

Nutrition and Health

Series Editor: Adrienne Bendich

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Victor R. Preedy *Editors*

Nutrients, Dietary Supplements, and Nutraceuticals

Cost Analysis Versus Clinical Benefits

 **Humana Press**

NUTRIENTS, DIETARY SUPPLEMENTS, AND NUTRICEUTICALS

NUTRITION AND HEALTH

Adrianne Bendich, PhD, FACN, SERIES EDITOR

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NUTRIENTS, DIETARY SUPPLEMENTS, AND NUTRICEUTICALS

Cost Analysis Versus Clinical Benefits

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Series Preface

The Nutrition and Health series of books has, as an overriding mission, to provide health professionals with texts that are considered essential because each includes: (1) a synthesis of the state of the science, (2) timely, in-depth reviews by the leading researchers in their respective fields, (3) extensive, up-to-date fully annotated reference lists, (4) a detailed index, (5) relevant tables and figures, (6) identification of paradigm shifts and the consequences, (7) virtually no overlap of information between chapters, but targeted, inter-chapter referrals, (8) suggestions of areas for future research, and (9) balanced, data-driven answers to patient /health professionals questions which are based upon the totality of evidence rather than the findings of any single study.

The series volumes are not the outcome of a symposium. Rather, each editor(s) has the potential to examine a chosen area with a broad perspective, both in subject matter as well as in the choice of chapter authors. The international perspective, especially with regard to public health initiatives, is emphasized where appropriate. The editors, whose trainings are both research and practice oriented, have the opportunity to develop a primary objective for their book; define the scope and focus, and then invite the leading authorities from around the world to be part of their initiative. The authors are encouraged to provide an overview of the field, discuss their own research and relate the research findings to potential human health consequences. Because each book is developed *de novo*, the chapters are coordinated so that the resulting volume imparts greater knowledge than the sum of the information contained in the individual chapters.

“Nutrients, Dietary Supplements and Nutraceuticals: Cost Analysis versus Clinical Benefits,” edited by Ronald R. Watson, Ph.D., Joe K. Gerald, M.D. Ph.D. and Victor Preedy, Ph.D. exemplifies the goals of the Nutrition and Health Series. Unlike many other books in the Series, this text provides a critical assessment of the economic value of dietary interventions studies. Each of the editors has extensive experience in nutrition research and cost analysis and the combined experiences in academia and clinical practice in the US as well as Europe provides a broad perspective on the role of food and food components, diet and diet modifications, nutrients, and many of the nonessential components of the diet on the economic impact of health and disease maintenance.

The editors have chosen 56 internationally recognized experts who are active investigators on the impact of overall diet and individual dietary constituents

on diseases and environmental stressors in different age groups, in different countries throughout the world, and in both sexes and the subsequent effects on health economics. This important, unique text provides practical, data-driven assessments of the cost effectiveness of nutritional interventions and the volume provides the reader with over 2,000 up-to date references and more than 150 well-organized tables and figures that assist the reader in evaluating the health economics associated with the use of vitamins and minerals and other dietary constituents, such as probiotics, long-chain fatty acids, conjugated linoleic acid, certain traditional Chinese medicines, plant polyphenols, tannins, and many other components of foods. Moreover, the critical value of nutrition for at-risk populations including those living with cancer, allergies and/or asthma, autoimmune diseases, the very young, and the very old are extensively reviewed in several unique chapters.

Each chapter begins with comprehensive bulleted Key Points followed by the list of key words, and includes an overview and historic review, examination of the literature with critical focus on comparisons between studies: discussion of the chemical composition of actives where appropriate and conclusions and perspectives on future research areas. The overarching goal of the editors is to provide fully referenced information to health professionals so they may have a balanced perspective on the value of many dietary components that are routinely consumed by patients and clients with the hope that healthy diets and prudent use of supplements and nutraceuticals can reduce overall healthcare costs. This important volume provides health professionals with balanced, data-driven answers to numerous questions about the validity of the science to date and also provides researchers with opportunities to clarify areas where many questions still exist about the effectiveness of specific nutrients/dietary factors on health outcomes and costs of disease prevention as well as treatment.

The editors have organized the volume into six sections that reflect the breadth and depth of current knowledge in the area of dietary factors that affect health and the cost effectiveness of improving nutritional status. In the first introductory section the editors have wisely included four chapters that examine cost effectiveness from a number of perspectives including nutritional options such as fortification, supplementation, and taxation of certain foods while providing subsidies for other, healthier choices. Areas reviewed include the calculation of daily adjusted life years (DALY) and a concept of the least-cost diet containing the minimal daily requirements recommended by national bodies. Unique areas of focus include an analysis of the potential effects of economic incentives on reduction of maternal and childhood under-nutrition. The second section on Influences on Preventive Nutrition Strategies includes three related chapters that describe the complex influences on choosing a healthy diet. Two chapters concentrate on fruit and vegetable choices and agree that price as well as economic status affect the purchase of fruits and vegetables. In depth analyses suggest that food price elasticity is of greater importance in lower and middle income families. Data from China, Brazil, as well as the United States are included. The third chapter examines the influence of ethnicity on the purchase of foods and food patterns. Social psychology models

are used and the theory of planned behavior is discussed as an example of how ethnicity can affect generations of dietary intakes. The third section provides in-depth, separate chapters devoted to the Potential for Cost Effectiveness with Food Interventions that are examined in four chapters. Two chapters discuss the potential for specific foods to be cost effective for children. Development of a lactose-free porridge that can be used as a ready to use therapeutic food in African malnourished children was found to be cost effective in reducing hospital stays. The use of fluoridated milk in needy children who already are provided milk in Chile has also been shown to be cost effective for reducing costs associated with dental care of young children. A broader based program is described for the US underprivileged children entitled the Supplemental Nutrition Assistance program (SNAP) managed by the USDA. By providing children nutrient dense foods and educational materials to parents, this program has shown that it is cost effective to be pro-active about nutrition. In contrast to these three programs, it is difficult to establish the cost effectiveness of nutrition interventions including increases in calcium and vitamin D intakes for improving bone health in children as a means to reduce the costs associated with osteoporosis. Perhaps an alternative strategy would be to look at the association of this intervention and reduction in costs of forearm fractures in prepubertal girls.

The fourth section on Antioxidant Nutrient and Bioactive Food Component Interactions: Potential Economic Benefits includes four chapters that examine the common thread of the importance of optimal antioxidant intakes throughout the lifespan for reducing disease risks and the dermal evidence of aging. One chapter provides a broad overview of the major dietary antioxidants and their concentrations in foods; the chemical structures of these important bioactive molecules are also included. There is a separate, in-depth chapter on zinc and its critical role as an antioxidant as well as a critical component of nonantioxidant enzymes. Options for enhancing zinc levels in the food supply are provided including genetic modification of plants with the goal of enhancing childhood immunity and enhancing the activity of tumor suppressor genes. Another source of antioxidant potential is reviewed in a chapter on a traditional medicine and food source from the hibiscus plant, Roselle. Teas made from parts of the plant have been used as an antioxidant, and also as an antibacterial especially in Mexico and other nations. The final chapter in this section is unique in its comprehensive review of the products used reduce the risk and treat the dermal signs of aging. There is an extensive discussion of the oxidative damage caused by UV light exposure and the importance of lifetime intakes of antioxidant rich diets to reduce environmental dermal damage. Authors of these chapters have been particularly inclusive and objective; extensive references to the published literature are provided.

The fifth section looks mainly at the Economic Effects of Dietary Components in Disease and Prevention Therapy in five chapters. Three of the chapters review the antiviral, antibacterial, antifungal, and anticarcinogenic properties of native plants that have been used as food sources and/or as medicinals. In-depth descriptions of the plants and the components identified as containing the bioactive component and its function are provided for more than 50

distinct plants. One possible way to utilize the antimicrobial properties of plant components is being utilized in food animal production practices. The use of citrus peels that are fed to livestock before slaughter to reduce food-borne pathogens before these enter the food supply is carefully described in another unique chapter. Secondary disease prevention and/or reduction in disease and surgical complications are examined in the last two chapters in this section. Chronic kidney disease is often a consequence of diabetes that is also often linked to obesity. Dietary changes to reduce cholesterol levels and insulin sensitivity can include supplementation with omega-3 fatty acids, antioxidants, B vitamins, and newer plant compounds that have been shown to be beneficial such as those from the olive leaf. These strategies have resulted in cost effective avoidance of dialysis and kidney transplants. Another proven cost effective strategy is the provision of preoperative immunonutrition formulas that contain arginine, omega-3 fatty acids, nucleotides, and other beneficial nutrients. Documentation of cost effectiveness has been shown in gastric cancer surgery patients and is reviewed in the final chapter in this section.

The final section of the volume contains eight chapters that examine the Cost Effectiveness of Dietary Intervention in Cardiovascular Disease and Diabetes. The economic value of the DASH diet is examined for hypertension reduction as well as a means to reduce the costs of care post myocardial infarction. Also, the WHO's evaluation of the global consequences of obesity and noncommunicable diseases are examined from a public health perspective. Changes in food industry choices and incentives for community health initiatives are reviewed. Diabetes prevalence is increasing globally and the potential for low glycemic, high satiety foods to enhance glycemic control are described in detail in two chapters. The third related pragmatic chapter provides practice guidelines and compilations of lifestyle interventions in prediabetics as well as for those with diabetes. The last two chapters explore the new findings from preliminary studies that examine the potential for a plant-based supplement to reduce the microvascular complications associated with diabetes and cardiovascular diseases and compare the cost effectiveness of this intervention with standard pharmacological agents.

Thus, it is clear that this volume contains a wealth of information concerning the potential for dietary interventions to reduce the costs associated with disease treatments. Additionally, the editors and authors have focussed on assisting those who are unfamiliar with the field of health economics in understanding the critical issues and important new research findings that can impact their fields of interest. Drs. Watson, Gerald, and Preedy have carefully chosen the very best researchers from around the world who can communicate the economic advantage of dietary components for both the maintenance of health and disease management. The authors have worked hard to make their information accessible to health professionals interested in public health, those practicing in medical specialties from pediatrics to geriatrics, those in general medical practice, health economists, public health practitioners, nurses, pharmacists and PharmD.s, educators, graduate students as well as nutrition-related allied health professionals.

In conclusion, "Nutrients, Dietary Supplements, and Nutraceuticals: Cost Analysis versus Clinical Benefits," edited by Ronald Ross Watson, Ph.D.,

Joe K. Gerald, M.D., and Victor R. Preedy, Ph.D. provides health professionals in many areas of research and practice with the most up-to-date, well referenced volume on the economic value of dietary intervention in evaluation of the importance of dietary factors for optimal health. This volume will serve the reader as the most authoritative resource in the field to date and is a very welcome addition to the Nutrition and Health Series.

Adrianne Bendich, Ph.D., FACN
Series Editor

Preface

Food and nutrition are vital keys to controlling morbidity and mortality from many chronic diseases affecting humankind. For millennia the relationship between famine and subsequent death due to disease has been known. Clearly food can be a key preventative agent for such dietary insufficiency-induced diseases. In the past decade, simple and very cheap vitamin A supplements not only prevented ocular damage but extended lifespan in children in developing countries. Documentation of the economic benefits of such dietary remedies is vital to their use in countries where there are insufficient health facilities and where adult diseases may take priority. In industrialized countries the cost to treat one person with a chronic disease like AIDS would pay for nutritional supplements preventing growth and development problems in thousands of children. Both are worthwhile but not always economically possible. Thus this book is crucial as it helps to document for health care agencies and individuals whether various *dietary supplements, nutrients and/or bioactive extracts promote health in a cost-effective manner or not.*

Biomolecules in dietary fruits and vegetables play crucial roles in health maintenance as well as in dietary supplements. They certainly could have different actions beyond their nutrient value in health promotion. For decades, it has been appreciated that oxidative pathways can lead to tissue damage and contribute to pathology. Fortunately, nature has provided us the mechanisms found predominately in plants to defend against such injury. Antioxidant nutritional agents have consequently attracted major attention and rightfully deserve to be studied carefully for possible beneficial roles. One of the main reasons for the interest in antioxidant agents in dietary vegetables, and their products, is their virtually complete lack of harmful side effects. This stands in stark contrast to many drugs that are promoted and studied for possible disease-preventive activity. However, are such bioactive molecules potent enough with an appropriate cost to be economically viable in health promotion? This book documents the potential cost-benefit relationship between major diseases and significant dietary supplements.

The US National Cancer Institute reports that only 18% of adults have the recommended intake of vegetables. Increasingly, Americans, Japanese, and Europeans are turning to the use of dietary vegetables, medicinal herbs, and their extracts or components to prevent or treat cancer. It has been known for decades that those populations with high vegetable consumption have reduced

risks of cancer and other diseases. However, which extracts or components are best to prevent disease or promote health? Some may be useful in experimental studies but the expenses of the supplements may outweigh the benefits. The goal of this book is to examine key ones for which health benefits are known to estimate their economic efficacy or lack thereof.

This book brings together experts working on the different aspects of supplementation, foods, economics and plant extracts and their potential for health promotion and disease prevention. Their expertise and experience provide the most current knowledge to promote future research. The conclusions and recommendations from the various chapters will provide a basis for using dietary supplements for which there is an economic rationale. By using vegetable extracts people can dramatically expand their exposure to protective dietary components and thus readily reduce their risk of multiple diseases. Specific foods, individual fruits or vegetables and their by products are reviewed in order to expand understanding and appropriate use. Yet are the benefits worth the increased costs of vegetables and their extracts? If so for which diseases? Which supplements are economically beneficial in treatment and/or prevention?

Plant extracts as dietary supplements are now a multi-billion-dollar business, built upon moderate research data. The bioactive extracts constitute many non-traditional medicines. In many cases these materials have been largely unregulated with limited requirements to show efficacy let alone economic efficiency compared to pharmaceutical drugs. Recently the US Food and Drug Administration has pushed this industry, with the support of Congress, to base its claims and products on scientific research. Therefore, the key area of dietary herbal medicine in this book will focus on efficacy or lack thereof in health promotion with emphasis on their economic benefits. Since common dietary vegetables and over-the-counter extracts are readily available, this book will be useful to health providers who treat clients and modify their lifestyles, as well as to the growing nutrition, food science, and natural product community. Increasingly, the lay public is requesting advice and is using more bioactive natural products in treatment and prevention of certain diseases including cancer, encouraging the medical community to become more knowledgeable. This book focuses on the growing body of knowledge on the role of diet, supplements and various dietary plants in reducing disease and whether the cost of such dietary changes equals or exceeds their economic benefits. As such the book will be essential reading for nutritionists, pharmacologist, health care professionals, research scientists, cancer workers, pathologists, molecular or cellular biochemists, physicians, general practitioners as well as those interested in diet and nutrition.

Our overall goal is to provide the most current, concise, scientific appraisal of the cost-benefits of nutritional supplements and bioactive components (nutriceuticals) of foods in improving the quality of life. The *basic outline* of the book involves concise chapters in sections: (A) *Introduction and Overview* which focuses on economics design in nutrition policy and value of dietary supplements; (B) *Influences on Preventive Nutrition Strategies* which focuses on benefits of fruits and vegetables versus costs; (C) *Cost-benefits of Food Interventions* which range from dental caries to malnourished children;

(D) *Nutrients and Bioactive Food Components and Interactions: Economic Benefits* which focuses on items such as natural antioxidants and zinc relative to their costs; (E) *Economic Effects of Dietary Components in Disease and Prevention Therapy* which focuses on cost benefits of citrus and vegetables on cancer and viruses; and (F) *Cost Effectiveness of Dietary Intervention in Cardiovascular Disease and Diabetes* which is the major section and shows the importance of dietary supplements relative to their costs. The excellent volunteer work of a wide variety of experts is greatly appreciated as it made this book possible.

Acknowledgments

The work of editorial assistant, Bethany L. Stevens, in communicating with authors, working with the manuscripts and the publisher was critical to the successful completion of the book and is much appreciated. Her daily responses to queries and collection of manuscripts and documents were extremely helpful. Support for her work was graciously provided by the National Health Research Institute as part of its mission to communicate to scientists about bioactive foods and dietary supplements was vital (<http://www.naturalhealthresearch.org>). This was part of their efforts to educate scientists and the lay public on the health and economic benefits of nutrients in the diet as well as supplements. Finally Nguyen T. Nga and Mari Stoddard of the Arizona Health Sciences library were instrumental in finding the authors and their addresses in the early stages of the book's preparation. The support of Humana Press staff as well as the input by the series editor, Adrienne Bendich is greatly appreciated for the improved organization of this book.

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Biography

Ronald R. Watson, Ph.D., attended the University of Idaho but graduated from Brigham Young University in Provo, Utah, with a degree in chemistry in 1966. He earned his Ph.D. in biochemistry from Michigan State University in 1971. His postdoctoral schooling in nutrition and microbiology was completed at the Harvard School of Public Health, where he gained 2 years of postdoctoral research experience in immunology and nutrition.

From 1973 to 1974 Dr. Watson was assistant professor of immunology and performed research at the University of Mississippi Medical Center in Jackson. He was assistant professor of microbiology and immunology at the Indiana University Medical School from 1974 to 1978 and associate professor at Purdue University in the Department of Food and Nutrition from 1978 to 1982. In 1982 Dr. Watson joined the faculty at the University of Arizona Health Sciences Center in the Department of Family and Community Medicine of the School of Medicine. He is currently professor of health promotion sciences in the Mel and Enid Zuckerman Arizona College of Public Health.

Dr. Watson is a member of several national and international nutrition, immunology, cancer, and alcoholism research societies. He is presently funded by the National Heart Blood and Lung Institute to study heart disease. In addition he has an NIH grant from NCCAM to study dietary supplements in modulating immune function and thus heart structure and function. For 30 years he was funded by Wallace Research Foundation to study dietary supplements in health promotion. Dr. Watson has edited more than 35 books on nutrition and another 53 scientific books. He has published more than 500 research and review articles.

Professor Victor R. Preedy is currently Professor of Nutritional Biochemistry in the Department of Nutrition and Dietetics, King's College London and Professor of Clinical Biochemistry in the Department of Clinical Biochemistry, King's College London. He is also Director of the Genomics Centre, Kings College London. Professor Preedy graduated in 1974 with a Degree in Biology and Physiology with Pharmacology. He gained his Ph.D. in 1981 in the field of Nutrition and Metabolism, specializing in protein turnover. In 1992 he received his Membership of the Royal College of Pathologists, based on his published works and in 1993 he gained a D.Sc. degree for his outstanding contribution to protein metabolism. At the time, he was one of the university's youngest

recipients of this distinguished award. Professor Preedy was elected as a Fellow to the Royal College of Pathologists in 2000. Since then he has been elected as a Fellow to the Royal Society for the Promotion of Health (2004) and The Royal Institute of Public Health (2004). In 2009 he was elected as a Fellow of the Royal Society for Public Health. Professor Preedy has written or edited over 550 articles, which includes over 160 peer-reviewed manuscripts based on original research and 85 reviews and 30 books. He has a wide interest in health related matters, particularly nutrition and diet.

Joe K. Gerald, MD, Ph.D., joined the Division of Community, Environment and Policy in the Mel and Enid Zuckerman College of Public Health in March of 2009. Dr. Gerald is the director of the undergraduate program in public health. His prior contributions to undergraduate education were recognized in 2001 as the recipient of the Ellen-Gregg-Ingalls/University of Alabama at Birmingham National Alumni Society Award for Excellence in Classroom Teaching. He currently teaches Health Care in the US and Health Economics and Policy.

Dr. Gerald completed a Ph.D. in Health Services Administration and post-doctoral fellowship in outcomes research at the University of Alabama at Birmingham. His research focuses on health outcomes, comparative effectiveness and economic research with an emphasis on the cost-effectiveness of interventions targeting children with asthma. His most recent work on the cost-effectiveness of school-based asthma screening was published in the *Journal of Asthma and Clinical Immunology*. This research used a novel short-cycle Markov Model approach to evaluate a 5 asthma health state model. He is currently investigating the cost-effectiveness of hand hygiene practices and their impact on asthma exacerbations.

Dr. Adrienne Bendich is Clinical Director, Medical Affairs at GlaxoSmithKline (GSK) Consumer Healthcare where she is responsible for leading the innovation and medical programs in support of many well-known brands including TUMS and Os-Cal. Dr. Bendich had primary responsibility for GSK's support for the Women's Health Initiative (WHI) intervention study. Prior to joining GSK, Dr. Bendich was at Roche Vitamins Inc. and was involved with the groundbreaking clinical studies showing that folic acid-containing multivitamins significantly reduced major classes of birth defects. Dr. Bendich has coauthored over 100 major clinical research studies in the area of preventive nutrition. Dr. Bendich is recognized as a leading authority on antioxidants, nutrition and immunity, and pregnancy outcomes, vitamin safety and the cost-effectiveness of vitamin/mineral supplementation.

Dr. Bendich is the editor of nine books including "Preventive Nutrition: The Comprehensive Guide For Health Professionals" coedited with Dr. Richard Deckelbaum, and is Series Editor of "Nutrition and Health" for Humana Press with 29 published volumes including "Probiotics in Pediatric Medicine" edited by Dr. Sonia Michail and Dr. Philip Sherman; "Handbook of Nutrition and Pregnancy" edited by Dr. Carol Lammi-Keefe, Dr. Sarah Couch, and Dr. Elliot Philipson; "Nutrition and Rheumatic Disease" edited by Dr. Laura Coleman; "Nutrition and Kidney Disease" edited by Dr. Laura Byham-Grey, Dr. Jerrilynn

Burrowes, and Dr. Glenn Chertow; “Nutrition and Health in Developing Countries” edited by Dr. Richard Semba and Dr. Martin Bloem; “Calcium in Human Health” edited by Dr. Robert Heaney and Dr. Connie Weaver and “Nutrition and Bone Health” edited by Dr. Michael Holick and Dr. Bess Dawson-Hughes.

Dr. Bendich served as Associate Editor for “Nutrition” the International Journal; served on the Editorial Board of the Journal of Women’s Health and Gender-based Medicine, and was a member of the Board of Directors of the American College of Nutrition.

Dr. Bendich was the recipient of the Roche Research Award, is a *Tribute to Women and Industry* Awardee and was a recipient of the Burroughs Wellcome Visiting Professorship in Basic Medical Sciences, 2000–2001. In 2008, Dr. Bendich was given the Council for Responsible Nutrition (CRN) Apple Award in recognition of her many contributions to the scientific understanding of dietary supplements. Dr Bendich holds academic appointments as Adjunct Professor in the Department of Preventive Medicine and Community Health at UMDNJ and has an adjunct appointment at the Institute of Nutrition, Columbia University P&S, and is an Adjunct Research Professor, Rutgers University, Newark Campus. She is listed in Who’s Who in American Women.

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Part I

Introduction and Overview

Chapter 1

Design of Economic Incentive Instruments in Nutrition Policy¹

Jørgen Dejgaard Jensen

Key Points

- Economic incentives are instruments to improve diet and reduce the fraction of people exposed to diet-related health risks.
- Proper targeting and design of economic incentive instruments is important, if such instruments are to be efficient and feasible policy measures for the improvement of dietary practice in industrialized countries.
- From a cost-effectiveness perspective, there is considerable potential for optimizing the targeting and design of economic incentive instruments in nutritional policy.

Keywords Cost-effectiveness • Economic incentives • Nutrition • Regulation • Taxation

1.1 Introduction

Inappropriate diet is a cause of increasing concern in many industrialized countries because of the increased risk of a range of health problems and diseases, including obesity, diabetes 2, cardiovascular diseases, and some forms of cancer. For example, during the last 40–50 years, the occurrence of obesity has increased considerably. Among the reasons for this increase are a ready supply of cheap food, an increasing consumption of convenience food and prepared fast-food meals [1–3], a change in the composition of the diet in the direction away from vegetables toward more saturated fats and sugar, and a change toward less physical activity, which has not been accompanied by a corresponding reduction in the energy intake.

Changed economic incentives may have been among the reasons for this development. The technological development of recent decades has lowered the costs of acquiring calories and increased the costs of expending these calories. Hence, the relative price between physical activity and calories has changed and consequently shifted the economic incentives in favor of higher calorie intake at the cost of calorie expenditure [3].

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In addition to the problems faced by individuals in terms of poor health, lack of social acceptance, and a number of inconveniences, diet-related health problems also induce external costs to society in terms of public financed costs to health care and reduced productivity. For example, it has been estimated that 5–8% of the total health care budget is used for obesity-related diseases in many industrialized countries [2, 4–10]. An increase in these costs may be foreseen because of future increases in the occurrence of such health problems.

Some of these costs are not taken into account in the decision making of consumers and suppliers in the market. In countries where health care is entirely or partially financed by the government – and in turn the tax payers – consumption decisions affecting the consumers' health status will impose a cost for the government in the future. Such so-called external effects have been recognized by economists as a key challenge since the work of Pigou [11]. When such external effects exist, they will distort the market mechanism and lead to a less than optimal utilization of the society's resources, and there is a need for policy intervention in order to correct for these externalities.

Several suggestions have been made in order to reduce the fraction of people with food intake deviating substantially from dietary recommendations and thus counter the challenge from diet-related health risks. Suggested measures include: instruments to change preferences, such as information campaigns; instruments to affect physical availability, such as tighter rules for advertising, promotion of healthier eating at schools; or instruments to change economic availability and incentives, such as modified food taxes or subsidies, etc. [12].

The idea behind modified food taxes or subsidies is to provide consumers with economic incentives to change their food consumption in a direction toward the nutritional recommendations, thus reducing the probability of being exposed to obesity or other health risks. However, in contrast to tobacco and alcohol, which have been subject to special taxation for many years in many countries, the use of nutrition-derived differentiated food taxes or subsidies has not been heavily represented on the agenda, and empirical experience with regard to differentiated food taxes – and thus empirical evidence about the effects of such food taxation on food consumption and health – is practically nonexistent. Despite the lack of empirical evidence, the following causality chain could however be presumed: tax change ! food prices ! food consumption ! fraction of people deviating from nutritional recommendation ! fraction of people exposed to health risks.

The objective of this chapter is to discuss economic incentives as a method to improve diet and thus reduce the fraction of people exposed to diet-related health risks. This goal is pursued in order to evaluate the importance of proper targeting and design if such instruments are to be efficient policy measures in the improvement of dietary behavior in industrialized countries.

The chapter is organized as follows. After this introductory section, [Sect. 1.2](#) will outline the general rationale for economic incentive instruments and introduce some of the main mechanisms that are important in the functioning of such instruments. [Section 1.3](#) will discuss the targeting of economic incentive instruments, whereas [Sect. 1.4](#) will discuss issues related to the design and magnitude of economic incentive instruments. In [Sect. 1.5](#), a quantitative example will illustrate some of the issues related to targeting and design, and finally, [Sect. 1.6](#) will draw some conclusions and perspectives.

1.2 The Rationale for Economic Incentive Instruments

Whereas arguments for nutrition policy intervention can be raised from many perspectives, the existence of external costs can be considered as the main reason for public intervention from a classical economic perspective.

Normally, we assume a positive relationship between price and supply, and a negative relationship between price and demand. Economic externalities exist when a transaction between two parties

have (positive or negative) economic consequences for a third party. Pollution is a classical example of an economic externality. If the production and marketing of a particular good implies pollution effects to the harm of other individuals, wildlife etc., these pollution effects are considered as externalities. If neither the producer nor the consumer of the product is held responsible for the costs due to the pollution effect, the market price of the product will in general not reflect the total costs to society of supplying this product – the cost of environmental damage is not included, and the production level will be beyond the optimal level from the point of view of society. Another example may be the long-term health effects of consuming certain unhealthy foods or beverages. To the extent that the long-term economic consequences of health degradation due to poor diet is not borne by the individual consumer – but by, e.g., their employers because of increased absenteeism or lower productivity, their families and relatives because of personal concern and discomfort, the surrounding society because of increased public health care costs, etc. – the dietary behavior can also be considered as an issue invoking economic externalities. During almost a century, economists, such as Pigou [12] have argued that the existence of such economic externality problems require regulation, if the behavior of producers, consumers etc. should not lead to suboptimal outcomes for society.

The theoretical foundation for using economic incentives as a regulation mechanism follows this line of thinking. As mentioned earlier, the existence of economic externalities implies that commodity market prices are not determined correctly from the point of view of society, because some of the costs for society are not included in the price setting. This provides economic incentives implying, e.g., that consumption of unhealthy foods exceeds the socially optimal level. Economic incentive regulation may attempt to “correct” market prices – or the consumers’ perception of the economic consequences of their behavior – by “internalizing” these external effects into market incentives (penalty), for example by adding the costs associated with long-term health consequences to the price of unhealthy foods.

Positive externalities can also be imagined, where a market transaction between two parties may have positive spill-over effects on third parties – for example that the consumption of a certain food product leads to positive health effects that will benefit employers etc. in the long run. In this case, an optimal socio-economic outcome would require a higher volume than the unregulated market outcome. One economic incentive regulation (reward) to stimulate such higher volume might be to subtract the value of positive externalities from the market price.

A basic premise for the use of economic incentive instruments is the assumption that agents act rationally, which implies that an economic reward or penalty mechanism will lead agents to adjust their behavior to increase rewards or reduce penalties. This also implies that demand curves are downward sloping, i.e., the higher the price, the lower the demand. Econometric studies for several countries suggest that higher prices on a commodity does have a negative impact on the consumption of this product [13–17], confirming this assumption.

In a structured review of the effect of economic incentives on consumers’ preventive behavior, Kane et al. [18] found that economic incentives worked 73% of the time, but that the rates varied by the goal and diffuseness of the incentive, with relatively high effectiveness in the short run for simple preventive care and for distinct, well-defined behavioral goals.

1.3 Targeting Economic Incentive Instruments

An overview of the potentials for targeting economic incentive instruments is given in Fig. 1.1. Individuals’ nutritional decisions are affected by a number of environmental factors, e.g., the provision of nutritional information from various sources, marketing, the availability of different foods, social and cultural norms, physical environment, time, etc.

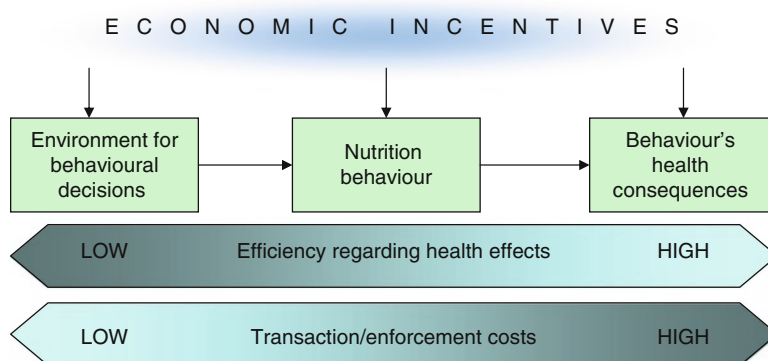


Fig. 1.1 Targeting economic incentive instruments in nutrition policy

Individuals' nutritional decisions may also be presumed to take into account the potential consequences (including long-term economic consequences) of their decisions, for example the risk of diet-related diseases such as cardiovascular diseases, diabetes, cancer, economic risk of future disability, enhanced unemployment risk, individual health care cost, risk of stigmatization, etc.

Hence, economic incentive regulation instruments could address the individual's decision making directly, for instance, by lowering the prices of healthy foods and increasing the prices of unhealthy foods, or by providing other types of direct rewards for desired behavior. But they could also address the decisions indirectly via the environment for the nutritional decisions or via the consequences of these decisions.

Economic incentives targeting the decision environment can be used to promote an environment that is more likely to lead to healthy decisions. For example, an economic reward to public authorities, nongovernmental organizations (NGOs), schools, workplaces etc. encouraging them to participate in nutrition education or intervention activities and provide stimulus for changes in social and cultural norms hampering individuals' healthy choices [19–23], an economic bonus to retail shops making an effort to promote the sales of healthy foods at the cost of unhealthy foods [24], a tax on advertising for unhealthy foods [25], all would be examples of economic incentive instruments that would address the decision environment as regards the contact between suppliers and consumers.

To the extent that individuals take the consequences of their decisions into account, their behavioral decisions may also be affected by economic incentives that relate to these consequences. For example, a higher degree of self-coverage of the costs associated with diet-related health problems [8] would provide individuals with an economic incentive to reduce the risk of getting such future health problems and hence choose a healthier diet. Such an approach would however raise a number of ethical questions, for example, related to income inequalities, fairness considerations etc.

An economic incentive argument might also be considered related to the sharing of responsibilities among different government authorities. Imagine, for example, that the financial situation of the authorities responsible for health promotion and prevention of certain life-style diseases were directly linked to the treatment costs invoked by those diseases, these authorities would have a strong economic incentive to maximize the effectiveness of their prevention efforts.

Economic considerations may guide the targeting of economic incentive instruments, and whether it would be most beneficial to address the decision environment, the direct short-term consequences of the decisions, or the long-term health consequences. Three aspects are important in this respect: (1) the effectiveness of the intervention for promoting long-term health induced by the regulation, (2) costs of distortions imposed by the regulation, and (3) transaction costs associated with the intervention (implementation, enforcement, monitoring, etc.).

A general finding from the economic literature is that a regulation is more *effective* the closer the regulation targets the ultimate goal [e.g., 26]. That is, if it is possible to target specific health consequences directly in a regulation, this will be more effective than targeting it indirectly, e.g., through selected dietary components. This rests on the reasoning that the more indirectly you target the regulation, the more the effects of the regulation will potentially occur in variables that are irrelevant for the goal. The more precisely the regulation targets the problem the smaller will be substitution effects (e.g., substitution from one unhealthy food type to another) etc., which may undermine the effectiveness of the regulation.

At the same time, the effectiveness also depends on the affected agents' possibilities to adjust to the regulation, and thus save costs, while still complying with the regulation, because a higher adjustment possibility within the regulation's aim implies a stronger incentive to comply. This relationship is also valid with regard to regulating the diet in order to improve the future health of the population and public health-care costs: The more directly and precisely the measures can be targeted towards these objectives, the more effective are the measures.

An important determinant for the effectiveness of intervention is how easily consumers can substitute different goods, measured by elasticities of the substitution. The larger the elasticity of substitution between two goods, the easier it will be for the consumer to replace consumption of one commodity with another commodity. This in turn implies that if the (physical or economic) availability of one commodity is reduced, consumers will tend to switch towards those goods with high elasticities substitution vis-à-vis the good, rather than towards those with low elasticities of substitution. Hence, the elasticities of substitution between different foods and beverages plays a crucial role for the effectiveness of policy intervention.

The effectiveness of intervention to promote consumers' preferences for healthy food (or dislike for an unhealthy food), e.g., information campaigns, commercial advertisements, press news, etc. depends not only on the extent to which such information affects the preferences, but also on the substitutability (elasticities of substitution). The latter has implications for which goods are replaced by the promoted good and the extent of this replacement. Interventions to affect the physical or economic availability of specific types of goods (e.g., restrictions on supply, regulation of space management in retail shops, differentiated taxes or subsidies, etc.) are also effective, if the affected goods can replace or be replaced in the desired direction, which again depends on the elasticity of substitution. Development of new food products as a health-promoting activity can be seen as an intervention to provide commodities with favorable health attributes (e.g., desired nutritional properties), but at the same time adopting some of the attributes of unhealthy products, which consumers find attractive (e.g., taste, convenience, brand, price). Hence, among such innovation activities, some can be interpreted as interventions aiming at affecting consumers' preferences, whereas others may affect the choice between healthy and unhealthy commodities.

As an example of economic policy measures with regard to the composition of diet is the imposition of taxes or subsidies on specific foods, for instance a VAT reduction on selected groups of food, like fruits and vegetables. A policy measure like this will provide consumers with an economic incentive to increase their intake of fruits and vegetables at the cost of other foods like meat, fish, and dairy products and thus lead to a less fat-intensive diet. However, the precision with respect to future health condition and public spending is more uncertain, because the health-enhancing effect varies across fruits and vegetables, and price-induced adjustments in diet composition may include changes that are not desirable from a nutritional point of view (e.g., decreased consumption of some other healthy foods). Furthermore, potential effects on physical activity are not taken into account. Thus, from a partial perspective, this effectiveness consideration suggests that economic incentives should address the consequences of nutritional decisions rather than the environment for these decisions or decisions *per se*.

Most regulations lead to *distortions* in behavior, which imposes costs on the individuals – compared to their choices without this regulation [27]. For example, if an individual would prefer an unhealthy snack over a piece of fruit, a regulation pushing him to choose the fruit will provide him with lower utility than if this regulation were not imposed – otherwise he would have chosen the fruit even without the regulation. It is not evident a priori, whether such distortions will apply more to some targeting versus another. However, the closer a regulation targets the final health goals, allowing flexibility in individual agents’ adaptation to these goals, the lower are these distortionary costs relative to the expected health effect, *ceteris paribus*. This is because such a regulation may use the fact that some individuals can more easily comply with a goal such as weight loss through reducing their intake of sugar-sweetened soft drinks and snacks, whereas others may find it easier to achieve weight loss through reduced intake of meat or fats. A regulation allowing for such individualized adaptation may be less costly than a regulation that does not allow for this. As the elasticities of substitution reflect individuals’ potential for such adjustments, the costs of change also depend on these elasticities.

The level of *transaction costs*, which are connected to the feasibility of an intervention, tends to increase as

- The more difficult it is to define and monitor the object of regulation.
- The more subjects that should be monitored.
- The more complicated the regulation scheme.

These considerations will in many cases suggest that transaction costs will be lower for incentive schemes introduced in the decision environment, and relatively high if the target is, e.g., individual health status in the population. Hence, partial transaction cost considerations would most often suggest interventions regarding the environment for nutritional decisions. Strnad [28] offers a useful review of some of the administrative and legislative challenges related to nutrition-related food taxation.

A changed VAT scheme was discussed earlier. Another type of economic measure is to impose taxes on specific detrimental components in the food commodities, e.g., the content of saturated fats or sugar (like the schemes proposed in Marshall, [29], or Jensen and Smed, [30]). Compared with the former type of economic measure, such a tax will be more closely connected to a final aim of improved future health. On the other hand, the administration of such a tax may be more costly because of higher requirements for documentation etc.

Other types of economic regulation might be to increase the economic incentives to physical activity, for instance by public support of sports [19], or to impose economic incentives with respect to the consequences of unhealthy lifestyle, for example a tax on the individual’s weight or BMI [8], or higher degree of payment on health care costs, which can be traced back to unhealthy lifestyle or obesity, possibly through insurance schemes where the premium depends on lifestyle etc.

The precision of the effects of taxes or subsidies on foods may be lower than for other measures, especially if very detailed objectives are pursued, e.g., by improving the diet of selected “risk segments” of the population. A potential barrier for the effectiveness of taxes and subsidies might be low response to price changes for targeted consumer segments, due to, e.g., imperfect information, habits, or lack of time. A range of studies document that the level of information and knowledge varies considerably across groups and such variations in the knowledge basis may have implications for consumers’ choices [31, 32]. Furthermore, economic ability or nutritional needs may vary across groups, and the use of economic instruments may lead to undesired regressive distributional effects, implying that poorer consumers become more heavily taxed than richer consumers, as illustrated by Leicester and Windmeijer [33] for example. Thus, “horizontal” policy measures that affect the price conditions equally for all consumers may give rise to undesired distributional effects that could be avoided by using more detailed “selective” regulations targeted at selected groups of consumers.

Despite these theoretical and empirical studies on food taxation, there seems to be only a few empirical studies dealing with the design of food taxation/subsidization instruments and thus the potentials for optimizing the efficiency of such instruments.

1.4 Design of Economic Incentive Instruments

In addition to the issue of targeting economic incentive instruments, there is also an issue of designing the incentive mechanism. One aspect to incentive design is whether a continuous or discrete approach should be used, i.e., whether there should be a positive continuous relationship between a stated goal and the reward, or, on the other hand, whether a fixed reward is triggered when some threshold concerning goal achievement has been reached. Incentives invoked by these types of design can be quite different. Whereas a discrete approach may provide a fairly strong incentive for reaching the stated threshold, it does not provide any incentive to go beyond this threshold, even if this would be desirable from a societal (health) point of view. In contrast, a continuous scheme may provide a somewhat weaker incentive to comply with the specified threshold, but may maintain an incentive to go beyond this threshold for some individuals.

Within the family of continuous schemes, it can also be considered, whether an incentive scheme should be proportional (e.g., VAT changes), progressive or digressive (cf. Fig. 1.2). In a progressive incentive scheme to stimulate a health-promoting behavior, the reward is relatively low for low levels of achievement, but accelerates with the level of achievement. For example, a reimbursement scheme, where the consumer's reimbursement per unit of fruits and vegetables gets higher, the more fruits and vegetables you buy, would be progressive in this sense, and the reverse is true for a digressive scheme.

As is the case with regard to targeting, feasibility is also an issue in relation to the design of incentive instruments. In general, a linear scheme is often more tractable than a progressive or digressive scheme from an administrative point of view. Whether continuous or discrete incentive instruments are most feasible depends on the nature of the instrument and the regulation object.

It is not a priori straightforward, whether economic incentives are best used to encourage healthy behavior or to discourage unhealthy behavior. Depending on the targeting of incentives, these two approaches may yield quite different outcomes. One explanation for this is the presence of substitution

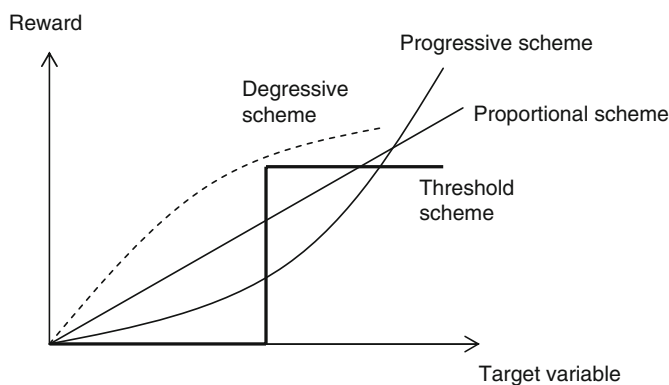


Fig. 1.2 Various design of economic incentive instruments

effects, including effects on the consumption of items that are not subject to intervention. This is illustrated in the quantitative example in the next section.

One issue that has not been explored much in the literature on dietary behavior is the provision of collective versus individual economic incentives. One exception is Brownell et al. [34], who investigate the effectiveness of worksite team-level weight loss-programs (with the pool of participation fees as the prize) and finds relatively high effectiveness and low attrition rates in team-oriented programs. Stunkard et al. [35], who compares individual, team-oriented, and organization-oriented weight loss competition schemes, also find that team-oriented competitions are more effective than individual and organization-level competitions. Imagine, for example, that all members of a certain group (e.g., a school class, a worksite, a local community) will receive a reward (or sanction) if a certain behavioral change has (or has not) been achieved for the group as a whole. Such an incentive scheme might invoke mechanisms of groups' discipline, peer encouragement etc. that could support the intended changes.

However, the success of such collective schemes may depend on the information framework surrounding the considered group [36]. In cases with asymmetric information (i.e., a situation, where group peers cannot perfectly observe the actions of every group member), such collective reward schemes may lead to "free-riding" behavior, e.g., if individuals' discomfort of complying with group incentives exceed the potential reward, after taking the risk of being discovered and the possible resulting sanctions into account. For example, assume that each member in a group of employees in a firm will receive a 1,000€ economic bonus, if the group as a whole achieves an average weight loss of 2 kg. Some of the employees in the group may already be fairly motivated to undertake weight loss activities, and this bonus may constitute the "tipping point" that makes them do it. But others may not be very motivated to lose weight, and they will get an incentive to go for the bonus while at the same time minimizing their own inconveniences related to participation in the weight loss program (i.e., they will as far as possible try to maintain their current life style and not engage much in weight loss activities) – they will tend to "free ride."

Another yet fairly underexplored issue in the field of dietary behavior is the distinction between permanent versus provisional economic incentives. Consider, for instance, a scheme where a short-run economic incentive is given to facilitate the transition from an unhealthy to a healthy diet, but once the healthier diet has been obtained, this is expected to be maintained without additional economic incentives. The rationale for such a scheme might be the existence of potential barriers to the transition from an unhealthy to a healthy diet. For example, such types of schemes may exist in relation to weight loss programs, where financial incentives may be included on the list of measures to obtain weight loss and life style changes, but once these changes have been achieved, the financial incentive is deactivated.

In addition to the issue of targeting economic incentive instruments, it should be noted that market prices result from the combination of demand and supply relations. Thus, the more price adaptable are the market supplies and demands for food commodities, the less will be the market price responses to a considered food tax change. The fact that most industrialized countries are members of the World Trade Organization, implies relatively free trade of food commodities between countries, suggesting that food supplies are fairly price flexible. This is supported by price transmission studies, where variations in domestic prices for many food commodities to a large extent can be explained by price variations in associated markets, indicating that domestic suppliers are facing competition from imported products [37]. To the extent that demand is not perfectly price flexible, an economic measure (e.g., tax reduction) may not be fully transmitted to the consumer price – some of the impact may be absorbed by increased margins in the food supply chain.

One final feature to the design of economic incentive instruments is the size of the instruments, e.g., tax or subsidy rate. On the one hand, the higher the tax or subsidy rates are, the stronger will also be the economic (and possible redistributive) impact for the affected individuals, of which

some may be unintended. On the other hand, a high tax or subsidy rate would be expected to yield a larger health effect than a low rate, although the marginal health effect of a higher rate may be decreasing.

1.5 A Quantitative Example, Comparison of Alternative Incentive Schemes

The previous sections have discussed a number of theoretical issues related to the use of economic incentives in nutrition policy. In order to illustrate some of the economic incentive mechanisms in a policy experiment, we now conduct a calculation of the effects of different formulations of a potential food tax reform aiming at the promotion of healthier diets.

The schemes are evaluated using a simple economic simulation model. Behavioral parameters (elasticities of substitution and derived own- and cross-price elasticities of food products) have been estimated econometrically on Danish data from the period 1971–1996 [38], and the model is calibrated to a situation broadly reflecting the current food consumption behavior in Northern Europe, distinguishing three food categories, healthy (fruits, vegetables, rice, pasta, fish, and potatoes), unhealthy (cakes, biscuits, sugar and sugar products, fats, and sugar), and neutral (meats, cheese products, and bread) [39]. Standard deviations reflecting heterogeneity among households are estimated on the basis of dietary survey data from the Danish National Food Institute [40].

Assumptions of the relationship between diet and health are inspired by various sources and reviews. Specifically, it is assumed that compliance with the assumed recommendation regarding healthy foods implies 0.01 lower relative risk of a number of diseases (e.g., cardiovascular disease and some forms of cancer). Similarly, complying with the recommendation on unhealthy foods also is assumed to imply a 0.01 lower relative risk of these diseases. It is furthermore assumed that the lower relative health risk for individuals complying with these recommendations implies that an increase in the share of population complying with these recommendations reduces the number of disability adjusted life years (DALY) in the population.

The assumptions of the model are summarized in Table 1.1. Note that in this example, we specify the consumption, as well as the recommended levels in monetary terms for tractability reasons. This solves a number of practical problems in the calculations of this illustrative example, but it is recognized that if such calculations should be conducted in relation to “real-life” instruments, it would be necessary to consider detailed quantities of the different commodities.

Now let us turn to the different incentive schemes. Specifically, we calculate the effects of five alternative economic incentive schemes:

1. A Reducing the price of healthy foods (VAT reduction)
1. B Increasing the price of unhealthy foods
2. A Discrete premium if household consumption of healthy foods exceeds a given threshold

Table 1.1 Model assumptions

	Healthy foods	Unhealthy foods	Neutral foods
Annual budget, € per capita	700	600	660
Std.dev. , € per capita	350	300	330
Threshold, € per capita	940	250	0
Impact on relative risk	−0.01	−0.01	
Elasticities of substitution			
Healthy foods		1,5	0,24
Unhealthy foods			0,1

2. B Discrete penalty, if household consumption of unhealthy foods exceeds a given threshold
3. Increased user payment on expected future health care services

The first two incentive schemes are assumed to affect the consumer prices of foods directly. For example, lowering the VAT on healthy foods is assumed to reduce the consumer price of these commodities by 20%, leaving the prices of other food commodities unaffected. This assumption implies that such change in taxation does not lead to changes in producers' or retailers' margins, neither on the group of healthy foods nor on other foods.

Incentive scheme 2A (2B) offers a bonus (penalty) to consumers complying (not complying) with the specified recommendation regarding the consumption of healthy (unhealthy) foods. In scheme 2A, consumers are offered a bonus, if their spending on healthy foods exceeds 940€/capita per year, whereas in scheme 2B, consumers will have to pay a fine, if their spending on unhealthy foods exceeds 250€/capita per year.

Finally, incentive scheme 3 assumes that the individuals will eventually have to pay a fee for obtaining health care related to diseases caused by unhealthy diet, that the individuals are aware of this future fee and that they take it into account in their consumption decisions. As consumers with an unhealthy diet face a higher risk of obtaining such diseases, this scheme also offers an incentive to eat healthily. But in contrast to the previous schemes, this scheme addresses the consequences of poor diet, not specific parts of the diet as such. Hence, the consumers are assumed to be free to choose how they would reduce the risk of developing these diseases – either by increasing the intake of healthy foods or by reducing the consumption of unhealthy foods. Again, it is assumed that the healthy choices differ from the actually observed choices, implying that the healthy choice yields a utility loss, compared with the current situation. As the individuals have larger flexibility than in the previous schemes – because they can choose between different health promoting lifestyle changes – the average utility loss is expected to be lower.

Table 1.2 provides some calculated consequences of the five incentive schemes, estimated by the model outlined in Table 1.1. All incentive schemes are scaled, such that they yield the same effect on aggregate disease burden – a reduction in the disease burden of 26 DALYper 100,000 inhabitants.

The first two schemes (1A and 1B) apply to the general market prices of healthy or unhealthy foods, and hence affect the entire population. This implies that the effects on total consumption of diverse foods are relatively strong, stimulating the consumption of healthy foods by 15–16% on average and reducing the average consumption of unhealthy foods by 10–12%. A reduction of the tax (and hence the price) on healthy foods (scheme 1A) naturally implies a reduction in consumers' spending on food, and hence an economic gain for consumers. However, the lower tax rate also leads to a reduction in tax revenue, which in turn implies either an increase in other tax rates or a reduction

Table 1.2 Estimated consequences of five alternative economic incentive instruments

	Continuous scheme		Discrete scheme		Health target
	1A	1B	2A	2B	3
Average consumption change – healthy	15.7%	15.4%	1.6%	3.2%	1.6%
Average consumption change – unhealthy	–10.7%	–11.3%	–1.1%	–2.3%	–1.4%
Average consumption change – neutral	–1.7%	1.0%	–0.2%	0.2%	0.0%
Change in disease burden – DALY per 100.000 inhab.	–26	–26	–26	–26	–26
Share of population affected, per cent	100%	100%	15%	15%	15%
Economic welfare loss, €/capita	34.2	46.7	3.5	9.7	2.5
Net public expenditure, €/capita	162.0	–109.0	5.0	–37.2	–73.9
Size of tax rate reduction/bonus, % or €/capita	20%	–	13.0	–	–
Size of tax rate increase/fine, % or €/capita	–	20%	–	138.6	110.9

in government service level, which in either case can be considered as an economic loss for consumers. The net economic welfare effect for consumers can be calculated by subtracting the government economic loss from the consumer economic gain, leading to an annual economic net loss of 34.20€/capita. Considering scheme 2B, which works in the opposite direction but with similar mechanisms, yields an economic net loss of 46.70€/capita. These economic net losses represent the value of the utility loss that consumers face, because the respective recommended diets deviate from the diet that the consumers would have chosen voluntarily.

Both food tax change schemes imply that a larger portion of consumers comply with the nutritional recommendations and hence reduce their future health risk. But for a considerable portion of the population, the dietary effects triggered by the tax changes are not sufficient to ensure this compliance, and are thus assumed not to yield health benefits, due to the threshold assumptions applied in the simplified model. Consequently, for this share of the population, the tax modifications involve an economic welfare loss, but do not yield health benefits, and this tends to reduce the cost-effectiveness of these incentive schemes.

In contrast, consider scheme 2A. In this incentive scheme, only those individuals complying with the recommendation on healthy foods become affected by the economic incentive, whereas those not complying do not feel any change at all. With regard to this scheme, the individuals can be categorized in three groups: those already complying with the recommendation (thus getting the reward without changing their behavior), those who are willing to modify their behavior to comply with the recommendation if they get the bonus, because the bonus is more than sufficient to offset their welfare loss due to changed diet (thus modifying behavior and getting the reward), and those who are not willing to modify their behavior to comply with the recommendation, because the reward is not sufficient to offset their utility loss (and thus do not change behavior nor receive the reward). In the reward scheme (2A), a compliance bonus of 13€/capita is calculated to yield the same health effect as a 20% price reduction on healthy foods. Fifteen percent of the model population will be affected, and consequently the average economic welfare loss is lower (3.50€/capita) than in the food tax reduction scheme.

In scheme 2B (penalty on noncompliance), a similar line of thinking can be applied. The size of the necessary fine is significantly higher (138.60€/capita) than the reward in the previous scheme, because the mean consumption of unhealthy foods exceeds the recommended threshold considerably. Fifteen percent of the population is affected, and the average economic net loss is calculated at 9.70€/capita.

In the final incentive scheme of this quantitative example (scheme 3), no specific taxes, subsidies, or bonuses are applied, but individuals are assumed to be held liable for part of the expected future costs due to disease induced by too low a consumption of healthy food or too high a consumption of unhealthy food. Thus, they have an economic incentive to reduce their future health risk, but they may choose which of the recommended thresholds they should prioritize in their diets. We assume that consumers take this liability into account in their current consumption decision and make a rational trade-off between the (financial) benefit of reducing this future liability and the utility of current consumption. The higher the future liability, the more willing will the consumers be to modify their current consumption to reduce the future health risk. It is calculated that if this future liability corresponds to an annual payment (annuity) of 110.90€/capita, the expected reduction in disease burden will correspond to that of the tax reduction on healthy foods (cf. scheme 1A). The scheme will affect 15% of the population, of which a little more than half will aim at increasing their consumption of healthy food to the recommended threshold, whereas a little less than half will aim at reducing their consumption of unhealthy foods below the recommended threshold for these foods. Because of the flexibility assumption that consumers can choose the most appropriate of these two strategies, the economic net welfare cost in this regulation scheme will be relatively low (2.50€/capita).

As mentioned earlier, the last scheme does not involve any taxes or subsidies at the time of consumption, but leads to a future extra liability corresponding to 110€/capita per annum. With a time horizon of 20 years and a 3% interest rate, this corresponds to an expected future liability of 3,000€/capita. This figure represents the future payment that the individual is statistically expected to be liable for after 20 years if he is not complying with the nutritional recommendations during this time period. How this expected payment should be implemented is yet another story that is not dealt with in this chapter.

The results in this example illustrate that the cost-effectiveness of economic incentive instruments in nutrition policy depends heavily on the targeting and design of these instruments. Carefully designed economic instruments may be substantially more cost-effective than relatively simple instruments, such as a general tax change on healthy or unhealthy foods. And targeting the health problem directly seems to be considerably more cost-effective than targeting individual sources of the health problem.

The analyses in this section focus on potential effectiveness and distortionary costs. As mentioned in the previous sections, also feasibility – and thus transaction costs – play an important role in the targeting and design of nutrition policy instruments – including economic incentive instruments.

These issues have been ignored in the example, but it is evident that the feasibility problems and associated administrative costs become larger the more complicated and individualized the instruments get. If, for example, a bonus (scheme 2A) should be issued conditional on passing a certain threshold, there is a need for individualized assessment of the consumption of healthy foods – an assessment that should be highly reliable and well-documented. This will involve considerable administrative costs.

It should also be underlined that this example is a artificial one, although the model assumptions and parameters are considered to correspond fairly well with empirical observations and statistical analyses. For this reason, it is expected that the qualitative lessons to be drawn from this example are plausible, but that quantitative relationships may differ considerably from the presented results, depending on country, classification of healthy versus unhealthy foods, existing policy framework, etc.

1.6 Discussion

Poor diet is a growing problem in most industrialized countries, and increasing portions of the population in these countries face nutrition-related health problems such as obesity, diabetes 2, cardiovascular diseases, various types of cancer etc. Consequently, substantial research efforts are devoted to solving these problems, with nutritional, medical, and pharmaceutical sciences as some of the most significant contributors. Social sciences are also involved, primarily in understanding consumers' attitudes, dietary and physical activity habits, etc. in an effort to improve behavior in these areas.

This chapter makes the claim that economics plays a role in the understanding and prevention of poor nutritional behavior. For example, during periods with increasing prevalence of obesity, food market conditions, such as physical availability or economic incentives, have developed in directions that are presumed to stimulate the consumption of unhealthy food at the cost of healthy food. To this extent, economic incentives contribute to food consumption behavior and hence to the development of corpulence, a deeper understanding of these incentives and policy instruments exploiting the incentives may also contribute to the solution of such health problems.

The use and selection of economic incentive instruments in nutrition policy involves a range of considerations, including cost, effectiveness, feasibility, target, design, scaling, flexibility, and ethics. In most cases, there is a trade-off between these different aspects. For example, one instrument might

be fairly easy to implement, but its health-improving effects would be modest. Another instrument might have a large health-improving potential, but is almost impossible to implement due to prohibitive administrative requirements. This chapter has discussed several of these aspects and some of the literature related to them. It is generally understood from economic theory – and to some extent illustrated by the above quantitative example – that the effectiveness of a regulation instrument is higher, the more precisely the instrument targets the objective of the regulation. But in many cases related to nutrition policy, the feasibility is also lower – and the associated transaction costs higher – for instruments that target health goals at the individual level.

Economic considerations make it clear that the economic environment has a say in the determination of peoples' behavior, including their dietary behavior. This is the case with respect to the environmental factors closely related to food consumption, e.g., food availability, food marketing, and food taxation. But also a large number of other environmental factors have an indirect role to play for the individuals' lifestyle and dietary behavior. Such environmental factors include family structure, education and income, market and policy conditions in the supply of foods (e.g., competitive conditions, agricultural policy, fishery policy, international trade, etc.), and physical conditions in homes, schools, worksites, institutions, sports facilities, etc. It is evident that economic interaction between these environmental factors can affect the consumption of healthy and unhealthy food and beverage, and that these interactions may also affect (positively or negatively) the effectiveness and costs related to introducing new economic incentive instruments. Such possible interactions should be taken into account in the consideration, targeting, and design of economic incentive instruments.

The use of economic incentive instruments in regulation is based on the individuals' behavioral response to these incentives. There is a need to distinguish between short-term and long-term effects of such incentives. In the short term, consumers are to some extent locked by habits and existing conditions (e.g., budget, restrictions on time, etc.), the availability and diversity of products is fixed, and hence consumers' room for making adjusted diets fit into their daily routines may be relatively limited. In the longer term, time or budget restrictions may be changeable, thus enabling larger adjustments, and food suppliers may have incentives to develop new food products that are in line with nutritional recommendations, following increased demand for such products.

One argument that is often raised against changes in commodity taxation is the aspect of border trade – if the consumer price of an unhealthy product increases in one country, its consumers will tend to buy these products in neighboring countries, thus undermining the health-improving effect of such a tax change. In general, the strength of this argument relies on three premises: that the price differential between the domestic and the foreign price is substantial, that the distance to the border is relatively short for a substantial portion of the population, and that the durability of the considered product is sufficiently long to avoid frequent border-crossing (which is related to the distance). It should be noted that this argument relates to the concrete targeting and design of an economic incentive instrument (a tax on specific foods), not to the idea of economic incentives in general.

Issuing economic incentives on food consumption behavior implies that the economic outcome for individuals depends on their current situation and on their behavioral adjustment. If, for example, an individual has a relatively large consumption of unhealthy foods, a tax on such foods will imply a relatively large economic loss for him – especially if his capability of substituting these unhealthy foods with healthier foods is low. In many countries, it seems to be a stylized fact that individuals with less education and lower income tend to have a relatively low consumption of healthy food and drink and a relatively large consumption of unhealthy food and beverage [40]. Consequently, the economic consequence of an increased tax on unhealthy foods would be expected to be relatively serious for people with less education and low socio-economic position [33]. On the other hand, a study by Smed et al. [41] suggests that the adaptability of substitution between healthy and unhealthy foods tend to be a decreasing function of the degree of education, and hence that food consumption

is more easily adjustable for people with less educations and lower economic social positions. But there is still a risk that nutrition-based food tax changes will tend to be regressive [39].

From an ethical standpoint, it can be argued, whether we, from a health perspective, should impose regulations that may contribute to increasing the economic inequalities in society. It should however be kept in mind that many other types of intervention to reduce nutrition-related health problems also have asymmetric effects on different socio-economic groups. For example, worksite health promotion programs most often tend to be biased towards some types of worksites, e.g., large worksites with many white-collar employees. Another ethical question is, whether society should intervene in people's dietary behavior at all, and to what extent is it justifiable to use instruments that affect the entire population – not only those individuals facing health problems from inappropriate diet.

As mentioned in the introduction, the issue of economic incentive instruments in nutrition policy is a fairly unexplored field of research. Some studies have been made regarding differentiated food taxes, but economic incentive instruments cover a much wider variety of possible instruments. The above discussions and the quantitative example suggests that there may be a potential for exploring such instruments more carefully. The main questions to be addressed would include different designs and sizes of incentive instruments, the feasibility of such instruments, and the associated transaction costs necessary to make the instruments work. Furthermore, there is a need for research in the adaptation of such incentive instruments in the current institutional and economic frameworks in different countries.

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Chapter 2

Nutrition Policy for the Prevention of Disease: Issues of Cost-effectiveness

Norman J. Temple

Key Points

- Governments should implement nutrition policies that will improve population health.
- These policies include reducing the salt content of processed foods, use of dietary supplements of proven value, eliminating hydrogenated oils that contain *trans* fatty acids from food.
- Implementation of the proposed policies would cost relatively little and should achieve significant health benefits within a few years.
- These policies therefore have a very attractive cost-effectiveness (i.e., they generate quality-adjusted life years [QALYs] at a fraction of the cost of many types of conventional medical treatment).

Keywords Cardiovascular disease • Coronary heart disease • Cost-effectiveness • Dietary supplements • Food advertising • Food labels • Food prices • Government policy • Health care • Health promotion • Hydrogenated oils • Hypertension • Nutrition policy • Population health • Public health • Quality-adjusted life years • Salt • Statins • Subsidies on food • Taxes on food price • *trans* fatty acids • vitamin D

2.1 Introduction

It has been well established since the 1970s that dietary factors play a major role in the causation and prevention of a spectrum of diseases. These diseases have been referred to as Western diseases, non-communicable diseases, and chronic diseases of lifestyle (CDL). The major CDL include most forms of cardiovascular disease (CVD) (including coronary heart disease [CHD], stroke, and hypertension), obesity, type 2 diabetes, and several major types of cancer.

The high prevalence of these diseases across the Western world has created immense pressures on health-care systems. This crisis is most severe in the United States where the cost of health care now exceeds \$2 trillion and accounts for more than 16% of GDP. This level of spending has created great strain on both public and private finances. Unless drastic measures are taken this spending is set to increase sharply over the next two decades. One factor driving this is that millions of baby boomers are now moving into their sixties. Another major factor is that the epidemic of obesity that has swept

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the world since the 1980s is now precipitating other health conditions such as type 2 diabetes. Compounding these problems the relentless cost inflation of medical treatment has shown little sign of being brought under control.

The economic crisis that swept the world in late 2008, the worst since the 1930s, created enormous budget deficits for governments in many countries. Thus, while the cost of health care is on an ever-rising trajectory, governments have a reduced capacity to pay these costs. This crisis of overspending is equally severe where medical costs are paid by individuals or by insurance companies: The individuals and companies who must pay the bills, whether directly or via insurance premiums, are also under much financial pressure resulting from the economic crisis.

There was one positive outcome from the economic crisis: A large section of the population woke up to the realization that the capitalist system requires careful government oversight. For many years banks and investments companies operated with complete freedom to conduct business as they pleased with minimal government regulation or oversight.

But what has this to do with nutrition policy? Actually, there are strong parallels between the problems of the financial system and that of the national diet. The economic interests of the food industry have been the dominant driver of nutrition policy in most countries, including the United States. This has frequently occurred in disregard of the health impact of these policies [1]. This has directly led to many of the health problems that are so prevalent in today's society, and their huge economic consequences. In brief, a lack of government oversight of the banks and investments companies played a major role in the economic meltdown, while the willingness of governments to place the economic interests of the food industry above the health interests of the general population has caused a deterioration in public health and the consequent expanded cost of medical treatment.

This chapter argues the case for a strategic shift on nutrition policy in relation to population health. It is essential to see the consequences of nutrition policy, not merely in terms of the economic interests of the food industry, but also in terms of the huge cost of medical treatment resulting from diseases that can be prevented by a healthy diet. In many cases it is possible to make a direct comparison between the cost-effectiveness of these policies with those of conventional medical treatments that target the same conditions. As we shall see, a nutrition policy approach often achieves far more benefit per dollar of expenditure than does medical spending.

2.2 The Cost-effectiveness of Medicine

Many analyses have been made regarding the cost-effectiveness of medicine [2]. Benefits achieved as a result of medical interventions are often quantified based on how many quality-adjusted life years (QALY) are generated. The use of QALY allows all types of interventions to be directly compared, both those that prevent deaths and those that improve the quality of life. The cost-effectiveness of medical interventions can then be estimated based on cost per QALY. In the United States interventions that cost in the range of \$50,000–\$100,000 per QALY are often regarded as being acceptable, though there is a lack of consensus on this. Other countries, such as the UK, often use lower cost thresholds.

The cost-effectiveness of medical intervention covers an extremely wide range. Here, we shall briefly examine some clinical preventative services, using estimates based on costs in the United States. Some such interventions are cost saving. Examples are aspirin therapy for the prevention of cardiovascular disease (CVD) in persons at elevated risk, immunization of children, and screening for tobacco use followed by a brief intervention [3]. Nicotine replacement therapy costs less than \$5,000 per QALY [4], clearly making it highly cost effective. Drug treatment of hypertension for nondiabetics is estimated to cost approximately \$53,000 per QALY [5]. Statins are a family of drugs widely prescribed for

the prevention of coronary heart disease (CHD). Their cost-effectiveness depends greatly on the level of risk of the patients being treated: The higher the risk, the lower the cost per QALY. Thus, for patients at high risk of CHD their cost-effectiveness translates to a rather modest \$20,000, or so, per QALY [6]. But this figure becomes tenfold higher for patients at intermediate risk of CHD [6]. For that reason statins are justified only for people at high risk of CHD [7]. Nevertheless, these drugs are heavily marketed for patients at intermediate risk of CHD as this allows pharmaceutical sellers to hugely increase total sales. Statins are far from being alone as an example of extravagant medicine: Around 1 in 11 preventative interventions cost more than a quarter million dollars per QALY [8].

While the focus above is clinical preventative services, the same problem of widespread use of medical procedures that exceed reasonable cost limits is seen in many other areas of American medicine. While this issue is much discussed in academic journals, there is seldom any serious attempt to bring this discussion into the public arena. A major reason for this is widespread opposition by politicians and others in the United States to the use of cost as a criterion for decision making [9].

Other countries take a very different approach on this issue. In the UK a cost-effectiveness analysis (CEA) is routinely performed as part of the process of determining whether particular interventions can be employed by the National Health Service and therefore paid for using tax money. Such evaluations are done by the National Institute for Health and Clinical Excellence (NICE) [10].

2.3 Nutrition Policy and Public Health

The lesson from the previous discussion is that unless serious efforts are made to constrain costs, medical interventions can often be extremely expensive; most cost in the range \$20,000–\$200,000 per QALY. A very different picture emerges when we examine what happens when governments implement policies designed to improve public health. These can often achieve widespread benefit at remarkably low cost. For example, a CEA has estimated that the mandatory use of daytime running lights and of motorcycle helmets is cost-saving [11], while a smoke-free workplace can prevent disease and do so at an estimated cost of a mere \$500 per QALY [4]. Much the same is seen with regard to nutrition policies: A strong body of evidence reveals that they can also deliver major health benefits at relatively low cost. Unfortunately, few CEAs have been carried out in this area.

Here we consider the nutrition policies where the evidence is strongest. The proposed interventions have been arranged in approximate order of cost-effectiveness, starting with the lowest cost. The policies have been broken into two groups:

Group A. There is a high probability that implementation of these policies will achieve significant health benefits within a few years and are cost-effective.

Group B. Here the cost-effectiveness is much less clear and/or the health benefits may be delayed by many years.

2.4 Group A Nutrition Policies

2.4.1 *Cutting the Salt Content of Food*

A substantial body of evidence reveals that the great majority of people across the Western world consume a grossly excessive quantity of salt in their diets and that this plays a major role in the causation of hypertension [12, 13] and cardiovascular disease (CVD) [13, 14]. Salt is also believed to be an important causative factor in stomach cancer [15].

In order to substantially reduce the salt intake of the general population it is necessary to cut the salt content of processed foods by at least half as this is where 75–80% of the salt in the diet comes from. Feeding studies demonstrate that consumers have little problem accepting food with a much reduced salt content [16, 17]. As it would cost extremely little to implement this policy and the potential benefits are so large, it clearly follows that the cost-effectiveness would be highly favorable. Based on an Australian estimate this policy would cost approximately (US)\$1,180 per QALY [18]. According to an American estimate cutting the sodium content of the diet to 2,300 mg/day would save around \$18 billion/year in health-care costs [19]. Another study estimated that a population-wide reduction in dietary salt of 3 g/day (1,200 mg of sodium) would prevent between 44,000 and 92,000 deaths per year [20].

Despite the strong case for the immediate implementation of this policy no action has been taken in the United States: There was no change in the salt content of food between 2005 and 2008 [21]. This contrasts with the UK where policy implementation has led to real progress. In that country the Food Standards Agency (FSA) embarked on an ambitious campaign to lower salt intake from 9.5 g/day in 2000/2001 to <6 g (roughly 2,300 mg sodium) by 2010. Actual intake by adults had fallen to 8.6 g in 2008 [22].

2.4.2 Dietary Supplements

There are several dietary supplements that have proven to be a highly effective, safe, and low-cost means to prevent disease. Iodide and fluoride are well-known examples. The prevention of spina bifida by the fortification of grain products with folic acid, a policy introduced in 1996, provides another illustration of the potential value of this strategy.

A strong case can be made that vitamin D has the potential to repeat this success. There is convincing evidence that the vitamin is of significant value in the prevention of osteoporosis. Strong evidence has emerged in recent years that the risk of cancer is significantly reduced when vitamin D levels are optimal [23]. This benefit may also extend to CHD [24, 25]. Based on this evidence a large section of the population would likely benefit from supplemental intake. This applies especially to people at risk of poor vitamin D status, notably people with darker skin color and inhabitants of northern latitudes, such as the northern states of the United States, northern Europe, and the whole of Canada [26].

There is much controversy as to the optimal intake of vitamin D. The RDA is currently 5 µg (or 200 IU) per day at age 50 or younger, and double that at ages 51–70. While we still need to see the outcome of long-term clinical trials, our best evidence suggests that a higher intake is more effective for the prevention of the diseases discussed earlier. For that reason a supplemental dose of 25 µg (or 1,000 IU) per day is indicated for those whose vitamin D status is likely to be suboptimal.

This policy has already been partially implemented in Canada where all adults over age 50 are advised to take a vitamin D supplement, though at a lower dose than that suggested here. It is important to appreciate that the potent form of vitamin D is D₃. Many supplements have D₂ but that is only one quarter as potent.

According to a 2003 estimate, vitamin D supplements decrease fracture rates at a cost of \$800 or less per vertebral fracture avoided [27]. This indicates that vitamin D supplements are highly cost-effective, especially for people aged over 40 or 50 who may be vulnerable to poor vitamin D status.

2.4.3 Trans Fatty Acids

Partially hydrogenated oils contain *trans* fatty acids. Major food sources of these fats include hard margarine, cakes, donuts, cookies, pastry, and deep-fried foods. Lesser amounts of *trans* fatty acids

are present in ruminant animals. *Trans* fatty acids are now recognized as adversely affecting multiple cardiovascular risk factors and contribute significantly to increased risk of CHD [28]. By one estimate if these fats were removed from the American diet, CHD rates would be reduced by 3–6%, possibly by as much as 12–22% [29].

There is nothing to stop governments implementing a policy requiring that hydrogenated oils containing *trans* fatty acids be removed from food. But as is often the case with important issues of public health, governments in several countries have chosen the path of relying on voluntary efforts by industry to reduce population intake of these fats [30]. Serious attempts have, however, been made in several jurisdictions to reduce consumption. Denmark stands as a fine example. New York City and San Francisco have enacted regulations banning these fats from food sold in restaurants while British Columbia (Canada) has gone further and imposed a ban that affects not only restaurants but also bakeries and other food outlets.

Implementation of a policy that leads to the removal of *trans* fatty acids should prevent at least 13,000 CHD deaths per year in the United States. According to an estimate made in 2003 there would be a one-time industry cost of \$139–\$275 million for testing, relabeling, and reformulation [31]. The above information leaves little doubt that such a policy, calculated as dollars per QALY, would deliver improved health at bargain-basement prices.

2.4.4 Health Promotion

Since the 1970s many health promotion interventions have been carried out in the United States and around the world [32]. These have been done in varied settings, including schools, worksites, physician offices, and in the community. Some have focused on just one or two lifestyle changes while others have been more wide ranging. The most common goals have been to reduce excess weight, lower the blood cholesterol and blood pressure, and encourage people to quit smoking and exercise more. Overall, the results have been mixed; typically, progress has amounted to no more than a few percentage points. This might be expected to reduce the risk of CHD by about 5–15% [32]. Despite this limited impact well-designed health promotion campaigns can be a cost-effective way to improve lifestyles and thereby positively affect the health of large numbers of people [33–35].

Much health promotion is carried out independently of governments. However, governments have the resources and authority required to implement health promotion programs across diverse settings. For that reason the expansion of health promotion programs is best done as government policy.

2.4.5 Improved Food Labels

Food labels used in the United States and many other countries leave much to be desired; many consumers find them confusing. In the United States and Canada labels mix together food components where intake should be limited (sodium, sugar, and saturated fat) and food components that are often lacking in the diet (fiber and omega-3 fat). Labels give information as quantity per serving but similar products often use different serving sizes, thereby making it difficult for consumers to make accurate comparisons.

A system which I consider much superior is based on traffic lights. This has been developed in the UK by the FSA [36]. With this system colored circles are placed on the front of the pack and show

at a glance if the food has a high (red), medium (orange), or low (green) content of fat, saturated fat, sugars, and salt. The label also indicates the actual quantity of these substances per serving. This system is not as yet in widespread use but has been adopted by some supermarkets and food manufacturers. Research studies have reported that traffic lights labels increase the ability of people to assess the health value of a food [37, 38].

One possible improvement to this system is to add an extra traffic light to indicate the global health value of a food. Such a system requires a standardized methodology for nutrient profiling so as to compare foods. Several such systems have been proposed [39]. A British group has developed a system based on a limited number of food components [40]. The NuVal Nutritional Scoring System is an algorithm developed in the United States that generates a score based on more than 30 different nutrients and nutrition factors [41].

The long-term health benefits of improved food labels are difficult to predict. However, as the cost of implementation is modest and the expected benefits may be significant, it can be confidently predicted that their cost-effectiveness will be very favorable.

A special issue of food labels concerns restaurants. These are where a substantial part of the population consumes much of their diet. Dinners in restaurants often supply huge amounts of food energy, as much as 1,000–1,500 kcal, but most people have little realization of this. Menus in restaurants are therefore another area where nutrition information is needed, especially the energy content of meals [42, 43]. Proposals to implement such a policy are usually restricted to restaurant chains with at least ten restaurants. Legislation has been passed to implement this policy in several cities (including New York, San Francisco, and Philadelphia) and several states (including California, Oregon, and Massachusetts). The new health care bill passed in 2010 turned this policy into federal law for all restaurant chains with at least 20 outlets.

2.5 Group B Nutrition Policies

We now examine nutrition policies where the cost-effectiveness is much less clear. This is often because the health benefits may be delayed by many years.

2.5.1 Nutrition Policy, Children, and Adolescents

Several important nutritional policies concern children and adolescents.

Food advertising on TV that targets children is overwhelmingly (80–90%) for unhealthy food choices or for fast-food restaurants [44, 45]. Not surprisingly, such advertising is often successful in inducing children to consume the advertised foods [46, 47] and is strongly associated with the risk of obesity in children and adolescents [48]. As the advertising of unhealthy foods is clearly detrimental to health, the obvious remedy is an outright ban. This has been done in Quebec (Canada), Sweden, and Norway [49]. A much more common approach, despite its limited effectiveness, is based on voluntary agreements and self-regulation by the food industry [49].

A study was recently carried out on 395 American public schools [50]. Vending machines were present in 82% and 97% of middle and high schools, respectively. Among schools where food was sold, approximately five in six of them permitted the sale of foods or beverages that are nutrient poor but high in energy (i.e., “junk food”). When schools permit the sale of unhealthy food they are – implicitly – conveying an educational message that is the diametric opposite of the one stated in

food guidelines. Schools should therefore be compelled to restrict the sale of unhealthy food. Likewise, where meals are served in schools, these should be of high nutritional quality. This can be justified as a means to directly improve the nutrition of children.

The cost of these policies on food advertising, on food sold in schools, and on school meals is difficult to estimate. For example, many school authorities may oppose restrictions on the sale of unhealthy food as those sales can be a valuable source of extra income. However, from a societal perspective the true cost of the proposed policies is likely to be reasonably low as spending lost in one area will be directed to other areas. In particular, as the sale of less healthy foods declines, sales of healthier foods will rise, and so will advertising for it.

The proposed policies should bring about a reduced prevalence of obesity. Another important benefit is that improved dietary habits of children and adolescents will, at least to some extent, carry over to middle age. Clearly, most of the health benefits of the proposed policies will accrue many years (~50 years) after the initial expenditures. As much is unknown with regard to both the cost and health benefits of these policies, their cost-effectiveness cannot be estimated with any accuracy. Nevertheless, much like environmental protection, expenditures today are justified based on their long-term benefits.

2.5.2 Food Prices

Changing food prices by means of taxes and subsidies is an attractive means to encourage healthier eating patterns. The price structure of food in the United States and other Western countries means that less healthy foods with a high energy density (energy per gram) are generally cheaper than healthier food choices. Refined cereals and foods with added sugar and fat are among cheapest sources of energy, whereas the more nutrient-dense foods, such as fish, lean meat, vegetables, and fruit, are generally much more expensive when the price is expressed as the cost of food energy (dollars per 1,000 kcal) [51–53]. For that reason people with a low income are pressured to select a relatively less healthy diet with a low content of several micronutrients (such as vitamin C and beta-carotene) and a high energy density [54]. This is probably an important reason why the poorest people are often the least healthy.

An important factor responsible for the current price structure of food is that government subsidies are paid to agricultural enterprises with little regard for their nutritional consequences. For example, the subsidies paid to American corn producers have made high-fructose corn syrup a cheap energy source and this has helped bring about a huge increase in consumption of soft drinks. [55]. Likewise, the Common Agricultural Policy of the European Union gives much higher subsidies to farmers for production of full-fat milk than for skimmed milk, while large quantities of fruit and vegetables are withdrawn from the market and destroyed so as to maintain high prices [56].

Studies on both smoking and alcohol have revealed “price elasticity” (i.e., consumption falls in response to a rise in price) [57–69]. The effect is stronger among the lower socioeconomic groups. What applies to tobacco and alcohol also applies to food [61]. We can reasonably assume that the judicious use of taxes and subsidies can shift eating patterns in a healthier direction. This was explored by Jeffery, French, and colleagues in a series of studies conducted at worksites and in high schools in the United States [62–64]. They observed that halving the prices of healthier food choices (low-fat snacks sold in vending machines and of fruit and salad ingredients sold in cafeterias) lead to a doubling or trebling of sales.

The above evidence points to the potential of government policies concerning prices of food to be an effective means to bring about desirable changes in eating patterns: The healthier choice must also

be the affordable one. Taxes and subsidies could be used as tools to persuade people, for example, to consume whole grain bread rather than white, low-fat milk rather than full-fat milk, and chicken rather than beef. A tax on sugar-sweetened beverages has been proposed [65].

This strategy is potentially one the most powerful nutrition policy approaches but is also one the most challenging. There is likely to be much opposition from industrial lobbies. Another challenge with regard to the use of taxes and subsidies is that the “law of unintended consequences” can rear its ugly head. For example, a British study based on computer simulations concluded that a reduction in consumption of saturated fat was likely to increase salt consumption, while taxation on milk and cream tends to cause a decrease in fruit consumption [66]. Clearly, while attractive, the use of taxes and subsidies as part of a nutrition policy needs to be carefully researched before being implemented.

The cost of the proposed changes to food prices may be quite high in the short term due to disruptions in patterns of agriculture and food production. However, in the longer term the cost should be minimal; depending on how the program is planned, extra costs in one area are canceled out by savings in other areas. As is the case with several of the other policy proposals discussed here, the long-term health benefits are very difficult to estimate. For these reasons more research is required before a realistic CEA can be made.

A variation of a strategy based on direct changes to food prices is the provision of healthy foods to people by more direct means. The US government gives food assistance to the more needy members of its population by way of several different programs. The largest of these is the Supplemental Nutrition Assistance Program (SNAP; formerly the Food Stamp Program). These programs are a potential vehicle by which people could be encouraged to consume healthier foods [67]. As an example of this, studies in both the UK [68] and United States [69] reported an increased intake of fruit and vegetables when low-income women were given vouchers that could be exchanged for these foods.

2.6 Conclusion

The policy proposals discussed here fall into two distinct groups:

Group A. There is a high probability that implementation of these policies will achieve significant health benefits within a few years and are highly cost-effective. These policies include reducing the salt content of processed foods, use of dietary supplements of proven value (perhaps starting with vitamin D for selected population groups, such as middle-aged and elderly people who have a lack of sunshine exposure), eliminating *trans* fatty acids from food, carefully selected health promotion interventions, and improving food labels so that they present clear information on the health value of food (e.g., traffic-light labels and adding nutrition information to menus in restaurants, especially the energy content of meals). These policies are likely to cost well under \$1,000 per QALY.

Group B. Here the cost-effectiveness is much less clear and/or the health benefits may be delayed by many years. These policies include nutritional policies that target children and adolescents and changes to food prices by means of taxes and subsidies.

The proposals made here, especially those in Group A, should be seen as the basis of a new overall nutrition strategy. They should help counter the burden of chronic diseases of lifestyle. This proposed strategy is best seen in the wider context: The objective of all policies and actions that impact on human health, whether carried out by government or the health-care industry, can be viewed as simply a means to generate QALYs. This encompasses policies as varied as improved road safety, removing hazardous chemicals from the environment, protecting the population from epidemics of infectious disease, giving dietary advice to the general population, and treating people

with drugs to treat hypertension or cancer. Seen in this context the proposed nutrition policies are a logical development of the above policies and actions.

Measured as dollars per QALY – or bang for the buck – the proposed nutrition policies generate QALYs far more cheaply than is achieved by many types of conventional medical treatment. By making comparisons as dollars per QALY it becomes clear that conventional medical interventions, such as the use of drugs for lowering blood cholesterol and controlling hypertension, typically cost many times more than nutrition policies to achieve comparable benefit: whereas medical interventions mostly cost in the range \$20,000–\$200,000 per QALY, the proposed nutrition policies are likely to cost well under \$1,000 per QALY.

There is one important barrier that stands in the way of the implementation of the policies discussed here, namely that health care is typically viewed as an essential service whereas improved nutrition policies are seen as having a much lower priority. We see this in the high priority politicians give to maintaining first class health care, at least for the majority of the population. Costs are seen as something that should be reduced where possible. Nutrition policies, by contrast, are discussed narrowly in terms of improving population health and have a far lower priority for most governments. One important factor responsible for this is pressure on governments by commercial interests: On the one hand, the pharmaceutical industry reaps vast profits from treating disease while the food industry has a vested interest in ignoring the health impact of its products. I argue here that it makes far more sense to evaluate the costs and potential value of health care and nutrition policies with the goalposts in a fixed position. Clearly, we need a paradigm shift.

In coming years it is likely that the total cost of health care will steadily become higher and suck in an ever-greater proportion of the national economic pie. A logical response to this will be policy initiatives to reject the use of medical procedures that exceed preset limits, measured as dollars per QALY. As mentioned earlier, this policy has already been implemented in the UK. Proposals along these lines have been made for the United States [70]. The bottom line is that what makes obvious sense is to direct finite resources to where they can be most usefully deployed; to do otherwise should be seen as irrational. The proposed strategic shift on nutrition policy and health should be viewed from that perspective.

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Chapter 3

Economics of Food Fortification

Annie S. Wesley and Sue Horton

Key Points

- The benefits of investments in micronutrient fortification far outweigh the costs: costs tend to be a few cents per person per year.
- Benefit: cost ratios (comparing the economic benefits of fortification to the costs) are very favorable. Cost-effectiveness is also high.
- This is true both in industrialized countries (for micronutrients such as iron, iodine, and folic acid) and developing countries (for the same three micronutrients, plus potentially zinc and vitamin A).
- Not all populations can be reached by fortification, and success requires an appropriate food vehicle.
- The chapter focuses on mass fortification, but special and targeted fortifications are also helpful to reach specific population groups.

Keywords Cost • Cost-benefit • Cost-effectiveness • Folate • Folic acid • Iodine • Iron • Vitamin A • Zinc

3.1 Introduction

Despite significant reductions in poverty in recent years, undernutrition remains widespread around the world. Recent estimates published in the Lancet [1] suggest that “maternal and child undernutrition is the underlying cause of 3.5 million deaths, 35% of the disease burden in children younger than 5 years, and 11% of total global DALY’s” (Disability Adjusted Life Years). One of the causes of undernutrition can be attributed to one or more micronutrient deficiencies, principally iron, iodine, vitamin A, folic acid, or zinc [2].

More than two billion people in the world suffer from micronutrient (vitamin and mineral) deficiencies caused largely by a dietary deficiency of vitamins and minerals. Also known as “hidden hunger,” the micronutrient deficiencies lead to long ranging effects on health, learning ability, and productivity. There are high social and public costs associated with reduced work capacity and higher healthcare expenditures due to high rates of illness and disability. Although people in all population

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groups in all regions of the world may be affected, the most widespread and severe problems are usually found among resource poor, food insecure, and vulnerable households in developing countries.

The solutions to address these deficiencies include ingestion of oral supplements (tablets, capsules, and syrups), public health measures, food fortification, and other food-based approaches. As national governments recognize and implement a combination of health and nutrition interventions, there has been a steadily growing level of interest in the costs and benefits of micronutrient interventions.

In the Copenhagen Consensus, 2008, a group of world-renowned economists ranked fortification of commonly eaten foods with vitamins and minerals, among the top three international development priorities [3]. This gives an opportunity to make strong economic and social arguments supporting increased investments in food fortification to meet the needs of essential micronutrients in developing countries.

The economic benefits of food fortification include reduced morbidity, improved work capacity, and improved cognitive ability. Reduced morbidity will reduce health care costs and days lost in school or at work; improve school attendance, concentration, and performance; and strengthen both production and consumption benefits. Reduced public health and public education expenditure, and reduced school dropout and retention rates will increase efficiency of public investment for essential social services and free resources for better uses. The economic value of fortification is expressed in improved work output due to increased work capacity and improved marginal productivity of labor. Last, improved cognitive ability will allow realization of the benefits of education expenditure; raise the number of years of schooling and academic performance; and, in a growing economy, will also raise wages and household income invested in the quality of the next generation of children [4]. The methodology for undertaking calculations is described in [Section. 3.2](#) below.

Important micronutrients with significant impact on public health include vitamin A, iron, iodine, zinc, and folic acid. Their significance is described in [Section. 3.3](#). Other micronutrients used in fortification of some staples in some countries include vitamin C, vitamin D, vitamin E, calcium, other B vitamins (thiamin, niacin, and riboflavin) and selenium. There are few or no economic studies available for these micronutrients. Fluoride has occasionally been added as a fortificant to food, but is more commonly added to drinking water. Although there are economic studies of fluoridization of drinking water, this is not covered here since this chapter focuses on food fortification.

Food fortification is a medium- to long-term solution to alleviate specific nutrient deficiencies in a population. It involves the addition of measured amounts of a nutrient-rich “premix,” which contains the required vitamins and minerals, to commonly eaten foods during processing. Within an integrated approach, micronutrient fortification of foods and condiments allows for an inexpensive and highly cost effective strategy to improve and protect the health and nutritional status of populations. The start-up cost for food fortification is relatively inexpensive for the food industry, and recurrent costs are rapidly passed on to the consumer. The benefits of fortification can extend over the entire life cycle of humans. It can thus be one of the most cost-effective means of overcoming micronutrient malnutrition. Although it is a fact that the first reason for fortifying foods with essential vitamins and minerals is this approach is safe and effective, the economics of food fortification has played an important role in its implementation in public policy.

To understand the economics of food fortification it is important to know the various ways in which fortified foods reach the consumers. Based on the population being reached and the type of industry compliance, several types of fortification are described in the World Health Organization’s (WHO) Guidelines on Food Fortification with Micronutrients [5]. This in turn has implications for calculating the economics of food fortification.

Mass fortification: When foods widely consumed by the general population are fortified. Flour fortification with iron and folic acid is a good example.

Targeted fortification: Since there are also age and lifecycle effects on peoples’ micronutrient requirements, to meet the additional nutritional needs of specific groups of population, foods

consumed by these groups can be targeted for fortification. Examples include complementary foods for young children or food rations for displaced populations.

Market-driven fortification: Food manufacturers take a business-oriented approach to fortify some of the products as value-added products thus complying with the specifications for permissible nutrients and quantities. This compares to the mass and targeted fortification programs that focus on those micronutrients that are needed the most by the general population. Cost becomes a factor for mass fortification thus it is important to have the collaboration of different stakeholders, particularly those in government and the milling industries. On the other hand, market-driven fortification might lean toward those micronutrients that have the greatest recognition and appeal to the intended market, usually the higher socioeconomic group that would purchase the premium products. Cost is generally not an issue in this situation.

Mandatory versus voluntary fortification: Based on legal considerations and compliance requirements, food fortification can be mandatory or voluntary. In mandatory fortification it is stipulated by a country's laws that certain foods should be fortified with specified nutrients and at specified levels. In contrast, with voluntary fortification the food industry is permitted to add micronutrients as long as it is within a framework of specifications. Mass fortification is generally mandatory, targeted fortification can either be mandatory or voluntary, and market-driven fortification is voluntary.

Industrially processed staple foods and condiments are the obvious choice for fortification given their consistent consumption by large sections of the population. A multifaceted approach of fortifying more than one food vehicle is a good strategy, especially when a universally consumed vehicle is not available.

Common food vehicles that can be fortified include: wheat and wheat products, corn, rice, milk and milk products, cooking oils, salt, sugar, breakfast cereals, and condiments. As processed foods gain popularity and market reach in the developing world, they offer new channels for micronutrient delivery. Industrially produced, fortified complementary foods are an option to reach infants and children under the age of 24 months because they have a different dietary pattern than adults. In countries or regions where there are few centrally processed complementary foods, alternative mechanisms include home fortification in which micronutrient mixes in daily dose sachets have been successful [6].

In this chapter we do not cover fortified foods developed for specialized populations such as the elderly, for participants in sports, or for populations with particular health risks or conditions. Some of these topics are covered in other chapters. We do not cover fortified products used for community-based treatment of severe, acute malnutrition (Ready-to-Use Therapeutic Food), or new products currently being developed for prevention and management of moderate malnutrition in young children (surveyed elsewhere) [7], or fortified foods for refugees.

The results from economic studies of fortification are reviewed in [Section 3.4](#). [Section 3.5](#) contains a brief conclusion.

3.2 Methodology for Calculating Economic Benefits of Fortified Foods

Realistic quantitative estimates of the economic consequences of micronutrient deficiencies can be defended on epidemiologic and economic grounds, and these estimates can be used to understand population-wide benefit – cost ratios and cost effectiveness for food fortification. Several studies have demonstrated that fortification is not only cost effective (i.e., is a cheaper way to increase micronutrient intake compared with other interventions that have the same aim), but also has a favorable *cost–benefit* ratio (i.e., is a good investment).

Cost-effectiveness is defined as the cost of achieving a specified outcome. In the case of food fortification, examples of the desired outcome might include the following: averting one case of

subclinical vitamin A deficiency, averting one case of anaemia, or averting one case of goitre or of iodine deficiency. Two outcome measures that are frequently employed in cost-effectiveness assessments of health interventions are the “cost per death averted” and the “cost per disability adjusted life year saved” (or cost per DALY saved).

Cost-effectiveness estimates are not directly obtained from interventions, but are constructed from what is known about the cost of interventions, effectiveness (in terms of micronutrient status) of interventions, and links between micronutrient status and morbidity/mortality outcomes. The analysis of program effectiveness requires the identification of the impact of the program on the outcome [5].

WHO’s CHOICE Project [8] is a useful tool for assessing cost-effectiveness. CHOICE stands for “CHOosing Interventions that are Cost-Effective,” and is a tool developed by WHO to help decision-makers select those interventions and programmes that provide the maximum benefit for the available resources. By generalizing the cost-effectiveness analysis, the application of the CHOICE model indicates which interventions either singly or in combination provide the best value for the money.

Cost–benefit: In its simplest form, a cost–benefit analysis compares the monetary cost of an intervention with the monetary value of the outcome (i.e., the benefit). It is expressed as the number of dollars gained (or saved), per dollar invested. Cost-effectiveness analyses are valuable tools for comparing interventions that share the same outcome; if however, the objective is to compare interventions with different outcomes, or to compare interventions whose potential benefits or outcomes extend beyond health, then a cost–benefit analysis is needed. The outcome or benefit may be increased productivity (e.g., iron fortification makes adults less anemic and hence more productive) or possibly lower health-care system costs (e.g., mothers who are less anemic will incur fewer complications during childbirth). Since cost–benefit analyses can be used to compare the relative merits of health intervention with other kinds of government spending, they are especially helpful for advocating the increased resources for nutrition and health.

The application of cost–benefit analysis requires information on the impact of a program as well as the input required to bring about this impact. Monetary values are attached to these impacts and inputs to get benefits and costs respectively, and finally costs and benefits are compared.

A cost–benefit ratio calculation requires much the same unit cost and effect data as a cost-effectiveness analysis. The cost data are typically easier and cheaper to obtain than the effect data. In addition, the benefit or rather the outcome of a health intervention (e.g., a reduction in prevalence of goiter or a change in the mean urinary iodine excretion of a population) has to be expressed in financial terms, that is to say, assigned a monetary value. Most cost–benefit studies do not do this directly, but rely on the findings of other studies that have linked the proximate health outcome to a financial benefit. For example, cost–benefit analyses involving iodine interventions, which seek to estimate the financial gain of eliminating one case of goiter (as an intermediate outcome), turn to studies that have estimated the costs associated with the loss of productivity per child born to a mother with goiter [5].

3.3 Economic Significance of Different Micronutrients

The important micronutrients that have significant impact on public health are briefly described in this section.

3.3.1 Vitamin A

Vitamin A deficiency is a major public health nutrition problem, affecting over 130 million preschool-aged children and likely at least that number of school-aged children and adolescents in

the developing world. Low vitamin A status affects an estimated 20 million women during pregnancy and the early phase of lactation. The most vitamin A-deficient populations are in Southern Asia and rural Africa. Chronically low vitamin A intake, from preformed and provitamin A carotenoid sources, is the major, underlying determinant of vitamin A deficiency. Vitamin A deficiency in newborn babies, infants, and children accounts for about 6% of under-5 deaths, 5% of under-5 DALYs (disability-adjusted life-years) lost, and 1.7% of total DALYs lost [1]. Since vitamin A is a fat soluble vitamin, fortification of oil and margarine are the foods traditionally fortified with vitamin A. Milk, sugar, and flour have also been used successfully.

3.3.2 Iron

One of the most widespread nutrient deficiencies is that of iron, which is estimated to affect one in three of the world's population. Iron deficiency anemia among pregnant women is associated with increased risks in childbirth, causing more than 20% of maternal mortality in Asia and sub-Saharan Africa and more than 20% of the deaths in the first week of life. There are two broad areas in which iron deficiency is considered to have important functional impact on humans, where economic consequences can be estimated: cognitive ability of children, and work capacity of adults. Iron deficiency has adverse effects on work productivity of adults, leading to losses in economic output. Iron deficiency also interferes with normal brain development and learning among children. Studies confirm that children with adequate iron status interact better with others and have better cognition, as well as perform better in school [10], and hence have potential for higher lifetime income. Women of reproductive age have a higher need for dietary iron so as to reverse the loss of body stores of the nutrient with monthly menstrual cycles. The common food vehicles for iron fortification are cereal flour, however other options that are successfully tested or being tested include soy/fish sauce, double fortified salt, and rice.

3.3.3 Iodine

Severe iodine deficiency in pregnancy is associated with significant cognitive loss in babies, with the most extreme outcome being cretinism, where the individual is mentally retarded and has almost no chance of a healthy and productive life. Even mild and moderate iodine deficiency among women during pregnancy can result in significant IQ loss and learning ability in their children. Adequate iodine intake is also essential for cognitive development in young children.

3.3.4 Folic Acid

Folic acid has been shown to be effective in the prevention of 50–70% of neural tube defect cases. Dramatic improvement in population-wide serum folate levels have been demonstrated in the USA and Canada since the addition of folic acid to flour was mandated. In South Africa, a significant reduction in neural tube defects has been documented following flour fortification in 2003 [11], and a similar benefit has been documented in the United States [12]. Additional benefits of folic acid fortification also include the correction of folic acid deficiency anemia and decreased homocysteine levels. Increased folic acid intake may also reduce the risk of other birth defects, and the incidence of stroke, heart disease, and some cancers. While concerns about potential negative health

consequences associated with folic acid fortification have arisen more recently, careful review of the of the information showed that most of the questions raised in recent literature on folic acid result from conditions where study participants received high dosages of folic acid in supplements, not levels typically found in fortified foods [13].

3.3.5 Zinc

Adequate zinc nutrition is necessary for optimal child health, physical growth, and normal pregnancy outcomes [14]. Notably, the recently published Lancet series on maternal and childhood undernutrition estimates that zinc deficiency is responsible for approximately 4% of deaths and DALY among children under five in lower income countries [1]. This places zinc intervention programs among the key strategies that have been suggested for ensuring greater child survival through improved nutrition. There is relatively little published information regarding the impact of zinc-fortified cereal products on biochemical or functional indicators of zinc status; and many of the available studies focused on specialized foods that might be used only in targeted fortification programs, rather than zinc-fortified cereal flours that are appropriate for mass fortification programs.

3.3.6 Other Micronutrients

Staple foods can be, and are, fortified with other micronutrients in selected countries. Many countries require some of the B vitamins lost in milling to be added back to flour (niacin, thiamine, and riboflavin). Vitamin D fortification of milk, dairy products, and margarine is frequently practiced, particularly in more northerly and southerly latitudes, as well as countries where exposure of skin to sunlight is culturally restricted. Ascorbic acid is sometimes added as an antioxidant, and vitamin C is added to some beverages, but higher cost and instability in storage make vitamin C less cost-effective as a fortificant. Calcium has been used to fortify juices and beverages (it is frequently added to soy milk, since this is used as a substitute for cows' milk but does not have the same calcium content). Selenium has been used to fortify salt in specific regions of China where it is known to be deficient in soil and associated with public health issues. Some B vitamins (niacin, riboflavin, and thiamine) are often added back to flour, since they are lost in the milling process. The WHO Guidelines mention these other nutrients [5]. There are however very few economic analyses of fortification using these other micronutrients, with the exception of two or three articles on the cost-benefit and cost-effectiveness of providing thiamine to combat Wernicke-Korsakoff syndrome, which is associated with alcoholism.

3.4 Economics of Fortification

3.4.1 Fortification of Staples

Fortification of staples is likely to reach some of the more deficient groups in the population, and economics is generally favorable.

Flour: Wheat and maize (corn) flour are widely and regularly consumed, and mostly processed in large industrial mills with established distribution and marketing networks that deliver the products to urban and rural populations in many countries. The small incremental cost of fortification can be easily passed on to the consumer. In situations when the incremental cost of fortification cannot be sustained by millers or passed directly to the consumer, governments may assist by assuring consistent enforcement of fortification regulations, subsidization, or tax exemptions. Other steps to be considered include bulk purchasing of premix for distribution to millers and the purchase of premix on a regional basis, when fortification standards are sufficiently compatible. Industrially milled wheat and maize flours are currently the most common products fortified with iron and folic acid. The flour fortification initiative (FFI) [15] estimates that in 2008 more than 63 countries are fortifying all or some of their wheat flour with iron, folic acid, and other nutrients covering 28% of the global market. Following a series of technical consultation and review of available impact studies, the WHO issued technical recommendations for wheat flour fortification for national governments. The recommendations provide guidance on the bioavailable forms of the nutrients to be considered based on diet and flour consumption levels [16]. It is important for countries to follow these guidelines in order to achieve the maximum impact.

A detailed incidence study for iron fortification [17, 18] estimated that the benefit to cost ratio has a median value of 6:1 for effects on physical productivity, which rises to 8.7:1 if cognitive benefits are also included. Cost of flour fortification is about \$0.12/person/year. The effects of iron are productivity increase in manual work and cognitive effects (maternal/perinatal mortality).

Salt: The most successful global fortification experience is the fortification of salt with iodine. Adding iodine to salt is a simple and low-cost manufacturing process. A significant proportion of the populations in more than 110 countries have access to iodized salt. Successful salt iodization has reduced the incidence of goiter and cretinism, prevented mental retardation and subclinical iodine deficiency disorders, and contributed to improved national productivity. Recent efficacy studies and economic analysis also show promise for salt that is double fortified with iron and iodine as a very attractive option for areas where fortification of wheat or maize flour in large scale mills is not an option [19]. Both the levels of iodine and iron in salt can be adjusted to the salt intake of the population consistent with other health goals such as reducing excessive sodium intake.

Rough estimates of the annual potential costs attributable to iodine deficiency in the developing world are \$35.7 billion prior to widespread salt iodization, as compared with an estimated \$0.5 billion annual cost for salt iodization, i.e., a 70:1 benefit to cost ratio [20]. Cost of salt iodization is about \$0.05/person/year. The effects are protection of brain development in pregnancy and young children. Adding iron to salt increases cost by \$0.20/person/year.

Soy sauce and fish sauce: Results from trials of fortification of soy sauce in China with iron (EDTA) suggest that consumption of fortified sauce can reduce anaemia by 30% or more (effect varies by demographic group) [21]. Fortification is inexpensive. To date, only voluntary fortification has been tried, and the take-up of fortified soy sauce has been modest except around the sentinel sites where promotion was extensive [22], but efforts are currently underway to reach poorer and rural households [23]. No benefit to cost calculations have been published, but given that the cost per person per year of the fortificant is \$0.007 [21], the benefit to cost ratio would be high if widespread use of the product could be achieved, provided that the social marketing costs were not excessive.

Effectiveness trials of similarly fortified fish sauce in Vietnam obtained a significant (33.8%) decrease in anaemia, compared to a non-significant decrease in the control group [24]. The cost of fortification is also modest (\$0.02/l), but production and consumption remain low [25]. No benefit to cost estimates are available, but as for soy sauce would likely be favorable if commercial production were feasible.

3.4.2 Fortification of More Specialized Products

The results presented so far are based on commercial fortification programs. There are various alternatives using specialized products targeted to meet a specific need. For such interventions, the unit costs tend to be higher than for commercial fortification. On the other hand, the intervention can be targeted, e.g., to weaning-age children who are particularly vulnerable to deficiency and who are unlikely to obtain enough of selected micronutrients from foods fortified for the general population.

3.4.2.1 Multiple Micronutrient Powders and Home Fortification

Single dose sachets containing micronutrients in a powder form called multiple micronutrient powders are easily sprinkled onto any foods prepared in the household. This practice is referred to as “home fortification” and is gaining popularity as a means of reaching children between 6 and 24 months. The iron (ferrous fumarate) is encapsulated with a thin lipid layer to prevent the iron from interacting with food so that there are minimal changes to the taste, color or texture of the food; other micronutrients, including zinc, iodine, vitamins C, D, and A, and folic acid, are added.

Cost-effectiveness and cost–benefit of home fortification approach is promising [26]. Costs include \$3.60/year/infant; \$7.20/year/child 12–23 months (based on \$0.03/sachet, three courses of 60 sachets, if distribution cost doubles cost of sachets). The effects include reduced anaemia, reduced mortality from diarrhoea. Estimates for Pakistan, when primarily targeted to children 6–12 months, suggest that cost per DALY saved could be as low as \$12 (based on the effects of zinc on averting diarrhea), and the benefit to cost could be 37:1 (based on the effects of iron on future productivity due to cognitive benefits), which are quite similar to estimates for commercial fortification. These estimates are based on intervention trials rather than a full-scale program and are for a country with high levels of deficiency, high infant mortality rates, and high rates of diarrhea. Larger scale trials would be worthwhile, and it would be also desirable to obtain distribution costs from program experience.

3.4.2.2 Fortified Complementary Foods

Though in some countries, micronutrient powders through home fortification are enough to improve nutrition (where food is less a limiting factor), in other developing countries, providing food along with micronutrients meets the calorie and micronutrient gap and improves growth according to a recent literature survey [26]. Fortified complementary foods being tried in developing countries include Plumpy’doz \$0.17/child/day (250 kcal); Ying Yang Bao \$0.10/child/day (40 kcal); Lipid-based nutrient spread (e.g., Nutributter) \$0.10/child/day (100–125 kcal) and India Ready-to-Use Food (WFP) \$0.13/child/day (250 kcal) [7].

Cost-effectiveness (cost per DALY) of fortified complementary food is less attractive than for micronutrients alone, since the annual cost per child is quite substantial (\$40–\$80 per child per year for providing 100–250 kcal/day each day from age 6–23 months). The main economic benefits are not averting deaths, but rather enhancing productivity; no recent benefit to cost data is available. If an investment of \$40–\$80 per child were able to reach similar benefits from the longitudinal study of supplemented children in Guatemala [27] where wages of adult men who were supplemented as children were 46% higher than those of controls, then benefit to cost ratios might be as high as 7:1. The benefit to cost and cost-effectiveness ratios discussed in this section are summarized in Table 3.1. Table 3.2 then compares the cost-effectiveness of selected fortification interventions, with those of

Table 3.1 Summary of Health Economic Impact if 1 DALY = \$1000

Intervention	Benefit:cost	Cost-effectiveness
<i>Fortification of staples</i>		
Salt iodization [20]	30:1	
Flour fortification – iron [17, 18]	8:1	
Flour fortification – folic acid [11]	46:1	
Sugar/oil fortification – Vit A [8]	(50:1)	\$17–22/DALY saved
Double Fortified Salt [19] (benefits of adding iron)	2:1 to 5:1	
<i>Home fortification</i>		
Multiple Micronutrient powders – effect of iron [6]	37:1	
Multiple Micronutrient powders – effect of zinc [6]	(13:1 to 80:1)	\$12.20–\$73/DALY
<i>Food based approach</i>		
Fortified complementary food	(2:1 to 1:1: mortality only) Up to 7:1 (authors' estimate using productivity)	\$500–\$1,000/ DALY ⁷

For sugar/oil fortification results are from WHO-CHOICE [8] project for Africa D region

() Implies results for cost-effectiveness are translated into benefit:cost using the value of \$1,000/DALY following Copenhagen Consensus 29 (Available at <http://www.copenhagenconsensus.com>. Accessed September 24, 2009)

Table 3.2 Cost-effectiveness of fortification as compared with other health interventions

Nutrition interventions	Health interventions (examples)
<i><\$20/DALY saved</i>	
Sugar fortification w' vit A; home fortification w' zinc (low estimate)	Intermittent treatment of pregnant women against malaria
<i>\$41–100/DALY saved</i>	
Home fortification with zinc (high estimate)	Screen and treat STDs to prevent HIV/AIDS (in sub-Saharan Africa)
<i>\$500–\$1,000/DALY saved</i>	
Complementary fortified foods	MCH package combined with neonatal care

Table 3.1 for fortification results: 30 for comparative health data

some health interventions for developing countries. Fortification is clearly an attractive intervention and comparable in cost-effectiveness to several high-priority health interventions.

3.5 Conclusions

The benefits of investments in micronutrient fortification far outweigh the costs: the costs tend to be a few cents per person. Economic analysis suggests that fortification is indeed a very high-priority investment. High benefit to cost ratios (comparing the economic benefits and costs of fortification) have likewise put fortification in the forefront in public policy regarding social sector investments. Also, provision of micronutrients to vulnerable groups is cheaper than spending public funds to treat the consequences of micronutrient deficiencies. To be successful, fortification requires a suitable food vehicle. It is also important to recognize that there are populations that are hard to reach with commercial fortification, particularly those living in more remote geographic areas and not utilizing purchased foods. Special and targeted fortification programs, though less cost-effective, are needed to ensure that the hard to reach and vulnerable populations are also covered. The chapter has focused more on economic aspects of fortification in developing countries, although one micronutrient (folic acid) is currently under evaluation for staple fortification in a number of industrialized countries also.

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Chapter 4

The Economic Value of Dietary Supplements

John F. Raffensperger

Key Points

- All nutrients can be obtained from food, without dietary supplements.
- Adding dietary supplements could reduce the cost of the diet only marginally, and only if the supplements complement the diet correctly.
- Most people could have a better diet and at lower cost simply by making different food choices.

Keywords Cost • Dietary supplement • Economics • Least cost diet • Linear program

4.1 Introduction: The Economic Value of Supplements?

What is the economic value of dietary supplements for Americans? To the supplements industry, this value is whatever Americans are willing to pay – about \$25.2 billion just for the year 2008 [1]. This is a high value! Fortunately for the industry, more than half of American adults take dietary supplements at least once per month [2].

Unfortunately for Americans, despite impressive and elaborate manufacturers' claims, doctors and scientists have long advised people to get their nutrients from food. Sales rely heavily on our gullibility. Worse, some supplements can cause harm. Toxicity of supplements is one type of cost, and a serious one. The safety of supplements has received considerable attention [3], while Americans have been reporting adverse events [4], and scientist have been reporting that the quality of dietary supplements is uneven [5].

The US Dietary Supplement Health and Education Act defines a dietary supplement as a product that is intended to supplement the diet, that contains one or more dietary ingredients, is intended to be taken by mouth as a pill, capsule, tablet, or liquid; and is labeled on the front panel as being a dietary supplement. That is a rather wide definition. Given the lack of evidence of effectiveness (and often good evidence of no effectiveness) of many supplements, this chapter will focus narrowly on only the 17 nutrients listed in the US government Dietary Supplements Ingredients Database [6]. This study makes an implicit assumption that any other nutritional supplement will not help anyone. The 17 nutrients have been rather well filtered by a host of previous science. If we consider only the high quality supplements, can we make a case for their economic value?

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The benefits of dietary supplements, at best, are similar to the benefits of food. Interventions that improve nutrition could help people to be healthier and more productive [7]. This is not controversial, especially for people in developing countries. We would expect that sick people, or people with special dietary needs, might benefit from supplements. Arguments about the economic burden of malnutrition are strong, but those are not necessarily good arguments for dietary supplements. For hospital patients, supplements can save money [8]. For elderly institutionalized people, a normal good diet is likely to be sufficient [9]. For elderly people who are home-nursed, supplements have been found to be of significant benefit [10–12]. What is uncertain, however, is whether supplements are of economic benefit to healthy Americans. Therefore, this chapter is rather narrowly focused.

We would expect that healthy people without special dietary needs would survive adequately without dietary supplements, as people have done for several hundred thousand years. However, a person selling dietary supplements could claim that we sometimes do not get enough nutrients, and therefore, supplements can ensure that we get what we need. The same salesperson might even claim that we could save money, because nutritious foods are expensive, while supplements are cheap. If someone takes a vitamin A supplement, he or she can eat fewer carrots. Can we save money on food if we take supplements? That is a relatively easy question to answer with a computer, as we shall see. Are we likely to lack nutrients, and if so, which ones should we take? The obvious answer is, “It depends.” In addition, this chapter aims to provide a study design that can be easily updated with any new scientific data.

This chapter will omit analysis of toxicity, placebo effects, side effects, supplements without at least one of the (RDA) required nutrients, ergogenic aids, interactions between supplements or between supplements and drugs, and substitution of prescription drugs with herbal remedies. The chapter will take existing required food fortification (e.g., vitamin D in milk) as given; fortified foods are not considered as a dietary supplement.

4.2 Literature Review: Diets and Math Models

Nutrition has long been studied with the operations research technique of linear programming (LP). In fact, LP’s inventor, George Dantzig, calculated a least-cost diet as one of the first problems solved with the new algorithm [13, 14]. He wanted to answer Stigler’s question, “What is the least cost of subsistence?” [15]. Other related important early work was done by Balintfy [16]. See also Lancaster [17].

Ferguson et al. [18] used LP to seek a mix of foods local to Ghana, Bangladesh, and Latin America, which would match or exceed the nutrient density of the nutrient-dense formula F100; the authors found no solution. Briend et al. [19] described how to use LP in a spreadsheet to plan children’s diets.

In an interesting paper, Santika et al. [20] used LP to show that Indonesian infants were likely to be short of iron, and the authors consequently developed complementary feeding recommendations. The authors stated that a food-based approach would not ensure iron sufficiency. Ferguson et al. [21] used LP in a four-phase approach to recommend better diets that are culturally appropriate and population-specific. They suggested supplements only in case their model could not satisfy nutritional requirements, but their model appeared to satisfy requirements based on their data.

Gao et al. [22] used LP to find diets which maximize vitamin E content for Americans, subject to constraints on other nutrients. They found that such diets were possible, but were quite different to the typical diet. However, it seems that vitamin E maximization may not be an ideal objective. Briend and Darmon [23] used LP similarly to determine which nutrients are likely to be short in a diet.

The study here is similar to this previous work. The model we wish to solve asks the following question: Please tell us which foods to eat to minimize cost, while ensuring that the minimum nutritional requirements are satisfied, and the maximum requirements are not exceeded. This question can be formulated mathematically as the following problem. The essential model remains the same in all these papers, all the way back at least to Dantzig’s.

Input Data

a_{fn} = amount of nutrient n in 100 g of food f . Source: The Food and Nutrient Database for Dietary Studies (FNDDS) [24] for foods, and Dietary Supplements Ingredient Database [6] for supplements.

b_n = required daily amount of nutrient n . Source: Dietary Reference Intakes, Otten et al. [25].

c_f = cost per 100 g of food f . Source: CNPP Food Prices Database [26].

d_n = maximum daily amount of nutrient n . Source: Dietary Reference Intakes, Otten et al. [25].

F = the number of foods.

N = the number of nutrients.

Decision Variables (Solution)

These results will come from solution of the model by computer.

x_f = 100 g servings to eat per day.

4.2.1 Model MCDP

Minimize total cost.

$$\text{Minimize } \sum_{f=1}^F c_f x_f \text{ subject to the following :} \quad (4.1)$$

The mix of foods must provide nutrients that exceed the minimum requirements.

$$\sum_{f=1}^F a_{fn} x_f \geq b_n, n = 1, \dots, N, \text{ dual price } y_n \quad (4.2)$$

The mix of foods must provide nutrients that do not exceed the maximum requirements.

$$\sum_{f=1}^F a_{fn} x_f \leq d_n, n = 1, \dots, N, \text{ dual price } z_n \quad (4.3)$$

Model MCDP is linear in the variables x_f and is easily solved with commercial or open source linear programming software. For this study, MCDP was solved with a commercial modeling language called AMPL [27].

Though this model is virtually the same as that in many previous papers, the assumptions are different, the data is different, and the questions we seek to answer are different.

4.3 Assumptions of this Study**4.3.1 Nutritional Requirements Come from the DRIs**

This study will take the nutritional requirements as given in the US Dietary Reference Intakes [25]. Rather than try to assume some kind of biological model that improves or is harmed in a nonlinear way, the cost of a shortage in these requirements (or an excess above the maximum requirements) is assumed to be almost infinite, and the value of excess above the minimum but below the maximum is assumed to be zero.

Any supplement that provides some chemical, say, ginkgo, other than those in the list of DRIs is assumed to have value zero. This assumption could be wrong if the weight of science to date were wrong, by missing a here-to-fore unknown necessary nutrient. Any dietary supplement which does not contribute toward at least one of the recognized required nutrients would be considered a pure

cost, with no benefit of any kind, by this study. Perhaps we could use the phrase “nutritional supplement,” which implies that we are considering only those chemicals which are currently recognized as genuine nutrients, rather than “dietary supplement,” which could be just about anything that a salesperson could hoodwink us into buying.

4.3.2 Food Data Comes from FNDDS [24]

This study will use the nutritional data for foods as listed in FNDDS as complete and authoritative.

4.3.3 Consider Only Nutrients in the Dietary Supplements Ingredient Database (DSID) [6]

This study will examine dietary supplements only for those nutrients listed in DSID. (However, model MCDP will still include all nutrients in the Dietary Reference Intakes). The DSID database provides estimates of actual nutrients, based on analytical testing, in dietary supplements for 18 key nutrients. These nutrients are listed in Table 4.1.

Table 4.1 Nutrients in the dietary supplements ingredients database

DSID ingredient name	USDA Standard Reference (SR) Nutrient Number	NHANES Ingredient ID Number
Calcium	301	10000070
Copper	312	10000103
Folic acid (adjusted)	431	10000980
Iodine (omitted)	314	10000191
Iron	303	10000192
Magnesium	304	10000248
Manganese	315	10000253
Niacin	406	10001266
Phosphorus	305	10000300
Potassium	306	10000303
Riboflavin	405	10001284
Selenium	317	10000338
Thiamin	404	10001283
Vitamin B-12	418	10002294
Vitamin B-6	415	10002293
Vitamin C	401	10000979
Vitamin E (adjusted)	340	10000386
Zinc	309	10000416

For purposes of this study, folic acid (SR Nutrient Number 431) was converted to folate (SR Nutrient Number 417), by multiplying the amount of folic acid by 1.67. Similarly, IU of vitamin E (SR Nutrient Number 340) was converted to mg vitamin E (SR Nutrient Number 323) by multiplying by $1/0.67=1.5$. Both of these changes would tend to make dietary supplements relatively more desirable. Iodine was omitted from the study, as it is not available in the food database FNDDS.

4.3.4 Costs Come from CNPP Food Prices Database

This study's primary weakness is its reliance on old price information. The price database used is the CNPP Food Prices Database [26], which is based on grocery scanner data from 2003 to 2004. Since that survey, the world has had big changes. These costs must be viewed as being hopelessly out of data.

We could multiply the prices by an inflation factor to adjust the prices crudely, as the USDA does to calculate the cost of Thrifty Food Plans. However, this will make no difference to the results of this study, because adjusting all prices by the same factor would not change the solutions to the model: maximize $5x + 3y$ (subject to constraints) would give the same solution as maximize $50x + 30y$ (subject to the same constraints). The change is only of scale. Most likely, and more importantly, prices have changed relative to each other. Further, CNPP lists some foods as free; these were all adjusted to \$0.01/100 g.

Food prices change quickly, and vary enormously by region and season. Further, the grocery stores have strong incentives to prevent disclosure of their prices. Indeed, this author's research assistants have been repeatedly chased away by grocery store managers. Therefore, we will have to make do, in the main, with the old CNPP data, while adjusting a few food prices by hand.

4.3.5 A Sample of Actual Diets Came from the National Health and Nutrition Examination Survey

In addition to answering our questions with computer-generated diets, we will also examine the effects of dietary supplements for a real diet, as sampled in the National Health and Nutrition Examination Survey (NHANES) [28]. Computer-generated diets, as we shall see, are quite different to what people actually eat.

4.4 The Least-Cost Diet Approach

It should be clear at this point that we have a restricting set of assumptions, a well-defined model of diet, and plenty of data. In this section, we will use MCDP to calculate whether dietary supplements can save us money.

4.4.1 The Least-Cost Diet

To motivate this approach, imagine a frugal 50-year-old man, who we will call John. John wants to get all his nutrients, including 2,000 cal/day, but John also wants to spend as little as possible in doing so. What should he eat, and how much will he have to pay?

If we solve model MCDP with prices from the CNPP Food Prices Database, we get the foods listed in Table 4.2, for a total cost of \$0.6095/day.

Table 4.2 Solution to model MCDP with prices from the CNPP food prices database

Quantity (g)	Price/kg	Food
381.1	\$0.20	Tortillas, ready-to-bake or -fry, corn
181.1	\$0.40	Pinto, calico, or red Mexican beans, dry, cooked, fat not added in cooking
164.8	\$0.20	Mixed vegetable and fruit juice drink, with added nutrients
119.2	\$1.50	Milk, dry, whole, with added vitamin D
44.7	\$3.20	Tomatoes, sun-dried
23.5	\$0.30	Rolls, dinner, rye
21.3	\$3.40	Peanut butter, vitamin and mineral fortified
3.4	\$3.00	Chicken liver, braised
2.4	\$6.80	Cereals ready-to-eat, Kellogg’s all-bran complete wheat flakes
Total cost \$0.6095/day		

Now this solution is rather preposterous for a couple reasons. First, the prices are far too low. Where can we buy tortillas for \$0.20/kg, or dinner rolls for \$0.30/kg? The computer is quite clever at seeking out the cheapest foods, taking nutrition into account. Therefore, we will have to update these prices. Second, this day’s diet may be okay for our frugal test subject John, but most people will probably not want to eat this. Nevertheless, let us carry forward with this method to see where it takes us.

4.4.2 Would the Computer Recommend a Dietary Supplement in a Least-Cost Diet?

Could frugal 50-year-old John save money if he took one or more supplements listed in DSID? Of course, that would depend on the cost of the supplements. If the supplements were free, perhaps he could save a lot of money. Note that John has to choose the best diet and matching supplement simultaneously, to minimize total cost. This is a difficult numerical problem, but one that model MCDP can do easily. This approach of finding complementary feeding recommendations is the same as the approaches of Santika et al. [20], Ferguson et al. [21], and Gao et al. [22].

Let us solve MCDP, adding all supplements from DSID as “foods,” and at zero cost. The solution, shown in Table 4.3, has a total cost of \$0.479/day, a savings of about 13 cents.

In DSID, a “serving” is what the manufacturer suggests be taken in one go. If we think of a serving as a tablet, then this solution suggests taking nine whole tablets, and fractions of seven tablets. John could save 13 cents if he could get all these tablets for free. This is far from plausible. John would have to work out how to eat a fraction of a tablet. Moreover, a casual review of a few discount supplement websites suggests that tablets cost about 10 cents each.

Suppose we assume that tablets cost 10 cents each, and must be consumed whole (no partial tablets). What should John do, and how much money will he save?

The solution, shown in Table 4.4, costs \$0.609/day, a savings of less than a penny a day. (If we assume that tablets in fact cost 11 cents each, rather than ten cents, the computer gives us the same solution as in Table 4.2, which had no supplements).

So what is supplement 1000607700? Its components are shown in Table 4.5. This is a big multi-vitamin. So far, it is not looking good for the dietary supplement industry. Their pills would have to be very cheap to be of interest to our frugal friend John, less than about 10 cents for a big multi-vitamin tablet. John has to get a lot for his 10 cents. (Data used in MCDP was the DSID predicted amount per serving, not the label amount).

Table 4.3 Solution to model MCDP, prices from the CNPP food prices database, with free supplements

Quantity (g)	Price	Food
530.3 g	\$0.20/kg	Tortillas, ready-to-bake or -fry, corn
148.7 g	\$1.50/kg	Milk, dry, whole, with added vitamin D
35.8 g	\$3.20/kg	Tomatoes, sun-dried
5.3 g	\$5.50/kg	Beef liver, braised
0.9 g	\$6.80/kg	Cereals ready-to-eat, Kellogg's all-bran complete wheat flakes
3.71 servings	\$0/serving	Supplement 1000594700
3.42 servings	\$0/serving	Supplement 1000620500
2.18 servings	\$0/serving	Supplement 1000664700
1.46 servings	\$0/serving	Supplement 1000527600
0.88 servings	\$0/serving	Supplement 1000474300
0.16 servings	\$0/serving	Supplement 1000076402
0.07 servings	\$0/serving	Supplement 1000660200

Total cost \$0.479/day

Table 4.4 Solution to model MCDP, prices from the CNPP food prices database, with supplements costing \$0.10/serving

Quantity	Price	Food
512.8 g	\$0.20/kg	Tortillas, ready-to-bake or -fry, corn
153.0 g	\$1.50/kg	Milk, dry, whole, with added vitamin D
46.3 g	\$3.20/kg	Tomatoes, sun-dried
5.2 g	\$5.50/kg	Beef liver, braised
1 serving	\$0.10/serving	Supplement 1000607700

Total cost, \$0.6087/day

Table 4.5 Components of DSID supplement 1000607700

Ingredient	Label amount/ serving	Unit	SR Nutrient Number	Predicted amount
Calcium	28	mg	301	36.0
Copper	2	mg	312	2.2
Folic acid	400	mcg	417	456.0
Manganese	3	mg	315	3.2
Niacin	20	mg	406	20.4
Potassium	100	mg	306	107.0
Riboflavin	4.2	mg	405	4.7
Selenium	80	mcg	317	100.0
Thiamin	6	mg	404	7.1
Vitamin B-12	100	mcg	418	108.0
Vitamin B-6	5	mg	415	6.3
Vitamin C	150	mg	401	162.0
Vitamin E	30	IU	323	31.8
Zinc	15	mg	309	15.6

The "Predicted amount" was calculated by a regression model, part of DSID

4.4.3 Updated Prices

Let us think about the price database. Remember, the prices look too low. Current prices seem to be much higher than those in the CNPP Food Prices Database. If food prices were higher, then John could possibly save more with a multi-vitamin.

Table 4.6 shows the result of a laborious process of price adjustment. Briefly, model MCDP was solved, and the solution examined, and if the price/kg of each food was deemed too low, it was adjusted upwards, and MCDP was solved again. Each time, MCDP would cleverly substitute some other food that was too cheap. So this process had to be done repeatedly, until all foods in the solution appeared to have reasonable prices. About 13% of the prices in the CNPP Food Prices Database had to be changed. The diet costs a total of \$2.16/day. The overall cost of diet has more than tripled, because prices of many cheap foods were raised.

What happens if we allow a supplement? Can John save any money? Yes, if tablets cost 10 cents, he can save about 14 cents, as seen in Table 4.7. The computer recommends one supplement 1000527600 (a multi-vitamin containing magnesium, manganese, potassium, selenium, vitamin C, vitamin E, and zinc).

Table 4.6 Solution to model MCDP, with prices updated from the CNPP food prices database

Quantity (g)	New price/kg	CNPP price/kg	Food
954.0	\$0.40	\$0.10	Flour and water gravy
166.0	\$5.00	\$2.50	Textured vegetable protein, dry
42.2	\$6.70	\$1.50	Milk, dry, whole, with added vitamin D
29.0	\$6.68	\$5.40	Guavas, common, raw
17.4	\$4.83	\$1.70	Oil, corn, industrial and retail, all purpose salad or cooking
14.5	\$6.80	\$3.40	Peanut butter, vitamin and mineral fortified
12.7	\$7.00	\$7.00	Braunschweiger (a liver sausage), pork
8.9	\$3.36	\$3.20	Bread, whole-wheat, commercially prepared, toasted
8.2	\$9.36	\$6.80	Cereals ready-to-eat, Kellogg's all-bran complete wheat flakes
8.1	\$3.70	\$3.70	Snacks, popcorn, home-prepared, oil-popped, unsalted
1.6	\$9.72	\$8.60	Cereals ready-to-eat, general mills, whole grain total
1.5	\$30.90	\$30.90	Tea, instant, unsweetened, powder
Total cost \$2.16/day			

Table 4.7 Solution to model MCDP, with prices updated from the CNPP food prices database, supplements costing \$0.10/serving

Quantity	New price	CNPP price	Food
1,064 g	\$0.4/kg	\$0.1/kg	Flour and water gravy
176.1 g	\$5/kg	\$2.5/kg	Textured vegetable protein, dry
41.7 g	\$6.7/kg	\$1.5/kg	Milk, dry, whole, with added vitamin D
17.9 g	\$3.7/kg	\$3.7/kg	Snacks, popcorn, home-prepared, oil-popped, unsalted
16.9 g	\$7/kg	\$7/kg	Braunschweiger (a liver sausage), pork
11.8 g	\$4.83/kg	\$1.7/kg	Oil, corn, industrial and retail, all purpose salad or cooking
8.8 g	\$9.36/kg	\$6.8/kg	Cereals ready-to-eat, Kellogg's all-bran complete wheat flakes
1.4 g	\$9.72/kg	\$8.6/kg	Cereals ready-to-eat, general mills, whole grain total
1 serving	\$0.10/serving	Not listed	Supplement 1000527600

Total cost \$2.02/day

Without taking the space to show another diet, when the tablets cost 10 cents each, and John were willing to eat partial tablets, the solution costs \$1.97/day. If all supplements were free, and our frugal John was willing to eat fractions of tablets, John could pay only \$1.88/day. The solution had just over 43 tablets. Thus, even if we raise food prices considerably, supplements would save our frugal John a few cents per day, and only if John were willing to take some small fraction of a tablet at a time, and only if the tablets were multi-vitamins that cost 10 cents per tablet or less. Further, John would have to work the least-cost mix of supplements and food.

4.5 Would Supplements Save Money for People on “Normal” Diets?

Our frugal test subject John was willing to eat whatever the computer told him to eat, and the computer’s recommendations probably did not look particularly palatable to most readers. So let us examine a “normal” diet, based on foods that a person actually reported eating.

4.5.1 *Jack’s Actual Diet*

Searching the 2005–2006 NHANES database, we find a 50-year-old male, respondent 38935, who reported eating the foods shown in Table 4.8, for Day 1 of the NHANES interview. Let us call respondent 38935 by the name Jack.

This diet looks quite conventional. Jack is a different fellow to our earlier test subject John. (John would probably say that the Sprite, coffee, tea, cookies, sugar, and whisky was a waste of money).

How is the nutrient profile for Jack’s menu of the day? Table 4.9 shows that Jack’s diet was short of a number of nutrients. (Nutrient calculations were taken directly from the FNDDB food database, not from the NHANES calculations of nutrients; the two differ slightly.) The table does not show the maximum limits, but Jack consumed 4,078 mg sodium, severely over his limit of 2,400 mg. With the old out-of-date CNPP prices, this diet cost about \$9.35/day. (If we updated the prices as we did some of John’s, the cost would be much higher, perhaps double).

Table 4.9 shows what is wrong with American diets: they are broken. We get too much of some nutrients (energy and sodium, for example), and not enough of some nutrients.

4.5.2 *Options for Fixing Jack’s Diet*

Could Jack eat only supplements to get the nutrients that he is missing? The supplements under study do not include fiber, vitamin D, or pantothenic acid, so Jack cannot get these within the assumptions of this study. If we ignore these nutrients (as they are all sold in the market place), and if tablets cost 10 cents each, then John could take 0.39 servings of supplement 1000413001, 5.6 servings of 1000601000, and 0.18 servings of 1000605401, at a cost of about \$0.62. Thus, he must pay even more to get the nutrients he needs, and he would exceed his requirements for sodium, niacin, and folate.

Could Jack eat some additional foods to get the nutrients that he is missing? If we ignore the upper limits on the nutrients, as he has already exceeded some limits, we can use model MCDP to choose additional foods that Jack could eat, which would ensure he is not short of any nutrients.

Table 4.8 Foods reported by NHANES respondent 38935, “Jack,” Day 1

Quantity (g)	Food
1355.2	Carbonated beverage, sprite, lemon-lime, without caffeine
625.2	Milk, cow's, fluid, 1% fat
384.8	Coffee, made from ground, regular
355.2	Tea, NS as to type, presweetened, NS as to sweetener
297.0	Lettuce, salad with assorted vegetables including tomatoes and/or carrots, no dressing
253.3	Coffee, decaffeinated, made from powdered instant
233.4	Orange juice, canned, bottled or in a carton
224.0	Whiskey
150.0	Peaches, raw
138.0	Apples, raw, with skin
112.0	Bologna, beef and pork
106.0	Fast foods, chicken tenders
73.2	Cookie, chocolate sandwich, reduced fat
56.2	Special K
56.0	Cheese, processed, American or Cheddar type
52.0	Bread, oat bran
30.0	Cream substitute, liquid
25.2	Sugar, white, granulated or lump
22.0	Honey mustard dressing
12.0	Croutons, seasoned

Table 4.9 Nutrients in Jack's diet

Nutrient	Units	Minimum requirement	Actual quantity	Excess (negative is a shortage)
Calcium, Ca	mg	1,000.0	1,455.2	455.1
Carbohydrate, by difference	g	130.0	450.2	320.2
Copper, Cu	mg	0.9	1.1	0.2
Energy	kcal	2,000.0	3,459.1	899.1
Fiber, total dietary	g	38.0	17.5	-20.5
Folate, total	mcg	400.0	1,054.5	654.5
Iron, Fe	mg	8.0	26.3	18.3
Magnesium, Mg	mg	420.0	340.6	-79.4
Manganese, Mn	mg	2.3	0.9	-1.4
Niacin	mg	16.0	35.2	19.2
Pantothenic acid	mg	5.0	2.6	-2.4
Phosphorus, P	mg	700.0	1,885.0	1,185.0
Potassium, K	mg	4,700.0	4,034.5	-665.5
Protein	g	56.0	99.9	43.9
Riboflavin	mg	1.3	3.8	2.5
Selenium, Se	mcg	55.0	141.8	86.8
Sodium, Na	mg	1,500.0	4,078.3	2,578.3
Thiamin	mg	1.2	2.4	1.2
Vitamin A, RAE	mcg	900.0	1,252.3	352.3
Vitamin B-12	mcg	2.4	16.6	14.2
Vitamin B-6	mg	1.3	5.3	4.0
Vitamin C, total ascorbic acid	mg	90.0	155.5	65.5
Vitamin D	IU	200.0	42.2	-157.8
Vitamin E (alpha-tocopherol)	mg	15.0	13.9	-1.1
Zinc, Zn	mg	11.0	12.0	1.0

The solution would be to eat some tea, peanut butter, and “Textured vegetable protein, dry,” at a cost of about \$0.54 (updated prices). Adding supplements (even still missing some fiber, vitamin D, and pantothenic acid) would be more expensive than adding food.

Suppose Jack were to eat the same set of foods, but in different quantities. What would the new diet look like? It turns out that model MCDP has no solution, because Jack’s menu has too little vitamin D. He could get some vitamin D from sunshine. (The NHANES scientists did not even calculate the quantity of vitamin D in the NHANES database.) But let us maintain the standard of requiring all nutrients.

Suppose Jack were to add just one more food, and rearrange all the remaining quantities. What would the new diet look like? Table 4.10 shows the solution and updated prices. The diet would cost \$6.68, much lower than his original diet, even with the higher updated prices. All Jack’s nutritional requirements are satisfied, and no upper limits are exceeded. The computer added the dried milk, partly to ensure that Jack would get his vitamin D. The point is that if Jack would make just a few adjustments, he could save money *and* eat more nutritiously. The quantity of fruit in this diet looks a bit much, that’s all. The tea still looks under-priced.

The point is that Jack could do a *better* job of getting all of his nutrients, without exceeding any upper limits, and at lower cost, if Jack were willing to eat a diet a bit more like John’s. Jack’s difficulty is not food availability or convenience, because he could easily get all of his nutrients – and save money – with only minor adjustments.

Suppose Jack were willing to adjust his diet slightly by changing the quantities, adding the one food, and also by taking supplements. Table 4.11 shows the new result. Assuming tablets still cost only 10 cents, this diet would cost about \$5.41.

Supplement 1000673200 has calcium, copper, magnesium, manganese, niacin, riboflavin, selenium, thiamin, vitamin B-12, vitamin B-6, vitamin C, vitamin E, and zinc. Note also that model MCDP choose the right supplement for Jack. If Jack were to enjoy the savings and the correct nutrients, he would have to know which nutrients were lacking in his diet, and find a matching supplement. This is a complicated nutritional analysis, followed by a difficult search for the right supplement.

The savings of \$1.27 compared to the previous solution is large. Why is this so large? It is because Jack’s chosen foods are expensive. He could save over a dollar by adding the tablet, because the cheap tablet substituted for expensive foods. (He could have saved even more money with a tablet if he had substituted it for *more* expensive food!) In effect, the tablet is a second “food.” However, if we ask the computer to add a second *real* food (switching out the croutons for whole wheat bread), the cost of Jack’s diet would fall to \$4.54, an even larger savings of over \$2.

Table 4.10 Improved version of Jack’s diet. Model MCDP was solved, but allowed to change only the quantities from Table 4.8, and add one more food (the dry milk)

Quantity (g)	New price/kg	CNPP price/kg	Food
851.5	\$2.20	\$2.20	Apples, raw, with skin
631.1	\$0.30	\$0.30	Tea, NS as to type, presweetened, NS as to sweetener
442.0	\$2.50	\$2.50	Peaches, raw
248.2	\$6.70	\$1.50	Milk, dry, whole, with added vitamin D
200.9	\$6.70	\$3.10	Bread, oat bran
51.4	\$8.00	\$8.00	Special K
13.2	\$7.20	\$7.20	Croutons, seasoned
Total cost \$6.68			

Table 4.11 Improved version of Jack's diet

Quantity	New price	CNPP price	Food
220.4 g	\$6.70/kg	\$1.50/kg	Milk, dry, whole, with added vitamin D
1,451.3 g	\$2.20/kg	\$2.20/kg	Apples, raw, with skin
44.2 g	\$2.50/kg	\$2.50/kg	Peaches, raw
32.1 g	\$7.20/kg	\$7.20/kg	Croutons, seasoned
37.5 g	\$8.00/kg	\$8.00/kg	Special K
1 serving	\$0.10/serving	Not listed	Supplement 1000673200

Model MCDP was solved, but allowed to change only the quantities from Table 4.8, and add one more food (the dry milk). Total cost \$5.41

4.5.3 Missing Issues

What else is going on? Jack does not eat only to satisfy his minimum nutrients. He eats partly for pleasure. Why else have cookies and whiskey? On the other hand, if Jack wishes to eat for pleasure, a tablet would not seem to help with that.

Jack does not have model MCDP conveniently available to him. He must choose his diet as people have done for a 100,000 years, by selecting the food that seems good from the food that is conveniently available. Hence, he is unlikely to get a diet with a perfect nutritional profile, unless he gives some attention to the task. Why did Jack over-eat so much in energy? To answer that, we probably need to look to the psychologists for answers.

In any case, Jack could save money and be much healthier – without dietary supplements – if he were willing to make a few changes. He does not need to eat a kilogram of peaches every day, but he could easily cut out the extra calories, and choose more fruits and vegetables.

4.6 Conclusion

Starting with an expensive bad diet, a person wishing to get any remaining nutrients is more likely to spend less by eating additional carefully selected foods than by taking a supplement. Assuming a very cheap price for dietary supplements of only ten cents per tablet, no one will save more than a few cents by relying on tablets instead of food, even if the diet is planned with a computer. The results depend on the nutritional content of food and food prices (relative to supplements). Nutritional requirements for different age and gender categories are similar, so these results would be the same, likely varying only by a few cents.

Furthermore, if a person wished to save money by taking supplements, he or she would have to get the *right* supplement, along with a complementary mix of foods. If we wish to save money on our food, the solution is to choose foods more wisely, not to use supplements. Healthy people can more cheaply and safely adjust their diets toward a better nutrition and cost profile by choosing different food, than by taking dietary supplements.

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Part II

Influences on Preventive Nutrition Strategies

Chapter 5

The Economic Value of Dietary Supplements

Tom Baranowski

Key Points

- All nutrients can be obtained from food, without dietary supplements.
- Adding dietary supplements could reduce the cost of the diet only marginally, and only if the supplements complement the diet correctly.
- Most people could have a better diet and at lower cost simply by making different food choices.

Keywords Cost • Dietary supplement • Economics • Least cost diet • Linear program

5.1 Introduction

Fruit and vegetable (FV) consumption is possibly protective of heart disease [1], some cancers [2], and accrued adiposity [3], among other adult diseases [4]. Since dietary intake levels track from childhood to the adult years [5], it is prudent to encourage children to eat more FV in order to establish healthy habits carried into the adult years.

Using the mediating variable model [6] to understand how interventions change behavior, interventions must influence the strong causal influences on behavior; these changes [6] induce changes in the behavior [7]. A large number of variables have been related to FV intake among children [8], but their “causal” status is unknown, and the strength of relationship is often diminished by using variables measured with low reliability [9]. One variable that has been consistently related to FV intake, with some evidence of causal influence, is home availability of FV (i.e., the number of different FV items in the home) [10]. Thus, increasing home FV availability should increase FV consumption. Increasing home FV availability, particularly in urban areas, requires more purchases of FV.

5.2 A Conceptual Model

To design interventions to increase home FV availability through increased FV purchases, we need to know its influences. Complex models predicting individual food choices have been proposed reflecting

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qualitative interviews [11]. Questionnaires have been generated to measure some of these influences [12]. Somewhat more complex models have been proposed to encompass both individual and family food choices [13]. Further investigation would be valuable to identify the specific factors influencing the purchase of FV to be available in the home, especially to influence children's FV consumption.

Qualitative research was initiated with ethnically diverse food shoppers with children. A synthesis of that research with subsequent more quantitative research suggested a model as in Fig. 5.1 [14]. This model is from the perspective of the household's primary food purchaser and interrelates four levels of influences including contextual (macroenvironmental), psychosocial, behavioral and microenvironmental variables. It proposes that FV consumption at home is a function of what foods are prepared for home meals and snacks. Home meal and snack preparation is a function of the FV preferences of the family members (primarily the home food purchaser [HFP]) and the foods found in the home food pantry or where ever foods are stored in the home. The home FV pantry is the source of "home FV availability." The foods contained in the pantry are a function of home pantry management practices (e.g., food replacement rules, use of coupons) and food purchases for the home.

What food items (e.g., FV) are purchased for the home is a complex integration of the food store(s) selected (and what foods, especially FV, are available therein, called neighborhood food availability), shopping frequency (e.g., every couple of days versus once a month), the outcome expectancies for the foods purchased (i.e., what people expect will happen as a result of eating the foods (FV) purchased, e.g., simply satisfy hunger, fulfill innermost cravings or desires, promote health), food shopping practices (e.g., pursuing sales, using coupons), and social support within the family for purchasing the FV (i.e., from the food purchaser's perspective, do family members support the purchases, which probably reflects the family members' food outcome expectancies). All these interrelationships occur within the context, or milieu, of what stores are available for food shopping, the socio demographics (including especially the financial resources available to the family) and social capital (i.e., the food shopper's network of friends and colleagues and their shared information and resources).

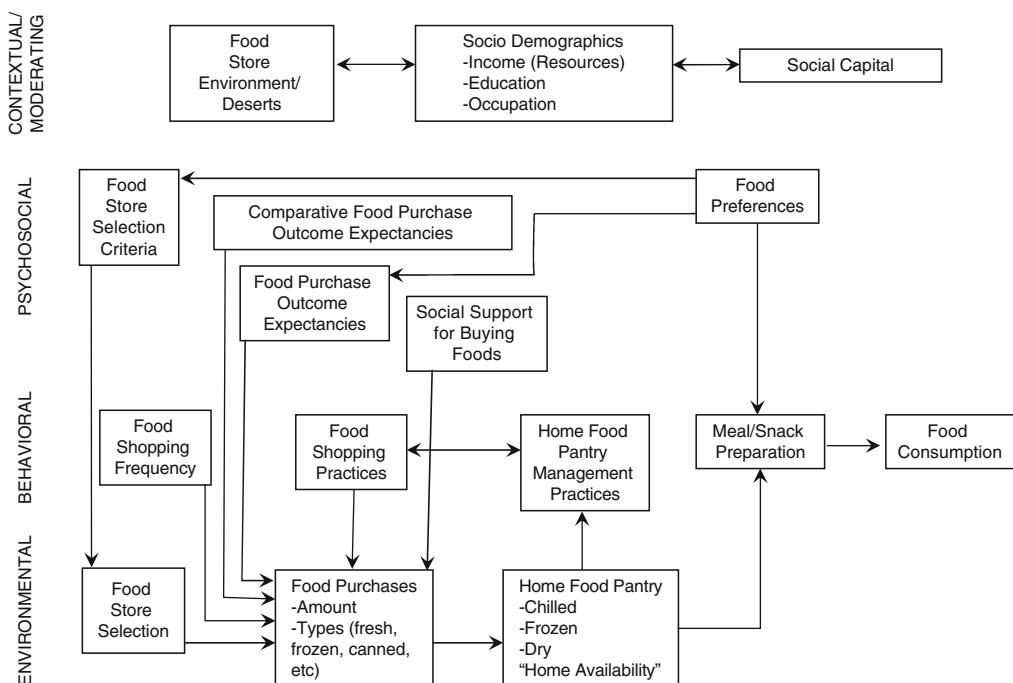


Fig. 5.1 Model of influences on home food availability and consumption

5.3 How Frequently Do People Shop for Food?

Conceptually, a key variable is the frequency of food shopping. Families that food shop infrequently, e.g., once a month, appear less likely to spend money on perishable items like fresh FV, but perhaps more on frozen, canned or dried FV. This may have implications for how much and what kinds of FV are available in the home. The nonperishable FV are more likely to be influenced by coupons, while the fresh FV should be more subject to seasonal store availability and sales, also likely influencing the amount and type of FV in the home. Since we wanted to collect grocery store receipts as a validation of self reported consumption, knowing the food shopping interval was important to know over what interval receipts should be collected.

To obtain this information a customer intercept survey was initiated with 823 primary food shoppers with children (≤ 18 years old) at home, at stores randomly selected within cells of a matrix of census tracts to maximize diversity on SES (high/low) and ethnicity (white, African-American, Asian, Hispanic) [15]. The substantial diversity in type and frequency of usual food shopping could be grouped into six categories: a big monthly shopping trip with a few small trips (8.3% of respondents), big biweekly shopping trips with no small trips (6.4%), big biweekly trips with a few small trips (21.9%), big weekly trip with no small trips (13.1%), big weekly trip with a few small trips (34.9%), and no big trips, food shopping as needed (15.4%). African American shoppers were most likely to report large monthly and biweekly shopping trips. Asian and Hispanic families were more likely to report the more frequent trips. The white families were almost evenly distributed as a percentage across all six categories (from 9.9% to 16%). Frequency of food shopping pattern was not related to educational attainment.

5.4 Creating Measures of Key Variables

A simple measure of home FV availability [16] was created and was demonstrated to have high validity [17]. In another survey with 162 participants recruited by means of grocery store intercepts, respondents reported home FV availability. A psychometric analysis of that scale, including item response modeling (IRM) procedures revealed that among 13 fruit items, bananas were most commonly reported to be in the home while dried fruit and Kiwi were least common; among three juices, orange juice was most commonly reported to be in the home, grape juice least with apple juice in between; and among 18 vegetables, lettuce and tomatoes were most commonly reported to be in the home, and greens, potato salad and cole slaw least commonly reported [18].

Simple home pantry management scales were created for fruit, 100% juice and vegetables [18]. IRM analysis of eight items in each scale revealed that it was easiest to agree to purchase each item when they were on sale, to keep a variety at home, or purchase when running out, but least likely to agree when having a coupon for the item or making a habit of purchasing the item on every trip. This suggested high reliance on in store sales; a low reliance on coupons; and regularly purchasing FV was not an established habit [18].

Since only about half of a family's FV expenditures are for fresh FV [19], four simple nine-item outcome expectancy scales were created separately for fruit and vegetables, and for fresh versus canned, bottled or frozen juice and vegetables [20]. Data were collected by telephone interview in the same 162 participants. IRM analyses revealed that it was easiest to agree that FV and fresh FV were good for your health and good sources of vitamins and minerals, and most difficult to agree they were inexpensive or that fresh were easiest to prepare. Respondents reported enjoying eating fruit, but not vegetables.

IRM analysis of a 12-item FV shopping practices scale revealed that it was easiest to agree to looking in refrigerator or pantry to see what was needed before going shopping and to check for FV on sale in the store, and most difficult to agree with using coupons for any purpose [21].

Separate five-item scales were generated for social support for purchasing FV. IRM analyses revealed it was easiest for respondents to agree with someone in the family approved their purchase of FV and they were asked to purchase FV, and most difficult to agree with someone in the family discussing purchasing FV for them [21].

5.5 A Test of the Model

A subset of the respondents in the home interview ($n=98$) with the sample obtained from grocery store intercepts had data on all scales at two time points [14]. One of these time points was used for the validation of the scales; the other was used to do a preliminary (admittedly underpowered) test of the model [14]. After controlling for all demographic characteristics, social desirability of response and body mass index, social support for purchasing fruit predicted an additional 14% of the variance in home fruit availability, and social support for purchasing vegetables accounted for an additional 16% of the variance in home vegetable availability. While not a complete test of the many pathways in the conceptual model, this test revealed the critical importance of social support in influencing home availability. None of the other newly created variables predicted the corresponding indicator of home availability.

Social support has been demonstrated to be a strong influence on a variety of human behaviors [22]. Social support is believed to have three components: informational, material and emotional support [22]. Our simple five item measure was a composite of all three types of support. Future research will need to build subscales for each of the social support variables and test which, or what combination of, social support types is most important.

While reducing the cost of FV might result in increased FV consumption [23], an important implication of our findings for intervention is that support for purchasing and consuming FV needs to be built within the family. This might be done with a large communication campaign that targeted specific family communication practices (e.g. “say something nice to your spouse today about what FV you enjoy eating, and why” (emotional support); “tell your spouse you’ll do the next food shopping if you can buy the FV you enjoy” (material support); “start a discussion at your next family dinner about why you all should be eating more FV” (informational support)) or by school based programs that encourage children to go home and ask their parents for FV (“mom, I wanted some orange juice for breakfast, and I could not find any; would you please buy some next time you shop?” (informational support); “mom, have I ever told you how much I really appreciated your buying the fruit I like?” (emotional support); and “mom, can I go shopping with you to help buy my favorite veggies?” (material support)).

5.6 Future Research

The variables included in the current model are similar to those identified in other investigations focused more on individual food choices [11–13]. The test reported in this manuscript was a weak test of the model because of the extremely small sample. Studies with larger samples need to be mounted both to test all the different pathways of influenced in the model, and to test for possible differences in the pathways by ethnic or socioeconomic status groups.

A recent review of the literature on the relationship of FV consumption to adiposity suggested that FV consumption influenced adiposity only when individuals were also actively pursuing overall lower caloric intake (i.e. increase FV intake was part of an overall lower caloric diet) [3]. This suggests that this type of research must assess and incorporate multiple characteristics of diet. This is possible by collecting all food purchase grocery receipts over some time interval (at least a month to be sure to capture the purchasing patterns of the least frequent shoppers). While manual collection and coding of grocery store receipts is possible [24] and free of self report error, it is tedious, and investigators can never be sure if the receipts are complete (among many other method problems). Research on methods for enhancing completeness of grocery store receipts over a month's interval, e.g., use of store courtesy cards and related files, would be valuable.

Future research needs to test possible differences in responses to these scales, and interrelationships across different ethnic, socioeconomic status and age/developmental groups. While the measures employed obtained interesting results, further research is needed to expand these scales to obtain more detailed assessments of the relevant constructs. Contextual variables were identified in the model. Research needs to understand how the model functions across different contexts, especially the recent findings on neighborhood food environment [25, 26]. To do this, economists should be involved in the research teams.

5.7 Conclusion

A variety of likely influences on home FV availability have been identified, preliminary measures have been formulated, and a model tested. More research is needed to better understand how these variables interrelate in alternative contexts so that future interventions have a stronger conceptual foundation for the design of interventions [27].

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Chapter 6

Fruit and Vegetable Prices, Dietary Intakes and Income: Potential Cost Versus Benefit

Qi Zhang and Youfa Wang

Key Points

- Fruit and Vegetable food price is correlated with the overall food price. It is important to put the F and V price in the context of the general food price to study the price effect on the dietary intake.
- Low and middle income consumers are more responsive to changes in F and V food price than higher income groups. Therefore, “fat tax” may not be effective in high income populations.
- Other environmental factors, such as the accessibility of alternative food stores, can explain the food price elasticity across income.

Keywords Dietary intake • Food price • Fruit • Socioeconomic status • Vegetable

6.1 Introduction

Adequate consumption of fruits and vegetables (F and V) is critical for good health [1]. Increased F and V intake can help reduce the risk of many diseases such as cancer, cardiovascular disease (CVD), [2, 3] and obesity [4–6].

The importance of consuming an adequate amount of F and V has been increasingly recognized by health professionals and policy makers, in particular, in developed countries. For example, in the US several national campaigns such as the Five-A-Day (i.e., to consume five servings of F and V each day) to promote F and V consumption have been implemented. However, thus far, they have achieved only modest success. Only 40% of American adults consumed F and V at the recommended daily level, five or more servings of F and V per day [7]. The percentage of children and adolescents that met the US Department of Agriculture’s (USDA’s) recommendations was much lower: It was only 1% of boys and 2% of girls aged 9–18 years old. People with incomes below the poverty line were at a greater risk of failure to consume the recommended amount of F and V. Previously our group analyzed data from the US National Health and Nutrition Examination Survey (NHANES) III (1988–1994) and NHANES 1999–2002. We found that higher income individuals (2.5 times above the poverty line) were significantly more likely to meet the USDA’s F and V

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recommendations compared to individuals below the poverty line [8]. Clearly a gap exists between the objectives of recent promotional efforts and the reality of F and V consumption. This highlights the need for more research to help understand what determines an individuals' F and V consumption.

Food cost is a major factor in affecting people's food choices [9, 10]. Healthier foods, such as F and V, are usually associated with higher costs, particularly in industrialized countries such as the USA [11], although in developing countries, animal sources of food such as meats, poultry and fish are usually more expensive than F and V. The relative cost disparity between F and V and energy-dense foods (e.g., processed foods) has lead to greater consumption of foods that are rich in fat and sugar [12]. Some limited previous studies indicated that consumers are responsive to differences or changes in F and V prices. For example, in an intervention study in middle school cafeterias, 50% price reductions were applied on fresh fruit and baby carrots. Consequently, the sale of fresh fruit increased by 450%, while the sale of baby carrots increased by over 208% during the intervention period [13]. A recent study also indicated the associations between food prices and nutrient deficits. Lakdawalla and Phillipson [14] found a positive and significant ($p < 0.05$) relationship between the prices of peach juice and orange juice and deficiencies in vitamin C and folate [14]. Studies have documented the socioeconomic disparities in obesity and unhealthy dietary intakes. Darmon et al. [15, 16] applied a linear programming approach to examine the food choice of a rational individual to maximize energy intake on a limited budget or income [15, 16]. The results indicated that a rational person increased energy intake from sweets and fats and reduced vitamin C intake by 25% and β -carotene intake by 10% given economic constraints. Poverty is significantly associated with obesity and low dietary quality [11]. Based on the US 1994–1996 CSFII (Continuing Survey of Food Intakes of Individuals) data, Drewnowski and Specter [17] reported that the USDA Health Eating Index (HEI) score had a positive linear relationship with the income/poverty ratio [17].

Previous study suggested that the relationship between prices of grain, egg, and pork with macronutrients, such as protein and fat, could vary across income levels [18]. However, few studies have specifically examined the interactive relationship between F and V price, income, and dietary quality. Poverty and high F and V price potentially can interact with each other to be a significant barrier to making quality food choices. Moreover, lower F and V price may benefit low-income groups in terms of their dietary intake. In this chapter, we review these related studies and examine how the relationship between F and V price and dietary intake varies by income levels. We highlight some research conducted in the USA, Brazil, and China. We focus on the USA, where more recent studies have been conducted, and we use it as an example to help indicate the situation in other industrialized countries. We use Brazil and China as examples of developing countries.

6.2 Economic Model

Economic theory suggests that a rational consumer will increase the consumption of certain foods to meet their daily energy need if the price for them is reduced. On the other hand, higher food costs can be a barrier to individuals' food consumption. Consumers have to make choices between different food categories, which are substitutes for each other. In the USA, the top-to-bottom ranking of the average prices of different food categories to provide the same amount of energy is as follows: vegetables, fruits/nuts, fish, meat, dairy, grains, sugars, and fats/oils [11]. Therefore, higher costs of F and V could become a barrier to a healthy diet.

The relationship between income and F and V consumption is, however, more complicated. A marginal increase in income among a low-income population will increase the demand for

energy-dense food to maximize energy intake rather than increase the demand for F and V. For example, in the USA, studies show that Food Stamp Program benefits distorted food consumption among participants who purchased fewer F and V but more sugars and fats. As a result, Food Stamp Program participants had higher obesity rate [19, 20]. If the baseline income is already over the poverty level, however, then the increase in income is positively associated with F and V consumption [14]. With a continuous increase in income, the marginal effect on F and V consumptions will decrease, which indicates a “ceiling effect” for top income holders [17].

In summary, it is widely believed that food prices and family income affect people’s F and V consumption. Higher F and V prices may reduce people’s F and V consumption, while higher income could either prevent or promote F and V consumption. The direction of the price and income effects also depends on the consumers’ levels of income, education, health- and nutrition- related knowledge and beliefs [21–24].

To better understand the interaction between food prices, income, and F and V consumption, appropriate data from population-based prospective studies will be needed for analysis. However, often such data are not available. In the following sections, we review some key related findings from studies based on national data in the USA.

6.3 The Associations Between Dietary Intake, F and V Prices, and Income in the USA

To our knowledge, most previous studies that examined the associations between dietary intake, F and V prices, and income were conducted in the USA. Few such studies have been conducted in other countries. In the following sections, we highlight two of the related recent studies our group has conducted, which are based on nationally representative survey data [21, 25].

Although rich data have been collected to survey dietary intake, household income and food prices in the USA, no single nationally representative survey has included all of these measures. Therefore, most available related studies, including ours, have linked dietary data from surveys with food price data from other data sources to study the associations between food price and dietary intake, including F and V. In our two recent studies to examine the association between food consumption and prices, we merged the contextual data on food prices (at county and city level) in the American Chamber of Commerce Researchers Association (ACCRA) Cost of Living data with individual-level data on dietary intake and income from two national surveys – Continuing Survey of Food Intakes among Individuals (CSFII) and National Longitudinal Survey of Youth 1997 (NLSY97). Using the federal information processing standard code (FPIC) assigned to each county, we matched the NLSY and CSFII data with ACCRA price data. Thus, the merged data had individual level data on F and V consumption and income and group/region level data on food prices.

6.3.1 Data on Individual Participants’ Dietary Intakes and Income in National Surveys

Continuing Survey of Food Intakes among Individuals (CSFII): CSFII was conducted by the USDA in 1994–1996 and in 1998 to collect information on 2-day dietary intake, nutrition knowledge, belief, and perceptions among 20,607 Americans. CSFII used multiple-pass 24-h recalls that were 3–10 days

apart to collect information on two nonconsecutive days' dietary intake. Dietary knowledge, attitude, and behavior data was collected by the Diet and Health Knowledge Survey (DHKS), a supplementary survey of the CSFII. The CSFII and DHKS were administered separately, at least 7 days apart. Although the CSFII was collected more than a decade ago, it is unique in providing comprehensive information on dietary-related information, such as nutrition belief and perceptions, which is not collected in other national surveys. As a nationally representative survey, CSFII also provides information on demographics, socioeconomic status, and other lifestyle variables.

National Longitudinal Survey of Youth 1997 (NLSY97): NLSY97 was a longitudinal survey of nationally representative adolescents aged 12–17 conducted in 1997. The survey has been administered annually by the Bureau of Labor Statistics since then to examine American youths' transition from school to work. Respondents are asked extensive questions related to their labor market behavior and educational experiences. Detailed information on individual and household income is also collected. The NLSY97 original cohort included 8,984 individuals. Frequencies of F and V consumption were asked in the 2002 wave of the survey, which included respondents between the ages of 18 and 23. There were 3,739 respondents who provided the F and V consumption information.

Individuals' dietary intake: For the NLSY97 data, F and V consumption was quantified as a frequency of eating fruits or vegetables in a typical week. Two questions were asked in NLSY97: (a) "In a typical week, how many times do you eat vegetables other than French fries or potato chips?" and (b) "In a typical week, how many times do you eat fruit? (Do not count fruit juice.)."

For the CSFII data, the dietary intake was based on two 24-h dietary recalls. Thanks to the rich dietary data in CSFII, more dietary quality indicators were created and studied, including daily intakes of total energy (kcal), fat (%kcal), fiber (g), and cholesterol (mg), as well as an overall dietary quality index score.

Individuals' income: We created several income measures. For the NLSY97 data, youth income and parental income were both used because some of the respondents had not entered the labor market and the youth income may not have fully reflected their socioeconomic status [25]. Moreover, tertiles can be created to indicate low, medium, and high income.

For the CSFII data, the poverty income ratio (PIR) was used, which was a percentage of the poverty line (which is published by the US federal government, such as the Department of Labor, annually). The absolute poor was defined as $PIR \leq 130\%$; the near poor, PIR is between 131% and 299%; while those with $PIR \geq 300$ were defined as not poor [26].

6.3.2 Contextual Data on Food Price: American Chamber of Commerce Researchers Association Cost of Living Data

The ACCRA data collects quarterly prices of consumer goods in approximately 225 metropolitan areas throughout the USA. The data includes prices of 21 foods typically consumed at home plus three foods typically consumed away from home. The 21 foods consumed at home include the following: meats, dairy products, F and V, white bread, corn flakes, and beverages. The three foods consumed away home are a ¼-lb McDonald's® hamburger, 12–13-in. thin-crust regular cheese pizza at Pizza Hut® or Pizza Inn®, and a fried chicken drumstick and thigh at Kentucky Fried Chicken® or Church's Fried Chicken®.

F and V Price Index: ACCRA lists seven F and V, including potatoes, bananas, lettuce, sweet peas, tomatoes, peaches, and corn. An expenditure weight was assigned to each food category based on the Consumer Expenditure Survey (CES), leading to a weighted price index created by using the absolute price of each food group and its expenditure weight.

6.3.3 Summary Results of the Interaction between F and V Price, Dietary Intake, and Income

In this chapter, “Food Price Elasticity” is defined as the percentage change in food consumption in response to a 1% change in food price. Since an increase in food price usually results in less food consumption, food price elasticity is negative. A greater absolute value of price elasticity suggests more responsiveness of food consumption to the price. In economics, a necessity, such as water, has less price responsiveness (i.e., lower absolute value of price elasticity) than a luxury, such as a perfume (i.e., higher absolute value of price elasticity).

6.3.3.1 F and V Price Elasticity across Income Tertiles in Young Americans

Figure 6.1 presents the F and V price elasticities across income tertiles using the 2002 wave of NLSY97 data and the ACCRA price data (raw numbers were adopted from Powell et al.)[25]. Young American adults with the lowest income were most sensitive to the F and V price: A 1% increase in the F and V price index decreased their F and V consumptions by 0.65% ($p<0.10$). However, those with middle or high incomes were much less responsive to F and V price differences. For the high income group, a 1% increase in the F and V price index only decreased their F and V consumption by <0.1% and the elasticity was not significant.

If parental income was used as a proxy for socioeconomic status (SES), young Americans with middle-income parents were most responsive to F and V price: A 1% increase in the F and V price index was associated with a decrease in their F and V consumption by 0.7% ($p<0.10$). Interestingly young adults with low-income parents were much less responsive to F and V price, with a price elasticity of -0.36 , which was not significant. Therefore, higher F and V price posts the most significant barrier for young American adults who were raised in middle-income households but ended up in poverty by themselves. High income young Americans from high-income families were almost immune to the fluctuation in F and V prices.

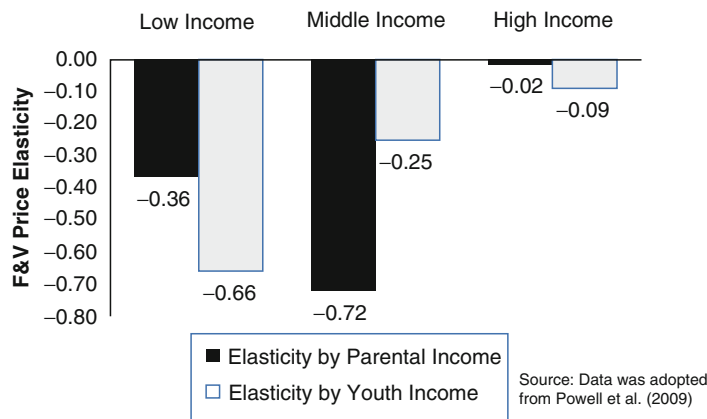


Fig. 6.1 Fruit and vegetable price elasticities by income in US youth (Original data is from the National Longitudinal Study of Youth 1997 Cohort and ACCRA Price data). The results indicated that the price elasticities were greater in low- or middle-income groups than in high-income groups. For example, a 1% increase in F and V price would reduce the F and V consumption among low-income youth American by 0.66%

6.3.3.2 Effect of Food Price on F and V Consumption and Other Dietary Intakes across Income Groups among US Adults

We analyzed data collected from 7,331 individuals in CSFII, which were merged with the ACCRA food price data [21]. We regressed multiple F and V-related dietary quality indicators on food prices by household poverty levels (poor, near poor, and non-poor). Since in our original report the daily dietary intake measures used different unit of measures (e.g., kcal/d, % kcal, g/d), it is difficult to compare the beta coefficient across dietary outcomes and income groups. Therefore, for this chapter, we constructed the Z-score from their beta coefficients and standard errors. The Z-statistics indicate whether the food price effects were significantly different from zero (see Fig. 6.2).

For the pooled analyses of individuals across all income levels, the Z-scores were all negative (−1.53, −1.10, −2.09, −0.44 for energy, fat, cholesterol, and fiber, respectively). The results suggest that the dietary intakes all decreased with higher F and V food prices regardless of the dietary intake measures, such as fiber, or unhealthy dietary outcomes, such as fat. The potential explanation is that the F and V food price index is an indicator of overall food price, i.e., F and V food price is correlated with other food prices, such as fast food. Therefore, higher F and V food prices indicate higher overall food prices, which may have a negative effect on consumption of all food items examined, regardless of whether they are healthy or unhealthy foods.

Our stratified analyses across income groups indicated that the price effects on dietary intake varied by income levels. For total energy, the negative effect of F and V price was strongest in the not-poor group (−2.35, $p < 0.05$), compared with −1.05 in the near-poor group and 0.88 in the poor group. It is interesting to observe the positive relationship between F and V food price and total energy for the poor group. This indicates that higher F and V food price may motivate the poor groups to shift from a healthy diet to energy-dense foods. For the near-poor group, the F and V food price effects were similar to those in the not-poor group but were not statistically significant.

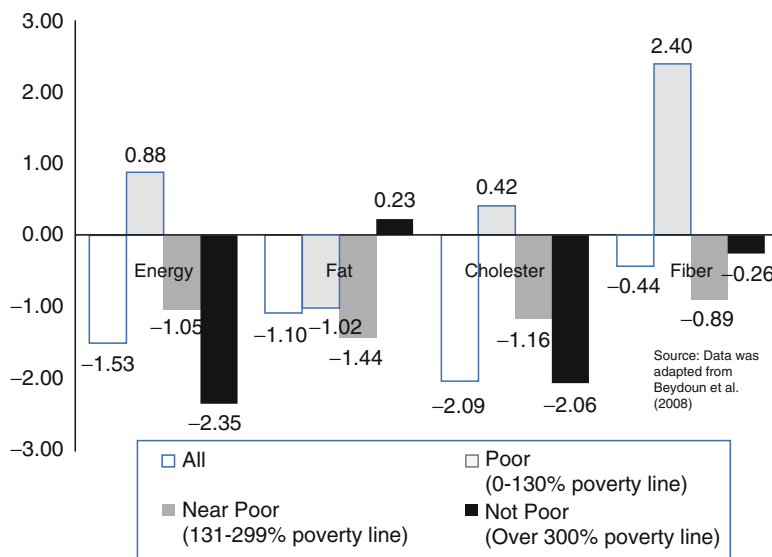


Fig. 6.2 Z-statistics of food price coefficients across income groups among US adults (Original data is from Continuing Survey of Food Intakes by Individuals (CSFII) and ACCRA price data) The results indicated that individuals across different poverty levels had different responses to F and V price changes as regards their dietary intake. For example, a 1% increase in F and V price would result in increase in energy intake by 0.88% in poor American adults

The effects of F and V food price on fat intake were negative among poor or near-poor groups and were the same as in our pooled analyses. The only exception is the not-poor group, which indicates that the higher F and V prices may promote increased fat intake. However, people with higher incomes may also substitute the consumption of F and V with other fat-dense food. The F and V price effects on cholesterol and fiber were negative among the near-poor and not-poor groups, but were positive in the poor group. For cholesterol intake, F and V food price had a greater negative effect in the not-poor group than in the near-poor group. However, there was a significantly positive association between F and V food price and fiber intake that was important ($Z=2.40$, $p<0.05$). A higher average F and V price index does not necessarily mean that all F and V groups were more expensive. Poor individuals could consume more lower priced fiber-rich F and V, such as bananas, when on average F and V became more expensive. This intra-group F and V substitution effect was only observed among groups with income less than 130% of the poverty line.

6.4 Findings of Associations between Dietary Intakes, F and V Prices, and Income in Other Countries

Our search of the related literature indicates that only very limited research on these topics has been conducted in other countries, and very few are from developing countries. Two developing nations that have conducted similar studies are Brazil and China.

6.4.1 Income, Food Prices, and Household Consumption of F and V in Brazil

Since 1974, the Brazilian Office of Geography and Statistics has conducted a series of national surveys entitled Household Budget Survey (HBS) [27]. The primary purpose of the HBS was to estimate the dietary intakes of Brazilians with various demographic and socioeconomic characteristics and in geographic regions. HBS collected data on 1-week food consumption and food expenditure from the responding families and also collected information on regional food prices.

Using the HBS 1998–1999 study in the city of Sao Paulo, Brazil, which covered 7,980 respondents in 2,351 households, Claro et al. [27] divided the respondents into quintiles based on household income [27]. The results indicated a significant difference in food expenditure across income quintiles. Households in the lowest quintile spent 39.3% of their income on food, while the top quintile households spent only 15.6% of their income on food. The F and V expenditure accounted for 3.4% of income in lowest income quintile versus 1.1% of income in top income quintile. Overall, Brazilians' consumption was more responsive to fruit price changes than to vegetable price changes (see Fig. 6.3). Moreover, low income households were less sensitive to fruit price than high income households, but the price sensitivity of vegetable were similar across income levels (the coefficient was -0.03 and -0.04 in the bottom and upper quintiles, respectively). The coefficient of fruit in the lowest quintile households was -0.08 , while in the upper quintile it was -0.16 . It is possible that Brazilians treated vegetables as a necessity, which means the demand changes little despite price changes. However, fruit may be more of a luxury, which makes it more price sensitive.

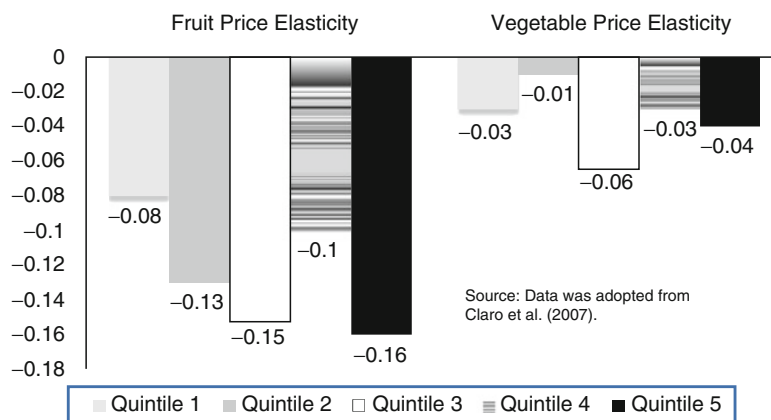


Fig. 6.3 Fruit and vegetable price elasticities in Brazil (Original data is from Household Budget Survey (HBS) in Brazil 1998–1999. Respondents were more responsive to fruit price changes than to vegetable price changes). For example, a 1% increase in fruit price would result in reduction of fruit consumption among lowest quintile individuals by 0.08%, while the same change in vegetable price would result in reduction of vegetable consumptions by 0.03%. Moreover, individuals in the highest income quintiles were more responsive to fruit price changes than individuals in the lowest income quintiles

6.4.2 F and V Price Elasticity Varied Across Income Groups in Rural China

There are few studies in the literature that examine F and V price responsiveness in China across income levels. The only study we found was Han et al. [28]. They used the 1993 National Rural Household Survey (NRHS), which was a national survey of 66,960 rural households in China. For each participating household, the NRHS collected rich information related to demographics, household income, expenditure, and food consumption. F and V were categorized as leafy vegetables, root vegetables, other vegetables, dried vegetables, apples, grapes, and other fruits. The F and V price was aggregated by community prices and expenditure share weights for each F and V group. Price elasticities were calculated across F and V categories and income tertiles. Root vegetables had similar price elasticities across income tertiles (-0.665 for the lowest tertile versus -0.666 for the highest tertile). However, the bottom tertile showed a strong price elasticity for leafy vegetable of -0.488 , while the top tertile had -0.076 . The results indicate that the low-income tertile households were more sensitive to the price of leafy vegetables than the high-income households. Fruit price elasticities were greater than vegetable price elasticities across income levels. For example, apples' price elasticities were -0.661 , -0.657 , and -0.725 across the tertiles, while grapes' price elasticities were -1.078 , -1.114 , -0.996 , respectively, which are the greatest price elasticities in all F and V categories. Therefore, rural Chinese were more price sensitive to fruits than to vegetables, which is similar to the situation in Brazil.

However, price elasticity for fruit was much stronger in China than in Brazil. This might be because of their different development stages and the different relative prices of fruits vs. vegetables (overall, cheaper than fruits in China). In China, the per capita GDP was \$1,183 in 1993, while it in Brazil was \$4,739 in 1999 [29].

In summary, F and V price plays a significant role in affecting people's F and V consumption, and the price effect significantly varies across income levels in developed and developing countries. Food price is not an isolated economic factor but is intertwined with other economic and environmental factors in affecting dietary intake [24]. Higher F and V prices could potentially present a significant barrier for low-income populations to have healthy diets.

6.5 Discussion

This chapter discussed the influence of F and V prices and income on F and V consumption and dietary intake. To our knowledge, there is no single nationally representative survey that includes all the measures of income, F and V price, and dietary intake in the USA. However, researchers can link related national representative data with national food price data using geographic indicators to study the relationships between F and V price, income, and dietary intake.

Economic theory suggests that higher F and V food prices can become a barrier for F and V consumption, while higher income could promote F and V consumption since F and V price is relatively lower. However, the existing evidence in the literature reveals more complicated relationship between the socioeconomic factors and dietary intake. First, F and V food price is an indicator of the overall food price. A lower F and V food price will contribute to a more healthy diet. However, due to the correlation with the overall food price, it might indicate a higher intake of energy, fat, and cholesterol as well. On the opposite side, a higher F and V food price is a barrier to F and V consumption, but because of the correlation it will also reduce the affordability of an unhealthy dietary intake. Therefore, it is important to put the F and V price in the context of the general food price to study the price effect on dietary intake.

Moreover, there are significant interactions between food price and income as regards F and V consumption and dietary intake. Lower-income and middle-income consumers are more responsive to differences in F and V food price than higher-income groups in the US. Food expenditure accounts for 12.8% of annual house expenditures [30]. Interestingly, low and high income households spend a similar share of their household budget on food items. For example, food expenditure in households with incomes less than \$49,999 accounted for 13.7% of their annual expenditure, while households with income more than \$90,000 spent 11.2% on food [31]. Therefore, high income households can spend a larger absolute number of dollars on food, resulting in less responsiveness to food prices. This finding has direct implications for the use of economic policy instruments to fight obesity across the income spectrum.

The interaction between F and V price and income as regards dietary intake also existed in developing countries. Different from the observations in the USA, high-income individuals in developing countries were more sensitive to fruit price changes than low-income individuals. However, vegetable price elasticities were similar across income levels and were smaller than fruit price elasticities. Therefore, in the developing countries, fruit was more like a luxury good, while vegetables were similar to a necessity. To promote healthy diet in developing countries, reducing fruit prices can achieve greater increase in fruit consumption than reducing vegetable prices.

In the USA, researchers suggested that a significant sales tax on so called “junk foods,” such as fast foods or soft drinks, may reduce fat and sugar intake [10, 19]. Twenty-seven states have passed or proposed similar taxes on sales or distribution of soft drinks and snacks. For example, Arkansas taxes \$2 on each gallon of soft drink syrup or \$0.21 on each gallon of bottled soft drinks [32]. This type of sales tax is also called a *fat tax*, which was one of the economic policy instruments to improve diet quality. However, based on the reviews in this chapter, the proposed increase in sales-tax may have a greater impact on low- and middle-income consumers, rather than on the high income groups. Previously we have reported that in the USA, the socioeconomic disparity in obesity has decreased in the last 3 decades [33–35]. In other words, the prevalence among middle- and high-income populations increased faster than among low-income populations. Due to the lower price elasticity among high-income consumers, the proposed fat tax may be less effective. But the tax may generate substantial revenues to cover the production of more healthy foods [19].

Other environmental factors may also help explain the varying food price elasticity across income levels. Accessibility to alternative food stores is remarkably different between low- and high-income neighborhoods. For example, in the USA, low-income individuals are more likely to live in the inner city, which lack supermarkets, yet supermarkets are significantly linked with better availability of F and V intake and therefore healthy food choices [36, 37]. In another sense, the current measured price elasticity does not fully reflect the real responsiveness among low-income individuals since they have limited food stores in their neighborhood. If low-income individuals had the same accessibility to food stores as high-income individuals, we suspect that they would be likely to have stronger price responsiveness with more food choices. Therefore, programs and policies aimed to promote healthy eating should promote comprehensive food environment approaches that would reduce healthy food prices and at the same time increase accessibility to healthy food.

In summary, policy makers can use F and V price as an effective policy instrument to promote healthy dietary intake, especially in low-income populations. Theoretically, rational consumers will optimize their dietary intake given the food cost and potential nutritional benefit. However, low income individuals were more responsive to the near-term food cost than to the long-term benefit of F and V, while high income groups were less responsive to the F and V cost. More research is needed to fully incorporate those different evaluations of F and V cost and benefit into health promotional policy and programs.

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Chapter 7

The Role of Ethnicity in Shaping Dietary Patterns: A Review on the Social and Psychological Correlates of Food Consumption

Giuseppe Carrus, Francesca Cini, Pierluigi Caddeo, Sabine Pirchio, and Anna Maria Nenci

Key Points

- Ethnicity and identification with the ethnic group is a cultural mediating and orienting framework relevant for understanding individual food consumption behavior.
- Empirical evidence, within social and behavioral sciences, confirmed the relationship between ethnicity, food choices, and dietary practices.
- There are important health implications of ethnicity and ethnic identification, in relation to food consumption patterns.
- Ethnic identity might play a crucial role in shaping (un)healthy behaviors across the lifespan, and particularly among younger generations.
- Different models for the explanation of individual food choices have been proposed in the field of cognitive and social psychology.
- Recent empirical studies have highlighted the role of identification with the ethnic group and social norms (e.g., perceived norms of the ethnic group) in predicting ethnic food choices.

Keywords Children • Dietary patterns • Ethnic food • Ethnic identity • Ethnicity • Food consumption • Health • Social norms

7.1 Introduction

Since behavioral patterns vary across different cultures, within social and psychosocial sciences it is nowadays widely accepted that values, beliefs, and lifestyles represent key-elements in shaping human attitudes and behaviors [1–3]. Even if this can be relevant at a national level, the cultural reality created by the worldwide phenomenon of immigration lead some scholars to stress the importance of understanding individual behavioral change, of those subcultural realities within given countries, thus evident at an intranational level (e.g., [4, 5]).

For example, the growing importance of the migratory phenomenon in the last decades lead many scholars in the social psychological field to investigate the attitudes, stereotypes, and prejudice that

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local people have about strangers. In this perspective the study on the development of ethnic identity is also highly relevant. Ethnic identity is part of an individual's self-concept derived from the individual acknowledgement of membership into a specific ethnic and cultural group, and the value or emotional significance attached to that membership [6].

Ethnicity is thus a mediating and orienting framework that can affect the way people think and act when they identify with a given social or cultural group (e.g., [7, 8]). Among the cultural dimensions connected to ethnicity, it is hard to deny the centrality of food in terms of food preferences, preparation methods, and consumption. Even in common sense thinking, food is considered a key expression of human cultures and subcultures. Far from being only a means of survival, the relation between human beings and food in Western countries has rather to be considered for its symbolic value connected to the development of personal and social identity [4, 9–14].

These kinds of assumptions can also be found in, and have been in the focus of, classical anthropological research on food habits and preferences (e.g., [15]). An example of this is offered by a study conducted by Kifleyesus [11] on the social and symbolic function of food among the ethnic group of Argobba in Ethiopia, a Muslim community of about 30,000 people. Also, in a period of socio-economic changes, food might represent a means of asserting one's own cultural identity: When foods from different ecologies and economies enter in the Argobba households, they get transformed in a uniquely Argobba meal, "a culturally domesticated product ready for consumption [...] The act of cooking food, and thus transforming it, is a means of expressing what the Argobba think of themselves, who they are as Muslims, where they live, and what their role is in the natural and social world of the escarpment and the political and economic systems of the Säwa and Wällo regions of the Ethiopia. Whenever the cultural identity of the Argobba is in question, symbols taken from the realm of their cuisine [...] become active in the arena of on-going discourse in which questions of cultural identity are confronted" (p. 271–272). Also scholars as Oswald [16], Sutton [17], and Gvion [18] highlighted the relevant role played by food preparation and consumption for the constitution of immigrants and minorities' identities, with regard to their cultural adaptation and modernization process. These contributions stressed how for many societies or social groups, food preparation and consumption often constitutes a way for complementing traditional elements, inherited from the culture of origin, with new ones derived from the contact with the host society.

Starting from these considerations, a strong relationship between ethnic identity and food choice and consumption can be assumed, specifically in view of identifying possible paths towards changing behavioral food patterns and decision-making styles at the level of cultural and ethnic subgroups.

Taking into account the social, medical, and economic implications, a review of the literature in this field allowed identification of two main research issues that have been the focus of empirical investigation:

1. Variations in intake patterns and food practices across different ethnic groups
2. (Un)healthy intake patterns and food practices typical of different ethnic groups

More specifically, the first issue concerns the role of ethnicity, in association with other factors, in shaping food consumption while the second one specifies the health dimension connected to different ethnic groups' dietary patterns. These aspects will be the focus of the next paragraphs.

7.2 Relations Between Ethnicity and Food Choice: A Review of Recent Empirical Research

A consistent number of studies analyzed the role of ethnicity in shaping food choices and consumption. Despite the central role ascribed to ethnicity in shaping food choices, such a role was mostly analyzed in association with acculturation, defined as a socio-psychological process of adaptation to a new

cultural milieu, with demographic and socioeconomic variables (e.g., gender, education, and income), and with individual lifestyles. The acculturation factor was introduced because it is strictly connected to the concepts of ethnicity and ethnical identity. According to this view, members of specific ethnic groups within a given society usually experience a complex form of adaptation, based on the interconnection between aspects that relate to the acculturation process (e.g., specific skills acquired to function within a host culture) and aspects related to the their cultures of origin (e.g., [13, 19–21]).

As an example, let us consider a study conducted by Bermúdez et al. [22] aimed at investigating the amount of energy and macronutrient intake of a representative group of Hispanic elders of different national origins (Puerto Rican, Dominican, and others), living in Massachusetts, USA. Participants differed for their ethnicity, acculturation, and length of residence in the USA. The study also compared the energy and macronutrient intake patterns with data collected from a group of non-Hispanic white individuals. Results suggested differences in energy intake between Hispanic and non-Hispanic, on the one hand, and among Hispanic elders of different national origins on the other hand. For instance, Puerto Rican men (with an average length of stay in the USA of more than 30 years, one of the longest among Hispanic groups) were the only group to report a fat intake of about 30% of total energy. The other Hispanic groups reported a value below the 30%, while non-Hispanic whites reported fat intakes above 30% of their total energy. With regard to the consumption of fiber-rich food, results revealed differences among the Hispanics in function of the acculturation level. For instance, the younger Hispanic group reported a mean of fiber intake below the amount recommended for a healthy dietary pattern.

Considering the acculturation aspect, even though the Hispanic group overall emerged as less acculturated, a small number of more-acculturated Hispanic elders showed macronutrient intake patterns similar to those reported by the non-Hispanic white group.

In conclusion, these findings showed that dietary patterns of Hispanic groups in the USA rely on few foods as suppliers of energy and macronutrients. Acculturation seemed to be a moderating factor of food consumption among them. To this regard, for example, more-acculturated Hispanic elders and less-acculturated Hispanic elders differed for the top food sources for simple sugars: added sugar for the former, sugar from milk for the latter. In this case, it appears that the acculturation process could have also negative effects, and lead to a less-healthy dietary pattern.

On the basis of these findings, Bermúdez et al. [22] outline how specific efforts are needed to promote better dietary patterns among the different groups of American Hispanics elders, according to a healthier mixture of ethnic and modern foods, which might be able to satisfy not only biological, but also emotional and social needs.

An anthropological study conducted by Satia et al. [23] investigated the factors affecting dietary choices and the determinants of food acculturation among Chinese-American women. Results of individual interviews and focus groups revealed that breakfast was the first meal to be westernized after immigration, and this was mainly due to convenience factors. The majority of participants maintained a lunch and dinner Chinese-style. The main sources of fat came from both the Chinese and the American cuisine. Convenience, costs, and food quality were identified as the most salient predictors of dietary changes after immigration. Participants sometimes stated to eat American food because the traditional Chinese one is not always so easy to be found. In addition, they declared to be aware of the health outcomes of dietary styles, and to consider some American food unhealthy and strictly connected to specific diseases such as cancer. Participants also stated not being familiar with American dietary guidelines, and to get much food information from Chinese journals and friends. The authors conclude stating that dietary acculturation among Chinese American women appeared mainly driven by daily life issues. According to Satia et al. [23], these findings are particularly relevant in order to promote healthier dietary patterns and to design specific intervention strategies among the specific ethnic group they involved in their study.

A work by Laroche et al. [24] proposed and analyzed a three-dimensional model of ethnic identity for Italian and Greek-Canadians, including: (1) ethnic language use with family members, (2) ethnic language media exposure, and (3) ethnic attachment. From their results, several

references to food preferences and consumption emerged in relation to the structure of ethnic identity. Therefore, the authors analyzed also differences in the dimension of food consumption between the two groups. To this regard, they hypothesized that ethnic identity is positively related with traditional food consumption and negatively related to convenience food consumption; this latter should be in fact more reflective of North American culture. Respondents from each ethnic group lived in various districts of a major metropolitan area of Eastern Canada. Results, in line with the main hypotheses, highlighted that ethnic identity emerged as a positive predictor of traditional food consumption, for both Italian-Canadian and Greek-Canadian samples. However, the second hypothesis was supported, but only among the Italian-Canadians sample. In fact, a negative correlation between ethnic identity and convenience food consumption emerged only for the Italian-Canadian group but not for the Greek-Canadian group.

Other studies have investigated also the interaction of ethnicity with other social and environmental characteristics in influencing food practices. For example, a recent work by Deshmukh-Taskar et al. [25] investigated food consumption patterns in groups with different ethnic origins, in relation to socioeconomic (e.g., income, education), demographic (e.g., gender), and lifestyle factors (e.g., marital status, physical activity). Participants were young adults from a semirural setting in Louisiana. The sample was composed by 1,266 individuals, aged 20–38 years, 39% male and 61% female: 74% were European American and 26% African American. With regard to the socioeconomic factor, young adults with higher income levels reported a significantly fewer serving of burgers, sandwiches, and mixed dishes. Similarly, young adults with an education level higher than 12 years, reported to consume significantly more servings of breads and cereals, dairy products (e.g., cheese and yogurt), fruits, 100% fruit juices, and vegetables compared to those with a lower education level. Differences in food consumption emerged also as a function of gender. Men showed higher consumption levels of burgers and sandwiches and alcoholic beverages than Women. By contrast, women consumed significantly more yogurt, fruits and 100% fruit juices, and vegetables compared to men.

Particularly relevant are the differences in food consumption as a function of ethnic origins. Findings revealed that European-American young adults consumed significantly more servings of dairy products (e.g., milk and cheese), vegetables, fats, mixed dishes, and sweetened beverages than their African-American counterparts. In contrast, African-American young adults consumed significantly more servings of fruits, 100% fruit juices, snacks, desserts, and alcoholic beverages than their European-American counterparts. These findings clearly suggest that food consumption varies across ethnic, socioeconomic, demographic, and lifestyle factors in young adults living in a semirural community. Therefore, Deshmukh-Taskar et al. [25] suggest that public health officers and research nutritionists, or other food and nutrition professionals, who encounter different populations should consider these factors when planning diets, nutrition education programs, and interventions targeting young adults groups and communities.

7.3 Ethnicity, Dietary Patterns and Health Implications

It is commonly assumed that a balanced diet is strictly connected to an overall individual well-being: for example, higher intake of fruit and vegetables is associated with a variety of health benefits, including the prevention of metabolic syndrome and the decreased risk of heart disease (e.g., [26]), the prevention of diabetes (e.g., [27]), and the decreased risk of cancer (e.g., [28]). Therefore, the findings of studies briefly reviewed above clearly suggest the possible health implications of the relation between ethnicity, dietary practice, and health outcomes. This relation has been more specifically the focus of the some other studies, which will be discussed in the following paragraphs.

The relations among factors such as ethnicity, age, education, and acculturation in shaping healthy dietary patterns was addressed in a study conducted by Satia-Abouta et al. [29]. The study reports findings from a cross-sectional survey of 244 women of Chinese ethnicity, living in Seattle, WA, USA and Vancouver, BC, Canada. The main results highlighted that older and less educated participants considered important the presence of low fat food, fruit, and vegetables in their dietary pattern. Also, younger respondents with an occupation outside the home did not consider Chinese diet healthier than the Western one. Coherently with the findings of Satia et al. [23] already discussed in the previous section, more western-acculturated women consider Chinese food less healthier than western one; for this reason, they reported that preparing Chinese meals is not recommendable, as they are aware of the relationship between diet and diseases (e.g., heart disease or cancer). Respondents with in-family normative pressure maintained Chinese eating patterns and consumed more fruits and vegetables. As emerged from this and other studies, cultural beliefs seem thus to play an important role in shaping dietary practices. Therefore, it is fundamental for designing and implementing culturally appropriate health promotion programs to take into consideration traditional health beliefs (e.g., Chinese), as well as other socioeconomic and environmental factors.

A study conducted by Cornelisse-Vermaat and Maassen van den Brink [30] was aimed at investigating ethnic differences in lifestyles and obesity among Dutch natives and immigrants in The Netherlands. More specifically, the authors hypothesized that factors affecting body overweight might differ across ethnic groups because of their different cultural backgrounds in terms of modern food habits, lifestyles (e.g., degree of physical activity), and socioeconomic status. The sample consisted in 2,551 respondents, coming from different ethnic groups. Results showed that the body mass index (BMI) was higher among immigrants (except Moroccans), compared to native Dutch. In line with previous findings, this was partly explained with the lower socioeconomic status and education level of immigrants. While there were not significant differences in relation to income, the level of education emerged as a relevant determinant of body overweight: across all the ethnic groups considered, a lower education level was associated to a higher level of BMI.

As expected, food habits contributed to the group differences in obesity. In fact, eating-out emerged as a more salient practice for native Dutch individuals, and this affected negatively their BMI. Consuming ready-to-eat meals emerged as significantly and positively associated to the BMI of Surinamese/Antillean immigrants, but negatively associated to the BMI of Moroccan immigrants. This was probably due to differences in the specific food consumed: meals with a high-calorie value were more frequently reported in the first case, while more healthy meals in the second.

Take-out food emerged as significantly and negatively associated to the BMI of Turkish immigrants. Concerning lifestyles, all the immigrant groups (especially the Turkish), reported a lower level of physical activity. Finally, among all groups, regardless of ethnicity, the BMI was positively and significantly associated to age. Again, it is important to note how findings like these can be useful in developing social campaigns against obesity, especially among those specific groups who appear as characterized by a higher risk for obesity: for example, less-educated native and immigrant subjects.

A qualitative study conducted by Yeh et al. [31] was aimed to highlight the barriers to and facilitators of fruit and vegetable consumption among African-American, Hispanic and Caucasian populations living in USA. Twelve focus groups, ranging from 9 to 16 participants, were conducted. As regards the ethnical origin of participants, some common barriers emerged across all groups. The most important ones were:

1. The high cost of fruit and vegetables
2. The lower energy and the higher preparation-time required for fruit and vegetables
3. The negative impact of mass media advertising (it is hard to see fruit and vegetables in TV)

Some ethnical differences in barriers to fruit and vegetable consumption also emerged. African-American participants reported a high-fat and a high-sodium preparation style, and a preference for foods with a longer shelf life. In addition, many of them reported a limited access to fresh production: this, in turn, inhibits their fruit and vegetables intake.

Hispanic-American participants lamented a lower accessibility to fruit and vegetables in the USA compared to their country of origin, as well as their poor quality; in addition the lack of familiar items and tools for traditional preparation styles was also mentioned. Therefore, these findings seem to suggest the need to improve the availability and access to fresh fruit and vegetables that are commonly available in the native countries of Hispanic immigrants.

Finally, for Caucasian immigrants the most important barrier was the fear of consuming fruit and vegetables that might be contaminated with pesticides.

For what it concerns the facilitating factors to fruit and vegetable consumption, all ethnic groups underlined their health benefits, recognizing that preparing them with added fat and salt might be unhealthy for adults and children. Therefore, enhancing the awareness of the health benefits of fruit and vegetable consumption, together with decreasing perceived barriers, might be a worthy aim for information campaigns. This aspect is particularly relevant for the younger segment of the population, as they represent the future generations.

The literature reviewed so far seems to converge in suggesting the importance of ethnicity and ethnic identity in shaping food consumption patterns among different social groups and categories, and how this, in turn, might have implications for the adoption of more or less healthier dietary styles. But what are the processes at the base of the acquisition of ethnic identity across the lifespan, and how might this impact on specific (un)healthy food consumption choices? This issue will be dealt with in the next section.

7.4 The Development of Ethnic Identity in Children and Its Relations to (Un)Healthy Food Choices and Consumption

The development of ethnic identity takes place in the individual lifespan as a result of a negotiation process triggered by the conflict between individual and social requirements. The first of these negotiations involves the child in her/his first social context: the relationship with parents [32]. Phinney [13, 21] proposes a perspective about the processes of identity development and about the factors influencing this development. This author suggests that the meaning that individuals attach to their ethnicity is of great relevance for the construction of identity. Ethnic identity has a central role in the individual psychological adjustment since it allows individuals to acquire a greater and more appropriate awareness of the self; it also helps to regulate interpersonal and social relationships, and contributes to the positive outcome of the adjustment process. The developmental process of ethnic identity has been mostly studied in adolescents (for whom the construction of identity is the main developmental task) belonging to minority groups. More recent research focused also on children, in order to identify the early precursors of ethnic identity (e.g., [33]).

Phinney [21] defines ethnicity as the values, customs, and norms derived by ethnic membership, assigning an important role to what such a membership means for the individual and to the experiences and attitudes attached to any eventual minority status. The individual involvement in the social and cultural practices of an ethnic group is the most widely used indicator of the development of ethnic identity e.g., [13]). There are many different social and cultural practices that people enact as a means of expression of ethnic identity that were focused on in the literature. Among them we can

mention factors such as language competence and use, the frequentation and background of friends, religious affiliation and practices, participation to ethnic societies or clubs, ethnic features of the residential area, and a wide variety of cultural practices. Among these cultural practices, food choices and cooking habits have been investigated as expression of ethnic identity [19]. However, most of the studies investigating these specific kinds of ethnic behaviors and choices from a psychosocial perspective were conducted on adults or, at a lesser rate, on adolescents.

There are, however, some exceptions. Young children have been found to use ethnicity to explain other's preference for novel food (i.e., a type of food children do not know if they would like). Asking children to rate how much they and others (ingroup and outgroup members) would like novel nonstereotyped foods, Lam and Leman [34] found that White children think that White children would like the foods less than children of another ethnicity would.

Research on the development of ethnic identity in children most of the time focused on ethnic identification, preferences, and attitudes toward ethnic ingroups and outgroups through the use of iconographic tasks and questionnaires, or sociometric testing [21, 33, 34]. However, as the findings of Lam and Leman [34] revealed, also food choices and the reasoning about one another's food choices can be a suitable context to investigate ethnic attitudes even in children. Food is in fact a central issue of the socialization practices: to be a member of a cultural or ethnic group means to share a common attitude about what to eat and what not to eat, and the family is the first place where this learning occurs. Some studies showed that the discourse during mealtime and about food preparation and consumption is a means by which children are socialized to the culture and social practices of their ingroup. In a study by Pontecorvo and Fasulo [35], cultural differences emerged between American and Italian families in attitudes about food: American families valued the food more as a means of nutrition, while Italian families considered the pleasure over other qualities of food. These different attitudes might end in different educational practices for children, where Italian children are encouraged to express and define their personal taste as an aspect of their identity while tastes of American children are considered different kind from the tastes of adults (e.g., [36]). A recent ethnographic study on fourth graders in two schools in Los Angeles focused on food economy, which has been found to be an autonomous and spontaneous way that children have to negotiate their social identities. Interestingly, in the process of giving, sharing, or trading ethnically marked food, children display and reinforce their ethnical boundaries and identities: "children learn to do ethnicity by making use of cultural objects (food) in the exchange system that they collaboratively create" ([37], p. 371).

With a different approach, several studies focused on children's and adolescents' food choices and healthy food consumption, starting from a medical perspective (e.g., [38–40]). Most of these studies have assessed the degree to which membership to a racial (e.g., Black vs White) or ethnic group (e.g., Hispanic vs Asian) may play a role in more or less healthy food consumption and obesity. These studies identified patterns of food consumption in children and adolescents with different ethnic background, stressing the important role the social environment may play in influencing individual's food choices. Unfortunately, in these studies individual's membership to an ethnic group is made upon its self-evidence (i.e., inclusion/exclusion). This means that very little is known on the role played by ethnic identity intended as the strength and the appropriateness of identification with, and attitudes towards, one's own ethnic group. A question that is relevant in this sense is then how individual participation in cultural and social practices typical of a specific ethnic group is linked with food consumption patterns. As we have seen from the literature reviewed so far, this aspect might have relevant implications for the assumption of specific dietary patterns, and it is therefore related to the adoption of more or less healthy food consumption choices and behaviors. The next two sections will illustrate more specifically the cognitive and social psychological factors involved in these processes.

7.5 Models of Food Choice in Social and Cognitive Psychology

The issue of the food choice and purchase has been deeply studied in the social and cognitive psychological literature, because of its social, health, environmental, and economic implications. Food choices have been often considered as not substantially different from the majority of other choices or purchasing behaviors, and therefore studied through general theories on decision making processes. However, one might argue that food choice conduct is only partly analyzable through general approaches, because it is often defined by the specific food category or by the specific food product. Food choices, in fact, are based mainly on the different characteristics and attributes of food products.

From a methodological point of view, the cognitive screening prior to the decision making and choice process has been studied mainly through the use of verbal protocols (e.g., [41]) and by investigating the monitoring strategies involved in the acquisition and selection of the information used in the decision process [42, 43]. According to these approaches, the cognitive processes involved are considered as continuous.

However, other evidences suggest that decision making about food might be a discontinuous process, characterized by different stages (i.e., [44]). As stressed by Janssen and Wander [45], different kinds of cognitive processes can interact with personal and social variables to influence the process of choice. Consumer decision making is anticipated by the attainment, monitoring, and analysis of information [43]. This process can be influenced by different elements, such as verbal labels [46, 47], even when the process of choice is focused on the product's features [48, 49].

Actually, the presence of different elements to be valued can result in different strategies that, in turn, can act at different levels of the course of action (or cognition). In a first step, the process can be characterized by a noncompensatory analysis of the possible options: in this step, only a few of the various item's attributes (or even only one of them) are considered. In a second step, a compensatory strategy can be adopted, comparing a reduced number of options. In this second phase, a wider range of the item's attributes are considered, and the decision maker balances positive and negative aspects of each of the different options available (i.e., [44, 50, 51–53]). A fundamental role in the decision process is also played by the frame in which the information is proposed (in terms of positive vs negative consequences, or gain vs losses, associated to the choice made under a condition of uncertainty) (see [54, 55]).

Coherently with the approach of discontinuity of the decision process, Levin and Jasper [56] developed an empirical method to analyze the different phases of the decision process. This method, described as *phased narrowing*, was specifically created to trace and measure the screening phases in realistic decision processes situations characterized by multiple sets of option with multiple attributes (i.e. cars, computers, foods).

This method was also empirically tested in a recent study by Caddeo [57], aimed at analyzing the decision process involved in the purchase of organic foods coming from specific regions in Italy. Results confirm the expected change of strategy during the decision process. In fact, an initial exclusion strategy based on negatives attributes was followed by a strategy based on the definition of the best attribute for the final choice. Besides, these findings confirm that the process varies in function of the characteristics of the specific product to be purchased. In fact, the compensatory strategy in the final decision phase was used only for those food products that were not prototypical of the specific participants' region, while the definition of only one choice attribute was fundamental for the more regionally prototypical food products (which might be assimilated to ethnic food products).

These findings suggest that other important elements should be taken into account in the food choice process. For example, recent work pointed out the importance of factors such as:

- The place of origin of the product, in which a stereotypical association between characteristic of the country are associated with characteristics of the product [58]
- The estimated health-related consequences of the consumption, in particular in consideration of the nature of food products defined as Organic or Genetically Modified [59, 60]
- Moral and ethical considerations of the purchaser [61–64]

Another line of research have focused more on the social psychological variables involved in ethnical food choices and decision, and pointed out the importance of individual attitudes and their relationship with food consumption behaviors. These aspects will be dealt with more thoroughly in the following paragraph.

7.6 The Role of Ethnic Identity and Perceived Ethnic Norms in Shaping Food Consumption: Some Recent Empirical Findings

Within the social psychology tradition, various approaches and models have tried to focus on the mutual interplay between individual and group variables in the formation of consumer's decision (e.g. [65]). A model worthy to mention in this sense is Theory of Planned Behavior (TPB [66–68]). The TPB has been applied with good results to the prediction of human deliberate action in several domains [69–71], including food purchasing conducts [72–74]. The TPB assumes deliberate processes and the evaluations of the possible alternatives and outcomes are at the basis of individual choices. More specifically, the TPB states that behavioral intentions are the most proximal antecedents of actual behaviors. In turn, behavioral intentions are based on three main elements: attitudes towards a specific behavior; subjective norms (i.e., the individual perception of what important others would or would not expect her/him to do or not to do); the perceived behavioral control.

Despite the huge empirical evidence supporting the sufficiency of the TPB, different authors suggested to improve this model by considering other predictors of intentions and behaviors [70, 71]. In the food consumption domain, for example, Cook et al. [75] tried to extend the TPB model by taking into account the role of self-identity for the prediction of the consumption of genetically modified (GM) food products. Likewise, in a study about fish consumption in Belgium, Verbeke and Vackier [74] investigated the role of personal characteristics together with the classical TPB variables in predicting purchasing intentions. Results showed that fish consumption and intention varies in relation to food involvement, and that this might vary across specific groups; in particular, it was found that health considerations were more relevant for women and that fish consumption increased with age.

But which is the specific role played by identification with the ethnic group in predicting the consumption of ethnic foods? Two empirical studies conducted by some of the authors of the present chapter have specifically addressed this issue [72, 76]. Both these studies tried to analyze the role of group and individual variables in the purchasing of ethnic food products by proposing an extended TPB model, inclusive of measures of past behavior, of ethnic identification and of perceived ethnic group norms regarding the target behavior (i.e., the individual perception that also other members of their ethnic group are purchasing ethnic food). The study conducted by Nenci et al. [76] was conducted on 135 Jamaican immigrants living in the Brixton neighborhood in London, UK, while the study by Carrus et al. [72] was conducted on 100 Indian immigrant women living in Rome, Italy.

The results of both studies confirmed the sufficiency of the original TPB model in predicting ethnic food choices. However, in both cases, a significant increase in the predictive power of the TPB model was detected when also other factors, such as ethnic identification and perceived ethnic group norms, were jointly considered. In particular a synergic interaction effect between these two variables

was found: in fact, the positive relation between the perceived norms of the ethnic group (i.e., the belief that many other members of the ethnic group are also purchasing ethnic food) and self-reported intentions to purchase ethnic food was particularly evident only for those individuals who strongly identified with their ethnic group.

Thus, these findings seem to confirm how food consumption patterns might also help individuals in order to comply with those norms and habits that are perceived as important (or even necessary) to define and express their membership into specific ethnic and social groups.

7.7 Concluding Remarks

The main assumption put forward in this chapter is the existence of a relationship between ethnicity and food choice. Indeed, empirical evidence accumulated so far across social and behavioral sciences suggest the importance of ethnicity in shaping food consumption patterns, among different social groups and categories. In addition, empirical findings reported here are suggesting the potential impact of ethnical identity on individual health and well being: identification with the ethnic group might in fact influence food choices and decisions of these choices, in turn, are at the basis of more or less healthy dietary patterns adopted by individuals, groups, and communities.

In general, studies focusing on the dietary patterns of immigrant populations started from the main assumption that immigrants groups might be less likely to adopt dietary patterns in line with current recommendations emerging from the medical and preventive medicine domain. This hypothesis has received only partial empirical support. Indeed, results of research in this field have highlighted a complex pattern in the relation between ethnicity and health-related food behaviors and habits. Therefore, further studies are needed in order to better analyze the association between ethnicity and other relevant variables involved in food consumption, such as, for example, acculturation, age, or length of residence in the hosting country.

Other findings relevant for understanding the relationship between ethnicity and food choices can be found in the social and cognitive psychological literature. For example, findings of social psychological research highlighted the role of factors such as ethnical identification and social norms (e.g., perceived norms of the ethnical group), in the prediction of ethnical food choices. In fact, a positive relation between perceived norms of the ethnic group and self-reported intentions to purchase ethnic food is evident in particular for those individual who strongly identify with their ethnic group.

The literature reviewed in this chapter provides insights for a better understanding of food consumption patterns of specific ethnic groups and communities. Particularly relevant is the issue of food choices and consumption among young people: children and adolescents are intensely involved in constructing their self and identity and they are constantly confronted with the instances of their social groups (e.g., family and peers), in negotiating this construction. Traditional values, heritage and cultural practices of the ethnic group, as well as individual and collective sense of membership to an ethnic group might be deeply involved in this process of identity construction. These factors help the individual to acquire social and personal resources that can guarantee an adequate personal and social adjustment, and positive social interaction experiences.

Food-related behaviors have indeed a strong symbolic meaning, as frequently highlighted by mainstream anthropological research. In addition, they might have a strong concrete relevance for individual health and well being. These aspects should therefore be seriously taken into account when planning interventions such as educational plans in schools, or general communication campaigns on healthy food consumption.

The findings of studies reviewed in this chapter can have relevant practical implications. For example, authorities concerned with public health and nutrition policies might be willing to consider factors related to membership into specific ethnic groups and cultures when planning diets, nutrition and food education interventions targeting specific social groups and communities (e.g., immigrants, children, adolescents, elder people). Identity processes and social norms shared among specific ethnic groups might also play a crucial role in this sense. In fact, findings reported here seem to confirm how food consumption patterns might also help individuals to comply with those norms and habits that are perceived as important (or even necessary) to define and express individual membership into specific ethnic and social groups. As a consequence, identity-related strategies could be pursued in marketing and advertising campaigns on healthy food choices, among these particular categories of people.

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Part III
Potential for Cost Effectiveness
with Food Interventions

Chapter 8

Low Cost Food, Recovery and Death in Malnourished Children

Luigi Greco and Valentina Fiorito

Key Points

- Malnutrition contributes to 53% of child mortality worldwide.
- According to WHO protocols, management of the severely malnourished is based on special formula diets based on the Modified Cow's Milk named F75 and F100.
- Many malnourished children have acute diarrhea after milk ingestion.
- There is high prevalence of lactose intolerance in Africans and this suggests that skim lactose-rich milk with added sugar may not be the best treatment for malnourished children with diarrhea.
- According to WHO recommendations we introduced in the rehabilitation protocol, in addition to the special milks, Nutricam, a porridge prepared with local low cost food.
- Nutricam feed has been accepted with enthusiasm by the local population and by the children.
- Children who received the porridge did better than those who was given only milk-based feeding: their edema disappeared more rapidly and they put on more weight daily.
- Crucially, the treatment-failure rate (deaths and withdrawals from treatment) declined by more than 50% after the porridge was introduced.
- In order to prevent and treat children with malnutrition, locally available low cost foods wisely prepared by reinforcing local tradition are more than often the single most cost-effective intervention.

Keywords Growth increments • Local foods • Malnutrition • Ready-to-use therapeutic food

8.1 Malnutrition: Inequalities in Human Rights at Global Levels

Malnutrition is one of the greatest public health problems facing the world today because of the number of children affected and the long-term consequences. There was much progress in the last decades. Malnutrition was reduced from 37% to 27% between 1980 and 1999, the percentage of those in rural areas with access to safe water has increased from 13% to 71% and in some countries, such as in China, income-poverty is reduced from 33% in 1978 to 7% in 1994 [1]. Despite this progress, poverty,

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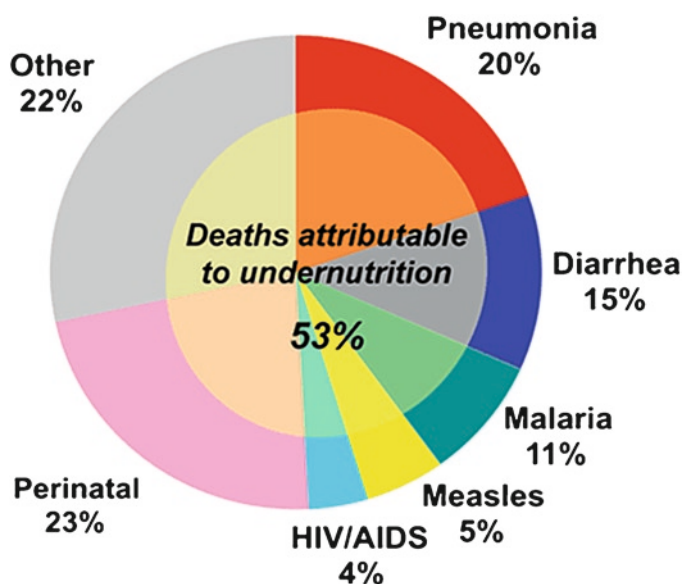


Fig. 8.1 Proportional mortality among under fives (WHO 2005)

malnutrition, healthcare and education are still hinge-topics in the international system because of global levels of inequality that are actually extremely high. Globalization limits the potential benefits of international markets to the poorest countries and gives to a limited number of people or countries the possibility of improving and growing. This means that global disparities in health, education and other human rights are day by day larger and, even if the global level of malnutrition is reducing, there are still countries whose children are under- or malnourished with scarce possibilities of improving without a specific commitment from international authorities. But the very factor underlying the actual status of widespread malnutrition is not indeed poverty or complete scarcity of resources: war, injustice, bad management are, by far, the most heavily responsible for children's malnutrition. United Nations in 2000 agreed on eight Millennium Development Goals and two of them are strictly linked with malnutrition aiming to halve those in extreme poverty and hunger by 2015 and reducing child mortality [2].

8.2 The Load of Malnutrition on Mortality

World Health Organization estimates that malnutrition contributes to 53% of child mortality worldwide [3] (See Fig. 8.1). There is a strong association between malnutrition and mortality in developing countries. The mean relative risk for severe malnutrition is 8.4, for moderate malnutrition it is 4.6, and for mild malnutrition it is 2.5 [4] and this means that even mild degrees of malnutrition double the risk of mortality for diseases such as respiratory tract infection, diarrhea, pneumonia, malaria and measles [5, 6].

8.3 Programs and Support for Malnutrition

WHO published several volumes in order to spread a simple classification of malnutrition and protocols for management [7–9]. The management of a malnourished child is the same for marasmus

Table 8.1 Nutritional status classification (WHO 2005)

	Wt/Ht	MUAC ^o	Edema	BMI*
Good nutritional status	>85%	>135 mm	no	
Mild acute malnutrition (at risk)	80–85%	125–135 mm	no	
Moderate acute malnutrition	70–80%	110–125 mm	no	16–18
Severe acute malnutrition	<70%	<110 mm	si	<16

MUAC^o = Mid upper Arm circumference (used for 6 months–18years old patients with length >65 cm)

BMI* = Body Mass Index (used only for adult)

(caloric restriction) and for kwashiorkor (protein restriction) despite their different etiology but the approach is different according to the degrees of malnutrition.

Table 8.1 shows how WHO defines a patient's nutritional status. *Mild Acute Malnutrition* benefits from health counseling and community mobilization. *Moderate Acute Malnutrition* is still manageable in community setting but needs a specific program: *Supplementary Feeding Program* (SFP). This program is based on *Supplementary Feeding Centers* (SFC) that monitor the patient every week and provide antibiotics, antihelminthics, vitamin A and supplementary food like Ready-to-Use Therapeutic Food (RUFT) a high energy fortified ready to eat food.

Severely malnourished children and infants less than 6 months old with specific features ($Wt < 4\text{ kg}$, $Wt/Length < 85\%$ and not able to suckle/not fed on breast-milk, mother died or mother has no or little milk or presence of edema) have to be admitted to a *Therapeutic Feeding Center* (TFC). In this center they are managed, according to a specific *Therapeutic Feeding Program* (TFP), with special milks called F75 and F100.

8.4 UNICEF_WHO Milks

Almost all severely malnourished children have infections, impaired liver and intestinal function, and problems related to imbalance of electrolytes when first admitted to the hospital. Because of these problems, they are unable to tolerate the usual amounts of dietary protein, fat and sodium. It is important, therefore, that children begin feeding on a diet that is low in these nutrients, and high in carbohydrate.

To this purpose UNICEF and WHO prepared two formula diets based on the Modified Cow's Milk F75 (starter 75 kcal/100 mL) and F100 (follow up 100 kcal/100 mL). These milks are given, in proportion of body weight, at 3-hourly intervals. F75 has a moderate protein and energy content and is given in the early phase of severe malnutrition, F100 has a higher energy and protein content and is useful for maintenance. The milks have to be given frequently and in small amounts to avoid overloading the intestine, liver and kidneys. Children unable to drink are fed by plastic syringes and nasogastric tube. The theoretical daily supply of energy is 140–200 cal/kg body weight. But this amount is very difficult to administer to any single child. Night feeds are generally not available.

Table 8.2 shows the composition of the two milk feeds: F75 starter, to be given for the first few days and F100 for follow up. From the table it is clear that the feeds are based on skimmed milk with added sugar and vegetable oil.

The mineral mix with potassium, magnesium and other essential minerals must be added to the diet. The potassium deficit, present in all malnourished children, adversely affects cardiac function and gastric emptying. Magnesium is essential for potassium to enter cells and be retained. The mineral mix does not contain iron as this is withheld during the initial phase.

Table 8.2 Composition of F-75 and F-100 diets

	F75	F100
Dried skimmed milk (g)	25	80
	100	50
Sugar	27	60
Vegetable oil	20	20
Electrolyte/mineral sol	1000	1000
Water: make up to (mL)		
<i>Contents per 100 mL</i>		
Energy	75 kcal _{th} (315 kJ)	100 kcal _{th} (410 kJ)
Protein	0.9 g	2.9 g
Lactose	1.3 g	4.2 g
Potassium	3.6 mmol	5.9 mmol
Sodium	0.6 mmol	1.9 mmol
Magnesium	0.43 mmol	0.73 mmol
Zinc	2 mg	2.3 mg
Copper	0.25 mg	0.25 mg
<i>Percentage of energy from:</i>		
Protein	5%	12%
Fat	32%	53%
Osmolarity	333 mOsm/L	419 mOsm/L

8.5 The Problem of Lactose and Lactase Deficiency

About 95.4% of African children have the C/C-13910 genotype of the lactase-Y-phlorizin-hydrolase gene that causes adult-type hypolactasia versus 14.5% of Finnish children. The decline of the lactase activity in African children occurred earlier than Finnish children, as 30% of the children already had low levels of lactase (<10 U/g protein) at the age of 5 years [10].

Ninety-one percent of the population of Sao Tome (West Africa) has lactose intolerance (homozygous CC genotype of adult type hypolactasia). Genetic data are 96% concordant with functional (Breath Hydrogen Test) data. In Portugal, on the contrary, lactose intolerance has 42% prevalence [11]. Many studies demonstrated that infants with acute diarrhea had chemical markers for lactose intolerance (positive reducing substances (Clinitest) in the feces and stool pH < 5) [12]. A randomized controlled study evaluated the effect of lactose-free formula versus ordinary milk on the outcome of 80 children with acute diarrhea. Lactose-free formula reduced by 20 h the duration of diarrhea, decreased stool frequency and increased the weight gain, as compared with lactose containing milk with otherwise the same composition. Unscheduled intravenous fluid could be decreased by 50% in the lactose-free group [13].

8.6 Is Milk the Sole “Drug” to Cure Malnutrition? What Does Happen in the Field?

While working at the Nutritional rehabilitation Unit of St. Mary’s Hospital, Lacor, Gulu, Uganda we observed acute diarrhea following milk ingestion in many malnourished children. We had to suspect that severely ill children could not fully absorb the energy provided by the milk containing full lactose and sugar. Chemical markers for lactose intolerance (positive clinitest and stool pH < 5) were suggestive, too.

These direct observations, supported by the awareness of high prevalence of lactose intolerance in Africans and the consideration that diarrhea is one of the main causes of fatality in severely malnourished children, suggested that skim lactose-rich milk with added sugar may not be the best treatment for malnourished children with diarrhea [14–16]. In this context, it is not surprising that milk alone is not the best treatment for severely malnourished children and indeed international agencies recommend supplementary feeding [7].

8.7 Supplementary Feeds: Official and Local Proposal

In addition to milk, supplementary feeding was encouraged to counteract malnutrition [7, 17]. Supplementary feeds are any types of food added to the standard diet: they can be based on cereals and legumes, can be prepared with locally available food in developing countries or packed industrially in developed countries as ready to use nutritional supplements. The efficacy of cereal-and-legume-based supplementary feeding in large-scale programs has yet to be demonstrated [18, 19]. Ready-to-use food in the form of a fortified spread is effective in treating malnourished children [20].

According WHO/UNICEF/WFP/SCN Ready-to-use food (RUTF) has to be a high energy, fortified ready to eat food suitable for treatment of severely malnourished children. (See Table 8.3)

Table 8.3 Ready-to-use therapeutic food (RUTF) composition

Nutritional composition	
Moisture content	2.5% maximum
Energy	520–550 kcal/100 g
Proteins	10–12% total energy
Lipids	45–60% total energy
Sodium	290 mg/100 g maximum
Potassium	1,100–1,400 mg/100 g
Calcium	300–600 mg/100 g
Phosphorus (excluding phytate)	300–600 mg/100 g
Magnesium	80–140 mg/100 g
Iron	10–14 mg/100 g
Zinc	11–14 mg/100 g
Copper	1.4–1.8 mg/100 g
Selenium	20–40 µg
Iodine	70–140 µg/100 g
Vitamin A	0.8–1.1 mg/100 g
Vitamin D	15–20 µg/100 g
Vitamin E	20 mg/100 g minimum
Vitamin K	15 to 30 µg/100 g
Vitamin B1	0.5 mg/100 g minimum
Vitamin B2	1.6 mg/100 g minimum
Vitamin C	50 mg/100 g minimum
Vitamin B6	0.6 mg/100 g minimum
Vitamin B12	1.6 µg/100 g minimum
Folic acid	200 µg/100 g minimum
Niacin	5 mg/100 g minimum
Pantothenic acid	3 mg/100 g minimum
Biotin	60 µg/100 g minimum
<i>n</i> -6 fatty acids	3–10% of total energy
<i>n</i> -3 fatty acids	0.3–2.5% of total energy

This food has to be soft or crushable, palatable and easy for children to eat without any preparation. At least half of the proteins contained in the industrial product come from milk products. To prepare locally RUTF four basic ingredients are suggested: Sugar, Dried Skimmed Milk, Oil, Vitamin and Mineral Supplement (CMV). In addition, up to 25% of a product's weight can come from oil-seeds, groundnuts or cereals like oats. As well as containing the necessary proteins, energy and micronutrients, RUTF should also have the following attributes:

- Taste and texture suitable for young children
- No need for cooking before consumption
- Resistant to contamination by micro-organisms and long shelf-life without sophisticated packaging. Product should be oil-based

Among Ready-to-Use Therapeutic Food is *Plumpy'nut*, a peanut-based food formulated in 1999. It is a high protein and high energy peanut-based paste in a foil wrapper. It tastes slightly sweeter than peanut butter.

There is no doubt that RUTF is a tremendous progress on the path to cure malnourished children. But we have to consider that:

- It is still based on lactose-containing milk.
- There is a remarkable load of simple carbohydrates (sugars).
- It is a typical western-style industrial packet which give to mothers more the message to be a “special drug” than a supplementary feed.

8.8 Nutricam: The Food-to-save

After a long frustrating work at the St Mary's Hospital Nutritional Unit in Lacor (Gulu, Northern Uganda) we attempted to find local solutions to improve nutritional rehabilitation in that setting [21, 22].

According to WHO recommendations [7], we decided to evaluate the possibility to introduce a new nutritional intervention, to be added to the UNICEF milk, for the following reasons:

- Results of the nutritional rehabilitation with the UNICEF milk were discouraging.
- The large amount of lactose and sugar of therapeutic milks might facilitate diarrhea, malabsorption and fatality.
- The UNICEF milk, as any other powdered milk, is not available outside the hospital: many children do relapse, because they are poorly fed when the milk is interrupted by the discharge from the hospital.
- Milk feeds are not available and not traditional to the Acholi children of North Uganda.

Following the observation of the traditional feeding habits of the Acholi people, and a further check of the availability of the food items at the local market, we purchased at the market outside the hospital maize flour, rice, millet, peas and beans, peanuts, small dry fishes, cow's meat, chicken and vegetable oil.

We prepared a thick semi-solid porridge, with a cereal flour base as carbohydrates, proteins (fish, legumes, meats on rotation) and fats (peanut butter and vegetable oil). The porridge was named NUTRICAM that in the local language, Acholi, means nutritional feed.

A 150-g serving of Nutricam made with 20 g flour (65 cal, 274 J), 10 g fish, meat or dry legumes (20 cal, 84 J), 5 g peanut butter (30 cal, 122 J) and 5 g oil (45 cal, 185 J), provides a total of 160 cal (665 J) and 6.3 g proteins (Table 8.4). Each child admitted in the Nutrition Unit according the WHO

criteria and in the face of rehabilitation II [7], was offered two 150-g servings of Nutricam each day in addition to the scheduled amount of milk. In this setting it was not practical to “dose” the porridge according to body weight. Milk was administered according to body weight. Feeds were given under surveillance in a purposely-built feeding hut, but we could not measure exactly the amount of food ingested. Most children consumed the whole feed within 1 h after distribution. Table 8.5 shows the week rotation of the feeds, in order to provide for different sources of proteins. 100 child/day/servings are prepared each morning and 100 each afternoon. A single daily feed (two servings) for a child costs about 5.9 cents of a Euro. The total monthly cost, including ingredients, fuel and salary for the cook is about 220 Euros (Table 8.6). Table 8.6 shows the cost of the milk feeds for the same 100 children and the ratio Nutricam/milk cost. The cost of NUTRICAM is about 8% of the actual cost of UNICEF milk.

The porridge can be made at home as follows: (1) cook two tablespoons of maize flour (or millet or rice) in 1 cup of boiling water; (2) cook for about 15 min then slowly add one tablespoon of powdered fish and a half a tablespoon of peanut butter, stir vigorously until a thick porridge is obtained; (3) add a half a tablespoon of vegetable oil to make the porridge more creamy. The source of protein can be fish, beef, poultry or beans depending on availability.

After the distribution of the NUTRICAM, each child was surveyed for his ability to eat the porridge and for the presence of vomiting or diarrhea. Mother’s attitude towards this feed was observed.

Table 8.4 Content of one 150 g serving of nutricam

Ingredient	grams	Calories (kJ)	Proteins (g)	Fat (g)	Carbohydrates	Fe (mg)	Zn (mg)
Cereal flour (ex. Mais)	20	64.8 (274)	1.4	0.6	13.3	0.5	0.1
Fish (or meat, poultry, beans)	10	20.0 (84.2)	2.4	0.6		0.2	0.2
Peanut butter	5	29.2 (121)	0.2	2.5	0.5	0.1	0.3
Vegetable oil	5	45.0 (185)	0	5			
Water	to 150 g	0					
Total		159 (664.8)	4.0	8.7	13.7	0.8	0.6

Table 8.5 Weekly menu of “Nutricam” for 200 servings/day

Day	Carbohydrates (kg/day)	Proteins (kg/day)	Fat (kg/day)
Monday	Maize 4 kg	Dry fishes 2 kg	Peanut Butter 1 kg + Oil 1 L
Tuesday	Rice 5 kg	Meat 2 kg	Peanut Butter 1 kg + Oil 1 L
Wednesday	Millet 4 kg	Dry fishes 2 kg	Peanut Butter 1 kg + Oil 1 L
Thursday	Maize 4 kg	Chicken meat 2 kg	Peanut Butter 1 kg + Oil 1 L
Friday	Rice 5 kg	Dry fishes 2 kg	Peanut Butter 1 kg + Oil 1 L
Saturday	Maize 4 kg	Beans 2 kg	Peanut Butter 1 kg + Oil 1 L
Sunday	Maize 4 kg	Peas 2 kg	Peanut Butter 1 kg + Oil 1 L

Table 8.6 Feeding cost for 100 children every day

EUROS			
	1 day	1 month	1 year
F75 milk	9.96	299	3,588
F100 milk	79.95	2,398	28,782
Total milk	89.91	2,697	32,370
Nutricam	7.35	220	2,648
Cost rate Nutricam/milk		%	8.18

The NUTRICAM feed was accepted with enthusiasm by the local population and by the children. They completely consumed two servings each day, while not interrupting the milk feed. We could not observe adverse reactions, as vomiting, diarrhea, food intolerance.

To evaluate the mean growth increments before and after the Nutricam intervention, to avoid seasonal effects, we randomly sampled 100 case files dismissed in the months October, November and December in the years 2001, 2002, 2003. For each case we reported the length of stay in the unit and the weight gain reached at discharge. To avoid complications with edematous children, we computed for all cases with edema $>1+$, the increment between the lowest weight reached and the weight at discharge.

The analysis of 20 weight growth curves of children without edema (Fig. 8.2) admitted to the Lacor hospital in June and July 2002, before the administration of Nutricam, did not show, in most cases, the expected catch-up growth after nutritional rehabilitation with milk. Finally, a significant proportion ($>10\%$) of mothers dropped out of the program, often because of discouraging results.

Figure 8.3 shows the weight curves, in grams of body weight, of 20 children, without edema, who received Nutricam starting from the first week of August 2002. There was a conspicuous improvement in the slope of many weight curves compared with pre-Nutricam values. The average daily edema-free weight gain was 21 g (12–29 g) with milk alone in 2001, 35 g (25–45 g) immediately after the intervention in 2002 and 59 g (51–68 g) at the end of the first year of intervention 2003 (See Fig. 8.4).

Table 8.7 shows the average increments in weight for each year of the study, corrected for days-in-care and age at admission (multivariate analysis). Days-in-care correlated with weight

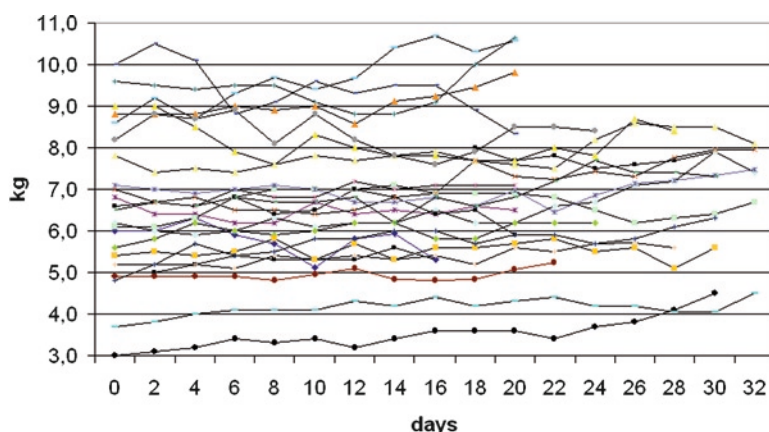


Fig. 8.2 Twenty individual weight curves (weight in kg) before Nutricam administration (July 2002)

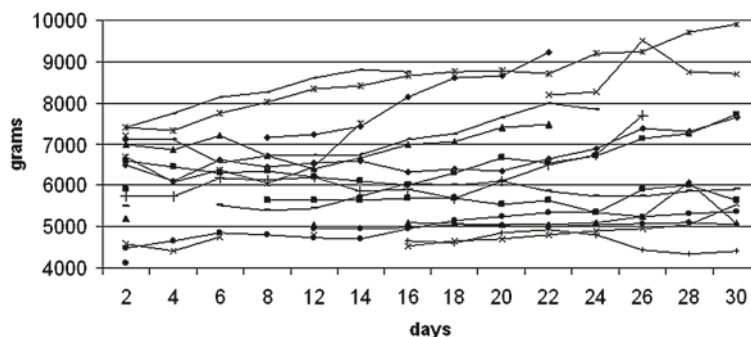


Fig. 8.3 Individual weight curves (weight in g) during Nutricam administration (August 2002)

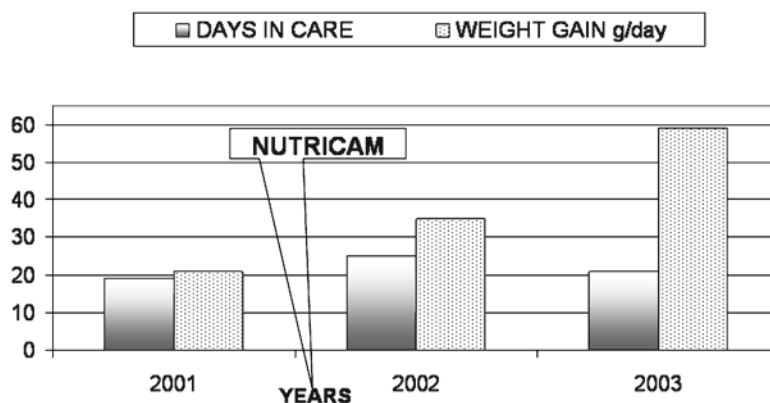


Fig. 8.4 Length of treatment (days in care) and mean daily weight increments before and after Nutricam

Table 8.7 Average weight gain: analysis of variance table

Year	Mean weight gain (g)	SE	95% Confidence intervals	
			Lower limit	Upper limit
2001	525	77.1	373	676
2002	771	78.0	618	925
2003	1274	78.0	1120	1427

Source of variation	Degrees of freedom	F	P	Partial ETA
Days in care	1	68.092	<0.0001	0.186
Age at entry	1	21.826	<0.0001	0.068
Year of study	2	24.057	<0.0001	0.139

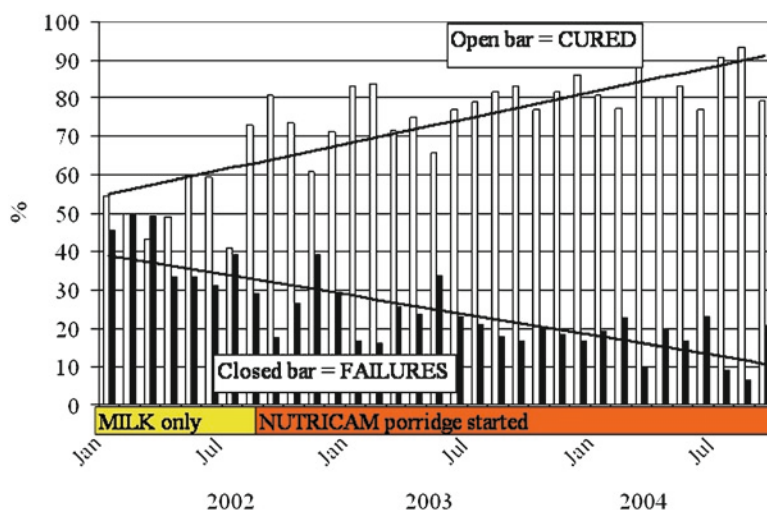


Fig. 8.5 Outcome of nutritional rehabilitation before and after Nutricam. The numbers and trends (regression line) of survival outcome are shown as per cent of cases admitted to hospital each month. The top regression line refers to cases discharged as “cured” (namely, children above the 85% weight for length). The lower regression line refers to overall failures (dead and lost cases)

increments, but did not change significantly over the 3 years of the study, whereas the mean weight increments during treatment (an average of 20 days) increased from 525 g in 2001 (before Nutricam), to 771 g in 2002, and 1,274 g in 2003. Mean growth increments increased significantly as the study

progressed ($F=38.0$ $P<0.0001$). Figure 8.5 shows the numbers and trend of survival outcome as a per cent of cases admitted to hospital each month. The top regression line shows the per cent of cases discharged as “cured” (namely, children who attained 85% weight-for-length, which increased from 54.5% in January 2002 to 93.3% in August 2004). The lower regression line shows the per cent deaths and per cent of “lost” cases. Mortality and “lost” rates are considered collectively as “overall failures”: these were 45.5% in January 2002 and 6.7% in August 2004. The death rate was 21.2% in January 2002 versus 2.9% in August 2004.

Table 8.8 shows the averages (and standard error) for each outcome variable (cure, death, lost–default) in the 3 years of the study after correction for the number of cases admitted in each study period (multivariate analysis). Again, the differences among years are highly significant.

The results were so good that the hospital decided to introduce permanently Nutricam in the nutritional rehabilitation.

In a further study, 6 years later, we demonstrate conclusively how Nutricam helped to treat malnutrition. In order to observe long term results, 5,620 patients admitted in the St. Mary’s Hospital in Lacor, Uganda, were studied from the second half of 2002 (after introduction of Nutricam) to 2007.

We included in the study all the patients admitted to the Nutrition Unit according to the WHO criteria [7] avoiding any selection bias. Over these 6 years 74.7% of patients were admitted because of marked edema, 17.3% because of low weight for height and 6.1% because of very low Mid Upper Arm Circumference.

As you can see in Fig. 8.6, the average edema-free weight gain was 1,694 g for cured patients. The average daily edema-free weight increment was 66.7 g for males and 62 g for females.

Table 8.8 Outcome at the nutritional unit over time

Year	% Cured (SE)	% Dead (SE)	% Defaulters (SE)
2002	59.6 (3.7)	17.0 (1.2)	18.2 (2.1)
2003	78.7 (1.7)	10.2 (0.9)	10.5 (1.3)
2004	83.5 (2.0)	9.2 (1.5)	3.7 (1.2)
ANOVA ^a	$F=21.2$ $P<0.0001$	$F=12.5$ $P<0.0001$	$F=10.9$ $P<0.0001$

SE standard error, F variance ratio

^aAnalysis of variance

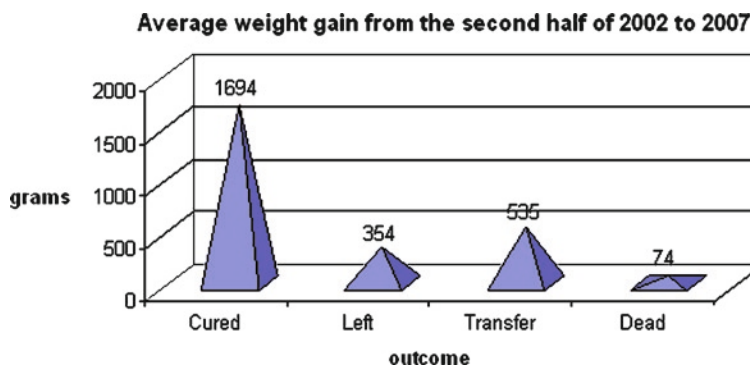


Fig. 8.6 Average weight gain over more than 5 years of Nutricam administration

The survival outcome is still confirmed, as in the previous paper. Figure 8.7 shows that the overall percent of children cured is 78% and the percent of died is 11%. These results are similar to those published in the previous paper and very different from those before-Nutricam period. Mortality in this setting is still very high. To understand the causes of this finding we explored the clinical data of the children. The average of days in care was 23.9 days/child but the distribution shows two peaks (Fig. 8.8).

The first high peak is in the first few days after admission: this is the cohort where most of deaths are endowed. They come to the Unit in extremely severe conditions and cannot take any advantage from the nutritional program. In our setting, more than 50% of dead patients did not survive to the sixth day after admission and the highest peaks of deaths is in the second and third day after

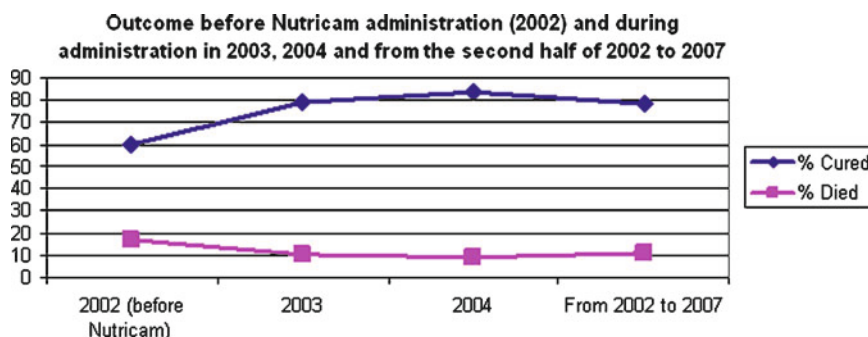


Fig. 8.7 Outcome of nutritional rehabilitation program without and with Nutricam administration

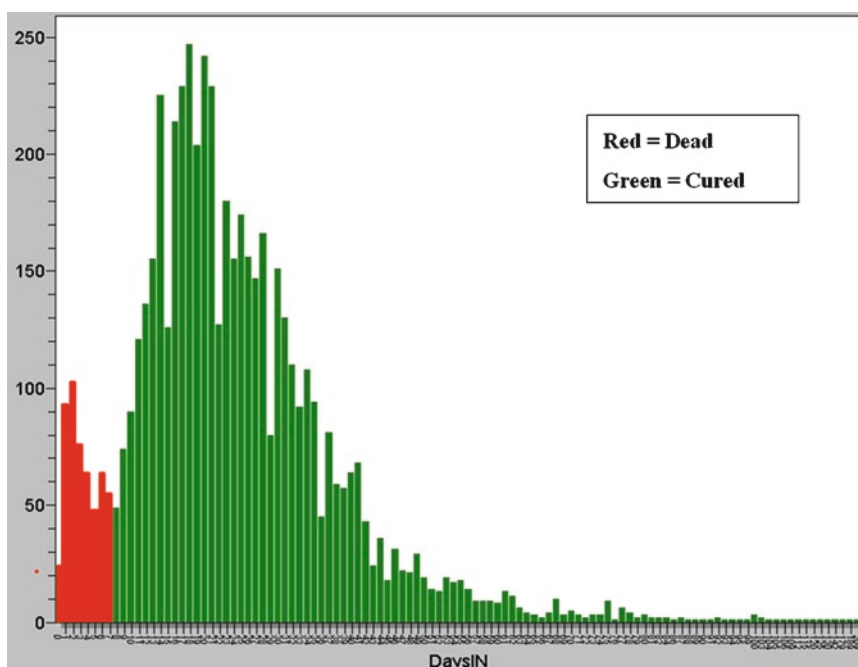


Fig. 8.8 Distribution of days in care over more than 5 years

admission. These data show that this high mortality cannot be attributed to a failure of the nutritional program but it is due to the late referral of the extremely wasted children with severe complications. Intensive care facilities, not yet available in the unit, could reduce these fatalities, but it will not be the most adequate solution to the problem.

It is clear that the best solution is to intensify the nutritional screening in the villages and, then, support community-based treatment for moderately malnourished children.

In conclusion, Nutricam plus milk was more effective than milk alone in nutritional rehabilitation of severely malnourished children. Edema disappeared rapidly and daily weight increments rose significantly compared to treatment with milk only. Nutricam did not affect the length of stay in the unit, probably because the children were severely ill and were affected by diseases typical of African countries (diarrhea, malaria, pneumonia, tuberculosis etc.) besides malnutrition.

The change observed over time in the outcome variables (increments in weight and survival) may not be entirely due to the nutritional intervention. During the 2 years after the intervention started, various improvements were made in the Nutritional Rehabilitation Unit, although the care of severely malnourished children remained unchanged. Moreover, the number and category of medical personnel in the Nutrition Unit did not change, and no additional motivation was given to medical personnel or caretakers/mother to improve care. During the study, the number of admissions increased and the status of the children at admission was worse, probably because warring factions had caused many families to abandon their villages. However, the disease pattern in these children and their management protocol did not differ from that of the other children studied.

Pre- and post-test HIV counseling was not routinely offered to all patients, and it was difficult to determine HIV prevalence among the children in the study. However, a cross-sectional investigation of patients in the same ward in 2004 showed an HIV prevalence of 10% (unpublished data). Therefore, it is unlikely that malnutrition in our study was HIV-related.

Nutricam is locally feasible at a low cost (about 0.056 Euro/serving, including labor and fuel). It is well accepted by the local population, easy to prepare and very effective for nutritional rehabilitation. Nutricam was not intended to supply all the daily energy requirements, but it is well suited as a supplement to mother's milk.

At the Nutritional Unit, mothers/caretakers are offered nutritional education twice daily by the Health Educator and they participate to the preparation of Nutricam for at least 5 days before their child is discharged from hospital. The nutritional intervention is not persistent if it is not handed to the mother's responsibility, in order to transfer this attitude to the daily village life. To comply with this priority, we reinforced the locally available health education activity: every other day a trained Health Education Nurse gives classes in Acholi. Inasmuch the mothers, in small groups, are actually directly involved in the preparation of the NUTRICAM: they prepare, by traditional procedures, the peanuts, legumes and cereals and attend to the cooking. The hospital management established four small charcoal kitchens, in order to facilitate the direct preparation of the food by the mothers.

Nutritional failures decreased by more than 50% after Nutricam. From August 2002 to September 2004, we estimated that 454 children were saved from nutritional failure: 216 less deaths and 238 patients less lost-to-treatment versus the period from January to July 2002.

This study demonstrates the efficacy of supplemental feeding with a varied protein source for severely malnourished children. The comparison of an "untreated" cohort with a different "treated" cohort could be seen as a limitation of our study. However, we could not divide each cohort into milk-only and milk-plus-Nutricam subgroups because the children were severely malnourished and in need of supplementation.

This intervention did not require a special project or sponsors, just one person at a cost of only 220 Euro/month for the entire action. The hospital management continued this intervention, which was also implemented in three district hospitals in the region. It cost about 3,000 Euros to build the

kitchen and purchase equipment for each new therapeutic feeding center. The cost of providing powdered milk by international agencies is 32,370 Euro/year for the same group of children who entered our study. The results of nutritional rehabilitation with milk alone are often disappointing. Moreover, milk is not always available out of the hospital, which means that many children relapse. The widespread use of the porridge together with milk, which resulted in better outcomes than milk alone, could produce savings thus releasing resources for other uses.

Lastly, nutritional rehabilitation is essential to survival for the many children with malnutrition in developing countries, but it cannot be based solely on powdered milk. The Lacor study highlights the need to involve local communities in the selection of locally available nutritious foods for children to prevent and treat malnutrition.

Few papers were published on local food in the rehabilitation of malnourished children. It's not impossible to imagine that the reason is in the poor economic interests. In 1988 a paper on the use of local food resources in the rehabilitation of children with malnutrition in Central African Republic was published. In this study 860 cases were followed-up with very good results after 6 years [23].

In 1997 Ashworth and Khanum in a paper in which they compared three approaches in a cost-effective analysis concluded that with careful training and an efficient referral system, home care preceded by 1 week of day care is the most cost-effective treatment option for severe malnutrition. In this home care approach no food supplements were given for feeding the child, otherwise, in the two other approaches, high energy nutrients were provided [24].

In 2008 a paper (written, among others, by the producer of one the most popular industrial supplementary food) compared F-100 with optimal combinations of local foods in different countries. They conclude that these combinations don't achieve the nutrient density of F100 and there is still the need to establish their clinical efficacy before promoting them [25].

In conclusion the most effective treatment of children's malnutrition is early local identification of at risk children and secondary prevention: which means to treat the moderately malnourished children before severe malnutrition ensues.

Immediately after this intervention the use of local ingredients to prepare supplementary feeds for breast fed children was proven to be an effective intervention at very low cost. Also in the hospital settings, especially in the Nutrition Rehabilitation units, widespread all over the developing world, supplementary feeds made by local ingredients are largely preferable to expensive, industrially packaged feed supplements. The solution to malnutrition is not to produce, transport and distribute "therapeutic" feed supplements: they are received as drugs and as such do not change the familial attitudes towards children feeding. These products are not available at home and are finally very expensive in terms of local currency. Many mothers sell their goats and garden products to pay for a tin of dried milk or few packages of RTUF on the black market. Western-type intervention is justified in emergency, but children malnutrition is often a chronic condition, which cannot be handled by the specialist's intervention only. Mothers and families have in their own hands the very solution to prevent and treat children malnutrition: locally available low cost foods, wisely prepared by reinforcing local traditions are more than often the single most cost-effective intervention to cure malnutrition.

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Chapter 9

Using Price Incentives to Increase the Consumption of Fruits and Vegetables Among a Low-Income Population

Karen M. Jetter

Key Points

1. Low socio-economic households eat fewer servings of fruits and vegetables a day and have a higher incidence of dietary related chronic diseases such as diabetes, cancer, and heart disease.
2. A price subsidy for fruits and vegetables for SNAP beneficiaries would lower their relative price, thereby encouraging healthier eating, and that may lower the rate of dietary related diseases among this high-risk population.
3. Price incentives have previously been used successfully to reduce the rate of tobacco use and alcohol consumption and provide a model for price incentives for healthier eating.
4. A price subsidy for SNAP beneficiaries would be justified from a budgetary perspective if greater fruit and vegetable consumption lowers Medicaid and Medicare expenditures on chronic diseases for people who participate in these programs.
5. A 25% price subsidy is estimated to increase net fruit and vegetable consumption by 6.9%, with the largest percentage increases for fruit, and deep yellow vegetables, and the smallest percentage increases for starchy vegetables.
6. A 40% price subsidy is estimated to increase net fruit and vegetable consumption by 11.1%.
7. The subsidy program is estimated to cost between \$1.745 billion and \$2.941 billion a year; however, the per person per month costs are only estimated to be \$8.45 under the 25% subsidy and \$14.25 under the 40% subsidy.
8. Total benefits will depend upon how changes in consumption affect the incidence of chronic disease and public expenditure on Medicaid and Medicare.

Keywords Chronic disease prevention • Economic incentives • Food stamps • Fruit consumption • Healthier eating • Price subsidies • SNAP • Vegetable consumption

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9.1 Background

9.1.1 Fruit and Vegetable Consumption and Chronic Disease

A public policy to subsidize the price that people on the USDA's Supplemental Nutrition Assistance Program (SNAP) pay for fruits and vegetables is one way to encourage healthier eating among a population at a higher risk of dietary related chronic diseases. Low socioeconomic status (SES) is strongly associated with higher rates of obesity and high rates of the leading causes of illness and death. Results from the National Health Interview Survey show that low-SES adults are more likely to have diabetes, cancer, heart disease, and hypertension compared to those with higher SES [1, 2]. They are also more likely to be diagnosed in the later stages of chronic diseases such as cancer and, consequently, have higher mortality rates than their higher income counterparts [3].

Increased consumption of fruits and vegetables has been linked to a decrease in dietary related chronic diseases such as heart disease, diabetes, and some cancers [4]. To reduce the incidence of dietary related chronic diseases The *Dietary Guidelines for Americans 2005* (DGA 2005) recommends between 4 and 5 cups of fruits and vegetables a day for women, and between 5 and 6 cups a day for men [5]. Eating certain types of fruits and vegetables has also been shown to provide specific health benefits. For example, eating dark green vegetables has been associated with a lower incidence of many chronic diseases, including lung and stomach cancers, non-Hodgkin's lymphoma, and stroke [3, 6–8]. As a result the DGA 2005 also recommends specific amounts of certain types of vegetables including legumes, dark green, and deep yellow vegetables.

Despite the known health benefits of a diet rich in fruits and vegetables, less than 10% of the U.S. population appears to meet the DGA 2005 general and subgroup recommendations for fruits and vegetables, and low-SES consumers are even less likely to meet them [9]. Using NHANES 2001–2002 survey data, people in households with an annual income over \$25,000 consume an average of 2.78 cup equivalents of fruits and vegetables a day while people in households making less than \$25,000 consume 2.52 cup equivalents a day. People in households with over \$25,000 in annual income consume fewer daily cup equivalents of starchy vegetables (0.64 vs 0.705), more dark green vegetables (0.29 vs 0.2), and more deep yellow vegetables (0.2 vs 0.16) than people in households with less than \$25,000 in annual income [10].

Low-SES consumers have reported cost as one barrier to consuming more fruits and vegetables [11, 12]. In a survey of nearly 800 low-income consumers, about one-third reported that cost was a constraint [13]. Observed expenditures seem to support this. American households allocate only 17–18% of their food-at-home budget to fruits and vegetables, and this proportion is consistent across income levels [14, 15]. With lower incomes though, a 17–18% food budget allocation among low-income consumers results in lower absolute levels of spending [15]. Average expenditures on fruits and vegetables by low-income consumers are about \$20 per person per month compared to \$25 for those with a household income over \$70,000 a year [15]. While absolute expenditures are lower, low-income consumers tend to economize by concentrating their spending on the relatively cheaper fruits and vegetables such as potatoes, corn, apples, bananas, oranges, and carrots [16]. They also tend to concentrate their spending in foods that provide the lowest relative price per calorie, rather than the lowest price per nutrient [17]. A price subsidy that targets low-SES SNAP households would lower the relative price of fruits and vegetables, thereby encouraging healthier eating, and that may lower the rate of dietary related diseases among this high risk population.

9.1.2 Economic Incentives to Increase Fruit and Vegetable Consumption

About half of all SNAP participants persistently receive benefits [18]. By subsidizing the price of fruits and vegetables, people chronically on food assistance could experience a long-term shift toward healthier eating. A policy to subsidize the price of fruits and vegetables for this population would thus be justified if the improved health status of SNAP beneficiaries decreases the amount of public monies used to pay Medicaid or Medicare costs as SNAP beneficiaries are often also enrolled in public health insurance programs. For example, the per-capita direct annual medical costs for obesity were estimated to be \$1,429 more per person when compared to people with normal weight [19, 20]. When broken down by insurance provider the increase in adult per capita spending attributable to obesity (again compared to normal weight) was \$1,723 for Medicare patients and \$1,021 for Medicaid [20]. The annual cost of heart diseases cost Medicaid \$4,179 per person for congestive heart failure, \$1,419 for hypertension, \$1,545 for stroke and \$1,499 for other heart diseases [21]. Medicare costs, except for hypertension, are even higher at \$5,881 for congestive heart failure, \$285 for hypertension, \$4,874 for stroke and \$3,127 for other heart diseases. While heart disease is the highest cost disease, the cost to treat other chronic diseases such as diabetes and cancer accounts for the largest increase in Medicare spending between 1987 and 2006 [22]. Even small changes in the incidence of these diseases could justify public subsidies of healthier foods.

In the past, regulatory policies to change prices paid by consumers have been shown to significantly change negative health related behaviors among smokers and drinkers through the imposition of a consumption tax. A 10% tax on the price of cigarettes is estimated to reduce cigarette smoking by 3–5% in the short run, and up to 10% in the long run [23]. A 10% tax on the price of alcohol is estimated to reduce beer consumption by 4.6%, wine consumption by 6.9%, and other spirits by 8% [24, 25]. Given the success of taxes in reducing the consumption of goods that increase the incidence of chronic diseases, a price subsidy on goods such as fruits and vegetables may result in healthier eating and a decrease on chronic disease.

Price subsidies have been shown to be more effective in bringing about a desired change in behavior than an income transfer. Blisard et al. estimated that an additional dollar of income in a low-income household (less than 130% of the poverty line) will probably be allocated to food groups other than fruits and vegetables, or to other items that are deemed more important by the household [26]. Conversely, in a review of environmental interventions, Seymour et al. determined that targeted assistance may be more efficient at effectuating dietary changes than more general assistance programs [27]. As reported in the review, interventions that offered discounts of 25–50% resulted in a significant change in consumption to healthier foods. Price subsidies of 10% did not have a significant effect. In a study on the effect of labeling and price subsidies on snack items in vending machines French et al. estimated that price subsidies of 25% and 50% lead to an increase in the purchase of healthier snacks by 39% and 93% respectively [28]. Labeling alone or in combination with price subsidies did not have a significant effect.

9.1.3 Expected Economic Effects of a Price Subsidy

A price subsidy functions by lowering the price of one good relative to the price of other goods. As relative prices fall consumers will shift their purchases toward the goods with the cheaper price, and away from the goods with relatively higher prices. By making the cost of fruits and vegetables relatively cheaper, SNAP beneficiaries will purchase more of the less expensive fruits and vegetables. The increase in total demand; however, will put upward pressure on market prices. The higher prices

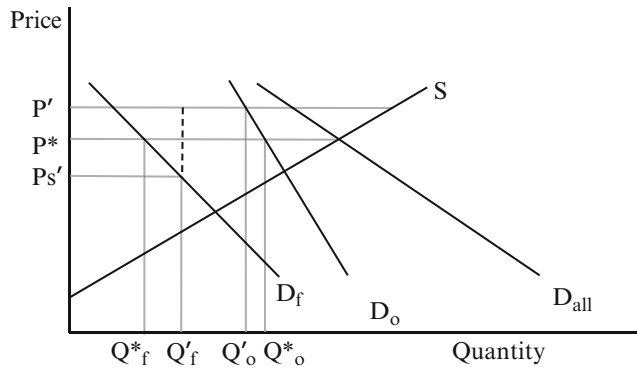


Fig. 9.1 The market effects of a price subsidy on fruits and vegetables for SNAP beneficiaries

will benefit producers, causing them to produce more fruits and vegetables, but cause all other consumers, including SNAP participants who purchase fruits and vegetables without an EBT card, to pay more. Public agencies, and ultimately tax payers, bear the cost of the program as they pay the difference between the retail price for the produce, and the subsidized price incurred by the SNAP beneficiary.

These effects can be shown graphically (Fig. 9.1). The graph above presents a model of the fruit and vegetable market in the United States. There are three demand curves shown in the graph. The first is the demand curve for SNAP beneficiaries, D_f , the next is the demand curve for all other consumers D_o , and the final is the sum of the demand curves over all consumers, D_{all} .

The demand curves are downward sloping because as prices fall, consumers will demand more of a good. The supply curve, S , is upward sloping because as prices rise, suppliers will produce more. The market is initially in equilibrium at P^* where the demand by all consumers, D_{all} , exactly equals the supply of fruits and vegetables. At P^* the quantity demanded by SNAP beneficiaries is Q^*_f , and the quantity demanded by other consumers is Q^*_o .

The price subsidy acts as a wedge between demand and supply, and is shown as the dotted line in Fig. 9.1. The wedge causes the final market price for fruits and vegetables to increase to P' . The price paid by SNAP beneficiaries though is only P'_s . Quantity demanded for fruits and vegetables by SNAP beneficiaries increases from Q^*_f to Q'_f while quantity demanded by all other consumers decreases from Q^*_o to Q'_o . The total cost of the subsidy is $(P' - P'_s) * Q'_f$.

9.2 Methodology

The effect of the subsidy on consumer demand, market prices, market supply, and, ultimately the cost of the subsidy depends upon what kind of subsidy is used to stimulate demand by SNAP beneficiaries, the share of demand by each consumer group, and how consumers and producers respond to changes in price. All of these considerations can be captured in a market model of the US fruit and vegetable industries.

9.2.1 Data Analysis Strategy

The market model developed for this analysis is based on models developed by Muth that set out supply and demand conditions in log-differential form such that $d\ln X = (X_1 - X_0)/X_0$, where the subscript 1 indexes the new price or quantity level, and the subscript 0 indexes the original level of

variable X [29]. The model is used to show how the equilibrium quantities, prices, and other variables respond to shocks to the system, such as a price subsidy. The model developed for this study includes a retail market with demand equations for fruits and vegetables by different consumer groups. These groups are the SNAP households and home consumption, SNAP households and away from home consumption, households at or below the 1.3 poverty ratio, and households above the 1.3 poverty ratio. People who receive SNAP benefits were separated into two consumer groups because the price subsidy will only apply in places where they can use their EBT cards. The NHANES data set that is used for this analysis only has consumption separated by whether the consumption of the food item was done at home or away. It was assumed that home consumption would more closely match the food items purchased with SNAP benefits. It is also assumed that all fruit and vegetable purchases would be made with an EBT card.

The supply side of the model contains equations for net US trade (US imports minus US exports), market quantity supplied from the agricultural marketing sector (processors and handlers), and production supplied to the marketing sector from growers in California and the rest of the United States. The result is a model that links supply and demand in the retail market to supply and demand in the marketing sector, and ultimately, to growers' production decisions. The solution to the system of equations is the percentage change in retail and grower prices, quantity demanded by each consumer group in the study, imports and exports, and production by growers in each region. The system of equations for this analysis is presented in an appendix at the end of this chapter.

A market model does not predict what the actual market quantity and prices will be because many other factors influence actual production (such as temperature, rainfall, etc.), demand, market price, and market quantity each year. Instead, a market model allows the economic effects of increased consumption to be modeled separately from all other market influences, treating the other market conditions and production costs as remaining constant when the change occurs. This is, in fact, the preferred measure of the effects of an isolated incident, even if interest is in a real-world demand shift, not a hypothetical one.

9.2.2 Simulations

This study will simulate the effects of a 25% and 40% price subsidy on the demand for individual fruits and vegetables. Based on the studies described above, price changes need to be at least 25% before consumers will significantly shift their consumption into those food items and two values were chosen for comparison purposes. The analysis will be done on individual commodities to examine how separate demand responses by commodity groups influence the demand for different types of fruits and vegetables. Size matters – at least in economics. The larger the budget share, the smaller will be the price response by consumers. The lower the price, the smaller will be the absolute value of the price change, and the lower will be the consumer response.

9.2.3 Data and Model Parameterization

Thirty-eight commodities were included in this analysis (Table 9.1). The final fruits and vegetables that were selected were those for which a complete demand and supply data set was available.

To parameterize the model and calculate the public cost of the price subsidy data were needed on the consumption of different food items by income and food assistance program, the current level of

Table 9.1 Commodities included in the analysis by USDA commodity group

Commodity Group	Commodities
Citrus/berry/melon fruit	Cantaloupe, grapefruit, honeydew melon, oranges, strawberries, tangerines and other citrus, watermelon
Other fruit	Apple, apricots, avocados, bananas, cherries, grapes, peaches and nectarines, pears, pineapples, plums and prunes
Starchy vegetables	White potatoes (net of chips and fries), corn, peas
Dark green vegetable	Spinach, broccoli, leaf lettuce
Deep yellow vegetable	Carrots, sweet potatoes
Tomatoes	Fresh market tomatoes, processing tomatoes
Other vegetables	Artichokes, asparagus, snap beans, celery, cucumbers, eggplant, head lettuce, onions, bell peppers, cabbage, cauliflower

Table 9.2 Comparison of NHANES 2001–2002 total consumption and the total consumed of the 38 commodities by sub-group and household economic status

	≥ 1.3 Poverty ratio		≤ 1.3 Poverty ratio		SNAP beneficiary	
	NHANES	Study	NHANES	Study	NHANES	Study
Total	2.64	2.17	2.86	1.90	2.59	1.95
Total fruit	1.10	0.91	0.97	0.81	1.14	0.82
Citrus/berry/melon	0.51	0.40	0.46	0.37	0.50	0.38
Other fruit	0.60	0.51	0.52	0.43	0.64	0.45
Total vegetable	1.54	1.26	1.89	1.10	1.45	1.12
Dark green	0.10	0.09	0.07	0.05	0.05	0.02
Deep yellow	0.08	0.06	0.07	0.06	0.05	0.03
Potato	0.39	0.39	0.38	0.38	0.44	0.44
Other starchy	0.08	0.06	0.09	0.06	0.07	0.04
Tomato	0.36	0.36	0.31	0.31	0.35	0.35
Other vegetables	0.54	0.31	0.97	0.24	0.49	0.25

retail prices, U.S. and California crop production and value, imports, exports, and demand and supply elasticities (used to measure the responsiveness of growers and consumers to price changes).

9.2.3.1 Consumption Data

The consumption data for fruits and vegetables were obtained from the NHANES 2001–2002 survey of food intake. This survey was used because it had the SAS routines available that would map the NHANES 24-h food recall surveys to the USDA pyramid servings. The limitation of using this data set is that it does not control for the place of purchase. It only distinguishes whether food was consumed within the home versus food consumed away from home. The consumption level by commodity was determined by a search through the NHANES food codes for those codes that contained 1 of the 38 commodities in the study, then running the SAS program with all the food codes for one commodity grouped together. In the case of a food code with more than one item in a food subcategory, the consumption was allocated equally across the commodities (i.e., orange/grapefruit juice was allocated 50% oranges and 50% grapefruit).

The NHANES data were used to calculate daily cup equivalents consumed for each of the four consumption groups in the model for each of the 38 commodities included in this study. These commodities account for 66% of total fruit and vegetable consumption for the consumers in households below the 1.3 ratio, 75% for SNAP beneficiaries and to 82% for households above the 1.3 ratio (Table 9.2).

To calculate the total amount of consumption by each group and their consumption shares, the U.S. census provided data on the total number of individuals in the United States, and the number below the 1.3 poverty ratio. The USDA reports on food stamp participation rates provided the data on the number of individuals participating in the food stamp program at the time of the NHANES 2001–2002 survey. Total consumption for each group was equal to the average daily cups consumed per person for that group multiplied by the number of individuals in that group. Consumption shares were calculated by dividing the total consumption for a consumer group by the total consumption for all groups.

9.2.3.2 Production and Trade

There are two production regions in the model, California and the rest of the United States, plus trade with the rest of the world. Data for the United States and California production and farm value were available from the USDA's Fruit and Nut Yearbook and Outlook reports, the Vegetable and Melon Yearbook and Outlook reports, and Agricultural Statistics [30–32]. The USDA data has California statistics for most, but not all crops. Additional data for California were available from the California Agricultural Statistics Service (2003–2005) [33].

9.2.3.3 Elasticities

Important parameters needed for this study were the elasticities of demand and supply. An elasticity measures the percentage change in a quantity variable for a 1.0% change in a price variable and is a key parameter in determining how consumers and producers respond to price changes. The data on demand elasticities were taken from Huang, and Huang and Lin [34, 35]. Huang estimated the own price, cross price, and income elasticities of demand for a variety of foods including beef, chicken, apples, oranges, lettuce, fresh and processed tomatoes, etc. Huang and Lin estimated own price, cross price and income elasticities of demand for low, medium and high-income households, but used a general fruit and general vegetable category. The elasticities of demand by household income type in Huang and Lin were used to weight elasticities for all commodities for households above the 1.3 poverty ratio, and an elasticity for the other households. Cross-price elasticities were calculated using the homogeneity conditions for demand functions.

There is no study that has estimated supply elasticities in a system that includes individual crops, though the fruit and vegetable sectors are included in studies that have estimated input and output elasticities of supply for US agriculture [36–38]. The supply elasticities for individual fruits and vegetables are extrapolated from this literature. The supply elasticities are determined for two different production groups: perennial and annual. Supply elasticities are more elastic for annual crops than the perennial crops. The own price elasticity of supply is 1.0 for annual crops and 0.8 for perennial crops. The cross-price elasticities of supply were calculated using the homogeneity conditions for supply equations. The remaining elasticities are in the appendix.

9.3 Results

9.3.1 Percentage Change in Consumption by SNAP Beneficiaries

A 25% price discount caused an estimated increase in fruits and vegetables purchased with EBT benefits of 10.9% (Table 9.3). Because fruit and vegetable purchases declined for items purchased

Table 9.3 The percentage change in fruit and vegetable consumption for a 25% and 40% price subsidy for SNAP beneficiaries

	25% Discount		40% Discount	
	Home	Total	Home	Total
Total	10.9	6.9	17.4	11.1
Fruit				
Citrus/berry/melon	19.3	12.0	30.8	19.3
Other fruit	13.8	8.9	22.1	14.2
Vegetables				
Dark green	8.0	8.0	12.8	12.8
Deep yellow	18.8	18.8	30.1	30.1
Starchy	4.4	2.5	7.1	4.0
Tomatoes	8.3	5.7	13.3	9.2
Other vegetable	7.2	4.6	11.4	7.4

for consumption away from home due to higher market prices, the net gain in consumption was 6.9%. The commodities with the largest net gains in consumption were citrus fruits (12.0%), other fruit (8.9%), and deep yellow vegetables (18.8%).

The commodities with the smallest gains in consumption were starchy vegetables (2.5%) and other vegetables (4.6%) category. The change in home and total consumption for dark green and deep yellow vegetables were the same because no away from home consumption by SNAP beneficiaries was recorded for the commodities included in this study. A 40% price subsidy caused an increase of 17.4% for home purchases and a net increase of 11.1% in consumption for all fruits and vegetables (Table 9.3). As was the case with the 25% price subsidy the largest gains were for the citrus/berry/melon group (19.3%), other fruit (14.2%) and deep yellow (30.1%). Similarly the smallest gains were for starchy vegetables (4.0%) and other vegetables (7.4%).

9.3.2 Cost of the Public Subsidies

The total annual public cost of the subsidies was estimated to be \$1.745 billion for a 25% subsidy and \$2.941 billion for a 40% subsidy. Even though the percentage increase in consumption was the lowest for starchy vegetables, the cost to subsidize the price of starchy vegetables accounted for almost 40% of the total program costs. The high cost was a reflection of the current high consumption rate of potatoes and other starchy vegetables in the American diet (Table 9.2), and that the discount was paid on all purchases, not just the additional purchases due to the price discount. In contrast the total cost of subsidizing dark green vegetable purchases was only \$36.2 million dollars for the 25% subsidy and \$61 million for the 40% price discount. Even though deep yellow vegetables had one of the highest percentage increases in consumption, the cost of the price subsidies was only \$63.9 million for a 25% subsidy and \$110 million for a 40% subsidy. The relatively low cost was due to the initial low consumption of deep yellow vegetables (Table 9.2).

The large cost of the program was a reflection of the number of people enrolled in the federal SNAP program as the cost per month per person was only \$8.45 for the 25% discount and \$14.25 for the 40% discount. The cost of the subsidy for the food subgroup with the lowest initial level of consumption, dark green vegetables, was only \$0.18 per person per month under the 25% subsidy and \$0.29 under the 40%. At the other end of values, the cost of the subsidy for starchy vegetables was \$3.36 per person per month for the 25% discount and \$5.51 for the 40% (Table 9.4).

Table 9.4 Public costs for a 25% and 40% price subsidy on fruits and vegetables for SNAP beneficiaries

	25% Discount		40% Discount	
	Total cost (in millions)	Cost per person per month	Total cost (in millions)	Cost per person per month
Total	1,745	8.45	2,941	14.25
Fruits				
Citrus	215	1.04	375	1.82
Other fruit	378	1.83	655	3.17
Vegetables				
Dark green	36.2	0.18	61	0.29
Deep yellow	63.9	0.31	110	0.53
Starchy	693	3.36	1,137	5.51
Tomatoes	119	0.58	202	0.98
Other vegetable	240	1.16	401	1.94

9.4 Discussion

By having a subsidy on the price of fruits and vegetables significant increases in consumption can occur, with large increases in consumption of food items particularly missing in U.S. diets such as deep yellow vegetables. This program will come at a substantial total cost and will run into the billions for either subsidy level. This high cost, however, is more a reflection of the number of people needing food assistance in the United States as the cost per person per month is less than \$15 for all of the commodities included in this study. If we assume that this cost represents 75% of the total cost in proportion to the 75% of fruit and vegetable consumption by SNAP beneficiaries (Table 9.2), then the total cost per person per month is still less than \$20, even under the larger 40% discount.

A more targeted subsidy may be one way to reduce the total costs of the program, while at the same time achieving the nutritional goal of increasing the consumption of healthier items lacking in U.S. diets. For example, a price subsidy could be paid on all items except starchy vegetables, or even more targeted to the citrus/melon/berry fruits, or dark green and deep yellow vegetables. A price subsidy on all fruits and vegetables except starchy vegetables would reduce the direct costs of the program by almost 40% while the subsidy restricted to citrus/berry/melon fruits, and dark green and deep yellow vegetables would reduce the direct costs by 82%.

Before the final costs and benefits are calculated it is necessary to know how the program effects the incidence of chronic diseases, or how it will be paid for if the public savings due to disease prevention is less than the cost of the program. The linkage between varying levels of fruit and vegetable consumption, chronic disease, and Medicaid and Medicare expenses is crucial in estimating the net benefits, but beyond the scope of this study. However, if the savings in reduced Medicaid or Medicare payments are less than the costs, there are other policy options that can provide funding, and at the same time reduce the consumption of foods that are often associated with poor eating habits. For example, the subsidy can be funded out of a tax on goods that are associated with an increase in obesity. The tax could be on soft drinks, fast food restaurants, etc. The revenues from the tax would then go into a fund from which the program costs of the price subsidy would be charged. This would reduce the consumption of high energy foods at the same time as encouraging the consumption of healthy foods.

Finally, quantifying net benefits will depend on how the price subsidy affects the purchase of fruits and vegetables, and all other purchases by SNAP beneficiaries. For example, if SNAP beneficiaries substitute the consumption fruits and vegetables for the consumption of sugary and fried

snacks, then there will be a decrease in energy consumed, and presumably, a decrease in obesity and obesity related medical expenses. This is the ultimate goal of the price subsidy program. On the other hand the price subsidy can allow SNAP beneficiaries to stretch their benefits. By deducting less than the market price for fruits and vegetables there is more net income available to increase purchases of all goods. If SNAP beneficiaries end up purchasing more of everything including fruits and vegetables, whole grains, meat, and sugary and fried snacks, then energy consumed will go up and, presumably, an increase in weight.

The net effect will probably be a combined effect of consumers making some substitutions in consumption and being able to stretch their SNAP benefits to purchase more food overall. Assuming a fixed stomach capacity; however, most people will probably consume less energy as consumption of fruits and vegetables increases and displaces higher energy foods in the diet. An empirical study is needed in order to determine the net effects and the final costs and benefits of a price subsidy program. However, significant increases in the consumption of healthier foods can be achieved through a subsidy program for SNAP beneficiaries.

9.5 Appendix

The market model used to estimate the response by SNAP consumers to the price subsidy, and the final direct public cost of the program is described below. This model contains separate equations for the retail market, trade, a marketing sector that combines the farm and marketing inputs for the final market, and the farm and marketing input markets.

9.6 Final Market Demand Equations

The quantity demanded, Y , for fruit or vegetable commodity j by consumption group k , depends upon its own-price P_j , the price of other commodities, P_{-j} , and an exogenous demand shifter ϕ that represents the price subsidy for fruits and vegetables (9.1)

$$Y_{jk} = d_{jk}(P_1, \dots, P_J; \phi_{jk}). \quad (9.1)$$

Total demand for commodity j is the sum of demand for each consumption group k (9.2)

$$Y_j^D = \sum_k Y_{jk}. \quad (9.2)$$

9.7 Final Market Supply Equations

The US market supply, Y^S , of commodity j comes from production, Q , by the marketing sector in region i , where i is California or the rest of the United States and from net trade, T , with other countries (9.3). Net trade is equal to total imports less total exports. If T is positive, the United States imported more than it exported. If T is negative, the United States exported more than it imported.

$$Y_j^S = \sum_i Q_{ji} + T_j. \quad (9.3)$$

In equilibrium total quantity demanded has to equal total quantity supplied (9.4).

$$Y_j^D = Y_j^S \quad (9.4)$$

Trade in commodity j depends on its US market price (9.5). As US prices increase, the amount of commodity j that goes to the US market also increases.

$$T_j = t_j(P_j) \quad (9.5)$$

9.8 Marketing Sector

The marketing sector takes the farm product and either packs it fresh for delivery to markets, or processes it to sell as juiced, canned, frozen or dried products. Marketing inputs such as labor, transportation, packing materials, machinery in processing plants, etc., are used to bring fruits and vegetables to market. The total cost of the marketing inputs is w_m . The price received by growers of fruits and vegetables, w_g , will change as the quantity demanded for fruits and vegetables changes in response to the price subsidy for SNAP beneficiaries. The retail price depends upon the cost of the farm and marketing inputs in each region i (9.6).

$$P_j = C_{ji}(w_{jgi}, w_{jmi}) \quad (9.6)$$

The marketing sector receives the farm commodity from growers and the marketing inputs from other suppliers. As demand for the final output changes, demand for the farm commodity and non-farm inputs changes. Using Shepard's Lemma, the derived demand for the farm commodity, x_{jgi} , (9.7) by the marketing sector in each region is

$$x_{jgi} = \partial C_{ji}(w_{jgi}, w_{jmi}; Q_{ji}) / \partial w_{jgi}. \quad (9.7)$$

Again using Shepard's Lemma, the derived demand for the marketing input, x_{jmi} , (9.8) in each region is

$$x_{jmi} = \partial C_{ji}(w_{jgi}, w_{jmi}; Q_{ji}) / \partial w_{jmi}. \quad (9.8)$$

The supply for the marketing input and grower inputs depends on the price for those inputs so that

$$x_{jgi} = x_{jgi}(w_{jgi}) \text{ and} \quad (9.9)$$

$$x_{jmi} = x_{jmi}(w_{jmi}). \quad (9.10)$$

Total quantity supplied for the marketing input by each region is the sum of quantity supplied by each region (9.11).

$$X_{jm} = \sum_i x_{jmi} \quad (9.11)$$

9.9 Model in Log-Linear Specification

The log-differential is taken of the system of equations specified above, and parameters converted into elasticities, and demand, supply and cost shares. The final simulation model, expanded for each equation, is:

$$d \ln Y_j^{sh} = \eta_{jj}^L d \ln P + \sum_{-j} \eta_{j-j}^L d \ln P_{-j} + \eta_{jj}^L d \ln \phi_j \quad (9.1)$$

$$d \ln Y_j^{sa} = \eta_{jj}^L d \ln P_j + \sum_{-j} \eta_{j-j}^L d \ln P_{-j} \quad (9.2)$$

$$d \ln Y_j^{tl1.3} = \eta_{jj}^L d \ln P_j + \sum_{-j} \eta_{j-j}^L d \ln P_{-j} \quad (9.3)$$

$$d \ln Y_j^{gt1.3} = \eta_{jj}^H d \ln P_j + \sum_{-j} \eta_{j-j}^H d \ln P_{-j} \quad (9.4)$$

$$d \ln Y_j = \sum_k \gamma_k d \ln Y_{jk} \quad (9.5)$$

$$d \ln Y_j = \lambda_{jC} d \ln Q_{jC} + \lambda_{jR} d \ln Q_{jR} + \lambda_{jT} d \ln T_j \quad (9.6)$$

$$d \ln T_j = \varepsilon_{jT} d \ln P_j \quad (9.7)$$

$$d \ln P_j = \alpha_{jgC} d \ln w_{jgC} + \alpha_{jmc} d \ln w_{jmc} \quad (9.8)$$

$$d \ln P_j = \alpha_{jgR} d \ln w_{jgR} + \alpha_{jmr} d \ln w_{jmr} \quad (9.9)$$

$$d \ln x_{jgC} = -\alpha_{jmc} \sigma_{jgmC} d \ln w_{jgC} + \alpha_{jmc} \sigma_{jgmC} d \ln w_{jm} + d \ln Q_{jC} \quad (9.10)$$

$$d \ln x_{jgR} = -\alpha_{jmr} \sigma_{jgmR} d \ln w_{jgR} + \alpha_{jmr} \sigma_{jgmR} d \ln w_{jm} + d \ln Q_j \quad (9.11)$$

$$d \ln x_{jmc} = \alpha_{jgC} \sigma_{jgmC} d \ln w_{jgC} - \alpha_{jgC} \sigma_{jgmC} d \ln w_{jm} + d \ln Q_{jC} \quad (9.12)$$

$$d \ln x_{jmr} = \alpha_{jgR} \sigma_{jgmR} d \ln w_{jgR} - \alpha_{jgR} \sigma_{jgmR} d \ln w_{jm} + d \ln Q_{jR} \quad (9.13)$$

$$d \ln x_{jgC} = \varepsilon_{jj} d \ln w_{jgC} + \sum_{-j} \varepsilon_{j-j} d \ln w_{-jgC} \quad (9.14)$$

$$d \ln x_{jgR} = \varepsilon_{jj} d \ln w_{jgR} + \sum_{-j} \varepsilon_{j-j} d \ln w_{-jgR} \quad (9.15)$$

$$d \ln x_{jmc} = \varepsilon_{x_{jm}} d \ln w_{jmc} \quad (9.16)$$

$$d \ln x_{jmr} = \varepsilon_{x_{jm}} d \ln w_{jmr} \quad (9.17)$$

$$d \ln X_{jm} = \beta_{jmc} d \ln x_{jmc} + \beta_{jmr} d \ln x_{jmr} \quad (9.18)$$

where the variables and parameters used in the analysis are defined below (Table 9.5).

The solution to the model is the percentage change in the price and quantity variables and directly estimates the percentage change in fruit and vegetable consumption for SNAP beneficiaries. The direct public cost of the subsidies is estimated from the price and quantity changes from the solution of the model and is calculated as where PD in the amount of the price subsidy, OP is the original

Table 9.5 Variable and parameter definitions for market model

Variable	Name
Y_j^k	Quantity demanded by income group k for commodity j
Y_j^D	Total quantity demanded of commodity j in the retail market
Y_j^S	Total quantity supplied to the retail market
Q_{ji}	Quantity supplied to the retail market by region i
T_j	Net imports
x_{jgi}	Quantity produced of the farm commodity in region i
x_{jmi}	Quantity supplied of the marketing input in region i
P_j	Retail price for commodity j
w_{jgi}	Input price for the farm input
w_{jmi}	Input price for the marketing input
ϕ_j	Shift parameter for the price subsidy
Shares	
λ_{ji}	Market supply share for region i
γ_k	Demand share for income group k

(continued)

Table 9.5 (continued)

Variable	Name
α_{vi}	Cost share of input v for region i
β_{jmi}	Marketing supply share
Elasticity	
η_{jj}^k	Own price elasticity of demand by income group k
ϵ_{jj}	Own price elasticity of supply for the farm commodity
$\epsilon_{x_{jm}}$	Elasticity of supply for the marketing input (value=10)
$\epsilon_{x_{jm}}$	Elasticity of trade (value=2)
σ_{gm}	Elasticity of substitution between the farm and non-farm input (value=.05)

price of commodity j , and OY is the original home consumption of commodity j by SNAP beneficiaries

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Chapter 10

Cost-Effectiveness of Nutritional Interventions for Bone Health in Children and Young Adults – What is Known and Where are the Gaps?

Tania Winzenberg and Graeme Jones

Key Points

- Maximizing bone mass from childhood into early adult life has important potential benefits for the prevention of osteoporotic fractures in the elderly.
- Nutritional factors that could improve bone health in childhood and young adults include maternal diet in utero, breast feeding, calcium and dairy intake, vitamin D, fruit and vegetable intake, and there are possible adverse effects of high dietary sodium intake and intake of carbonated beverages.
- These factors have most frequently been investigated in children to date, but many remain incompletely understood and current evidence does not include cost-effectiveness data.
- In premenopausal women and men, evidence is very limited and insufficient to inform an assessment of cost-effectiveness.
- The substantial challenges of determining the very long-term impacts of interventions in childhood and young adult life on fracture outcomes in the elderly are a major barrier to determining cost-effectiveness.

Keywords Adolescents • Age-related bone loss • Bone • Bone development • Breastfeeding • Calcium • Children • Diet • Essential fatty acids • Fruit • Osteoporosis • Peak Bone Mass • Pregnancy • Premenopausal • Salt • Soft drinks • Vegetables • Vitamin D

10.1 Background

Osteoporosis is a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture [1]. It is a major, growing global public health problem [2], particularly in women [3, 4]. This is because it is both a common disease, and a disease with significant associated morbidity, mortality, and economic costs mainly as a consequence of the occurrence of fragility fractures. In the year 2000, there were an estimated 9.0 million osteoporotic fractures globally [2]. Based on Australian data, the residual lifetime fracture risk for a person aged 50 years is 27% for men and 44% for women [3]. Morbidity includes reductions in mobility and reduced ability to perform personal care and housework with prolonged restrictions occurring in more than

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half of women with hip fracture [5]. Osteoporotic fractures are costly. In the United States [6] more than 2 million incident fractures at a cost of \$17 billion were predicted for 2005, with 25% of these costs arising from fractures in men. In Australia direct health costs are estimated at \$1.9 billion with a further \$5.6 billion in indirect costs [7]. The hospitalisation costs of vertebral fracture alone in the European Union was estimated at Euro 337 million (2001 values) [8].

10.2 Bone Development from Childhood to Early Adult Life and its Implications for Osteoporosis Prevention

Bone mineral density (BMD) is one of the major predictors of osteoporotic fractures [9, 10]. BMD in later life is a function of peak bone mass (the maximum bone mass attained in a person's life) and the rate of subsequent bone loss [11, 12]. Suboptimal bone growth in childhood and adolescence appears at least as important as later bone loss in the development of osteoporosis [1]. Premenopausal bone mass is at least as important as bone loss in the post menopausal period for prediction of fracture [12]. Bone density is also a risk factor for fracture in children [13–15], and in premenopausal women [16–20]. Furthermore, several studies have shown that a history of fracture prior to menopause is associated with a higher risk of subsequent osteoporotic fracture [16, 21–23]. For example, a fracture sustained between age 20 and 50 years increases the risk of risk of fracture after age 50 by 74% [22]. Therefore, maximizing bone mass throughout life has important potential benefits for the prevention of fracture throughout the lifespan.

10.2.1 Peak Bone Mass and Childhood Bone Development

Childhood and adolescence is an important time to intervene to maximize peak bone mass and so potentially reduce the impact of age-related bone loss. In addition, because low BMD is a risk factor for fractures in childhood and adolescence, there are likely to be more immediate public health benefits from improving children's bone mass. The full-grown fetus at term contains about 21 g (range 13–31 g) of calcium [24]. Cross-sectional data from infants aged 1–391 days suggest that total body bone mineral content (TB BMC) increases by 389% and total body BMD increases by 157% during infancy [25]. While bone mass increases occur throughout childhood, puberty is a key stage for bone mass acquisition with skeletal mass approximately doubling between the onset of puberty and young adulthood [26]. At least 90% of peak bone mass is obtained by age 18 years [27]. The pattern in bone growth in boys differs from that in girls in two ways [28]. Puberty is of later onset in boys (age 14 years compared to 12 years) resulting in a longer period of prepubertal growth. The pubertal growth spurt in boys is also longer, lasting 4 years compared to 3 in girls. This results in boys having a greater peak bone mass. Peak bone mineral content velocity occurs approximately 6–7 months later than peak height velocity [27, 29].

10.2.2 Bone Development in Pre- and Perimenopausal Women

The exact temporal course of bone density changes in young adult women is not well defined. The reasons for this are:

1. Uncertainty around the timing of attainment of peak bone mass, i.e., a definitive answer to the question “At what age does bone acquisition cease?” is not known.

2. Uncertainty around the timing of commencement of age-related bone loss.
3. Variations in the estimates of the rate of premenopausal bone loss at different sites.

Estimates of the age at which peak bone mass is reached have varied widely in cross-sectional studies, ranging from as early as from late adolescence to into the late 1930's and varying with site of measure [30, 31]. The time at which bone loss begins after attainment of peak bone mass is not clear – bone loss at the femoral neck may potentially begin as early as age 24, but at the lumbar spine this may commence at the older age of 38–39 years [32]. Cross-sectional estimates range from late adolescence [33] to age 39 years for the femoral neck or 49 years for the lumbar spine [34]. Peak bone density in women at the radius occurs at between 36 and 38 years [35]. There may also be racial or ethnic differences in the age at which peak bone mass is reached, with one study suggesting femoral neck bone mineral density and bone mineral content peaks earlier in white women than in black or Hispanic women [36]. Regardless of the exact timing, even though the bulk of peak bone mass is acquired in childhood and adolescence [27], there remains scope for further improvements on peak bone mass into adult life until age-related bone loss commences. This is shown by the longitudinal study of 156 healthy women aged 19–29 years followed for 5 years by Recker et al. [37] in which the median gain in bone mass for the third decade of life (% per decade) was 4.8% for the forearm, 5.9% for lumbar BMC, 6.8% for lumbar BMD, and 12.5% for total body bone mass ($p < 0.0001$ in all cases).

It is estimated that over their lifespan women lose approximately 42% of their spinal and 58% of their femoral bone mass [38] and although bone mineral density is lost most rapidly postmenopausally through oestrogen-dependent bone loss, a substantial amount of bone is lost premenopause. In one study, age-related bone loss (independent of oestrogen-dependent bone loss) accounted for 44% of total bone loss over the perimenopausal period at the femoral neck and for 39% of the loss of TB BMC [39]. In other longitudinal studies examining the natural history of BMD loss in younger, premenopausal Caucasian populations (aged <45 years) [32, 35, 40–46] estimates of bone density changes have ranged from small increases in TB BMC and radial BMD, to no effect or losses of up to 0.3% p.a. at the femoral neck and 1.3% p.a. at the lumbar spine. Bone loss may be higher in older, perimenopausal women [41–43, 47, 48] though this has not invariably been demonstrated [32]. If premenopausal bone loss can be reduced, or potentially reversed, then this has important implications for the long-term prevention of osteoporosis and fracture.

Thus in premenopausal women, both continued bone gain and bone loss are factors which will determine bone mass at different sites at different ages. Improvements in bone density, regardless of whether they come from increased bone acquisition or from reduced bone loss, have the potential to prevent osteoporosis and reduce fractures in later life. As changes in acquisition or losses are potentially incremental over decades, even small annual changes have potential for important long-term clinical and public health effects. For example, in the lumbar spine, a very small decrease in age-related bone loss of 0.03% p.a. (from 0.25% p.a. loss to 0.22% p.a. loss) from the age of 30 years has been predicted to delay the onset of osteoporosis by 2 years [49].

Therefore, osteoporosis prevention needs to be addressed throughout the life course, to improve peak bone mass in childhood and early adult life and reduce age-related bone loss over adult life.

10.3 What Nutritional Interventions in Childhood could or do Improve Peak Bone Mass?

There are a number of nutritional factors that potentially influence children's bone development and may affect peak bone mass. These include maternal diet in utero, breast feeding, calcium and dairy intake, vitamin D, fruit and vegetable intake and possible adverse effects of high dietary sodium intake and intake of carbonated beverages. In theory, interventions in the form of supplementation

programs or behavioural interventions to improve diet could be used to address these factors, but the evidence to support this is of variable strength. This section provides an overview of the current epidemiological and clinical evidence for these factors.

10.3.1 Potential Influences of Maternal Diet In Utero

There are few studies addressing the effects of maternal diet in pregnancy on childhood bone development. This is an important evidence gap, as in utero influences may not just affect early skeletal development, but also the acquisition of bone mass throughout childhood. This is because of the potential impact of in utero programming or developmental plasticity, i.e., the potential for environmental factors impacting at critical times in development to cause persistent changes in structure or function. There is a body of evidence supporting a role for this in bone development [50].

Calcium supplementation is the only intervention known to the authors to have been tested by randomized controlled trials (RCT) in pregnancy. In a randomized controlled trial (RCT) of calcium supplements (600 vs 300 mg/day vs placebo) in 87 pregnant women of low socioeconomic status, calcium supplements resulted in higher neonatal bone density of the ulna, radius, fibula, and tibia (measured by x-ray), with a dose response apparent in the fibula [51]. Another RCT in 72 healthy pregnant adolescents compared 1,200 mg/day of dietary calcium intake from either calcium supplemented orange juice/calcium carbonate supplements or dairy foods. Only the dairy supplemented group had higher total body calcium (g) measured by DXA than the control group, which may have been due to higher vitamin D intake in the dairy group compared to the supplemented orange juice group [52]. A RCT of 2 g elemental calcium vs. placebo in 256 healthy mothers did not demonstrate any effect of calcium supplementation on neonatal total body or lumbar spine BMC, but in mothers whose baseline intake was <600 mg/day, TB BMC was higher with calcium supplementation (55.7 vs 64.1 g for placebo and calcium groups respectively) [53]. Lastly, in a double-blind RCT, calcium supplementation (1,500 mg/day as calcium carbonate) given to 125 pregnant rural Gambian women with low calcium intake did not have any benefits for whole body or radial BMC or BMD [54]. From these data it is unclear whether improving calcium intakes in pregnancy is beneficial for in utero bone development.

Studies describing other maternal nutritional influences on bone development are predominantly observational. An exploratory study reported associations between maternal dietary intake of magnesium, phosphorus, potassium, protein, and fat in the third trimester of pregnancy and bone density in children at age 8 [55]. Maternal fat intake was negatively and the remaining four nutrients were positively associated with bone density. In the same cohort at age 16, femoral neck BMD (FN BMD) was positively associated with magnesium density and negatively associated with fat density in the maternal diet in pregnancy (all p -values <0.05). Lumbar spine BMD (LS BMD) was positively associated with calcium, magnesium, and phosphorus density and negatively associated with fat density (all p -values <0.05). Maternal milk intake was significantly positively associated with LS BMD. After considering all significant nutrients in the same model, fat density remained significant negatively for the femoral neck and lumbar spine, whereas magnesium density remained significant positively for the femoral neck. No nutrient was significant for the total body (Jing, in press *European Journal of Clinical Nutrition*). A subsequent study examined associations between maternal diet at 32 weeks gestation and BMC and BMD at age 9 years [56]. This found that maternal magnesium intake was positively associated with total body BMC and BMD but not when adjusted for child's height, and that maternal intake of potassium was positively associated with spinal BMC and BMD, until adjusted for child's weight. An alternative analysis approach using

principal component analysis of maternal diet in the same study identified a pattern of dietary intake consisting of a diet high in fruit, vegetable and wholemeal bread, pasta and rice and low in processed foods which was consistent with advice for healthy eating. A score termed the prudent diet score was derived to measure this. A high prudent diet score was associated with higher total body and lumbar BMC and areal BMD and accounted for between 2% and 6% of the variance in bone outcomes [57]. Similar results were seen in a cohort of rural Indian mother-child pairs, in which intake of milk products, pulses and fruit were all positively associated with spine BMD in the children at age 6 years [58].

In one of the same cohorts previously described [56], maternal serum 25-hydroxy vitamin D in late pregnancy was positively associated with whole body and LS BMC in the same children at age 9 [59]. Maternal folate intake at 32 weeks was positively associated with spinal BMC adjusted for BA after adjusting for both weight and height of children [56] in 9 year olds, and maternal red blood cell folate at 28 weeks gestation with spine BMD in 6 year olds [58]. Recently published data in a prospective cohort of UK women of childbearing age reported that maternal serum 25-OH D levels was associated with alterations in femoral development (determined by high resolution three-dimensional ultrasound) in the fetus as early as 19 weeks gestation [60]. Maternal vitamin D supplementation in pregnancy has also been shown to be associated with lower bone specific alkaline phosphatase levels and smaller fontanelle size (suggesting improved skull ossification) [61] in infants, and in lower cord serum alkaline phosphatase [62] and greater crown-heel length [62] in neonates. Zinc supplementation in pregnancy in a poor area in a developing country resulted in increased fetal femur diaphysis length [63].

Though limited, these data indicate that nutritional interventions in pregnancy could be beneficial for bone development in children. Further research is needed to determine which such interventions might be effective and the size of effects it is possible to obtain.

10.3.2 Breastfeeding

The importance of very early life influences on long term bone development is also seen with breast feeding. For example, in a RCT of early diet in pre-term infants, those exposed to breast milk, even for as little as 4 weeks, had higher bone mass in later life (up to 8 years of age) compared to non-breast fed infants. As for in utero effects, this is postulated to be due to changes in bone cell programming from early exposure [64]. This is consistent with other data showing that while, in general, human milk-fed infants have lower bone accretion compared to formula fed infants, possibly due to low vitamin D content and decreasing phosphorus content of human milk with continued lactation [65], studies of the long-term effects of breastfeeding on bone health in children born at term suggest that any initial lower bone accretion is temporary, with catch up growth occurring later in childhood. Such data includes results of a RCT of infant feeding comparing two different formulae and breastfeeding showing that initial differences in BMC accretion did not persist past 12 months of age [66]. Similar patterns are seen in longitudinal observational data. In 8-year-old children born at term [67], breast fed children had higher femoral neck, lumbar spine, and total body BMD compared with bottle fed children, particularly in children breast fed for more than 3 months. In 7–9-year-old children born at term, being breast fed was not associated with ultrasound measures of bone outcome (BUA or SOS), but in breast fed children, duration of breast feeding was positively associated with metacarpal diameter [68]. Observational studies with bone measures at younger ages [69, 70] did not find associations between breast feeding and bone density. However, in a retrospective study, premenopausal women who had been breast fed for more

than 3 months had greater cortical thickness at the radius and a trend towards greater cortical area and cortical BMC at the radius, but not at other sites [71]. Importantly, breast feeding was protective for childhood fractures in a longitudinal study of prepubertal children [72] and in a case control study of children aged 4–15 years [73], though this was not observed in a longitudinal study of fracture risk from birth to 18 years [74].

It may be possible to augment bone development in breast feeding infants through vitamin D supplements – a retrospective cohort study of the use of vitamin D supplements in the first 6 months of life in girls who were breast fed was associated with increased BMD at the distal radius and femoral neck, though not lumbar spine [75] at 8 years of age. This remains to be confirmed in a randomized controlled trial.

10.3.3 Calcium

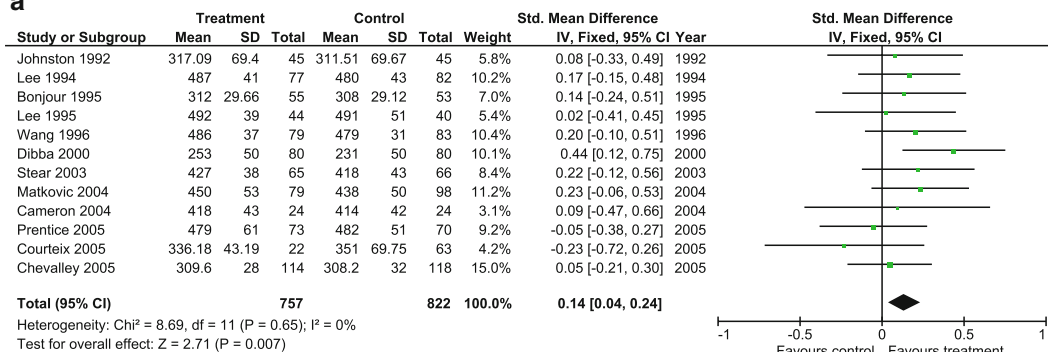
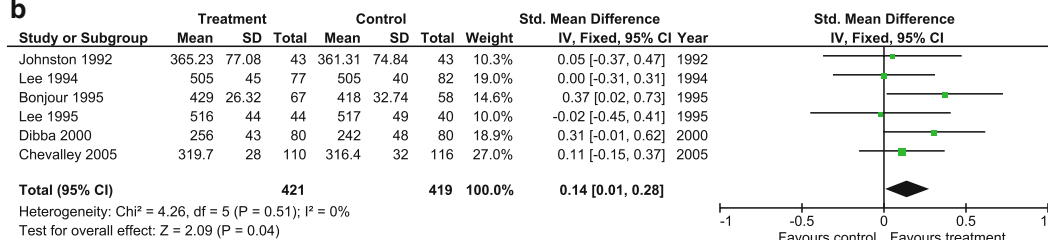
The importance of an adequate childhood calcium intake to bone development is widely accepted. However, the evidence from observational and intervention studies is mixed [76]. Case–control studies have found that low calcium/dairy intake is associated with increased fracture risk in 11–13-year-old boys but this result has not been confirmed in other groups [14, 15, 77]. In both males and females, low calcium/dairy intake has been found to be associated with recurrent fracture [73, 78]. However, a meta-analysis of randomized controlled trials (RCTs) [79, 80] found that calcium supplementation had no effect on BMD at the femoral neck or lumbar spine, which are two important sites for osteoporotic fracture (Table 10.1). Supplementation had a small effect on total body BMC, but this did not persist beyond the period of supplementation. Upper limb BMD increased by a small amount, equivalent to a 1.7 percentage point greater increase in BMD in the supplemented compared to the control group that did persist after supplements were ceased (Fig. 10.1). However, an effect size of this magnitude would be estimated to reduce the absolute risk of fracture at the peak childhood fracture incidence by at most 0.2% p.a. Furthermore, the evidence did not suggest that increasing the duration of supplementation led to increasing effects, or that the effect size varied with baseline calcium intakes, down to a level of <600 mg/day. Thus, the small increase in bone density at the upper limb from increasing intake from an average 700 to 1,200 mg/day is unlikely to result in a clinically significant decrease in fracture risk. The meta-analysis only included placebo-controlled trials. This means that some RCTs of calcium supplementation using dairy products were not included [81–87]. However, qualitatively, the results of these studies were not dissimilar, mainly demonstrating no effect [81] or only small to moderate short term effects [83–86], which did not persist after supplementation ceased [84, 87]. One study did report a larger effect, but in the results were potentially confounded by substantially higher levels of vitamin D intake [82] in the intervention group. It was therefore uncertain what effect was due to calcium supplementation and what was due to vitamin D.

10.3.4 Vitamin D

Vitamin D has a key role in bone metabolism and its impact on bone health in adults is well accepted [88]. Overt vitamin D deficiency in children leads to rickets and there is increasing evidence that subclinical vitamin D deficiency may also affect bone mineralisation [75, 89–92]. Vitamin D

Table 10.1 Main effects of calcium supplementation at different sites [80]

Site	No. studies	N ^a	Effect size ^b at end trial	No. studies	N	Effect size after supplement ceased
Femoral neck BMD (g/cm ²)	10	1,073	+0.07 (−0.05, +0.19)	5	617	+0.10 (−0.06, +0.26)
Lumbar spine BMD (g/cm ²)	11	1,164	+0.08 (−0.04, +0.20)	5	617	−0.01 (−0.16, +0.17)
Total body BMC (g)	9	953	+0.14 (+0.01, +0.27)	1	96	0.00 (−0.40, +0.40) ^c
Upper limb BMD (g/cm ²)	12	1,579	+0.14 (+0.04, +0.24)	6	840	+0.14 (+0.01, 0.28)

^aN number of participants^bBold denotes statistical significance at the 5% level; effect given as standardised mean difference (95% confidence interval (CI)); an SMD of 0.3 is regarded as small [160]^cSingle study only**a****b****Fig. 10.1** (a) Effect of calcium supplementation in the upper limb at the end of trial. (b) Effect of calcium supplementation in the upper limb at longest point after supplementation ceased

deficiency is most easily diagnosed by measurement of serum 25-hydroxyvitamin D (25-OHD) [93]. Serum levels above 50 nmol/L are considered normal and prevent secondary hyperparathyroidism and elevated BAP levels although there remains debate about where the level of this threshold. Vitamin D deficiency is considered mild at 25–50 nmol/L, moderate at 12.5–25 nmol/L and severe at <12.5 nmol/L [93]. Evidence is growing that low vitamin D levels in children are common enough to be considered a significant public health issue in many parts of the world and across a range of latitudes, including numerous European countries [75, 89–91, 94, 95], the United States [96], Lebanon [97], Australia (see below), and New Zealand [93, 98, 99].

The prevalence of vitamin D deficiency is higher in late adolescence [96, 98, 100, 101].

Despite this, the effectiveness of using vitamin D supplementation to improve bone development and peak bone mass in children remains uncertain. RCTs of vitamin D supplementation as the sole intervention in healthy children with bone density outcomes give inconsistent results. This may be due to variation in compliance, doses given and baseline vitamin D levels [86, 102–104] in different studies as well as small sample size [104]. In studies reporting statistically significant effects, effect sizes were 1.3% over 2 years for total body BMC [86], 2% for lumbar spine (LS) and femoral BMC in 1 year [105] and 5% for total hip BMC in 1 year [103]. These results suggest that vitamin D supplementation could deliver improvements in bone health and childhood fracture incidence that are of clinical and public health significance. However, no studies have been powered for fracture; it is not known if effects accumulate with ongoing supplementation and there are no cost-effectiveness data available.

10.3.5 Fruit and Vegetables

There are a number of mechanisms by which fruit and vegetable intake could affect bone. These include the induction of a mild metabolic alkalosis, vitamin K, vitamin C, antioxidants, and phytoestrogens, though phytoestrogens alone have little effect on bone turnover in children [106]. Evidence from cross-sectional studies suggests there is a positive relationship between fruit and vegetable intake and bone outcomes in children. In 8-year olds [107] urinary potassium was positively associated with both fruit and vegetable intake and BMD. Girls at Tanner stage 2 [108] who consumed at least three servings of fruit and vegetable daily had higher bone area, lower urinary calcium excretion and lower parathyroid hormone levels than those consuming fewer than three, though there were no differences in BMD or the bone turnover markers urinary deoxypyridinoline and serum osteocalcin between these two groups. A second study reported that 12-year-old girls consuming high amounts of fruit had higher heel BMD than moderate fruit consumers [109]. In adolescent boys and girls [110] higher fruit intake was associated with higher spine size-adjusted BMC (SA-BMC) and, in boys, with higher femoral neck SA-BMC as well.

Longitudinally, over 7 years, fruit and vegetable intake was an independent predictor of TBBMC in boys but not girls [111]. In children aged 10–15 years [112] followed for 1 year, stiffness index (SI), measured by quantitative ultrasound, was positively associated with fruit, vegetable, and soybean intake. Girls increasing fruit intake had a 4.7% greater increase in SI than those who did not, girls increasing vegetable intake had a 3.6% greater increase, and boys increasing vegetable intake had a 2.4% greater increase. In a study retrospectively measuring childhood fruit and vegetable intake, femoral neck BMD was higher in women who had consumed high amounts of fruit in their childhood than in women who had consumed medium or low amounts [113]. There is randomised controlled trial evidence to show that fruit and vegetable intake can be increased in children, ranging from increases of 0.3–0.99 servings per day [114], so taking such an approach to improving peak bone mass could be feasible. However, further research is needed to confirm if bone health is changed by clinically significant amounts by increases of this size.

10.3.6 Salt

Urinary sodium excretion has been shown to be associated with a high bone turnover state in adolescent boys [115]. In this study, urinary sodium accounted for 3–6% of the variation in bone turnover

markers, specifically bone specific alkaline phosphate and urinary pyridinoline. Urinary sodium excretion is also associated with urinary calcium excretion in girls [116-118] though urinary calcium excretion is not immediately affected by an acute sodium chloride load [118]. However, in the few studies assessing bone density outcomes in children, urinary sodium excretion has not in turn been shown to be associated with bone density [107, 117], though dietary sodium intake was associated with size-adjusted bone area but not BMC in a cross-sectional study of 10-year-old girls [119]. Therefore, it is uncertain whether high dietary sodium intake has clinically important adverse impacts on bone outcomes in children and initially further longitudinal studies are needed to determine if this is so.

10.3.7 Soft Drinks and Milk Avoidance

Higher carbonated beverage intake is associated with decreased BMD in girls but not boys [120, 121]. In both males and females, carbonated beverage consumption is associated with increased fracture risk. Other studies have reported increased fracture risk with higher cola intake but not non-cola carbonated beverage intake [122, 123]. It is unclear if this effect is due to milk replacement. In one study [77] the association between cola drinks and fracture persisted after adjustment for milk intake but not after adjustment for television, computer and video watching, suggesting the latter mediates the effect on fracture risk. In another, low milk intake and a higher consumption of carbonated beverages were independent fracture risk factors in children with recurrent fractures [73]. Milk avoidance itself appears detrimental to bone development. Pre-pubertal children who avoid milk have lower total body BMC and areal BMD [124] as well as an increased risk of childhood fracture [125]. Low milk consumption in childhood may have effects which extend into adult life – low childhood milk intake has been shown to be associated with lower BMD [126] and higher risk of fracture in adult life in women [127].

Overall, while there is evidence linking a number of nutritional factors with children's bone development, many of these are incompletely understood. Calcium supplementation has been investigated to the greatest extent, but its effects are of limited public health significance. This makes the exploration of other nutritional approaches to improving peak bone mass in order to determine which are effective of key importance. Until this is better understood, cost-effectiveness cannot be addressed.

10.4 What Nutritional Interventions in Premenopausal Women could or do Improve Bone Density?

As described above, bone density can potentially be improved in premenopausal women through a combination of improving peak bone mass in early adult life, and slowing age-related bone loss in older premenopausal and perimenopausal women. The range of potential nutritional interventions to improve peak bone mass and slow age-related bone loss in premenopausal women, as in childhood, includes improving calcium intake and improving serum vitamin D levels. The evidence regarding other potential nutritional factors, such as fruit and vegetable intake, salt intake, alcohol intake, intake of animal and vegetable proteins, and the calcium/phosphorus ratio in the diet is very limited in premenopausal women and insufficient to inform an assessment of cost-effectiveness. These issues will not be discussed further in this chapter but are discussed elsewhere [128, 129].

A single placebo-controlled RCT of an essential fatty supplement (evening primrose oil 4.0 g and marine fish oil 440 mg with calcium 1.0 g compared to a control of calcium 1.0 g) did not demonstrate any effect on total body BMD or bone turnover markers [130].

10.4.1 Calcium

As in children, the results of observational studies investigating the relationship between calcium intake and bone density in premenopausal women are mixed [131, 132] though meta-analyses suggest there is small effect [132, 133]. There are several controlled trials of increasing calcium intake in premenopausal women, either by using supplements or by dietary advice (Table 10.2). A meta-analysis of 4 of these [45, 134–136] gave an effect size of 1.3% per year across a combination of sites [133]. However, examining the different sites investigated in these studies, it is apparent that there are conflicting results (Table 10.3).

For cortical bone, an effect was seen when measured by metacarpal cortical thickness [134], and at only one of six upper limb sites (the left humerus) for BMC [136], but not other sites and not at the left humerus for BMC/W (equivalent to BMD) was used. For TB BMC, a short-term increase was seen with supplementation over 1 year, but no longer term data is given to determine whether this was a transient or persistent effect [135]. This is an important concern with regards to long-term fracture prevention, because of the phenomenon of the bone remodeling transient. This is a temporary alteration in the balance between bone formation and bone resorption, which can result from changes in any factor that affects bone remodeling, though most commonly described with

Table 10.2 Characteristics of randomised controlled trials of increased calcium intake (by supplements or dietary changes)

Study	<i>n</i>	Age (years)	Participants	Design	Calcium Intervention	Duration
Smith 1989 [136, 161]*	35	Mean 42.3	Premenopausal women	RCT, placebo control	1.5 g Ca/day (CaCO ₃)	4 years
Baran 1990 [45]	59	Range 30–42	Premenopausal women	RCT	Instructions to increase dairy intake vs. usual diet	3 years
Rico 1994 [135]	72	Mean 39	TB BMC Z score < -1.5	Controlled trial, alternate enrolment, usual diet control (no placebo)	1.0 g Ca/day (calcium pidolate)	1 year
Elders 1994 [134]**	112	Range 46–55		RCT	Either 1.0 or 2.0 g Ca/day (several preparations)	3 years
Prior 1994 [138]	61	Range 21–45	With menstrual cycle disturbance	RCT with 4 arms***	1.0 g Ca/day ((CaCO ₃))	1 year

TB total body, BMC bone mineral content, BMD bone mineral density, LS lumbar spine, RCT randomised controlled trial, Ca calcium, CaCO₃ calcium carbonate

Table only reports results in *premenopausal or **premenopausal and early perimenopausal, participants in the study

***Medroxyprogesterone 10 mg/day for 10 days/month/calcium; Medroxyprogesterone 10 mg/day for 10 days/month/calcium placebo; Medroxyprogesterone placebo/calcium; Medroxyprogesterone placebo/calcium placebo

Table 10.3 Results of randomised controlled trials of increased calcium intake (by supplements or dietary changes)

Study	Outcomes	results	Comment
Smith 1989 [136, 161]*	Radius, ulna and humerus BMC, width(W) and BMC/W	Left humerus BMC loss was less in treatment than control group (−0.62% vs. −1.53% respectively ($p < 0.05$). There were no significant differences in other measures between groups	
Baran 1990 [45]	LS BMD	LS BMD loss of 1% p.a. in control group c.f. no loss in group with increased dairy intake	Vitamin D intake and serum vitamin D not measured. Unclear whether wholly a calcium effect. Large loss to follow up (37%). Difference in calcium intake was small (70 mg/day) between groups.
Rico 1994 [135]	TB BMC	TB BMC increase by 2.6% in calcium group c.f. 0.6% increase in control group	
Elders 1994 [134]**	LS BMD, Metacarpal cortical thickness	Difference in LS BMD change over 3 years between supplemented and control groups was 4.8%. Loss of metacarpal cortical thickness was 1% less in supplemented groups c.f. to controls	
Prior 1994 [138]	LS BMD	No statistically significant effect.	

TB total body, BMC bone mineral content, BMD bone mineral density, LS lumbar spine
 *premenopausal or **premenopausal and early perimenopausal, participants in the study

interventions involving changes in calcium intake [137]. Increasing calcium intake causes a decrease in the activation of new bone resorption while existing areas of resorption are still being replaced, resulting in bone temporarily being in positive balance. The rate of activation of new areas of resorption and bone formation then reach a new steady state which reflects the true increase in bone mineral density from the intervention. The effect of the remodeling transient, which results from increased calcium intake, is greatest in the 6–18 months after increasing calcium intake [137] so it is not possible to determine if the effect of calcium on bone density during a 1 year study is indicative of long-term gain in steady-state bone mass. Lumbar spine BMD loss was reduced with increase dairy intake [45], but this could have involved factors other than calcium intake such as: vitamin D intake if the dairy foods were fortified; effects of protein or other nutrients contained in dairy foods; or the increased weight gain in the dairy group. However, a similar effect size equivalent to about 1.6% p.a. at the lumbar spine was seen with calcium supplements in healthy premenopausal women, though no effect was seen in women with menstrual irregularities treated with medroxyprogesterone [138].

We have shown that it is possible to use feedback of fracture risk based on bone density combined with either leaflet based or more intensive group education intervention to improve femoral neck but not lumbar spine BMD in premenopausal women. We observed FN BMD changes of 0.9% per annum in women receiving feedback of being at high risk, regardless of which additional educational intervention they received. These changes were mediated through changes in osteoporosis preventive behavior, namely increased use of calcium supplements (1.3% p.a.) and increases in self-reported physical activity (0.7% p.a.).

10.4.2 Vitamin D

Vitamin D deficiency in young women is common across a range of latitudes. Prevalence rates of up to 50% have been reported. We have data from the controls of the Tasmanian MS case–control study (1999–2001) [139] who were randomly drawn from the Tasmanian Electoral Roll and matched on sex and birth year to prevalent MS cases. These included 132 women $\leq$ aged 50 years, 55% of whom were vitamin D deficient (<50 nmol/L). This is higher than seen in a population-based sample of Geelong women, of whom 20% aged 20–39 years and 25% aged 40–59 years were deficient [140], but similar to the prevalence of 51% reported in New Zealand women aged 19–44 years [98]. In the United States, 18% of women aged 20–39 years were deficient in summer at low latitudes (median 39° N), rising to 40% in winter at 32° N [96]. At all latitudes, there was marked seasonal variation – in the Geelong study the prevalence was up to 41% in winter.

Despite vitamin D deficiency in premenopausal women being common, its impact on bone health in younger women has not been adequately examined [141]. This is a serious evidence gap given that its detrimental effects on bone density and fracture in postmenopausal women are well known and the increasing evidence (described previously) that subclinical vitamin D deficiency is detrimental to bone development in childhood and adolescence. There are few published data reporting associations of vitamin D and bone outcomes in younger women. In a cross-sectional sample of white US women aged 20–49 years, there was a 4.1% higher total hip BMD in the highest compared to the lowest quintile of serum vitamin D levels [142], and in a small sample ($n=21$) of premenopausal Arabian women (mean age 34 years), those women with a serum 25 OHD <30 nmol/L had lower spine and hip BMD about 10% lower than those whose 25 OHD were at this level or above [143]. Most recently, Australian data in 861 women aged 20–94 years demonstrate a positive association between serum 25 OHD and spine, femoral neck and whole body BMD after adjustment for age [144], though the association in the subgroup of premenopausal women was not given. The potential bone benefits from improving vitamin D levels are demonstrated by an RCT in which vitamin D 800 IU and 2,000 mg calcium given daily to female Navy recruits aged 17–35 years during 8 weeks of training at latitude 41° N resulted in a 20% reduction in stress fractures [145]. Levels of vitamin D deficiency and bone outcomes other than stress fracture were not measured in this study. The only other RCT was performed in vitamin D deficient Pakistani immigrants in Denmark [104]. It included 89 women aged 18–52 years given placebo, 10 or 20 μ g of vitamin D₃ daily of whom 27 dropped out over 12 months. This trial reported no differences between treatment groups for lumbar spine BMD, BMC or bone area, but reduced whole body BMD and BA in the 20 μ g supplement group. Given the small numbers and high dropout rate in the study, this result should be interpreted cautiously. Trials in other populations of premenopausal women with bone density outcomes are lacking.

10.4.2.1 Men

Osteoporotic fractures are a substantial problem in elderly men, with men having a residual lifetime risk for fracture after the age of 40 years of 25%, and of 42% if their T-score is less than -2.5 [146]. Moreover, mortality after hip fracture is higher in men than in women [147]. As in women, in older men (age over 50 years) BMD is risk factor for osteoporotic fracture. Longitudinal data from 93 men aged 20–49 years suggest that bone loss at the hip begins before age 50 and that bone loss at this site occurs at a similar rate from 20 to 49 years [148], but that lumbar spine and total BMD remains unchanged over this period. Another longitudinal study in 17 year olds followed for 7 years 8 months demonstrated increases in total body and lumbar spine BMD until age 19 years, at which time a plateau was seen, and increases in femoral neck and hip BMD until age 19 after which bone loss was

observed at these sites [149]. A longitudinal study over 3 years measuring volumetric BMD in 21–49 year old men reported substantial losses of trabecular bone (median of -0.38 , -0.40 and -0.84% per year at the distal radius, distal tibia and lumbar spine respectively) but not of cortical bone. An estimated 42% of total lifetime trabecular loss occurred in men prior to the age of 50 years [150]. Thus it appears that in men, as in women, early intervention to improve or maintain BMD is an important approach to prevent osteoporotic fractures in later life. Despite this, in comparison with women, ways to improve peak bone mass or slow age-related bone loss are severely underinvestigated in young adult males. Serum vitamin D has been shown to be positively correlated with femoral neck BMD but not BMC, or bone size at the distal forearm in 19–54-year-old men [151]. In the same cohort, daily calcium intake was not associated with bone size, BMD or BMAD at any site [151]. There are no nutritional intervention studies known to the authors in young adult males. The available evidence therefore precludes any estimate of the cost-effectiveness of such interventions.

10.5 The Challenges of Assessing Cost-Effectiveness of Nutritional Interventions in Children and Young Adults

Even in the more established field of economic evaluation of osteoporosis treatments in later adult life, there are substantial challenges to be overcome. These include determining the costs and quality of life changes of fractures in different countries with different health systems and how to take into account adherence in the real world (as compared to the RCT) setting [152]. There are no cost-effectiveness studies known to the authors assessing nutritional interventions in children, in premenopausal women or in young (<50 years of age) men. Two recent systematic reviews of the cost-effectiveness of the treatment and prevention of osteoporosis [153, 154] have also failed to identify any such studies. Given the substantial research interest in prevention of osteoporosis through early intervention, why are cost-effectiveness data lacking? There are a number of potential reasons for this evidence gap, related to the additional challenges of assessing cost-effectiveness in this context.

10.5.1 Absence of Fracture Outcome Data

The health costs associated with osteoporosis predominantly are related to the substantial morbidity and mortality caused by osteoporotic fractures. These fractures occur predominantly in elderly men and women. However fractures are not uncommon in children, particularly in the teenage years [155] and also need to be considered in the economic evaluation of interventions in childhood and young adult life.

In the elderly, in the economic evaluation of osteoporosis treatments BMD was used in the past as a surrogate measure of fracture risk, in the absence of studies with fracture outcomes [156]. However, while the association between BMD and fracture risk is strong, there are other factors affecting fracture risk which create a level of uncertainty about this relationship when used in economic modelling [154]. For this reason, current modelling recommendations are based on fracture risk reductions achieved by interventions. Clearly, this approach is problematic when attempting to assess interventions in children and young adults. As discussed above, there are only a few observational studies linking nutritional factors with fracture outcomes and no evidence from clinical trials with fracture outcomes in children or young adults. Relevant trials in young women and children to

date have not been powered to look at short-term fracture prevention, and for obvious logistical reasons have not been of sufficient duration to look at very long-term fracture prevention, i.e., following participants for decades until they are elderly and at high risk. It is not impossible to design studies measuring determine fracture outcomes in childhood and early adult life and clearly consideration needs to be given to this in the design of future clinical trials. Such trials would need to be much larger, be longer in duration or be targeted to high risk subgroups, such as people who have sustained a fracture. However, the logistics of such studies will remain challenging and the costs of performing them substantial.

10.5.2 Modelling Using Peak Bone Mass as a Predictor of Osteoporotic Fracture

The alternative to using fracture outcomes in childhood and early adult life is to use bone mineral density as a surrogate outcome and model reductions in fracture risk from this. There are data available to support such an approach. For example, from a case-control study in 9–16-year olds with upper limb fracture, for each standard deviation reduction in areal BMD at the total body, femoral neck and lumbar spine, the odds ratio for fracture was 1.6, 1.5, and 1.6, respectively [13]. Prospective data have shown a similar relationship but not at all sites. For example that the hazard ratio for upper limb fracture at age 16 per standard deviation decrease in lumbar spine BMD at age 8 is 1.52 [157].

More problematic is the issue of how to estimate fracture benefits in old age from bone density improvements in childhood and young adult life. Not surprisingly, given the lengthy period of follow-up that would be required, there are limited direct data addressing this issue. The only study to address this issue failed to demonstrate an association between childhood fracture between the ages of 8 and 18 years and incident fracture in a cohort of men and women of mean age 63 years followed for a median of 3 years [158]. However, in this study data on childhood fracture relied on self-report, collected retrospectively some 50 years after the event making errors of recall in the data very likely. Hernandez et al. [49] used a computer simulation of bone remodelling in cancellous bone to provide an estimate of the effects of improving peak bone and slowing age-related bone loss in the premenopausal period on osteoporotic fracture. This study suggested that a 10% increase in peak bone mass would delay the onset of osteoporosis by 13 years, and a 10% decrease in age-related bone loss before menopause would delay its onset by 2 years. For the 10% variation in peak bone mass, this could translate to approximately a 1 SD higher bone density at the lumbar spine from the age of 60. Data suggests that per 1 SD decrease in lumbar spine BMD there is a 60% increase in hip fracture risk [159], so an increase of this magnitude could translate to an estimated 50% reduction in the relative risk of hip fracture. However, this relationship relies heavily on extrapolating from computer modelling and indirect data and the reliability of this approach would be open to question. Further research is needed to improve the evidence base for such modelling of fracture reductions based on BMD in earlier life.

10.5.3 Effectiveness Evidence

Even if the major problems of extrapolating early life BMD changes to osteoporotic fracture outcomes in old age can be overcome, unfortunately the evidence supporting the effectiveness of

interventions on bone outcomes for many of the potential nutritional interventions at different ages, as described previously, is limited and not robust. Randomized controlled trial evidence is lacking for many potential factors, and where RCT evidence exists it is often inconsistent. Further research is required to synthesis existing evidence to clarify inconsistencies and RCTs of the most promising potential modifiable nutritional factors is urgently needed in these age groups.

In conclusion, while it is clear that there is great potential to improve bone outcomes through nutritional interventions in childhood and early adult life, robust evidence to quantify their effectiveness is lacking to date. This combined with the substantial challenges of determining the very long-term impacts of any such successful interventions on fracture outcomes in the elderly means that the cost-effectiveness of nutritional interventions in childhood and early adult life remains to be investigated, and should be a high priority for future research.

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Chapter 11

Economic Evaluation of Dental Caries Prevention Programs Using Milk and its Products as the Vehicle for Fluorides: Cost Versus Benefits

Rodrigo Mariño, Jorge Fajardo, and Mike Morgan

Key Points

- Milk fluoridation represents an example of the use of potential nondental resources in achieving oral health objectives.
- For the situations equivalent to those prevailing in Chile, milk fluoridation would be successful within the setting of existing food programs, largely acceptable to the community, likely to be sustainable with minimal external input, and could be readily integrated into the food program activities.
- From a societal perspectives, milk-fluoridation produce health improvements in a cost-effective way. From an economic perspective, it offers good value for money for public health programmes.
- This study estimates that a milk-fluoridation programme targeting children living in nonfluoridated areas of rural Chile would have savings to the society, and that the concerned with dental caries averted would implied health gains to the community.
- Public health policy and practice have the potential of bringing considerable monetary and human benefits. There is a lack of studies evaluating the economic as well as the health consequences of community-based dental caries prevention in developing countries.

Keywords Chile • Dental caries prevention • Economic evaluation • Fluoridation • Milk fluoridation • Oral health

11.1 Introduction

Oral health is defined as the “standard of health of the oral and related tissues which enables an individual to eat, speak and socialise without active disease, discomfort or embarrassment and which contributes to general well-being” [1]. Two major threats to oral health are dental caries and periodontal disease (gum disease). However, oral health involves more than just having healthy teeth and gums. Pain, infection, and tooth loss are the most common consequences of oral disease. It is becoming clear that oral health is integral to general health and should not be considered in isolation.

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Oral diseases and conditions cause difficulties with chewing, swallowing, and speech, which affect the way in which people look and sound, with a significant impact on self-esteem, psychological and social well being, interpersonal relations, and quality of life [2].

Oral health is also concerned with ensuring that people's lives are not affected by a range of conditions including dentofacial anomalies, diseases of the oral mucosa, oral cancer and precancerous lesions, maxillo-facial trauma, xerostomia (dry mouth), and other less common conditions such as oral manifestation of the HIV infection; defects of the dental hard tissues, birth defects, and temporomandibular joint disorders.

Dental caries, is one of the most widespread chronic, nonlethal diseases affecting humankind. Reports would indicate that a large proportion of the population suffer or have suffered from it during their lifetime. While sugar was responsible for the rise of dental caries in the first half of the last century, during the second half of the last century several countries have demonstrated significant reductions in dental disease levels. This caries decline is considered to be the result of dental a number of public health measures and behavioral changes. One of the most important factors in this decline has been the use of fluorides. Fluoride plays a central role in the prevention of dental caries. The evidence overwhelmingly supports fluoridation as a safe and effective mechanism for dental caries prevention. Yet, in many parts of the world, the incidence of dental caries is still on the increase: the main reasons identified are the increasing consumption of sugar coupled with an inadequate exposure to fluorides [3].

Consequently, an important goal of oral health programs has been to increase the fluoride coverage in the population. Fluoride can be delivered to individuals as a dental preventive measure through a variety of mechanisms, one of which is drinking water where the fluoride level is adjusted to optimal levels for dental caries prevention (0.6–1.0 ppm or 0.6–1 mg/L) [4].

While the practice of adjusting fluoride content in water to the optimal level to prevent dental caries is widely adopted, fluoride should be used in the way most appropriate to local circumstances, to benefit people in different communities of the world. Where traditional forms of community-based fluoride are not feasible, possible, or recommended, fluoride can be made available to individuals via other mechanisms. These mechanisms include school water fluoridation, fluoride mouthrinses, topical application of fluoride solutions, fluoride gels, and milk fluoridation [5–8].

Fluoride was first added to public drinking water in the mid-1940s as a public health measure to prevent dental caries. Since then, it has been introduced in several countries around the world. In the 1950s, some countries in Latin America and Europe introduced salt fluoridation. Later, fluoride was added to toothpastes and other dental products. Currently more than 300 million people in 39 countries benefit from adjusted fluoridated water. In addition, 40 million would receive this benefit from water supplies that are naturally fluoridated [9].

From the point of view of public health, the use of community water supplies to provide fluorides is regarded as the most practical and effective vehicle for fluoride [10, 11]. However, the lack of reticulated water supply is not an insurmountable obstacle to receiving the benefits of fluorides. Several studies and public health programs have shown that alternative methods are effective in preventing dental caries [11, 12]. When the community does not have access to a public water supply, some countries have tested and applied other community-based fluoridation programs at local, regional, or national levels. An example is salt fluoridation. Salt fluoridation was first used in Switzerland in the 1950s and later elsewhere in Europe and the Americas [13]. In fact, in many Latin American and European countries (Colombia, Costa Rica, France, Germany, Hungary, Jamaica, Mexico, Spain, Switzerland, and Uruguay), salt-fluoridation is the preferred community-based program [13–15]. Today, salt fluoridation is provided to over 100 million people in Europe alone and to millions in Latin America (e.g., Colombia, Costa Rica, Ecuador, Jamaica, Mexico, Uruguay, Venezuela). In addition, more than 500 million people worldwide use fluoridated toothpaste [16].

For many countries milk fluoridation offers a way of ensuring that optimal exposure to fluorides is achieved. Regarding milk fluoridation, until recently, the cost of such a program has been repeatedly

cited as one of the main disadvantages of this vehicle for fluorides. For example, the WHO (1994) classified milk, together with water and salt, as a highly cost-efficient vehicle for fluorides, supporting its implementation as a community health measure.

Economic evaluation is an integral component of the overall process of decision-making about any preventive program [17–19]. Because of the importance of an economic analysis in the evaluation of any publicly funded preventive program [17], this chapter will provide an economic evaluation of milk-fluoridation schemes used for dental caries prevention of children living in a nonfluoridated community in rural areas of Chile, a country with a long successful history of milk fluoridation, with low fluoride concentration in their potable water. From a public health perspective, this information will not only increase present knowledge regarding the use of fluorides and in particular milk fluoridation, but it will also provide the necessary evidence to support maintenance, future expansion, or the introduction of fluoridation schemes under conditions such as those prevailing in Chile.

This chapter will provide a brief rationale for the use of milk fluoridation, and will describe and illustrate some aspects of the Chilean milk fluoridation schemes. It will also present the results of two economic evaluations of the schemes, a cost-effectiveness analysis and a cost-minimization study. It will further present the results of an economic evaluation model for a milk fluoridation program in 12-year-old children living in rural areas of Chile

11.2 Milk Fluoridation

Milk fluoridation represents an ideal mechanism for children living in communities where water fluoridation or other forms of systemic fluoride are not feasible or possible [5, 7]. Furthermore, according to several researchers [20–22], when a suitable water supply is not available milk should be placed first among alternative mechanisms of fluoridation. For example, after water, milk is considered to be the most important contribution to total fluid intake [20–26]. It is also an important and essential food for infants and children during the period of teeth formation [24, 27].

Several attributes of milk fluoridation make it an ideal alternative to water. Milk (like salt) can provide an alternative method of administration in areas where there is no suitable community water supply. However, it requires an established milk distribution program. It is a particularly suitable vehicle for community fluoridation for rural areas, where it is unlikely that the population has access to fluoride-adjusted water supplies. This is consistent with the idea of locally significant solutions [5, 28].

On the other hand, there is not total agreement about milk as a fluoride vehicle. Some authors have concluded that milk fluoridation is not appropriate as a vehicle for fluorides, mainly because of fluoride's decreased bioavailability from sodium fluoride (NaF) when ingested with meals rich in calcium, such as milk [30–32]. However, Ericsson [20] and Villa et al. [29] proved that fluoride accumulation in calcified tissues does occur after ingesting fluoride dissolved in milk. Furthermore, Villa et al. [29] administered fluoride to rats, as MFP in milk and NaF in water, finding that femur fluoride concentration was almost twice as high in the milk group compared with the water group, under normal feeding conditions. This was a very important finding as it opened the possibility of using milk as an alternative vehicle for fluoride and discredited the myth that it would not work. Table 11.1 summarizes advantages and limitations of using milk as the vehicle for fluoride for the purposes of dental caries prevention. Some of both advantages and disadvantages are common to other community-based fluoridation programs.

The evidence from several researchers indicates that fluoride consumed using milk as the vehicle increases the fluoride concentration in plaque and saliva. In plaque at the tooth surface, fluoride acts in several ways to prevent enamel demineralization and promote remineralization. Furthermore, in some cases, a superior effect in remineralizing enamel lesions *in vitro* has been demonstrated when

Table 11.1 Advantages and limitations of using milk as the vehicle for fluoride for dental caries prevention**Advantages of milk fluoridation**

- It provides an alternative method of administration in areas where there is no suitable community water supply.
- It is particularly valuable for rural areas, where it is unlikely that the population has access to fluoride-adjusted water supplies.
- When there is a milk program running, such as in schools or kindergartens, no additional costs are involved for the milk fluoridation program.
- It does not require changes in food composition, behaviors/pattern.
- It gives individuals a free choice over the intake of fluorides.

Limitations of milk fluoridation.

- A suitable milk distribution system is required.
- Where an existing milk distribution system is used, it will limit:
 - (i) The delivery of fluoride to those parts of the population that are receiving the milk.
 - (ii) The length of time over which fluoridated milk can be consumed.
 - (iii) The frequency of consumption to the number of days that milk is provided.

fluoride is in milk, than when fluoride is in other vehicles (e.g., water), further highlighting the importance of milk as a vehicle.

The value of milk as an alternative vehicle for the administration of fluorides for caries prevention in humans has been reported since the 1950s. In vivo and in vitro experiments indicate that milk can be used as a vehicle for fluorides and also demonstrated that milk is a suitable vehicle for fluoride delivery. Evidence from animal, and human experiments, as well as community trials, show that fluoridated milk can achieve its caries-protective role in fluoride deficient areas.

Clinical studies using this method have been performed in a range of countries such as Israel [33], Scotland [34, 35], Switzerland [36, 37], Brazil [38], Japan [39], Hungary [40–42], and United States [27, 43, 44]. Results from these studies show that fluoridated milk is effective in preventing caries development in both permanent and primary dentitions. Milk fluoridation has been successfully shown to have cariostatic potential on experimental tooth decay in vitro, in vivo and in small-scale clinical trials. However, as there has been some concern as to whether findings obtained in the controlled environment of clinical experiments are robust enough to be applied in the complex, non-controlled community environment, long-term community-based studies have also been undertaken in collaboration with the WHO/Oral Health Program. The world's first community project for milk fluoridation was established in Bulgaria in 1988. Other community demonstrations have been planned or conducted in Chile, China, Russia, Thailand, and the United Kingdom.

Recently, a Cochrane review was conducted by Yeung and his collaborators [45] to determine the effectiveness of fluoridated milk as a vehicle for delivering fluoride. The authors reviewed almost 200 publications using Cochrane's based criteria. The conclusion was that fluoridated milk was beneficial to schoolchildren by helping prevent caries in the permanent dentition and they called for more randomized clinical trials (RCT) in this area, which are the level of evidence that satisfy the Cochrane's criteria. However, the authors of the review also stated that this shortage of studies satisfying the criteria, did not "imply that milk is ineffective in caries prevention, merely that high quality RCT evidence is lacking in the area."

11.2.1 Addition of Fluoride to Milk

Fluoridated milk can be produced both in liquid and powder forms. Several fluoride compounds can be used, including calcium fluoride, sodium fluoride (NaF) and disodium monofluorophosphate (MFP) [46, 47].

Most programs use liquid milk and NaF as the fluoride compound (Bulgaria, China, Russia, Thailand, UK) [48]. Powdered milk and MFP are used in the Chilean milk scheme. The selection depends on many factors, including the nature of the food supplement program itself, human resources available, training, etc. The concentration of fluoride required in these products will depend on several factors, including age of the children, fluoride concentration of local water supplies, and volume of fluoridated milk ingested daily.

The feasibility and sustainability of a milk fluoridation scheme depends largely on the existence of food and/or milk supplement programs. Any kind of milk can be fluoridated; therefore any delivery system which provides a regular supply of milk to children could potentially provide a vehicle for fluoride. Clearly, an existing milk distribution scheme or a national nutrition program would simplify the implementation of a milk fluoridation scheme.

11.2.2 The History of Milk Fluoridation in Chile

In Chile, as in many other countries, water fluoridation has been one of the cornerstone strategies for the prevention and control of dental caries [49, 50]. The goals set by the Chilean Ministry of Health include a measured reduction of dental caries and an increase in water fluoridation coverage [50]. However, circumstances prevalent in Chile prevent the extent of water fluoridation reaching total population exposure. In fact, 82.3% of the Chilean population have access to water fluoridation [51]. Those without exposure include those living in rural areas and those in small localities in particular, who are left without any method of continuous fluoride exposure, beyond home use of fluoridated toothpaste. To address the issue of equity, these children should be targeted to have an alternative effective mechanism of fluoridation.

It is estimated that about one and a half million Chileans live in small rural areas where water fluoridation is neither currently available nor likely to be introduced in the future. This represents approximately 78% of all the country's rural areas [52, 53]. This population forms the target group for many fluoridation modalities known to effectively prevent dental caries. These mechanisms include, among others, fluoridation of table salt, school water fluoridation, milk fluoridation [5, 7].

Chile has the advantage of two established nutritional programs which deliver, on a free basis, powdered milk and milk derivatives. These food programs have been in operation for more than 50 years; and provides a unique situation to use milk as the vehicle for fluoride. In one of these programs, the "Programa Nacional de Alimentación Complementaria" (PNAC) (National Complementary Feeding program), which has been operating since the 1950s, every child from birth to 6 years old is entitled to free nutritional supplements. In the PNAC, children from birth until 2 years of age are supplied with 2 kg of powdered cow's milk (Purita™) per month. One kilogram of a milk derivative (Purita Cereal™) is delivered monthly to children aged 2–6 years. The national coverage of PNAC is about 80% of the national population of infants under 2 years of age and 70% of preschool children, pregnant women, and nursing mothers [54, 55]. PNAC has universal coverage, no specific targeting strategy is in place, although self-exclusion of high-income beneficiaries does occur [54].

The other food supplement program is run by the National (Chile) Board of Students Assistance and Scholarships (Junta Nacional de Auxilio Escolar y Becas [JUNAEB]). It has successfully implemented the school food program (Programa de Alimentación Escolar or PAE), and has been operating since 1964. Under this program, school children from Year 1 to Year 8 (ages 6–14) are entitled to a free breakfast, which includes dairy products. The fluoridated products are delivered to school children in the rural areas of the country using the standard PAE. Under PAE, children are expected to drink 200 mL of milk or milk derivatives per day for 200 days/year.

In the year 2000, the Ministry of Health and JUNAEB agreed on a program that ensured exposure to fluoride for school children living in rural areas of the Chilean IX Region¹ by enriching the milk used in the school food program with fluoride (PAE-F) to prevent dental caries (Resolución exenta No. 460, dated 28/02/2000). This decree represents the first legislation authorizing the addition of fluoride to a food supplement program (i.e., dairy products), at a national level, and would allow the gradual inclusion of children attending rural schools located south of the IV Region (32°02' South). The first expansion of the program occurred in March 2004 involving the IX Region. At March 2009, the milk fluoridation program reached 3,600 rural schools in 194 municipalities located in the nine Regions of the country, with 235,000 children participating.

11.3 Prevention of Dental Caries Through Fluoridated Powdered Milk Trial in Codegua, Chile, 1994–1999

As early as the 1970s in Chile, there was an interest in milk fluoridation; however, the fluoridation of milk products was precluded by the complexity of technical aspects of adding fluoride to powdered milk. In the 1980s, Villa and his collaborators demonstrated that fluorides in the form of disodium monofluorophosphate (MFP) could successfully be added to milk, providing evidence of the potential viability of this vehicle for fluoride. However, although a number of trials examining the efficacy of milk fluoridation in the prevention of dental caries were available in Europe, the success of this approach had not been clinically demonstrated, under the conditions then prevalent in Chile.

At the beginning of 1995, the Institute of Nutrition and Food Technology (INTA) at the University of Chile, under the technical supervision of the Oral Health Department, Ministry of Public Health, and through a Technical Services Agreement with the Oral Health Unit/WHO, started a community trial to test the feasibility and effectiveness of using milk as the vehicle for distributing fluoride to a community, and to demonstrate that caries reduction could be achieved through the addition of fluorides to milk routinely distributed in the free milk program PNAC.

This program included all children living in a rural community where milk is distributed free of charge under PNAC, which has been operating in the country for decades.

The unique characteristics of this fluoridation scheme are:

1. It represented the first instance of the use of fluoridated *powdered* milk reconstituted at home
2. MFP was the fluoridating agent [22, 29]
3. Every child participating in the scheme received fluoridated milk and milk derivatives from 6 months to 6 years of age, that is for 365 days/year
4. Fluoride exposure of participating children was monitored through urinary fluoride excretion

The selection of the intervention (Codegua) and control (La Punta) communities was influenced by several factors considered to be present in any rural community in central Chile, e.g. similar conditions of fluoride exposure, rural environment, food supplement programs, etc. Consequently, it is argued that the sample is representative of the rural population of central Chile.

Fluoridated powdered milk products were prepared by a dairy company under contract to the Regional Health Service, adding previously specified MFP concentrations to the current PNAC products. Milk distribution is the responsibility of the dietician/nutritionist of the community health centers, as part of the normal PNAC procedures. The average daily fluoride ingestion was estimated to be 0.25 mg F/day among infants; 0.5 mg F/day for children 2–3 years old; and 0.75 mg F/day among 3–6 year olds. These powdered milk products are prepared with boiled tap water in a 1:10 ratio at home.

¹ Chile is divided administratively in 15 Regions

In 1994, baseline examinations were performed in 177 children, aged 3–6 years, in Codegua. Baseline examination, in La Punta, the control community, was conducted in 189 children aged 3–6 years in 1997. In 1999, 252 children aged 3–6 years were examined in Codegua, and 240 children in the same age groups in La Punta. After 4 years of children being exposed to fluoridated milk, there were statistically significant differences in terms of the dmft,² dmfs, and the proportion of children free from dental caries. Children in Codegua, the test community, showed a decrease in the mean number of tooth surfaces affected by dental caries. At the same time, those children in the control community who did not participate in the milk fluoridation program maintained a very similar pattern of dental caries throughout the study. Children in the control community also had higher dental caries indices than the children in the test community at the end of the study (Year 4).

11.3.1 Cost-Effectiveness of a Fluoridated Milk Trial in Rural Areas of Chile

The aim of this section is to estimate the cost-effectiveness, from a societal viewpoint, of adding fluoride to milk products distributed as part of a National Complementary Feeding Program (PNAC) to prevent dental caries in the primary dentition of children 6 months to 6 years old and comparing this attempt with nonintervention (or status quo) in two rural areas of the VI Region of Chile. It was considered that comparing costs and benefits with other vehicles of fluoride would not be as relevant as testing against the status quo for the purpose of policy development. This was because small, rural localities such as the one considered in this study would never have access to other vehicles of fluoride (i.e., water). A more detailed description of this study has been published elsewhere [48].

The form of economic evaluation (EE) used in this study was cost-effectiveness analysis (CEA). In CEA, costs of alternative programs are measured as economic costs and outcomes are valued in units of effectiveness (dmfs) [56].

11.3.1.1 Costs

Using a societal perspective, data from the Codegua milk fluoridation scheme together with all the costs of running the milk supplement program were used to determine the program cost-effectiveness when compared with the control (status quo) alternative. All the important and relevant costs of the milk fluoridation intervention, at different phases of the project, were identified and accounted for. This included the preimplementation costs, project coordination costs, etc. Similarly, the costs of fluoridation material equipment and staff for implementation of the program, and quality control were taken into account. The costs were identified in appropriate physical units, that is, weight of the fluoride used, number of urine examinations carried out, etc. They were then costed using the current market costs in the area as well as from the project budgets. All costs were calculated in Chilean pesos (1 US\$ = RCH (1999) \$527.70).

The shared costs were apportioned appropriately. The staff costs were apportioned on the basis of staff time spent on the intervention. The office space and use of vehicles were apportioned on the basis of their actual use for the program. The analysis excluded resources used for protocol-driven activities.

A summary of the estimated cost of operating the milk fluoridation program for 1,000 children (i.e., 250 children for each age cohort) in Codegua is presented in Table 11.2.

²The dmft index is the sum of deciduous teeth (t) that are decayed (d), missing (m), or filled (f) due to dental caries. The dmfs index is the equivalent for tooth surface (s).

Table 11.2 Summary of total program costs over 4 years associated with the milk fluoridation program

Cost category	Amount (RCH\$1999) ^a	% of total
Salaries		
Program coordinator (part-time 0.10 full-time equivalent [FTE])	1,398,746	19.03
Dentist examiner (6 weeks @ RCH\$488,710 FTE per month)	676,675	9.21
Dental assistant (6 weeks @RCH\$156,034 FTE per month)	216,047	2.94
Data analysis (40 h @RCH\$5,041/h)	161,600	2.20
Laboratory services		
Urine excretion analysis (50 samples)	200,000	2.72
Milk analysis (80 samples)	463,458	6.31
Consumables		
Program coordinator office rent	834,225	11.35
Program coordinator office expenses	210,000	2.86
Dental instruments	356,700	4.85
Examination expenses	91,981	1.25
Program consumables	2,497,819	33.99
Overheads		
Program coordinator office's services	251,041	3.29
Total	7,358,292 (US\$13,944.08)	100.00

^a(RCH\$) [1 US\$ = RCH (1999) \$527.70]

11.3.2 Effectiveness

The outcome after 4 years indicates that children aged 3–6 years from Codegua (the test community) who had access to milk fluoridation during the eruption of their deciduous teeth showed a decline in dental caries experience from 4.83 in 1994 to 2.08 in 1999, which represents a reduction of 57% [57]. In contrast, among children living in La Punta, the nonfluoridated community, the mean dmft index was 3.49 in 1999 and did not vary significantly from baseline. In 1999, there was a difference of 1.41 dmft between the two communities.

The time horizon for costs and outcomes was from time of commencement of fluoridated milk distribution (1995) until the end of the scheme in 1999. Thus, the time horizon would be 4 years for each child.

The savings in costs of dental treatments due to reduced caries experience were calculated on the basis of the fillings avoided as well as extractions prevented due to reduced caries experience. The avoidance of dental procedures thus estimated was then costed using the current local rates for fillings and extractions. The savings in expenses for the family for treatment, in terms of production/wage losses avoided as well as transportation costs for traveling to the dental treatment facility were also taken into account. The estimated cost of dental treatment over the 4 years for the intervention and control groups, using a discount rate of 3%, is shown in Table 5.5. Costs were about 65% higher in the control group (RCH\$28,351,391 or RCH\$7,087.85 per child per annum) compared with the intervention group (RCH\$17,191,589.78 or RCH\$4,297.90 per child per annum).

11.3.3 Cost-Effectiveness Ratio

Combining the costs of the operation of the preventive program with dental treatment costs and comparing them with the costs in the control group resulted in an overall net saving of RCH\$ (1999) 3,801,509.80 (or RCH\$3,801.15 per child) (i.e., [RCH\$28,351,391 – RCH\$24,549,881/1,000]) attributable to the preventive program over the 4 year study period. Thus, a public investment of RCH

\$1,839.57 (7,358,292/1,000/4) per annum per child resulted in an approximate RCH\$950.38 reduction in dental treatment costs per child per annum (i.e., [RCH\$28,351,391 – RCH\$24,549,881/1,000/4]).

The incremental cost-effectiveness ratio for the intervention group compared to the control group for the overall program was estimated to be saving RCH\$2,695.61 per dmft (i.e., [RCH\$28,351,391 – RCH\$24,550,583]/1,410 = 2,695.61). Thus, an investment of RCH\$1,839.75 per annum per child resulted in a net saving of RCH\$2,696.11 per dmft prevented. That represents, not only a reduction in disease, but also a net saving to the community.

A sensitivity analysis was undertaken to test the robustness of the results to different methodological assumptions. The most favorable result was established by using the lower boundary of the effectiveness assumption, that is, using the lower extreme in the test community and the upper boundary in the control community. Conversely, the least favorable result was found using the lower extreme in the control community and the higher boundary in the test community. In conclusion, while the analysis has inherent limitations as a result of its reliance on a range of assumptions, the findings suggest that there are significant health and economic benefits to be gained from the use of fluoridated milk products in nonfluoridated rural communities. That is, after 4 years, children who received fluoridated products had significantly lower levels of dental caries than those who did not. This improvement was achieved at a yearly cost of RCH\$1,839.57 per child. On average, this program would result in a return to society in dental treatment costs of RCH\$950.38 per child per annum. This represents a favorable incremental cost-effectiveness ratio for the intervention group of RCH\$2,695.61 per diseased tooth averted after 4 years.

11.4 Caries Reduction in Rural School Children Exposed to Fluorides Through a Milk Fluoridation Program in Rural Areas of Chile: Expansion of the Program

The experience gained in the Codegua community trial proved to be a powerful tool for the development of a national program (PAE-F) to prevent dental caries. The Codegua experience not only generated new knowledge, but provided opportunities to build new skills and test a particular technology, providing the basis of a model that could be used in other communities across the country.

In 1991 JUNAEB introduced a dental caries prevention program which consists of the provision of acidulated fluoride gel to 80,000 children from school with no access to fluoridated water. Nine years later, the Fluor Gel Topical Application Program (APF-Gel) has produced benefits that prove that it is a valid preventive mechanism for school students, where dental caries are highly prevalent. However, this program was difficult to implement in some areas due to a lack of dentists to apply the product and the number of hours that dentists need to be away from health care centers to make the applications.

When the Codegua scheme was in its third year (1998), the convenience of expanding fluoridated milk preventive programs to primary school children³ was acknowledged by JUNAEB. The JUNAEB Oral Health Unit initiated a wider fluoridated milk pilot study in rural areas of the IX Region, in the Southern part of Chile, using the school food program (PAE). The Chilean IX region is highly rural. Rural parts of that region are among the most economically deprived areas in the country. In addition, according to a report on oral health, the IX Region yielded a very high prevalence (higher than 95%) of dental caries in the deciduous dentition of 6-year-old children, and higher than the national

³In Chile primary education is from Year 1 to Year 8.

average DMFT⁴ scores, for 12-year-olds [58]. Thus, a fluoridated milk food program (PAE-F) was proposed to enhance the integral care provided by JUNAEB to its beneficiaries.

In 1999, JUNAEB commenced the PAE-F, involving 35,000 students enrolled in Year 1 to Year 8 of rural primary schools of the Chilean IX Region (Araucania) and living in 25 municipalities of that Region. In addition, about 6,000 children of the same ages and living in equivalent conditions were the positive control group (APF-Gel).

The methodology of this scheme differs from the Codegua scheme in several aspects. The unique characteristics of this fluoridation scheme are as follows:

1. It represents an instance of the use of fluoridated powdered milk reconstituted on school premises.
2. Every child participating in the scheme received fluoridated milk and milk derivatives from Year 1 (6 years of age) to Year 8 (14 years of age), approximately 200 days/year.

Under these conditions, the daily fluoride dose from fluoridated milk products (PAE-F) was estimated at 0.65 mg/day, which is equivalent to 200 mL with a fluoride concentration of 3.13 ppm. Fluoridated powdered milk products were prepared by two dairy companies under contract with the JUNAEB, adding previously specified MFP concentrations to the current PAE products prior (premix) to the final dry-mixing process.

Thirty-six months later an evaluation of this scheme was conducted. The aims of this evaluation were twofolded. Firstly, to test if a reduction in dental caries experience was possible using fluoridated dairy by-products delivered through the PAE to children enrolled in rural and remote schools, to whom other sources of community fluoride were unavailable. Secondly, the evaluation aimed to compare the effectiveness of two different JUNAEB dental caries prevention programs for rural school children, namely, the milk fluoridation program and the APF-Gel program.

The details of this pilot study have been published [59]. Briefly, in 2003, examinations were performed in 308 children, aged 6, 9 and 12 years, under the PAE-F program, and 330 children aged 6, 9 and 12 years, under the APF-Gel program. After 3 years of children being exposed to either program showed a statistically significant reduction in the DMFT indexes. However, differences in caries experience done at the third year of the scheme between children living in the control municipalities (APF-Gel program), and those living in the test municipalities (PAE-F), did not reach statistical significance. That is, the effectiveness of the PAE-F and the APF-Gel programs, in terms of dental caries prevention, was equivalent. Thus, findings support the contention that it is possible to obtain comparable results in caries prevention in the permanent dentition using either milk or APF-Gel as vehicles for fluorides.

11.5 Cost-Minimization Analysis of a Fluoridated Milk Trial in Rural Areas of Chile

The objective of this section of this chapter is to estimate the cost-savings, from a societal viewpoint, of adding fluoride to milk products distributed as part of a National School Feeding Program (PAE) to prevent dental caries in the permanent dentition of 12 years old children compared to an acidulated gels program in two rural areas of the IX Region of Chile with low levels of fluoride in their drinking water after a 3-year period.

The question being examined was:

What would be the cost and outcome if 6000 9-year-old children living in a rural nonfluoridated community took part in a dental caries prevention program over three years, using milk as the vehicle for fluorides vs. an acidulated gel program?

⁴The DMFT index is the sum of permanent teeth (T) that are decayed (D), missing (M), or filled (F) due to dental caries. The DMFS index is the equivalent for tooth surface (S).

The form of economic evaluation (EE) used in this study was cost-minimization analysis (CMA). In CMA, economic costs of alternative programs with the equivalent effectiveness are measured and compared. The comparator used in the study was the intervention group (PAE-F) and the control (APF-Gel) group.

11.5.1 Costs

Using a societal perspective, all the important and relevant costs from the PAE-F milk fluoridation and the APF-Gel schemes in the IX Region, at their different phases, were identified and accounted for. All costs were calculated in Chilean pesos (2008) (1 US\$ = RCH(2008)\$600). This included the preimplementation costs, project coordination costs, etc. Similarly, the costs of programs consumables, equipment and staff for implementation of the program, and quality control were taken into account. They were then costed using the current market costs in the area as well as from the project budgets. The shared costs were apportioned appropriately. The staff costs were apportioned on the basis of staff time spent on the intervention. This was determined on the basis of office records, and vehicle logbooks, as well as interviews with the field staff. All costs were deflated and discounted to 2008 value, using Chilean Central Bank figures.

The time horizon for costs and outcomes was from time of commencement of fluoridated milk distribution (2000) until the evaluation of the pilot scheme in 2003. Thus, the time horizon would be 3 years for each child. A summary of the estimated cost of operating the PAE-F milk fluoridation and the APF-Gel schemes in the IX Region for 6,000 children is presented in Table 11.3.

11.5.2 Effectiveness

Comparisons of caries experience in the dentition of the 12-year-old under PAE-F, between Year 3 and Year 0 indicated a statistically significant reduction in the DMFT index (2.98 vs 4.02; $p < 0.01$).

Table 11.3 Summary of total programs costs over 3 years associated with the milk fluoridation and APF-Gel programs

	PAE-F		APF-Gel	
Salaries	RCH\$ (2008)	% del Total	RCH\$ (2008)	% del Total
Program coordinator	2,191,118.30	29.90	365,186.44	0.72
Dentist examiner	1,107,692.31	15.12	1,107,692.31	2.18
Dental assistant	346,153.84	4.72	346,153.85	0.68
Data analysis	1,268,040.00	17.30	1,268,040.00	2.49
Dentist (operator)			28,095,005.74	55.22
Assistant (operator)			8,779,689.29	17.25
Laboratory services				
Urine excretion analysis	264,200.00	3.61		
Milk analysis	450,213.95	6.14		
Consumables				
Program coordinator office rent and services	401,705.02	5.48	66,950.84	0.13
Program coordinator office expenses	182,593.19	2.49	30,432.20	0.06
Dental instruments	600,000.00	8.19	600,000.00	1.18
Examination expenses	20,000.00	0.27	20,000.00	0.04
Transport team			4,214,250.86	8.28
Program consumables	496,197.00	6.77	5,989,056.68	11.77
Total	7,327,913.61	100	50,882,458.15	100

A similar effect was observed in the 12-year-old groups exposed to APF-Gel who showed a decline in dental caries experience from a mean DMFT of 3.09 in 1999 to 2.47 in 2003, which represents a reduction between 24% and 20%, respectively [59]. However, a comparison between children living in the control municipalities (APF-Gel program), and those living in the test municipalities (PAE-F) did not find any statistically significant differences in caries experience.

11.5.3 Cost-Effectiveness Ratio

The estimated costs of the pilot study to prevent dental caries and its associated cost by type of scheme are shown in Table 11.4. The cost of the PAE-F scheme for 3 year was RCH\$(2008) 7,327,913.61 (US\$12,213.19). The cost the APF-Gel scheme for 3 year was RCH\$(2008) 50,882,458.15 (US\$84,804.10). As this analysis assumes that alternative programs have equal efficacy to prevent dental caries, according to the cost ratio, the APF-Gel scheme was more than six times higher (more expensive) than the PAE-F in achieving the same result.

Findings from this cost-minimization analysis show that the PAE-F scheme was cost-effective compared with the standard than the APF-Gel program. The cost-minimization analysis indicated an overall net saving for the society of RCH\$43,554,544.46 (US\$72,590.91) program over 3 years. That is, after 3 years, on average, this program resulted in a societal savings cost of RCH\$7,259.10 (US\$12.10) per child. Furthermore, the analysis found that the use of PAE-F resulted in a net saving of RCH\$4,452.00 (US\$7.42) per DMFT prevented compared to the APF-Gel program.

The effective and efficient use of resources has been increasingly emphasized from society, health plans, and health care providers. This finding suggests that there is an economic benefit to be gained from the use fluoridated milk products distributed through the PAE-F in nonfluoridated rural communities in Chile compared to an APF-Gel program.

11.6 Cost-Effectiveness Analysis of a Fluoridated Milk Program in Rural Areas of Chile

The purpose of this section is to model the cost-effectiveness, from a societal viewpoint, of adding fluoride to milk product distributed as PAE to prevent dental caries versus a nonintervention in the permanent dentition of children from 6 to 12 years old living in the Araucania Region of Chile, a Region with low levels of fluoride in their drinking water. Specifically, we aim to estimate the

Table 11.4 Total costs in RCH\$ (2008) for the overall milk fluoridation and APF-Gel programs

	PAE-F	APF-Gel
Total program cost	7,327,913.61	50,882,458.15
Net saving	43,554,544.46	
Saving per child after 3 years	7,259.10	
Saving per DMFT avoided	4,452.00	
Program cost per child	1,221.32	8,418.00
Program cost per child per year	408.00	2,826.00

costs of performing the program, and the savings due to prevented dental caries. The results in terms of events averted (dental caries) were modeled from the first year a child is exposed to PAE-F (6 years of age) until the children reached 12 years old. Estimates of the child population living in small rural areas of the Araucania Region, where water fluoridation is not available, would be about 35,000. Therefore, about 6,000 children would be 12 years of age, consequently, the evaluation attempted to answer the following research question:

What would be the cost and the effectiveness if 6,000 12 year-old children took part in a dental caries prevention program over 6 years using milk as the vehicle for fluorides to prevent dental caries?

This analysis was considered to have greater external validity than the Codegua study presented previously, because this study conditions reflects better real-life conditions and not the controlled conditions of the Codegua evaluation.

11.6.1 Costs

Standard cost-effectiveness analysis methods were used. The costs associated with implementing and operating the program, using a societal perspective, were identified and measured. The comparator used was nonintervention (or status-quo). Health outcomes were measured as dental caries averted over a 6-year period. That is, from the time of first exposure of fluoridated milk distribution (6 years of age) until a child reached 12 years of age.

As with the other examples presented previously in this chapter, the costs of the PAE-F program included administration, salaries, epidemiological surveillance costs, program coordinator office, and program consumables. Costs of time in traveling for child plus parents' cost of productivity due to travel and treatment time were also estimated.

Program cost categories over 6 years associated with the milk-fluoridation program are summarized for the test community in Table 11.5. All costs were estimated in 2008 prices and discounted to their present value using an annual discount rate of 8% (<http://www.bcentral.cl/eng/>).

Table 11.5 Summary of total program costs over 6 years associated with the milk fluoridation program

Cost category	Amount (RCH\$2008) ^a	% of total
Salaries		
Program coordinator (part-time 0.10 full-time equivalent [FTE])	4,685,381	40.51
Dentist examiner (6 weeks @RCH\$800,000 FTE per month)	1,107,692	9.58
Dental assistant (6 weeks @RCH\$250,000 FTE per month)	346,154	2.99
Data analysis (40 h @RCH\$31,701/h)	1,268,040	10.46
Laboratory services		
Urine excretion analysis (50 samples @RCH\$5,284 per sample)	264,200	2.28
Milk analysis (20 samples per year @RCH\$7,397 per sample)	962,716	8.32
Consumables		
Program coordinator office rent and services expenses	858,986	7.43
Program coordinator office expenses	390,448	3.38
Dental instruments	600,000	5.19
Examination expenses	20,000	0.17
Program consumables	1,061,043	9.17
Total	11,564,660 (US\$19,274.43)	100.00

^a(RCH\$) [1 US\$ = RCH (2008) \$600]

11.6.2 Effectiveness

The outcome after 6 years indicates that children aged 6–12-years from the Araucania Region who had access to milk fluoridation during the eruption of their permanent teeth, though the PAE-F program, would show a decline in dental caries experience compared with the nonfluoridated community from 3.09 to 1.46, a reduction of 53%.

The health effects used in this analysis were based on the results from the Cochrane review [45] and on the prevalence of dental caries at 12 years old in rural areas of the Araucania Region as reported by Weitz [59]. The Codegua trial showed a reduction in the prevalence of dental caries of 53%, with extremes reported in the literature from 31%, as the worst scenario of dental caries reduction, and 78% [45, 57], as the best scenario of dental caries reduction.

For the purposes of the economic evaluation, we used the total number of DMFT averted for a reference population of 6,000 12-year-old children, based on the number of children enrolled in the PAE-F program. The savings in expenses for the family for treatment, in terms of production/wage losses avoided as well as transportation costs for traveling to the dental treatment facility were also taken into account (see Table 11.6).

11.6.3 Cost-Effectiveness Ratio

We estimated that if a dental caries prevention program using milk products from the PAE-F were available for 6,000 children from 6 to 12 years of age, the net saving in dental treatment would total RCH\$10,043.75 (US\$16.74) per DMFT avoided over 6 years. These societal savings, in the form of improved oral health, would be achieved at a yearly cost to a government sponsoring agency (for example, Ministry of Health) of RCH\$321.24 (11,564,660.62/6000/6) per annum per child.

A sensitivity analysis was undertaken to test the robustness of the results to different methodological assumptions, using one-way and two-way sensitivity analysis [60]. The parameters that were changed were the discount rate, using rates of 0% and 15%, the best and worst scenario of dental caries reduction for each program, and the employment basis of the coordinator of the program.

Two-way sensitivity analysis resulted in incremental cost–effectiveness ratio ranging from a net saving of RCH\$12,383.71 (US\$20.64) to RCH\$7,509.96 (US\$12.52) per DMFT avoided. This range of variability of the cost-effectiveness ratio was produced by uncertainties of the effectiveness of the milk-fluoridation scheme. The most favorable result was gained by using the higher boundary of the dental caries reduction, plus a 15% discount rate. Conversely, the least favorable result was found using the lower boundary of the dental caries reduction, together with a 0% discount rate.

Table 11.6 Summary of costs of dental treatment in the PAE-F community and control communities after 6 years of program

Treatment item	Total test community (RCH\$)	Total control community (RCH\$)
Restorations	59,347,373	126,271,007
Extractions	5,623,381	11,964,640
Costs of travel to community health center	19,910,915	42,363,650
Cost of productivity losses	12,641,851	26,897,555
Total costs	97,523,520	207,496,852

In conclusion, the cost-effectiveness ratios of this milk fluoridation program are highly favorable. These findings are likely to hold for other settings where the PAE-F is implemented provided efficacy rates and intervention costs resemble those evaluated in this study. The findings suggest that there are significant health and economic benefits to be gained from the use of fluoridated milk products in nonfluoridated rural communities. That is, after 6 years, children who received fluoridated products would have a significantly lower level of dental caries than those who did not. This improvement would be achieved at a yearly cost of RCH\$321.24 per child. This represents a favorable incremental cost-effectiveness ratio for the intervention group of RCH\$10,043.75 per diseased tooth averted after 6 years.

11.7 Final Remarks

The results of the Chilean milk fluoridation studies were unequivocal, both in terms of the dental caries prevention achieved using fluoridated milk and the feasibility of using the existing food programs to deliver the fluoridated products. In both schemes, after exposure to fluoridated milk, there were significant reductions in both the prevalence and severity of dental caries. These results may be expected in a fluoridated community. However, the most significant aspect of the findings for policy makers and health authorities is that this dramatic health benefit was achieved without any technical or administrative changes to the normal operation of the PNAC program in Codegua or the PAE in the IX Region. Thus, it seems reasonable to suggest that this preventive measure could be successfully extended to other rural or semi-rural areas of the country where water fluoridation is not adequate or possible for technical, geographic, or economic reasons and where data on dental caries epidemiology indicates the need for prevention programs. Furthermore, this effort represents an example of the use of potential nondental resources in achieving oral health objectives.

Food programs are essential for countries' ability to maximize the impact of the health sector in reaching national health objectives and/or priorities, and to meet health and social challenges. This chapter has focused on the Chilean experience of using this program. In many countries, however, milk fluoridation may not be suitable or cannot be accommodated within these programs, as it was the case in Chile. There may still be many logistic or practical situations which might render milk an unsuitable vehicle for fluorides.

There is much more that needs to be done to improve oral health in developing countries. However, our contention throughout this chapter is that, for the situations equivalent to those prevailing in Chile, milk fluoridation would be successful within the setting of existing food programs, largely acceptable to the respective communities, likely to be sustainable with minimal external input, and could be readily integrated into the food program activities. As such, this approach represents a cost-effective intervention aimed at ensuring a reduction in oral health treatments and teeth mortality, which in turn would ensure better quality of life.

Glossary

DMFS: Decayed, missing and filled permanent teeth surfaces

dmfs: Decayed, missing and filled deciduous teeth surfaces

DMFT: Decayed, missing and filled permanent teeth

dmft:	Decayed, missing and filled deciduous teeth
FDI:	Federation Dentaire Internationale/International Dental Federation.
INTA:	Instituto de Nutrición y Tecnología de los Alimentos (Institute of Nutrition and Food Technology), University of Chile
JUNAEB:	Junta Nacional de Auxilio Escolar y Becas (National Board of Students Assistance and Scholarships)
MFP:	Disodium monofluorophosphate
PAE:	Programa de alimentación escolar (School food program)
PAE-F:	Programa de alimentación escolar fluorurado (School food program with fluoride)
PAHO:	Pan American Health Organization
PNAC:	Programa Nacional de Alimentación Complementaria (National Complementary Feeding Program)
ppm:	parts per million
WHO:	World Health Organization

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Part IV
Antioxidant Nutrient and Bioactive Food
Component Interactions: Potential Economic
Benefits

Chapter 12

Cost Effective Natural Antioxidants

Dhan Prakash and Neeraj Kumar

Key Points

- Reactive oxygen species can damage nucleic acids, proteins, lipids and carbohydrates that consequently affect the immune functions causing degenerative diseases.
- Antioxidants act as free radical scavenger leading to reduced risk of oxidative stress and associated disorders.
- Antioxidant phytochemicals such as carotenoids, tocopherols, ascorbates, lipoic acids and polyphenols offer protection against oxidative stress associated degenerative diseases like cancer, diabetes mellitus, inflammation, neurodegenerative disorders and aging.
- Cereals, legumes, oilseeds, fruits, vegetables and beverages are the main sources of dietary polyphenols. Carrots, tomatoes, parsleys, orange and green leafy vegetables like amaranth, chenopods, mustard, fenugreek, spinach, cabbage, radish and turnip are the rich sources of Carotenoids.
- Medicinal plants also contain several phytochemicals with antioxidant activities, which can be used for the prevention or treatment of many diseases, including cancer.
- Tocotrienols and tocopherols mainly found in oils are associated with the reduced risk of cancer, Alzheimer's and cardiovascular diseases, cholesterol lowering ability and inhibited LDL oxidation.
- Some sulfur containing compounds like glutathione, lipoic acid and dihydrolipoic acid present in meat, liver and heart also offer protection against oxidative stress.

Keywords Anthocyanins • Apigenin • Astaxanthin • Butylated hydroxy toluene • Caffeic acid • Carcinogens • Carotenoids • Catechin • Catechins • Chemo preventive • Chlorogenic acids • Cyclooxygenase • Daidzein • Ellagic acid • Epicatechin • Epidemiologic • Ferulic acid • Flavonols • Free radicals • Genistein • Glutathione • Glycosides • Isoflavones • Kaempferol • Limonoids • Lipoic acid • Myeloperoxidase • Neurodegenerative • Oryzanol • Phenolic acids • Polyphenols • Quercetin • Reactive oxygen species • Resveratrol • Sterols • Terpenes • Tocopherols • Tocotrienols • Xanthophylls • Zeaxanthin

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12.1 Introduction

Reactive oxygen species (ROS) are products of normal cellular metabolism and participate in various redox-regulatory mechanisms. Oxygen is essential for survival and about 5% of its inhaled part is converted to ROS such as $[O_2]^-$, H_2O_2 and $[OH]$ by univalent reduction. They are also produced on exposure to sunlight, X-rays, ozone, tobacco smoke, automobile exhaust, environmental pollutants and by several other physiological processes. Presence of unpaired electron in their outer orbit makes them highly reactive to damage nucleic acids, proteins, lipids and carbohydrates that consequently affect the immune functions causing degenerative diseases [1–4].

Antioxidants are known to defuse free radicals (Table 12.1) leading to limited risk of oxidative stress and associated disorders. At cellular and molecular levels, they inactivate ROS and inhibit or delay oxidative processes by interrupting the radical chain reaction of lipid peroxidation [5–7]. Phytochemicals with antioxidant capacity naturally present in food are of great interest due to their beneficial effects on human health as they offer protection against oxidative deterioration [6, 8]. Epidemiological and animal studies suggest that the regular consumption of fruits, vegetables and whole grains, reduces the risk of chronic diseases associated with oxidative damage [9, 10]. Carotenoids, tocopherols, ascorbates, lipoic acids and polyphenols are strong natural antioxidants with free radical scavenging activity. Endogenous antioxidant enzymes like super oxide dismutase (SOD), catalase, glutathione peroxidase, glutathione reductase, minerals like Se, Mn, Cu, Zn, vitamins A, C and E, carotenoids, limonoids and polyphenols exert synergistic actions in scavenging free radicals. Synthetic antioxidants such as butylated hydroxy anisole (BHA) and butylated hydroxy toluene (BHT) play a useful role in food and pharmaceutical industries [11–13].

Present chapter comprises cost effective natural antioxidants including carotenoids, tocopherols, ascorbates, lipoic acids and polyphenols and their protective effects against various diseases, including cancer, diabetes mellitus, inflammatory diseases, neurodegenerative disorders and aging.

Table 12.1 Reactive oxygen species (ROS) and corresponding neutralizing antioxidant

ROS	Remark	Neutralizing antioxidants
Hydroxyl radical ($\bullet OH$)	Highly reactive, generated during iron overload	Vitamin C, glutathione, polyphenols, lipoic acid
Superoxide radical ($O_2^{\bullet -}$)	Generated in mitochondria, and cardiovascular system	Vitamin C, glutathione, polyphenols, SOD
Hydrogen peroxide (H_2O_2)	Formed in several reactions and yields potent species like hydroxyl radical	Vitamins C, E, glutathione, β -carotene, CoQ10, polyphenols, lipoic acid
Lipid peroxides ($ROO^{\bullet}$)	Highly reactive, formed from lipids, proteins, DNA, sugars, during oxidative damage	β -carotene, vitamin E, ubiquinone, flavonoids, glutathione, peroxidases
Singlet oxygen ($^1O_2$)	Highly reactive, formed during photo-sensitization and chemical reactions	Vitamins C, E, polyphenols, glutathione
Organic hydro-peroxide	Reacts with transient metal ions to yield reactive species	Vitamins C, E, glutathione, β -carotene, CoQ10, polyphenols,
Ozone	An atmospheric pollutant, react with various molecules, yielding Singlet oxygen	Vitamins C, E, β -carotene, CoQ10, polyphenols, lipoic acid

12.2 Cost Effective Natural Sources of Antioxidants

Antioxidants act as radical scavenger, hydrogen donors, electron donor, peroxide decomposer, singlet oxygen quencher, enzyme inhibitor, synergist, and metal-chelating agents [1, 2, 14]. Polyphenols are considered to be the most effective antioxidants; they can also intensify the activity of other antioxidants. The most popular polyphenols are flavonoids, among which quercetin, kaempferol and apigenin glycosides dominate. Some antioxidants are made in our cells and include enzymes and the small molecules glutathione, uric acid, coenzyme Q-10 and lipoic acid [15, 16]. Other essential antioxidants such as phenols, carotenoids, vitamin C, E and lipoic acid must be obtained from diet. Whole varieties of phenolic compounds, in addition to flavonoids, are widely distributed in grains, fruits, vegetables and herbs (Tables 12.2 and 12.3).

12.3 Vegetables

Among vegetables, the best sources of natural antioxidants are tomatoes, red pepper, *Brassica* vegetables, onion, garlic and red beet. Anthocyanin pigments are found only in few vegetables. They give characteristic color of red cabbage, onion and lettuce with red leaves. They can also be found in peel of radish, aubergine and colored potatoes. Potato, varieties with pink or violet colored pulp are also cultivated. Anthocyanin pigments found in vegetables are acyl derivatives of cyanidin (red cabbage, red onion, radish and lettuce), pelargonidin (radish and potatoes) and delphinidin (aubergine). Generally, the flavonoids group dominate among vegetable polyphenols and it was found that flavonoids share in total content of polyphenols in vegetables was in range of 51–79% [17, 18]. The non-processed vegetables flavonoids are rarely present in aglycon form. Kaempferol in free form was present only in tomatoes and free isorhamnetin in onion. Among glycosides of flavonol in onion were identified as 4-glucoside of quercetin and 3, 4-glucoside of quercetin consisting from 83% to 93% of total polyphenol amount [19–22]. Derivatives of quercetin were found also in lettuce. Main polyphenol compounds of broccoli are quercetin 3-sophoroside and kaempferol 3-sophoroside [19–23]. Over 20 compounds of quercetin and kaempferol were found in cabbage. In red pepper, two derivatives of quercetin, three – luteolin and one – apigenin were found [24, 25]. From phenolic acids group in vegetables are mainly spread derivatives of hydroxycinnamic acid. Chlorogenic acids in potatoes constitute 90% of all phenolic compounds. In the case of carrots, the amount of chlorogenic acid depends on vegetable color – with the highest amount in carrot with purple color, and the lower – in yellow and white. Chlorogenic acid is also present in aubergine and tomatoes. Neochlorogenic acid is present in high amount in broccoli. In carrot, besides chlorogenic acid, caffeic acid and its derivatives were identified [26, 27]. Red pepper is appreciated mainly because of high content of vitamin C (144 mg/100 g) and cryptoxanthin, and tomatoes as a source of lycopene. Lycopene is present in tomatoes peel in amount of 3,025 µg/100 g, however, considerably higher amounts, and better absorbed form is supplied by tomatoes preserves, for example ketchup (9,900 µg/100 g) [28, 29]. Considering vitamin C or β-carotene content, parsley roots, kale, carrot and pumpkin are excellent sources of these phytochemicals among vegetables [30, 31]. Tomatoes are also a source of polyphenols, mainly flavonols and it has been reported that 98% of flavonols present in tomatoes are in fruit peel, from which 96% of it consists the quercetin. In pulp and seeds, compounds of quercetin consist about 70%, and kaempferol 30% of total flavonols [21, 31, 32]. *Brassica* vegetables such as white cabbage, kale, cabbage, broccoli sprouts, kale or cauliflower are known for their pro-healthy properties due to the presence of antioxidant compounds in high amounts.

Table 12.2 Cost effective natural dietary sources of polyphenols

Class and subclass	Polyphenol	Sources
Flavonoids, anthocyanidins	Cyanidin 3-glycosides Malvidin, delphinidin, pelargonidin	Black berries, black currant, blue berries, black grape, elder-berries, straw-berries, cherries, plums, cranberry, pomegranate, juice, raspberry, red wine
Anthoxanthins Flavonols	Myricetin, fisetin, quercetin, kaempferol Isorhamnetin	Celery, chives, onions, fennel, peppers, cherry tomatoes, spinach, sweet potato, lettuce, broccoli, kale, buckwheat, beans, apples, apricots, grapes, plums, berries, currants, cherries, black currant juice, ginkgo biloba, red wine, tea, cocoa
Flavanones Flavones	Naringenin, eriodictyol, hesperetin Apigenin Luteolin	Citrus fruits and their juices, grapes, tangerine juice, peppermint Celery, olives, peppers, celery hearts, fresh parsley, oregano, rosemary, dry parsley, thyme
Flavanols (Flavan-3-ols)	Morin, procyanidins Prodelphinidins, catechin, epicatechin, and their gallates	Apples, apricots, grapes, peaches, nectarines, pears, plums, raisins, berries, cherries, red wine, tea, chocolate
Isoflavones (Flavans) Flavonoid glycoside Phenolic acids,	Genistein, daidzein, equol Rutin, hesperidin, naringin Caffeic acid, chlorogenic acid, ferulic acid, <i>p</i> -coumaric acid, sinapic acid	Grape seeds/skin, soybean, soy products, soy cheese and sauces Lemon, orange, orange juice, grapefruit, tangerine juice Bluberry, cranberry, pear, cherry, cherry juice, apple, apple juice, orange, grapefruit, lemon, peach, potato, lettuce, spinach, coffee beans, tea, coffee, cider
Hydroxy-benzoic acids Trihydroxy-stilbenes Tannins	Ellagic acid, gallic acid, corilagin Resveratrol, <i>trans</i> -resveratrol Catechin, epicatechin polymers, ellagitannins, proanthocyanidins, tannic acids	Strawberry, raspberry grape juice, longan seed, pomegranate juice grapes, peanuts, red wine Grape seeds and skin, apple juice, strawberries, raspberries, black-berry, pomegranate, walnuts, peach, olive, plum, chick pea, peas, lentils, haricot bean, red wine, cocoa, chocolate, tea, coffee, immature fruits
Diferuloylmethane	Curcumin	Turmeric

Table 12.3 Polyphenolic contents (mg/100 g) and their class in some cost effective natural sources

Source/class of phenol	mg/100 g	Source/class of phenol	mg/100 g
Parsley/flavones	1.2–9.2	Beans/catechins	35–55
Celery/flavones	4.5–28.2	Apricot/catechins	10–25
Capsicum/flavones	0.5–1.2	Cherry/catechins	5.2–22.8
Onion/flavonol	35.5–120.8	Grape/catechins	3.1–17.5
Curly kale/flavonol	30.3–60.9	Peach/catechins	5.1–14.7
Leek/flavonol	3.1–22.5	Apple/catechins	10–43
Leek/flavonones	1.5–20.3	Red raspberry/catechins	2–48
Broccoli/flavonol	4.3–10.7	Strawberry/catechins	2–50
Tomato/flavonol	0.2–1.5	Blackberry/catechins	9–11
Apple/flavonol	2.1–4.3	Green tea/catechins	10–8
Black tea/flavonol	3.5–4.5	Black tea/catechins	6–50
Green tea/flavonol	2.1–3.5	Red wine/catechins	8–30
Black grape/flavonol	1.5–4.6	Aubergine/anthocyanins	750
Blueberry/flavonol	3.2–16.7	Black berry/anthocyanins	100–400
Orange/flavanones	21.5–68.5	Black currant/anthocyanins	130–400
Grape juice/flavanones	10.3–65.9	Blueberry/anthocyanins	25–500
Lemon juice/flavanones	5.1–30.7	Black grape/anthocyanins	30–750
Soy cheese/isoflavones	6.4–31.3	Cherry/anthocyanins	35–450
Soy flour/isoflavones	131.2–177.9	Strawberry/anthocyanins	15–75
Soy bean/isoflavones	59.8–145	Red wine/anthocyanins	20–38
Tofu/isoflavones	22.6–48.4	Red cabbage/anthocyanins	17–25
Chocolate/catechins	46–61	Plum/anthocyanins	2–27

It is considered that a higher content of vitamin C among vegetables is in peppers. Kale is a better source of carotenoids (17–34 mg/100 g) than that of carrot, tomatoes or spinach [32, 33]. Plants of cabbage family like kale, broccoli and brussels sprouts are rich sources of polyphenols. *Brassica* vegetables also contain derivatives of hydroxycinnamic acids like caffeic, chlorogenic, ferulic, and sinapic acids [33, 34] and flavonols.

12.4 Oilseeds

Tocopherols (Table 12.4), carotenoid pigments and some sterols are found in most of the crude oils. The most important group of natural antioxidants present in crude and refined edible oils are tocopherols [35]. The most active antioxidant *in vivo* among them is α -tocopherol. On the contrary, the most active antioxidants in bulk food lipids are γ -tocopherol and δ -tocopherol, but the last phytochemical is usually present only in very small amounts. The closely related tocotrienols, present in palm oil and oil from cereals, possess antioxidant activities similar to that of tocopherols [35–37]. Carotenoid pigments present in crude oils also have antioxidant activity, especially in the sun light [38]. Sterols, present in some oils, contribute to the resistance against oxidation. Sesamol and related compounds present in sesame oil, are contributing excellent resistance against rancidity [38–40]. Oryzanol a group of esters of phenolic acids, found in rice bran oil acts as antioxidants. A group of derivatives of hydroxyl-tyrosol is present in olive oil. These are formed by decomposition of more polar precursors, which remain in the residue after the removal of oil. Their content decreases during ripening of olives so that the olive fruits used for oil production are less rich in antioxidants than green olives. In addition of these oils, rich in antioxidants other than tocopherols can increase the resistance against oxidation under both storage and frying conditions [41–44].

Table 12.4 Tocopherol contents and antioxidants identified in some oilseeds [36, 60]

Oilseed	Tocopherol contents (mg/kg oil)				Antioxidants in seed cakes
	α	β	γ	δ	
Olive	Up to 90	Tr	Up to 10	Tr	Hydroxyl-tyrosol, secoiridoids, flavonoids, lignans
Peanut	49–373	<41	88–389	Up to 50	Phenolic acids and esters, such as <i>p</i> -hydroxybenzoic, <i>p</i> -coumaric, syringic, ferulic, caffeic acids
Rapeseed	100–385	<140	189–753	Tr–25	Benzoic, sinapine and cinnamic acid derivatives, phenolic acid esters and glycosides
Sunflower	405–935	<45	Tr–35	Tr–10	Syringic, gallic, chlorogenic, caffeic, <i>p</i> -hydroxybenzoic, <i>p</i> -coumaric, cinnamic, <i>m</i> -hydroxy-benzoic, vanillic, and vanillic acids, epicatechin, catechin
Soybean	10–355	Tr–40	90–2310	155–935	Vanillic, ferulic, salicylic, <i>p</i> -coumaric syringic, acids, their esters, chlorogenic, caffeic, sinapic acids, isoflavones and their glucosides
Sesame	Tr–3	Tr	521–983	4–21	Lignans, coumaric, ferulic, vanillic, sinapic acids

Tr traces

Extracted oilseed meals contain only negligible residues of lipid soluble antioxidants. More polar antioxidants, present in extracted meals, consist of phenolic acids, either free esterified or condensed in insoluble forms. Another important antioxidant fraction is flavonoids, which can be detected in nearly all extracted meals, at least in small amounts. The minority of extracted meals contain lignans and their decomposition products. Some substances possessing antioxidant activities have been detected in most expeller cakes and extracted meals, such as phenolic acids, like caffeic, dihydrocaffeic, ferulic and sinapic acids, or flavonoids. Rapeseed meal is very rich in phenols (77–81 mg/kg), mainly sinapic acid [45, 46]. Mustard seed also contains similar antioxidant phytochemicals. Soybean flour or defatted flour has been used as an antioxidant due to the presence of isoflavones and cinnamic acid derivatives. The antioxidant activity of aqueous extracts is attributed to genistein and glycitein 7-O-monoglucosides [47, 48]. The antioxidant activity of soybean hydrolysates is probably mostly due to isoflavone aglycones. The antioxidant activity of peanuts is mainly due to phenolic acids [49, 50]. Defatted sunflower meal contained 3.0–3.5 g/kg phenolics; chlorogenic and caffeic acids constitute about 70% of phenolic antioxidants [51]. The main antioxidant in defatted rice bran flour is γ -oryzanol, which is a mixture of steryl ferulates with related phytochemicals [41]. Defatted grape seed meal contains a mixture of catechins and procyanidins [52]. Evening primrose seeds are used for the extraction of oil and extracted meal is rich in phenols like proanthocyanidins, catechins, polymerized polyphenols, and isoflavones [53, 54]. The main precursors of sesame seed antioxidants are lignans, such as sesamol. The defatted extract of sesame flour contained 41 mg/kg free phenolic acids, 325 mg/kg esterified acids and 14 mg/kg insoluble phenolic acids. Olive fruit is rich in phenolic antioxidants [40, 55] like hydroxytyrosol, tyrosol, secoiridoids, such as oleuropein and its aglycone, flavonoids, and lignans [43, 54, 55].

Husks have relatively high contents of phenols in some cases, usually higher than are their contents in seeds, so it can be used as a source of antioxidants. In husks and skins of oilseeds, the similar compounds are usually present as those in kernels, tannins and proanthocyanidins. Several types of proanthocyanidins and flavonoids were identified in peanut skin [56]. High molecular weight oleoresins found on the surfaces of oilseeds are co-extracted with phenolics and contribute significantly to

the antioxidant activity of the extracts [57]. Rapeseed hulls have a high content (2–6%) of condensed tannins [46, 58]. Peanut hulls are particularly rich source of phenols, containing tannins, procyanidins, catechin, epicatechin oligomers, resveratrol, and some other phenolic compounds [59, 60]. Sunflower seed shells are rich in chlorogenic acids and caffeic acid that can be isolated from the aqueous-ethanolic extract after saponification. Ethanol extracts of rapeseed meals were more efficient antioxidants than BHA, BHT, and mono-acyl-glycerol citrate [61, 62].

12.5 Fruits

Majority of fruits are rich source of vitamin C, carotenoids and polyphenols, especially berry fruits are precious in this regard. They contain high amounts of vitamin C, in range of 120–215 mg/100 g, and significant amounts of carotenoids, mainly lutein and α -carotene [63, 64]. Phenolic compounds present in seeds and peel of grapes, are mainly anthocyanins and derivatives of hydroxycinnamic acid, flavonols and stilbenoids. Among polyphenols present in grape seeds are gallic acid, catechins and epicatechins, while in peel ellagic acid, myricetin, quercetin, kaempferol and *trans*-resveratrol predominate [65]. Resveratrol influences the inhibition of tumor growth and metastasis of malignant tumors. From grape kernels, para-pharmaceutic preparations recommended in prevention of ischemic heart diseases are produced. In blackcurrant fruits, phenols present are mainly anthocyanins and up to the level of about 25 mg/g [63–65]. *Aronia melanocarpa* fruits are considered as rich source of polyphenols (40–70 mg/g) with over 50% share for anthocyanins. The other polyphenols are the derivatives of hydroxycinnamic acid, represented mainly by chlorogenic and neochlorogenic acids and epicatechins. In mature guava leaves, the greatest concentrations of flavonoids found were myricetin (208.44 mg/kg), quercetin (2883.08 mg/kg), luteolin (51.22 mg/kg) and kaempferol (97.25 mg/kg) [66]. The antioxidant phytochemicals of strawberry fruits were with high amounts of vitamin C (35–104 mg/100 g), and phenolic compounds (20 mg/g), with biggest share of anthocyanins, ellagic acid, their glycoside and ellagitannin derivatives. Among anthocyanins, present are mainly pelargonidin 3-glucoside and cyanidin 3-glucoside. Ellagic acid makes up also over a half of polyphenols amount in raspberries. Bilberries a very popular fruits contain vitamin C and carotenoids, but the most important antioxidants are phenols (30 mg/g) with 70% consisting of anthocyan, and about 10% derivatives of hydroxycinnamic acid [67–69]. The other rich source of phenolic compounds (20 mg/g) are cranberries. They contain anthocyanins (peonidin and cyanidin), flavanones and procyanidin, and from flavonols – quercetin, myricetin and derivatives of hydroxycinnamic acid [70]. Crowberry fruits are valuable source of vitamin C (18 mg/100 g). They contain also carotenoides α -lutein (3.6 μ g/g) and β -carotene (2 μ g/g) and phenols (26–46 mg/g) [64]. Among phenols, flavanols and procyanidins, cinnamic acid, *trans*-resveratrol and *p*-coumaric acid dominate. Polyphenolics (23 mg/g) of blackberry are mainly responsible for its antioxidant activity [63, 71]. Besides anthocyanins and flavonols, ellagic acid has the biggest share and the next in turn are procyanidins and epicatechins stored in seeds [53, 63, 71]. Citrus fruits, grapes, lemons, and oranges are rich sources of antioxidants, due to the presence of vitamin C (40–50 mg/100 g) and phenols, among which flavanones (hesperidin, naringenin, eriodictyol) predominate. Pink grapefruits show relatively high content of lycopene, an antioxidant of nutraceutical importance [29, 72]. Apples a source of phenols (5.0 g/kg), with about seven times higher content in peel than that of pulp. Almost 80% of apple polyphenols contain polymeric procyanidins and monomeric flavanols, with dominating epicatechin and its dimmer procyanidin. The other phytochemicals are phenolic acids, dihydrochalcones and flavonols. Main phenolic acid in apples is chlorogenic acid, among dihydrochalcones – phloridzin and phloretin-2-xyloglucoside and they influence juice quality especially color and taste [72–74].

12.6 Cereals and Legumes

Among polyphenols found in cereal grains, phenolic acids play important role, and especially ferulic acid is dominating in grains (wheat and rye). Besides this compound, vanillic and *p*-coumaric acids play important role, even though they are present in smaller amounts. In the case of oats, the presence of other polyphenols called avertramidin was recorded, while rutin is the main polyphenol of buckwheat. Phenolic acids are present as ester and glycoside forms. The cereal grains are also a source of catechins; the higher amounts of these compounds were found in seeds of buckwheat, oats, rye, and wheat [75, 76]. Catechins are present in seeds of beans, which contain phenolic acids (ferulic, sinapic), quercetin, tannins, anthocyanins and isoflavones (genistein, daidzein, glycitein), of which soybean is the richest source [46, 77–80].

12.7 Beverages, Medicinal plants and Spices

Beverages, such as cocoa, coffee, tea, red wine, and beer can supply high amount of antioxidants. Phenols are present in high amounts (12–18%) in cocoa seeds and procyanidins consist about 60% of them, while quercetin and its glycosides are in lower amount. These flavonols and procyanidins (70–170 mg of flavonoids/100 g) are also present in chocolate and their contents depend on the kind and color of chocolate [81]. The content of phenols in roasted coffee reaches 8%, from which chlorogenic acid is dominant. Main phenolic compounds present in tea are catechins and generally, green tea contains more of these compounds than black or red tea with more than two times higher antioxidant activity. Red wine is a very good source of antioxidants that contains resveratrol a valuable polyphenols [82]. Antioxidants phenols present in beer are mainly derived from barley, malt (80%) and hop (20%). The most important phenolic compounds present in beer are phenolic acids like cinnamic, chlorogenic, vanillic, ferulic, gallic, caffeic, syringic, *o*- and *p*-coumaric acids, and derivatives of flavan-3-ol such as catechin, epicatechin, procyanidin prodelphinidin and flavonoglycosides. The chemically most reactive phenolic compounds of beer are derivatives of flavan-3-ol [83].

From folk medicine and traditional system of medicine, medicinal plants were adopted into modern system of medicine after they have been found effective drugs through chemical and pharmacological screening. The medicinal plants contain several phytochemicals such as vitamins A, C, E, carotenoids, terpenoids, flavonoids, polyphenols, alkaloids, tannins, saponins, enzymes, minerals, etc. These phytochemicals possess antioxidant activities, which can be used for the prevention or treatment of many diseases, including cancer. Herbal drugs are also known to have good immunomodulatory properties. These act by stimulating both non-specific and specific immunity [84]. Ellagic acid and a whole range of flavonoids, carotenoids and terpenoids present in *Fragaria vesca* (strawberries) and *Rubus idaeus* (raspberries) have been reported to be responsible for antioxidant activity. These chemicals block various hormone actions and metabolic pathways that are associated with the development of cancer [85–87]. *Osmarinus officinalis* (rosemary) contains substantial amounts of carnosol and ursolic acid, the potent antioxidants that possess antitumor activity [88]. Rich sources of quercetin are *Terminalia bellerica* fruits, *Ocimum sanctum* leaves and *Ficus carica* aerial parts. Quercetin possesses both anticarcinogenic activity and the ability to inhibit LDL oxidation [74, 84]. Whole varieties of phenolic compounds, in addition to flavonoids, are widely distributed in spices, herbs and medicinal plants. Phenolic compounds such as caffeic, ellagic and ferulic acids, sesamol and vanillin have been reported to exhibit antioxidant and anticarcinogenic activities and inhibit atherosclerosis [12, 84, 89–92].

12.8 Animal Sources

Important group of natural antioxidants from animal derived food sources are amino acids, peptides and proteins. Antioxidant activity of these compounds is connected mainly with specific amino acids like methionine and cysteine, which possess thiol groups. Antioxidant activity of proteins from animal-derived products can be also connected with value addition of concentrates and isolates obtained from high-protein plants (legumes seeds) and animals (milk, eggs) raw materials. Isolated soybean proteins, because of their good functional properties, are widely used in meat industry and they can inhibit reaction of lipid oxidation [93]. In several studies, the ability of casein and whey proteins of milk to inhibit auto-oxidation of lipids was confirmed. Casein inhibits enzymatic, as well as non-enzymatic oxidation of lipids [94]. Main non-protein thiol of animal tissues is glutathione (GSH). Its basic function in organism is protection of thiol protein groups from oxidation. Glutathione and other reduced thiol compounds can regenerate oxidized α -tocopherol radical to vitamin E [95].

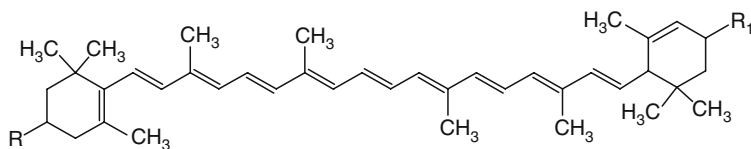
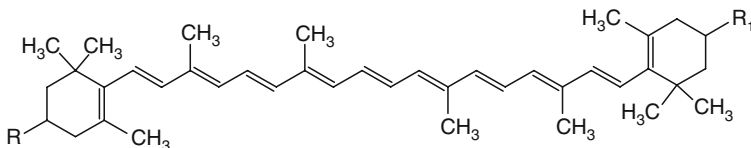
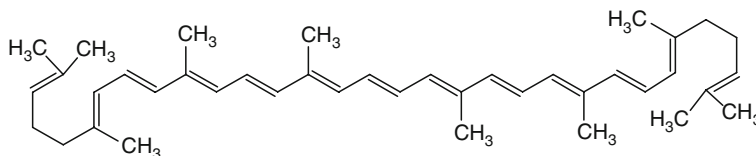
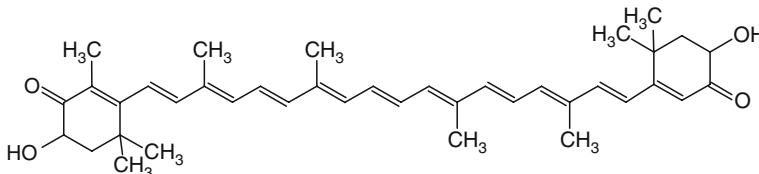
12.9 Antioxidant Phytochemicals

Phytochemicals with antioxidant capacity naturally present in food are of great interest due to their beneficial effects on human health as they offer protection against oxidative deterioration. Epidemiological and animal studies suggest that the regular consumption of fruits, vegetables and whole grains, reduces the risk of chronic diseases associated with oxidative damage [8, 9, 15]. Carotenoids, tocopherols, ascorbates, lipoic acids, and polyphenols are strong natural antioxidants with free radical scavenging activity.

12.10 Carotenoids

Terpenes are the largest class of phytochemicals with carotenoids and limonoids being its two major subclasses. There are more than 700 naturally occurring carotenoids that act as biological antioxidants and protect cells and tissues from the damaging effects of free radicals. Carrots, tomatoes, parsleys, orange and green leafy vegetables like amaranth, chenopods, mustard, fenugreek, spinach, cabbage, radish and turnip are the rich sources of carotenoids (Fig. 12.1). They have been classified into two major groups on the basis of their structure carotenes like β -carotene and lycopene containing only carbon and hydrogen that may be cyclic or linear and oxycarotenoids (xanthophylls, lutein) containing carbon, hydrogen and oxygen in the form of hydroxy, epoxy or oxy groups [28, 96]. In carotenoids, the polyene chain contains up to 15 conjugated double bonds, which are responsible for their characteristic absorption spectra and specific photochemical properties. They are found in linear or all *trans* configuration and exposure to light or heat facilitates the *trans* to *cis* isomerisation of one or more double bonds [97, 98].

Among the carotenes, only alpha, beta and gamma carotenes possess vitamin A activity and out of them β -carotene is the most active. Natural β -carotene is the precursor of vitamin A and has preventive action against eye diseases and cancer. Carotenes enhance immune response and protect skin cells against UV radiations. They help to lower the risk of cardiovascular diseases, age related vision disorders, asthma and reduce inflammation [4, 9]. Lycopene gives tomatoes their red color and is particu-

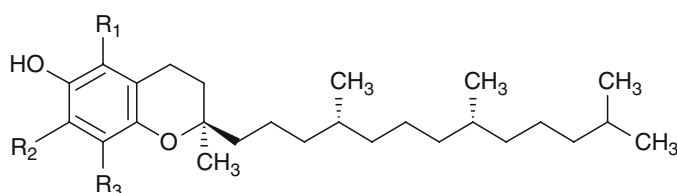
**Fig 1.1** α - Carotene**Fig 1.2** Lutein (Xanthophyll)**Fig 1.3** β - Carotene**Fig 1.4** Zeaxanthin**Fig 1.5** Lycopene**Fig 1.6** Astaxanthin**Fig. 12.1** Carotenoids. (a) α -Carotene, (b) lutein (Xanthophyll), (c) β -carotene, (d) zeaxanthin, (e) lycopene and (f) astaxanthin

larly effective at quenching the destructive singlet oxygen. Along with carotene and lutein, it provides protection against lung, breast, uterus and prostate cancers. Green leafy vegetables and corn are best source of xanthophylls like lutein and zeaxanthin that are believed to function as protective antioxidants for the retinal part of human eye. Astaxanthin, a xanthophyll found in salmon, shrimp and other seafood's with potent antioxidant properties [28, 99, 100]. Limonoids, the second major subclass of terpenoids, are the biologically active phytochemicals present in citrus, which act as antioxidant and protect lung tissues from free oxygen radicals. In vitro studies show that limonin, nomilin and limonoid glycosides have significant ability to inhibit proliferation of human breast cancer [101, 102].

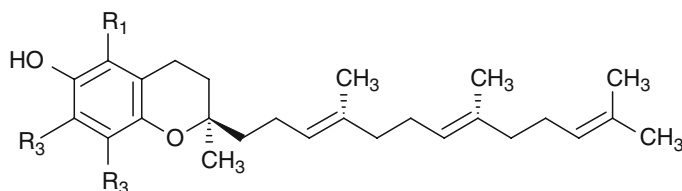
Moreover, foods containing provitamin A carotenoids are the primary source of vitamin A. Epidemiologic studies suggest that dietary intake of carotenoids influences the risk for certain types of cancer, cardiovascular disease and other chronic diseases [103]. Increased intake of fruits and vegetables that contain carotenoids is associated with a decreased risk of many types of cancer including lung, breast and those affecting the gastrointestinal tract, a decreased risk of cardiovascular disease, less incidences of age-related macular degeneration and reduction in xerophthalmia in areas with low preformed vitamin A intake [103–108].

12.11 Vitamin E (Tocopherols and Tocotrienols)

Tocopherols and tocotrienols are non-polar constituents of biological membranes that exist in nature (Table 12.4) in lipid phase. Tocopherols (vitamin E) consist of a chromane ring and a long saturated phytyl chain. The α -, β -, γ , and δ - tocols and tocotrienols differ in the number and position of methyl groups attached to the 5, 7 and 8 position of the ring structure (Fig. 12.2). α -tocopherol is the most abundant form, with high vitamin E activity and singlet oxygen quenching ability than other forms of tocopherols but is less effective in scavenging superoxide anion generated by xanthine oxidase [96, 108–110]. γ -tocopherols can reduce the concentration of nitrogen dioxide most effectively that is involved in carcinogenesis, arthritis and neurologic diseases. Efficiency of scavenging hydroxyl, alkoxyl and peroxy radicals by α -tocopherol is approximately 10^{10} , 10^8 , and 10^6 (M/s) respectively [37, 97]. Antioxidant mechanisms of tocopherols mainly involve the transfer of hydrogen at



	R ₁	R ₂	R ₃
Fig 2.1 α - Tocopherol	CH ₃	CH ₃	CH ₃
Fig 2.2 β -Tocopherol	CH ₃	H	CH ₃
Fig 2.3 γ -Tocopherol	H	CH ₃	CH ₃
Fig 2.4 δ -Tocopherol	H	H	CH ₃



	R ₁	R ₂	R ₃
Fig 2.5 α - Tocotrienol	CH ₃	CH ₃	CH ₃
Fig 2.6 β - Tocotrienol	CH ₃	H	CH ₃
Fig 2.7 γ -Tocotrienol	H	CH ₃	CH ₃
Fig 2.8 δ - Tocotrienol	H	H	CH ₃

Fig. 12.2 Tocopherols and tocotrienols. (a) α -Tocopherol, (b) β -tocopherol, (c) γ -tocopherol, (d) δ -tocopherol, (e) α -tocotrienol, (f) β -tocotrienol, (g) γ -tocotrienol and (h) δ -tocotrienol

6-hydroxyl group of a chromane ring, scavenging of free radicals and regeneration in the presence of ascorbic acid. Their phytyl chain adjusts itself in membrane bilayer while active chromane ring is closely positioned to the surface. This unique structure enables them to act as effective antioxidants and to be regenerated through reaction with other antioxidants [107, 111].

Tocotrienols mainly found in palm oil, cereal grains and kale are also potential antioxidant and their mechanism of action is similar to tocopherols. They are associated with the reduced risk of cancer, Alzheimer's and cardiovascular diseases, cholesterol lowering ability and inhibited LDL oxidation. α -tocotrienol is preferentially absorbed as compared to its γ - and δ -form. Tocotrienols have a higher radical scavenging activity than tocopherols but they are less bio-available as compared to the latter [107, 111]. Moreover, there are many biological functions of tocopherols, and the different forms do not have the same relative activities for each function. In the cancer prevention effect of vitamin E studies, it was stated that gamma-tocopherol was found most potent form for preventing breast cancer [108, 111]. The biological activity of vitamin E, which attracts the most interest, is the prevention of lipid peroxidation. Alpha-tocopherol is the most active tocopherol against peroxy radicals and delta-tocopherol is the least active ($\alpha > \beta > \gamma > \delta$). As an antioxidant that protects the membranes of cells and mitochondria, vitamin E would be expected to boost the immune system and to protect against cancer. The main rationale for the use of vitamin E to prevent atherosclerosis and coronary heart disease is based on the idea that α -tocopherol prevents oxidation of LDL cholesterol. Better results were seen in a clinical trial that combined vitamin E with vitamin C presumably because the vitamin C provided a means to neutralize the tocopheroxyl radicals [37, 96, 108–112].

12.12 Ascorbic Acid

Ascorbic acid (vitamin C) is a leading natural antioxidant that can scavenge ROS and has anticarcinogenic effects. It first changes to semi-dehydroascorbic acid by donating one hydrogen and an electron, followed by conversion into l-dehydroascorbic acid by donating a second hydrogen atom and electron (Fig. 12.3). Both l-ascorbic acid and l-dehydroascorbic acid retain the vitamin C activity [97, 113, 114]. The antioxidant mechanism of ascorbic acid is based on hydrogen atom donation to

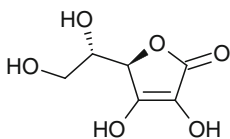


Fig 3.1 Ascorbic acid

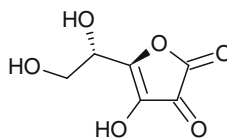


Fig 3.2 Semi-dehydroascorbic acid

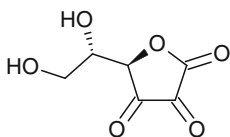


Fig 3.3 Semi-dehydroascorbate radical

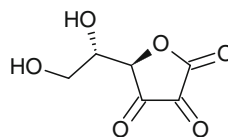


Fig 3.4 Dehydroascorbic acid

Fig. 12.3 Sequential 1-electron reduction of l-ascorbic acid. (a) Ascorbic acid, (b) semi-dehydroascorbic acid, (c) semi-dehydroascorbate radical and (d) Dehydroascorbic acid

lipid radicals, quenching of singlet oxygen and removal of molecular oxygen. Scavenging aqueous radicals and regenerating α -tocopherol from the tocopheroxyl radical are also one of its well known antioxidant properties. It is an excellent electron donor because of low standard one electron reduction potential, which makes generation of relatively stable semi-dehydro ascorbic acid possible and its easy conversion from dehydroascorbic acid to ascorbic acid [115, 116]. It can donate a hydrogen atom to a tocopheroxyl radical at the rate of 2×10^5 M/s. Synthetic antioxidants were found less effective than ascorbic acid [112, 114]. Oxidation of ascorbic acid is highly influenced by heat, light, water, pH, oxygen concentration and metal ions like Cu^{+2} and Fe^{+3} . It may be related to the prevention of some forms of cancer and heart diseases. Ascorbic acid and tocopherol supplementation can substantially reduce oxidative damage [116, 117].

12.13 Lipoic Acids

Some sulfur containing compounds like glutathione (GSH), lipoic acid (1, 2-dithilane-3-pentanoic acid) and dihydrolipoic acid (Fig. 12.4) present in meat, liver and heart show antioxidant activities. They prevent oxidative damage of proteins; regenerate GSH in liver, kidney and lung tissues. There are evidences to show that they reduce diabetic related complication and thus play an important role in reduction of blood glucose concentration. Lipoic acid improves mitochondrial membrane potential,

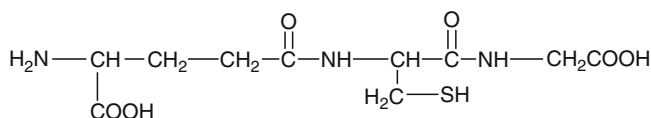


Fig 4.1 Glutathione

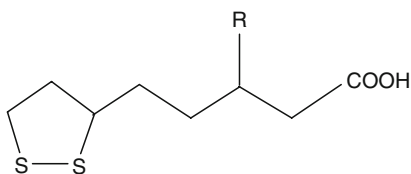


Fig 4.2 Lipoic acid

R = H

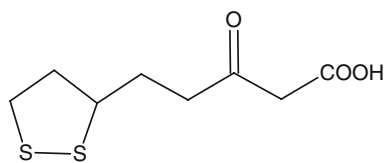


Fig 4.3 3-Ketolipoic acid

Fig 4.4 3-Hydroxylipoic acid

R = OH

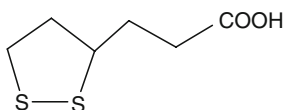


Fig 4.5 Bisnorlipoic acid

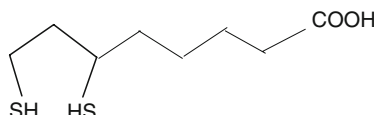


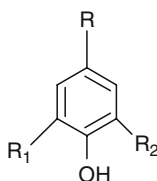
Fig 4.6 Dihydrolipoic acid

Fig. 12.4 Lipoic acids and its metabolites. (a) Glutathione, (b) lipoic acid, (c) 3-ketolipoic acid, (d) 3-hydroxylipoic acid, (e) bisnorlipoic acid, (f) dihydrolipoic acid

age related memory loss and brain ailments, including Alzheimer's and Parkinson's disease [97, 118]. Racemic lipoic acid has been widely used in the treatment of cirrhosis, mushroom poisoning and in case of metal intoxication. Both oxidized (3-hydroxylipoic acid, 3-ketolipoic acid and bisnor-lipoic acid), reduced (dihydrolipoic acid) forms of lipoic acid (Fig. 12.4) act as antioxidants, and have abilities for radical scavenging and metal chelation. Due to its essential role in health, alpha-lipoic acid may very well join the ranks of vitamins C and E as part of first line of defense against free radicals [117–119].

12.14 Polyphenols

The term polyphenols or phenolics refer precisely to those chemical compounds, which have an aromatic ring with hydroxyl substituent(s), including their derivatives like esters, methyl ethers and glycosides. Based on chemistry, they can be classified into phenolic acids, flavonoids, stilbenes and lignans. They are the most abundantly occurring polyphenols in plants (Tables 12.2 and 12.3), of which flavonoids and phenolic acids accounts for about 60% and 30% of total dietary phenols respectively. Derivatives of hydroxybenzoic or hydroxycinnamic acids are the most common phenolic acids in plants. Protocatechuic acid, gallic acid, syringic acid and vanillic acid are some of the examples of phenolic acids derived from hydroxybenzoic acid while *p*-coumaric acid, caffeic acid and ferulic acid (Fig. 12.5) are derivatives of hydroxycinnamic acids [10, 11]. Ellagic acid (Fig. 12.6) a dimer of gallic acid is the most potent natural chemo preventive agent, which prevents oxidative damage of connective tissue and repairs damaged proteins present in the walls of blood vessels



	R	R ₁	R ₂
Fig 5.1 Protocatechuic acid	COOH	OH	H
Fig 5.2 Gallic acid	COOH	OH	OH
Fig 5.3 Syringic acid	COOH	OCH ₃	OCH ₃
Fig 5.4 Vanillic acid	COOH	OCH ₃	H
Fig 5.5 <i>p</i> -Coumaric acid	CH=CH.COOH	H	H
Fig 5.6 Caffeic acid	CH=CH.COOH	OH	H
Fig 5.7 Ferulic acid	CH=CH.COOH	OCH ₃	H
Fig 5.8 Chlorogenic acid	CH=CH.COO-quinic acid	OH	H

Fig. 12.5 Phenolic acids. (a) Protocatechuic acid, (b) gallic acid, (c) syringic acid, (d) vanillic acid, (e) *p*-coumaric acid, (f) caffeic acid, (g) ferulic acid and (h) chlorogenic acid

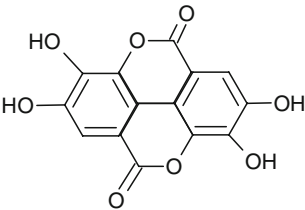
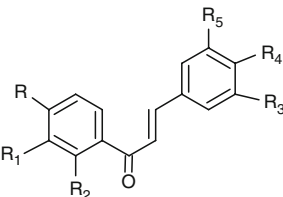
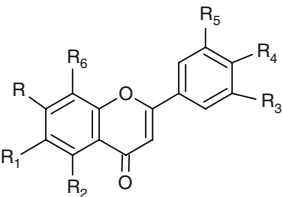


Fig. 12.6 Ellagic acid



	R	R ₁	R ₂	R ₃	R ₄	R ₅
Fig 7.1 Butein	OH	H	OH	H	OH	OH
Fig 7.2 Isoquirtigenin	OH	H	OH	H	OH	H

Fig. 12.7 Chalcones. (a) Butein and (b) isoquirtigenin

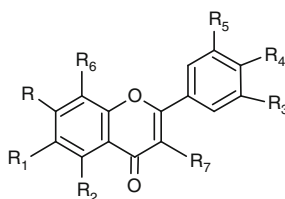


	R	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆
Fig 8.1 Apigenin	OH	H	OH	H	OH	H	H
Fig 8.2 Vitexin	OH	H	OH	H	OH	H	O-Glucose
Fig 8.3 Isovitexin	OH	O-Glucose	OH	H	OH	H	H
Fig 8.4 Luteolin	OH	H	OH	H	OH	OH	H

Fig. 12.8 Flavones. (a) Apigenin, (b) vitexin, (c) isovitexin and (d) luteolin

[119]. Antioxidant activity and biological properties of polyphenols from berries, red wine, ginkgo, onions, apples, grapes, chamomile, citrus, dandelion, green tea, hawthorn, licorice, rosemary, thyme, fruits, vegetables and beverages have been studied. They are rich sources of phenols that can enhance the efficacy of vitamin C, reduce the risk of cancer, act against allergies, ulcers, tumors, platelet aggregation and are effective in controlling hypertension [13, 120].

Flavonoids may be classified into flavones, flavonols, flavanones, flavanols, isoflavones, anthocyanidins and proanthocyanidins. Chalcones such as butein, isoquirtigenin (Fig. 12.7) are considered members of the flavonoids [12]. Flavones (Fig. 12.8), flavonols (Fig. 12.9), flavanols (Fig. 12.10), flavanones (Fig. 12.11), Isoflavones (Fig. 12.12) and anthocyanins (Fig. 12.13) are important classes



	R	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆	R ₇
Fig 9.1 Kaempferol	OH	H	OH	H	OH	H	H	OH
Fig 9.2 Quercetin	OH	H	OH	H	OH	OH	H	OH
Fig 9.3 Quercetrin	OH	H	OH	H	OH	OH	H	O-Glucose
Fig 9.4 Rutin	OH	H	OH	H	OH	OH	H	O-Rutinoside
Fig 9.5 Myricitin	OH	H	OH	OH	OH	OH	H	OH

Fig. 12.9 Flavonol. (a) Kaempferol, (b) quercetin, (c) quercetrin, (d) rutin and (e) myricitin

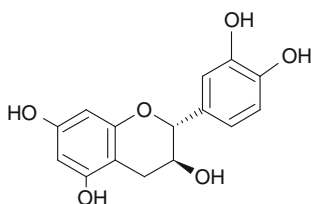


Fig 10.1 Catechin

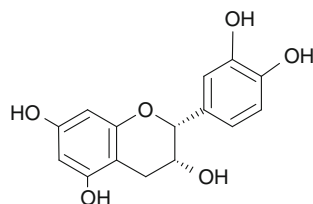


Fig 10.2 Epicatechin

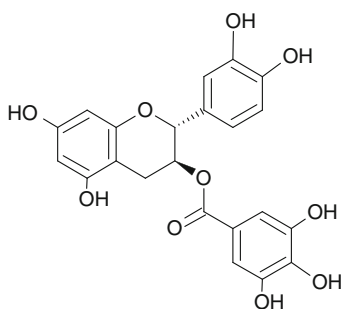


Fig 10.3 Catechin gallate

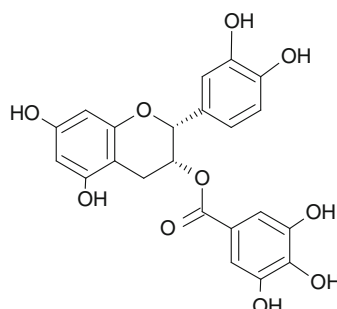
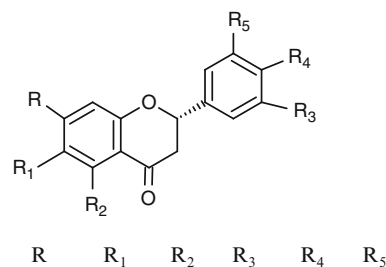


Fig 10.4 Epicatechin gallate

Fig. 12.10 Flavanol (Flavan-3-ols). (a) Catechin, (b) epicatechin, (c) catechin gallate, (d) epicatechin gallate

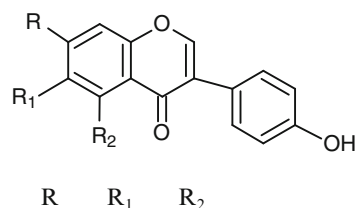
of polyphenols found in nature. Anthocyanins are composed of aglycon called anthocyanidins and sugar moiety(ies). Proanthocyanidins are condensed tannins or polymeric flavonols, which are generally formed because of coupling between electrophilic and nucleophilic flavanyl units. Flavonoids possess an ideal structure for free radicals scavenging activity and have been found to be more effective antioxidants *in vitro* than tocopherols and ascorbates [10, 121, 122].

Fig. 12.11 Flavanone. (a) Naringenin and (b) hesperidin**Fig 11.1** Naringenin

OH	H	OH	H	OH	H

Fig 11.2 Hesperidin

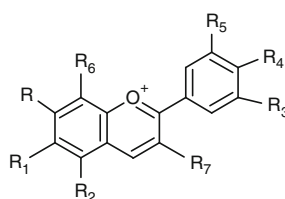
OH	H	OH	H	OCH ₃	H

Fig. 12.12 Isoflavones. (a) Daidzein and (b) genistein**Fig 12.1** Daidzein

OH	H	OH

Fig 12.2 Genistein

OH	H	H

Fig. 12.13 Anthocyanins. (a) Pelargonidin, (b) cyanidin and (c) delphinidin**Fig 13.1** Pelargonidin

OH	H	OH	H	OH	H	H	OH

Fig 13.2 Cyanidin

OH	H	OH	OH	OH	H	H	OH

Fig 13.3 Delphinidin

OH	H	OH	OH	OH	OH	H	OH

The position and number of hydroxyl groups also plays an important role in antioxidant activity. For example in apigenin (Fig. 12.8a), the three hydroxyl groups at position 5, 7, 4' were associated with a small but definite antioxidant effect, while kaempferol (Fig. 12.9a) with an additional hydroxyl at position 3 was more potent than apigenin. Quercetin (Fig. 12.9b) with additional hydroxyl group at 3' and myricetin at 3', 5' positions (Fig. 12.9e) were still more effective [12, 96, 121].

More than 4,000 flavonoids have been identified in plants, which are responsible for the color of vegetables, fruits, grains, seeds, leaves, flowers, bark and products derived from them [11, 97]. Luteolin (Fig. 12.8d), kaempferol, quercetin, quercitrin, rutin, myricetin (Fig. 12.9) and vitamin C (Fig. 12.3a) are powerful antioxidants that inhibit the oxidation of low-density lipoprotein (LDL), a major factor in the promotion of atherosclerosis, which is the plaque build up in arteries that can lead to heart attack or stroke. In general, the aglycones were found with greater antioxidant potential than their glycosides [8, 9]. Use of comet assay to assess DNA damage during oxidative stress showed that quercetin was more potent antioxidant as compared to rutin and vitamin C. Isoflavones like daidzein (Fig. 12.12a) and genistein (Fig. 12.12b) found abundantly in legumes such as lentils, chickpeas and soybeans, have nutraceutical properties against tumor growth and cancer and they form one of the main classes of estrogenic substances in plants. Anthocyanins (Fig. 12.13), another major group of flavonoids play a significant role in collagen protein synthesis and sport medicines. Athletes who exercise a lot produce free radicals that can be tackled by anthocyanidins [78, 79, 122, 123].

12.15 Antioxidant Activity

Flavonoids are powerful metal chelators and scavengers of free radicals and act as anti-inflammatory, anti-ulcer, antitumor and anticancer agents. They act as potent chain breaking antioxidants and possess vitamin C stabilizing activity by increasing its absorption. Their activity depends upon the arrangement of functional groups in nuclear structure [1, 121]. They interact with cellular signal pathways that control cell cycle, differentiation and apoptosis. Their antineoplastic effects can improve antioxidant activity, induction of phase II enzyme activity, inhibition of protein kinases and interaction with type II estrogen binding sites [12, 124]. Therapeutic usefulness of flavonoids has been demonstrated in gastrointestinal hemorrhages, radiation reactions, ethyroblastosis, menorrhagia, bleeding cystitis, tuberculoses, hemophysis, periodontal diseases, epistaxis and ophthalmic disorders [125, 126].

The antioxidant activity of flavonoids can be explained through their chelating action. They bind with transition metal particularly iron and copper and thus inhibit of transition metal-catalyzed free radical formation. Chelated transition metals would be unavailable to interact with other compounds and initiate biologically damaging reactions. Flavonoids inhibit lipid peroxidation, oxidation of linoleic acid and Fe^{+2} catalyzed oxidation of glutamine synthase, through free radical scavenging and removal of metal ions from catalytic sites via chelation [12, 127, 128]. Flavonoids are also known to modify the activities of enzymes like protein kinase C, protein tyrosine kinase, aldose reductase, myeloperoxidase, NADPH oxidase, xanthine oxidase, phospholipase, reverse transcriptase, ornithine decarboxylase, lipoxygenase, and cyclooxygenase. Some of these enzymes are involved in immune functions, carcinogenesis, cellular transformations, tumor growth and metastasis. The antioxidant function and enzyme modifying actions of flavonoids account for many of their pharmacological activities [10, 12, 129, 130].

Biological effects of phenols are of great interest since evidences were found that they offer protection against gastro-duodenal pathogenesis, premature aging, inflammation, metabolic dysfunction, cancer, neuro-degenerative and cardiovascular diseases. Polyphenols have the potential to inhibit oxidation of LDL in vitro that is considered a key mechanism in atherosclerosis. Flavonoids are effective scavengers of free radicals, responsible for DNA damage and tumor promotion. They metabolize a significant number of carcinogens and play a major role in the activation of carcinogens, such as polycyclic hydrocarbons and heterocyclic amines [1, 9, 129, 130].

Flavonoids were found to have beneficial effect in rheumatoid arthritis flavonols and flavone inhibit cytochrome P-450 enzymes while genistein and quercetin inhibit protein tyrosine kinase involved in cell proliferation. Apigenin, luteolin and quercetin have been shown to cause cell cycle arrest and apoptosis by p53-dependent mechanism [96, 129, 131]. Thus, multiple mechanisms have been identified for the anti-neoplastic effects of flavonoids, including anti-inflammatory and anti-proliferative. However, these effects were often obtained with concentrations, which are greater than what can be achieved in humans through dietary means [9, 79, 126, 132, 133].

12.16 Dietary Polyphenols

Epidemiological studies provide convincing evidence that diet rich in antioxidants is associated with a lower incidence of degenerative diseases. Cereals, legumes (barley, corn, nuts, oats, rice, sorghum, wheat, beans, and pulses), oilseeds (rapeseed, canola, flaxseed and olive seeds), fruits, vegetables and beverages (fruit juices, tea, coffee, cocoa, beer and wine) are the main sources (Tables 12.2 and 12.3) of dietary polyphenols [8, 11, 134–140]. Fruits like apple, grape, pear, cherry and various berries contain up to 200–300 mg polyphenols/100 g fresh weights. A glass of red wine or a cup of coffee or tea contains about 100 mg polyphenols. Their total dietary intake may be about 1 g/day, which is about ten times higher than that of vitamin C and 100 times higher than that of vitamin E and carotenoids [13, 116, 125, 141]. The major constituents of tea polyphenols are flavonols (catechin, epicatechin, catechin gallate and epicatechin gallate), flavanols (quercetin, kaempferol and their glycosides), flavones (vitexin, isovitexin) and phenolic acids (gallic acid, chlorogenic acid). They constitute up to 30% of the dry weight of green leaves and 9–10% of the dry weight of black tea leaves [11, 129, 142]. Ferulic acid is associated with dietary fiber linked with hemi cellulose of the cell wall via ester bonds. Caffeic acid in the form of caffeoyl esters and coumaric acids are common in apples, pears, and grapes. In addition, apples and pears are rich in chlorogenic acid and grape in gallic acid. Apples contain high levels of quercetin among fruits [137, 142–145]. Grain-derived products are very important in human diet as they have higher concentration of phenolic acids in the outer layers of kernel that constitute the bran [80, 144]. Most of the phenolic acid derivatives are hydrolysable tannins and are usually esterified with glucose [80, 140, 146]. Citrus fruits are main sources of flavonones and hesperidin is found in abundance (120–250 mg/L) in orange juice [101, 147, 148]. Quercetin occurs in its glycosylated form as rutin in fruits, vegetables and particularly onions are its rich source [10, 78–80, 136]. Anthocyanins are pigments of fruits such as cherries, plums, strawberries, raspberries, black berries and red currant and their content varies from 0.15 to 4.5 mg/g in fresh berries. Occurrence of some of the flavonoids is restricted to a few foodstuffs like the main source of isoflavonoid is soy, which contain ~1 mg/g of genistein and daidzein and have received considerable attention due to their suggested role in prevention of cancer and osteoporosis. People who consume traditional diets rich in soy and tea rarely experience breast, uterus and prostate cancer. Although there are a range of potentially antimutagenic fruits, vegetables and cereals but their intake is generally below the level necessary to protect from various mutagens [78, 79, 98, 137, 148].

12.17 Conclusions

Over production of ROS, most frequently either by excessive stimulation of NADPH by cytokines, or by the mitochondrial electron transport chain and xanthine oxidase result in oxidative stress.

Oxidative stress is a deleterious process that can be an important mediator of damage to cell structures and consequently various disease states and aging. ROS appear to be key regulatory factors in molecular pathways linked to neurodegenerative and cardiovascular diseases. Antioxidant phytochemicals of nutraceutical importance such as ascorbic acid, carotenoids, flavonoids, polyphenols, tocopherols, lipoic acid and other potent natural products may play key role to control several diseases induced by oxidative stress and might aid in the design of novel therapies targeting the respective molecular pathways. Since continued research is needed to better understand the mechanisms and specific pathways involved in ROS-induced diseases, and to determine the most rational and effective combination of antioxidants. Antioxidants can also offer suitable answer to the question of the anticancer, antidiabetic, anti-ulcer, anti-inflammatory and antimutagenic effects and other oxidative stress related health problems. Several clinical evidences, together with epidemiologic observations, suggest that for example tomato consumption may have organ-specific chemo-preventive effects with antioxidative phytomolecules exerting protective effects on to tumor development, tumor dissemination, neurodegenerative and cardiovascular diseases. The recent advances in biochemistry and molecular biology techniques provide new, powerful tools for studying the expression of tissue antioxidant enzymes and for elucidating the mechanisms of the actions of antioxidants. In a number of clinical trials the importance of daily consumption of whole grains, fruits, vegetables, nuts, and unsaturated fatty acids rich vegetable oils with controlled diets in the prevention or treatment of various diseases have been observed. Randomized clinical trials and evidences from epidemiological studies on naturally occurring antioxidants have shown protective effects. Thus the future of cost effective natural sources of antioxidants hold a great promise to ensure a better disease free lifestyle for the man kind by scavenging free radicals and consequently preventing mutagenic changes and associated disorders.

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Chapter 13

Zinc Intervention Strategies: Costs and Health Benefits

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Key Points

- Zinc is required for such processes as growth, immunity and reproduction. Even in developed countries, many people have a marginal intake of zinc and several common dietary constituents can impair its absorption. Attention to the zinc nutrition of at-risk groups such as the malnourished, children, pregnant women, the elderly and immuno-compromised individuals is therefore required.
- New information about zinc and cancer risk has emerged. Zinc deficiency has been shown to upregulate expression of the tumor suppressor protein, p53; and impairs the DNA binding abilities of p53, NFκB, and AP-1 transcription factors. These studies suggest that a decrease in cellular zinc alone results in a loss of DNA integrity, increasing the potential for cancer risk. Conversely, zinc supplementation decreases oxidative stress and improves immune function, which may be a mechanism for its cancer preventive activity.
- Successful programs to increase global zinc intakes through a combination of supplementation, dietary diversification, fortification, biofortification, zinc-fertilizers, phytate reduction and/or utilizing enzymes like phytase are necessary.
- Industry should help to define feasible, affordable fortification strategies, identify appropriate food vehicles and fortificants, develop quality assurance systems, and implement educational campaigns to reach target populations.
- Fortification of staple foods, such as bread or breakfast cereals, offers a means of increasing zinc intake among the majority of the population that consume these foods and can help to ensure dietary adequacy.
- Biofortification is an alternate strategy for improving zinc content in staple crops, provided that there is adequate genetic biodiversity/natural variation in concentrations of relevant micronutrients. Crops with enhanced micronutrient content are most relevant to developing countries, where micronutrient deficiencies are widespread.
- Scientific community members need to determine the country-specific prevalence of zinc deficiency, the sensory acceptability and efficacy of the chosen zinc compound and food products, develop and implement educational campaigns to reach target populations, and verify the overall effectiveness of zinc-supplementation program(s).

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Abbreviations

AMD	Age-related macular degeneration
AREDS	Age-Related Eye Disease Study
BCR	Benefit-to-cost ratio
DALYs	Disability adjusted life years
EAR	Estimated average requirement
GA	Geographic atrophy
IZiNCG	International Zinc Nutrition Consultative Group
NPK	Nitrogen phosphorus and potassium
UNICEF	United Nations Children's Fund

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13.1 Introduction

The Office of Dietary Supplements at the US National Institutes of Health (<http://dietary-supplements.info.nih.gov>) defines dietary zinc as “an essential mineral that is naturally present in some foods, added to others, and available as a dietary supplement.” Zinc is involved in numerous aspects of cellular metabolism – it is required for structural and functional integrity of more than 300 enzymes [1] and 2,000 transcription factors [2]. Therefore, almost every signaling and metabolic pathway is in some way dependent on at least one, and often several, zinc-requiring proteins. Zinc plays assorted roles in human health, including immune function [3, 4], protein synthesis [5], wound healing [6], DNA synthesis [7, 8] and cell death [9]. Zinc also supports normal growth and development during pregnancy, childhood, and adolescence [10–12] and is required for proper sense of taste and smell [12]. An adequate daily intake of zinc is required to maintain a steady state because the body has no specialized zinc storage system [13]. Zinc deficiency increases the risk and severity of a variety of infections, restricts physical growth, and affects specific outcomes of pregnancy. Global recognition of the importance of zinc nutrition in public health has expanded dramatically in recent years, and more experience has accumulated on the design and implementation of zinc intervention programs.

This review details advances in knowledge of zinc nutrition, human health benefits and the link between moderate zinc deficiency and cancer. As the fifth top ranking factor contributing to the burden of disease in the developing world, zinc deficiency is increasingly acknowledged as one of the most serious public health challenges. Recently, a panel of world-renowned economists produced the Copenhagen Consensus on Hunger and Malnutrition – a project to establish priorities for advancing global welfare [14]. The Copenhagen Consensus statement ranked micronutrient supplements, specifically zinc and vitamin A supplements, as the top international development priority, out of more than 40 interventions considered, to help combat malnutrition among the 140 million children who are undernourished. More recently, the International Zinc Nutrition Consultative Group (IZiNCG; www.izincg.org) completed a second Technical Document [15] that re-examined the latest information on intervention strategies developed to enhance zinc nutrition and control zinc deficiency.

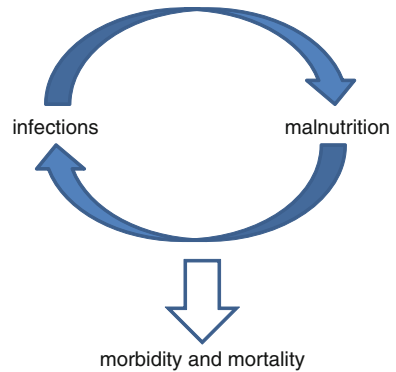
In particular, the document reviewed evidence regarding preventive zinc supplementation and the role of zinc as adjunctive therapy for selected infections, zinc fortification including the promotion of biofortification, and dietary diversification or modification strategies. Hence, this chapter will also summarize the outcomes of these two important assessments of population zinc status, and review critical zinc-intervention strategies.

13.2 The Importance of Zinc for Human Health

13.2.1 Recent Advances in Knowledge of Zinc Nutrition and Human Health

The head of Global Health Program at the Bill and Melinda Gates Foundation, Dr Tachi Yamada, was recently quoted as saying “The food and financial crises have refocused the world on how we deal with nearly one billion people who go to bed hungry.” But his listeners, a gathering of nutrition scientists in Bangkok (19th International Congress of Nutrition, 4–9 October 2009), did not focus on the hungry, in the usual sense of people whose intake of calories is low. Instead they tackled a problem that is far larger, but possibly simpler. Perhaps a third of the world’s people suffer from a lack of micronutrients, substances that help bodies and brains to grow and resist disease. These micronutrients include zinc, folic acid, iron, iodine, and vitamin A. The following review examines recent advances in knowledge of zinc nutrition and human health.

Zinc deficiency affects about 1.2 billion people worldwide [16], and has been shown in epidemiological trials to increase the risk of diarrhea in young children by 33%, pneumonia by 69%, and malaria by 56% [17]. The link between diarrhea and zinc deficiency is a perfect example of the feedback loop between malnutrition and disease: the amount of zinc lost through defecation increases threefold with diarrhea, resulting in imbalances with other micronutrients such as magnesium [18]. The overall result of nutrient deficiencies aggravated by, and/or aggravating disease progression, results in three million deaths annually from diarrheal disease among children under the age of 5 years. In the developing world, the combination of lack of clean water, crowding, poor sanitary conditions, and environmental conditions that favor bacterial cross-contamination leads to the vicious cycle in which malnutrition increases the risk of diarrheal diseases which aggravate malnutrition – and both contribute to early death (Fig. 13.1). A good example is the Irish famine of the 1840s, where as many as one in seven of those who died were recorded as having died not of food shortage (“starvation”), but of diarrheal diseases, including dysentery [19]. Similarly, diarrheal diseases were the prime cause of mortality in Afghanistan during the 2001 famine [20], in the Democratic Republic of Congo from 1999 to 2002 [21] and in Bangladesh during three consecutive floods: 1988, 1998 and 2004 [22]. Unfortunately, humanitarian emergencies establish the conditions whereby water sources are easily contaminated, but so too are food sources, as they become exposed to pathogens associated with unsanitary food handling, pests, flies, and unclean cooking utensils. As a result, diarrheal outbreaks in emergencies must be controlled through hygiene and sanitation measures to protect water and food supplies, as well as by treating the individual. The power of zinc and vitamin A to reduce diarrhea should be re-emphasized, as both are essential to immune function. In addition to reducing child morbidity associated with infectious diseases, controlling vitamin A deficiency in at-risk populations reduces child mortality by an average of 23%, equivalent to more than 600,000 deaths averted in sub-Saharan Africa alone. A recent review [10] showed that providing zinc supplements reduces overall child mortality by 6% in deficient populations and reduces deaths of children over 1 year by 18%. In a large trial in Bangladesh, mortality

Fig. 13.1 Micronutrients and infection**Micronutrients and Infection**

rates (excluding deaths from injury) were 51% lower in the cluster with therapeutic zinc supplementation for diarrhea, than the control [23]. Bhutta and colleagues [24] have estimated the mortality reduction associated with therapeutic zinc at 42% for persistent diarrhea, and Robberstad et al. [25] modeled the effect of a 50% reduction. The most recent Copenhagen Consensus statement on Hunger and Malnutrition [14] ranked zinc and vitamin A supplementation as the top contender for advancing global welfare – this involves the provision of therapeutic zinc supplements and vitamin A capsules for children under the age of 2 years. In a follow-up, the Vice-president for the Helen Keller International, Shawn Baker was quoted as saying “Clearly the time has come to eliminate all micronutrient deficiencies, from A to Z.”

Is zinc-deficiency linked to malnutrition, or undernutrition, defined as an inadequate intake of certain nutrients? Despite significant reductions in income poverty in recent years, undernutrition remains a major issue in developing countries. Recent estimates from the United Nations Children’s Fund (UNICEF) are that one out of every four children under the age of five (approximately 146 million children in the developing world) is underweight for his/her age [26], with undernutrition being the underlying cause of 3.5 million deaths each year [27]. However, undernutrition associated with inadequate micronutrients in poor quality diets is even more widespread than that indicated by underweight alone. It is estimated that over one billion people are susceptible to zinc deficiency [28], and up to 219 million children are vitamin A deficient [29]. Children with these deficiencies are significantly more likely to experience morbidity and mortality, which in turn has negative effects on income and on economic growth.

Micronutrient malnutrition has increasingly taken center stage in policy discussions on food security. It is recognized that food security refers not merely to adequate energy intakes, but also to ensuring sufficient intakes of essential micronutrients. In determining cost-effectiveness, the Disability-Adjusted Life Years (DALYs) framework is used to capture both morbidity and mortality outcomes in a single measure. Relatively underutilized in the economics literature as a metric for welfare, the use of DALYs obviates the need for monetization of health benefits. Instead, benefits can be quantified directly using DALYs averted, and costs per DALY averted offer a consistent way of ranking a range of alternative interventions that affect health outcomes [30]. Zinc deficiency accounts for about 4% of under-5 deaths and DALYs and 1% of total DALYs lost, while vitamin A deficiency accounts for about 6% of under-5 deaths, 5% of under-5 DALYs, and 1.7% of total DALYs lost [27]. Zinc deficiency affects many cellular systems in the host because of zinc’s essential role in many aspects of cellular metabolism. Zinc deficiency can occur in populations with low dietary zinc intake and/or a high concentration of phytate, a powerful chelator of divalent metals. The pathological signs

of zinc deficiency include stunted growth, dystocia (impaired parturition), neuropathy, decreased food intake, diarrhea, dermatitis, hair loss, bleeding tendency, hypotension, and hypothermia [31]. Although severe zinc deficiency is rare, mild-to-moderate zinc deficiency is highly prevalent even in developed countries. Populations that are at high risk include individuals at early stages of the life cycle (i.e., infancy and childhood) when requirements for zinc are high. In addition, the elderly have an increased risk of zinc depletion due to the consumption of a low-zinc diet as well as impaired zinc absorption [32, 33]. Foods rich in zinc include red meat and poultry. Other good food sources include beans, nuts, and certain types of seafood such as crab and lobster, whole grains, fortified breakfast cereals and dairy products. Several plant sources, such as whole grains and legumes are good sources of zinc, however, the zinc is much less bioavailable due to high phytate content. Thus, vegetarians may also be at risk for zinc deficiency [34].

The recommendation for this lifesaving intervention of zinc supplementation follows on the joint statement by WHO-UNICEF in 2004, recommending the use of zinc for 10–14 days for all episodes of diarrhea among children under 5 years of age [35]. However, this highly beneficial intervention has not yet been widely adopted, despite the low cost – providing zinc as part of case management carries an estimated incremental cost of US \$0.47 per treatment, ranging from \$0.33 to \$0.62. Zinc as an adjunct therapy in the management of diarrhea is very cost effective, with an average cost of US \$73 per DALY gained and \$2,100 per death averted [25]. Sustained support in the form of policy advocacy, technical assistance, capacity building, demand creation, product registration and supplies are needed to support the scale-up of zinc supplementation for the treatment of diarrhea and the reduction in child mortality in developing countries [36]. Although there is good evidence for the efficacy of zinc in treatment of diarrhea, and most studies have shown mortality, morbidity and growth benefits, there still remain a number of information gaps as to the size of the effects and the optimal pattern of intervention.

Currently 1.87 million children die annually due to diarrhea [37], hence there is the potential for saving a considerable number of lives. Recent meta-analyses demonstrate the effectiveness of zinc in treating acute, persistent and dysenteric diarrhea in children in both developed [38] and developing [39] countries. Lukacik et al. [39] used a pooled relative risk of 22 studies in children – 16 studies examined acute diarrhea ($n=15,231$), and six examined persistent diarrhea ($n=2,968$), while Patro et al. [38] used combined data from 18 studies in children – 13 studies examined reduction in diarrhea duration ($n=5,643$), and eight studies examined the risk of diarrhea lasting longer than 7 days ($n=5,769$). Overall, mean duration of acute diarrhea and persistent diarrhea was significantly lower for zinc compared with placebo. At day 3, diarrhea presence was significantly lower for zinc in persistent diarrhea trials, but not in acute diarrhea trials. Overall, children who received zinc reported an 18.8% and 12.5% reduction in average stool frequency, 15.0% and 15.5% shortening of diarrhea duration, and a 17.9% and 18.0% probability of reducing diarrhea over placebo in acute and persistent trials, respectively. No significant reduction in stool volume was observed for those receiving zinc compared with placebo. The authors do provide a cautionary note – vomiting after therapy was significantly greater for those receiving zinc (vs. the placebo), and when the agent is zinc gluconate (vs. zinc sulfate or zinc acetate). While both studies conclude that zinc supplementation significantly reduces the duration and severity of acute and persistent diarrhea in children, the mechanism(s) by which zinc exerts its anti-diarrheal effect have not been fully elucidated.

The choice of a particular chemical form of supplemental zinc should be based on its solubility in water, intragastric solubility, taste, cost, side effects and safety [40]. Water-soluble compounds are preferable because they are absorbed more efficiently. A number of studies have been conducted to assess the absorption of different chemical forms of supplemental zinc (zinc acetate, aminoate, ascorbate, citrate, gluconate, histidine, methionine, oxide, picolinate, and sulfate), although results have been variable and sometimes conflicting in terms of their relative absorption [41–44]. In general,

water-soluble compounds, such as zinc acetate, zinc gluconate, and zinc sulfate, are considered to be more readily absorbable than compounds with limited solubility at neutral pH [45]. Some studies suggest that zinc oxide is poorly absorbed because its low solubility at the basic pH of the small intestine may prevent it from dissociating in the gastro-intestinal tract [42, 43, 46]. However, this may only present a problem when gastric acidity is reduced, as may occur in malnourished children.

Single-micronutrient studies have shown significant reductions in all-cause mortality, but combination studies are needed. Studies using vitamin A supplementation in children under age 5 at risk of deficiency have shown a significant 23% reduction in all-cause mortality [47]. This has been further supported by the recent *Lancet* journal series on child survival that identified vitamin A supplementation as one of the key proven interventions to reduce child mortality [27]. In combination studies (zinc and vitamin A supplementation), the reported effects on clinical and immune response outcomes associated with diarrheal pathogens do appear to be pathogen- and even outcome- specific [48, 49]. These findings may result from the differential effects that vitamin A and zinc have on the pathogen-specific immune response. Vitamin A-deficiency induces an upregulation of the Th₁ cell-mediated response, while supplementation up-regulates the Th₂ response and downregulates the Th₁ response [50–52]. The down-regulated Th₁ response may underlie the reductions in childhood mortality and diarrheal disease severity associated with vitamin A supplementation. The dysregulated production of pro-inflammatory cytokines during a dominant Th₁-response can cause tissue damage, organ failure, and, in some cases, death [53]. The effect of vitamin A on the mucosal immune response may be modified by the type of enteric pathogen infecting the child [51]. Zinc deficiency leads to a reduced Th₁ response, while supplementation up-regulates this response [54, 55]. Zinc positively mediates interferon- γ mRNA expression in monocyte-macrophage cell lines, in lipopolysaccharide-exposed human peripheral blood mononuclear cells, and in activated T-lymphocytes [54, 56–58]. An up-regulated Th₁ response is more protective against many of the invasive diarrheal pathogens such as *Salmonella* and *Shigella* [59, 60]. Overall, there is a need to further define the effects that these micronutrients have on both general and pathogen-specific diarrhea and on the mechanisms underlying these associations, because the studies examining these relationships are not comprehensive, or systematic.

In 2008 a panel of world-renowned economists produced the Copenhagen Consensus on Hunger and Malnutrition – a project to establish priorities for advancing global welfare [14]. The 2008 Copenhagen Consensus statement ranked micronutrient supplements as the top international development priority, out of more than 40 interventions considered, to help combat malnutrition among the 140 million children who are undernourished. Specifically, therapeutic zinc supplementation for children with diarrhea (10–14 days of supplementation, up to the age of 5), and high-dose vitamin A supplementation for children (every 4–6 months, from age 6 months to 5 years) were considered the highest priority. The criteria used included the benefit-to-cost ratio (BCR), as well as feasibility and sustainability of the interventions. The Copenhagen Consensus proposed solutions/priorities for advancing global welfare, with ballpark estimates of costs and benefits [14]. The most promising solution, titled “Micronutrient Supplementation,” involves the provision of therapeutic zinc supplements and vitamin A capsules for children under the age of 2 years. This would cost a total of US \$60.4 million annually, with benefits worth more than \$1 billion yearly (BCR of more than 17:1). The second solution offered, titled “Micronutrient Fortification,” entails the provision of iodized salt and iron. For an annual cost of \$286 million, the corresponding benefits are \$2.7 billion (BCR of 9.5:1). Their third solution, titled “Biofortification” involves improving agricultural technology, with annual costs of \$60 million and benefits of \$1 billion (BCR of more than 16:1). Estimating costs is an important step in planning a food fortification program. Estimates must include both the costs to industry (for example, capital investment and recurrent costs, such as the purchase of fortificant) as

well as the public sector costs (for example, enforcement, monitoring and evaluation). In the case of mass zinc-fortification programs, which tend to rely on staples and condiments as the food vehicles, cost is often the most significant limiting factor. Staples and condiments are consumed frequently and in large amounts, not only by the population directly, but also by the food industry. Even small variations in price can thus have profound consequences, and experience has shown that mass fortification in an open market economy is most likely to be successful when the increase in the price of the fortified product, relative to the unfortified one, does not exceed 1–2% [61]. The addition of zinc adds very little to the fortification cost and hence, for this micronutrient, cost is not a restrictive factor. In a recent review of the current costs to supply the Estimated Average Requirement (EAR) of nutrients to women of reproductive age through food fortification, it was concluded that zinc (as zinc oxide) is one of the least expensive nutrients [62]. Zinc seems to be absorbed equally well from foods fortified with zinc oxide or zinc sulfate, the two cheapest sources of zinc that are generally recognized as safe for human consumption [63]. When taking the expected micronutrient loss during production, distribution, storage, and food preparation into account, it is estimated that a woman could receive her entire yearly requirement of zinc through food fortification at an annual cost of US\$0.006–US\$0.013. The time is now ripe to convert this awareness into tangible results.

13.3 Systematic Review of Zinc Intervention Strategies

Zinc deficiency, resulting from an inadequate dietary intake of zinc, is now widely recognized as a leading risk factor for morbidity and mortality [64], and much attention has been given to improving zinc intakes. Like other micronutrient deficiencies, three main factors have been cited for zinc deficiency in low-income and/or developing countries: inadequate dietary consumption (or absorption) due to the intake of largely plant-based diets, or suboptimal breastfeeding practices; disease states that either disrupt zinc utilization or induce excessive losses; and physiological stressors that elevate zinc requirements, such as rapid growth during childhood and pregnancy [65]. Strategies employed to improve zinc intakes include supplementation, fortification, biofortification and dietary diversification/modification. Fortification and biofortification strategies are reviewed in Sect. 3.4. Implementation of these strategies require sustained effort in developing countries and the commitment of resources from government, industry, public health educators, donors, scientists, nongovernmental organizations and consumers [66]. The following section provides a review of current knowledge of zinc intervention strategies and recommendations from programs that have used them.

13.4 Zinc Supplementation

According to the WHO, supplementation describes the provision of relatively large doses of micronutrients, usually in the form of pills, capsules or syrups. It has the advantage of being capable of supplying an optimal amount of a specific nutrient or nutrients, in a highly absorbable form, and is often the fastest way to control deficiency in individuals or population groups that have been identified as being deficient [61]. Zinc supplementation has been studied most extensively with regards to reducing diarrheal morbidity in young children. Recent meta-analyses [38, 39] support the earlier findings of the Zinc Investigators' Collaborative Group that in children with acute diarrhea supplemented with zinc, there was a 15% lower probability of continuing diarrhea when compared to the

control group [24]. The results of these analyses confirm a beneficial impact of preventive zinc supplementation for reducing the incidence of selected childhood infections and increasing children's physical growth [10], and of therapeutic zinc supplementation for reducing the duration and severity of diarrhea [64]. In particular, preventive zinc supplementation reduces the incidence of diarrhea by approximately 27% among young children over 12 months of age and decreases the incidence of acute lower respiratory tract infections by approximately 15%. Preventive zinc supplementation may also reduce the incidence of malaria, but the number of available studies is still relatively small, so more research is needed to confirm this outcome. Overall, zinc supplementation reduces child mortality by approximately 6% [36]. This impact of preventive zinc supplementation is restricted to children over 12 months of age (in whom the mortality reduction is approximately 18%) and possibly to small-for-gestational-age infants. Preventive zinc supplementation also increases linear growth and weight gain of young children, thereby contributing to reduced rates of stunting and underweight. Importantly, available studies show that preventive zinc supplements provided in recommended amounts do not have adverse effects on the status of other micronutrients or cause any detectable functional abnormalities.

Additional trials have showed similar results, providing strong support for international recommendations of zinc supplementation for reducing diarrhea in children. Zinc supplementation studies that were pivotal in advancing these recommendations included studies to reduce the severity and duration of diarrhea as well as studies to prevent subsequent diarrheal episodes. For instance, of 12 studies that examined the effect of zinc supplementation on acute diarrhea, 11 demonstrated a reduction in diarrhea duration, with eight showing statistically significant reductions. Furthermore, zinc supplementation during and until cessation of a diarrheal episode had a significant beneficial effect, reducing the severity of diarrhea. Finally, studies examining zinc supplementation to prevent subsequent diarrheal episodes reported that 10–20 mg of zinc daily for 10–14 days reduced the number of diarrheal episodes in the subsequent 2–3 months following supplementation [35].

Based on these findings, in May 2004, UNICEF and WHO issued a joint statement recommending the use of zinc with oral rehydration therapy to treat diarrhea in children. Twenty milligrams of zinc are recommended for 10–14 days in children 12–59 months of age; and 10 mg of zinc for infants less than 6 months of age [35]. It has been estimated that implementing zinc supplementation as an adjunct treatment with oral rehydration therapy to combat diarrhea, could prevent 88% of deaths attributable to diarrhea [67].

Breastfeeding is an important zinc intervention strategy in reducing zinc deficiency in infants and young children [68], as breast milk alone is a sufficient source of zinc for infants up to 3 months of age and possibly up to 6 months of age. The WHO considers breastfeeding an unequalled way of providing ideal food for the healthy growth and development of infants [69]. Even after complementary feeding has begun and into a child's second year, breast milk continues to provide about 50% of zinc requirements.

Zinc supplementation of infants, preschool -age and pre-pubertal children have also been investigated. The results have been variable depending upon the study objectives and population characteristics. A summation of a series of meta-analyses on the impact of preventive zinc supplementation on morbidity, mortality and physical growth were reported recently [10]. The supplementation periods reviewed ranged from 2 weeks [70] to 15 months [71], and the number of subjects per study ranged from 18 to 94,359. The periodic zinc supplementation doses ranged from 1 to 70 mg per dose (median, 10 mg). These doses were provided daily ($n=50$ studies), several times per week ($n=30$), or once per week ($n=6$), resulting in a daily dose equivalents ranging from 0.9 to 21.4 mg of zinc/day. Most studies provided zinc as zinc sulfate ($n=36$ studies), although a few distributed other compounds, including zinc acetate ($n=5$), zinc gluconate ($n=5$), zinc amino acid chelates ($n=3$), and zinc oxide ($n=1$). Zinc supplementation reduced diarrheal incidence by

approximately 20% in children 12 months or greater, and the relative risk of diarrhea was reduced by 27% in children 12 months or older. Other outcomes examined included: incidence of acute lower respiratory tract infection, which was reduced along with pneumonia by 15%; malaria incidence, which yielded inconsistent results; and overall child mortality which was reduced 6%. The greatest benefit was for children over 12 months of age, where deaths was reduced by 18%, and physical growth increased by a small, but significant amount [10]. There was no evidence of adverse effects of zinc on iron or copper status – therefore it can be administered singly or with other micronutrients formulations (as preferred), as many children suffer from multiple micronutrient deficiencies [72].

The challenges of zinc supplementation programs include product availability, coverage, training, endorsement, and treatment compliance [73]. Zinc sulfate tablets have most commonly been used in supplementation programs because they are inexpensive, easy to transport and accepted by mothers and children; however, for program sustainability, local production or technology transfer is needed, which is already being reported in Bangladesh and India [73]. Treatment compliance is essential and many factors may influence compliance including the form of supplement (tablet, powder, or syrup), dosing frequency, acceptance by community leaders and medical staff [10]. Health care providers who treat children for diarrhea will require training and motivation on the promotion of zinc supplementation. This ensures adequate counseling and product endorsement to recipients thus improving their likelihood of compliance [10, 73]. In addition, the health care delivery system used to distribute the supplements is critical. Constraints such as limited access and poorly utilized health care services must be addressed, as well as identifying programs that zinc supplements can be distributed through with the required contact frequency necessary [10, 73]. For instance, vitamin A supplementation which has been shown to be successful is a potential program that may facilitate zinc supplementation integration. However, since vitamin A supplementation usually occurs in twice yearly campaigns, this schedule would be challenging for compliance with zinc supplementation, which requires daily, or at least weekly, dosing [10]. Social marketing campaigns may be useful in promoting zinc supplementation in communities [73]. Finally, zinc supplements must also be available to health care providers at the local health facilities in order to reach the intended recipients. This will require close consultation and political support from governments in partnership with aid agencies to finance and distribute zinc supplements for maximal uninterrupted coverage [73].

Since many food staples in the developing world are high in phytate, studies have been conducted to measure zinc absorption from high- or low-phytate foods that have been fortified with zinc [74–76]. These studies indicate that the phytate:zinc molar ratio of the meals explains most of the observed differences in the percentage of dietary zinc that was absorbed. The results suggest minimal ability for humans to adaptively increase zinc absorption from diets high in phytic acid. Hunt et al. [74] report that when the phytate:zinc ratio is >15 – 20 , the unbound zinc available to absorptive transporters may be insufficient for biological up-regulation to increase zinc absorption. Their data also suggest that diets with a phytate:zinc ratio ≥ 12 do not provide an amount of absorbed zinc that meets the mean physiologic requirement for absorbed zinc estimated by the Food and Nutrition Board [7]. In practical terms, a study in Swedish adults [75] reported that the percentage of dietary zinc absorbed from a zinc-fortified, low-phytate, refined wheat bread was significantly greater than that from the zinc-fortified, high-phytate, whole-wheat bread (13.2% vs 8.2%, respectively). In a more recent study [76], the percentage of zinc absorbed from a refined-wheat, yeast-fermented bread was approximately twice as much as that absorbed from a whole-wheat, unfermented porridge despite similar zinc content (3.1–3.7 mg of zinc/serving). These results indicate that phytate reduces zinc absorption from zinc-fortified foods; however, more zinc is still absorbed with zinc fortification, than without [63].

13.5 Dietary Diversification and Modification

Dietary diversification or modification of diets is aimed at enhancing access to, and utilization of, foods with a high content of absorbable zinc [77]. As such, diversification or modification strategies are categorized under agricultural interventions, complementary foods enhancement and behavioral change [77]. Improvements in dietary intake due to agricultural changes have been studied primarily in relation to vitamin A status, with negligible research on zinc. One study in Egypt examined 31 types of agricultural interventions to increase productivity of local crops and reported an increase in maize, peanuts, wheat, protein and iron in the intervention group as compared to the control group. Zinc intake was not specifically measured and although higher intakes of protein and iron sources may result in higher zinc intakes, an increase in phytate consumption is also assumed due to higher grain intake [78]. The challenge is to encourage increased plant intake while including a strategy to deal with the resultant increase in phytate content and therefore, decreased zinc bioavailability. Additionally, including nutrition education as part of an agricultural intervention has resulted in increased or greater intakes of vegetables and vitamin A-rich foods; however, several of these studies did not have a control group, which hampers the interpretation of such results [77].

Agricultural interventions that aim to increase production or promote animal-source foods through animal husbandry or aquaculture have been shown to increase the consumption of animal-source foods when they are culturally appropriate and include nutrition education or behavior change components [77]. Providing red meat compared to milk or fish, can lead to an increased intake of more bioavailable zinc for infants and school-age children, although recent studies have shown there are some indigenous fish species in Cambodia and Bangladesh that are rich sources of zinc, vitamin A and iron [79]. It would be helpful if future studies determined whether such fish species are a valuable source for increasing zinc intake.

Dietary diversification/modification strategies to improve dietary zinc intake may focus on either the commercial or household level. While phytate reduction strategies have been demonstrated to reduce phytate by about 50% with soaking of pounded maize or maize flour or fermenting maize porridges, more in vivo isotope absorption studies are needed [80]. Additionally, research suggests that phytate reduction strategies without a corresponding increase in animal-source foods for infants and young children are unlikely to achieve recommended zinc requirements [81].

The impact of dietary diversity/modification on improving the health, development and zinc status of children and women of reproductive age have been assessed [77]. Enhancing diets of infants and young children by adding animal source foods or promoting their use positively affect body composition, growth, cognitive functioning, and intakes of bioavailable zinc [82]. There is insufficient research available to draw similar conclusions for women of reproductive age.

Both short-term measures (supplementation and fortification) and long-term solutions (i.e., dietary diversification or *modification* and biofortification) can be used to alleviate zinc deficiency in developing countries. While there is too little evidence to ascertain that dietary diversification/modification can impact nutritional status in the long-term, in the short-term, interventions have been shown to be successful in improving certain nutritional measures [83]. For instance, a notable study in Peru [84] showed a significant effect on behavior change which resulted in improvements in length and weight in the intervention vs control groups. The intervention included nutrition education to increase the intake of thick purees and animal-source foods and increase the practice of responsive feeding. Demonstrations of preparation of the purees were provided to the control group. The intervention group as compared to the control group had higher intakes of energy from animal-source foods with fewer children failing to meet their energy, iron, and zinc requirements. However, the long-term sustainability of this behavior change was not evaluated.

Finally, it is unknown if dietary diversification strategies are modified by related factors. Baseline nutritional status has been shown in micronutrient supplementation studies to modify responses to dietary diversification; however, in most intervention studies reviewed related to zinc enhancement, baseline status was not measured [77]. Infections may modify response to dietary diversity by decreasing appetite and intake, altering the gastrointestinal permeability and thereby, decreasing absorption, resulting in decreasing serum zinc. Unfortunately, few interventions that promoted dietary diversification/modification have measured the existence of an infection, the exceptions being studies in Ghana [85] and Kenya [86]. Age is another potential modifier of the influence of dietary diversity/modification interventions. A study in Chinese infants that included nutrition education and counseling to increase breastfeeding rates and improve the nutritional content of complementary foods showed that before 12 months of age, there was no difference in growth between groups, but at 12 months, infants in the education group showed better growth in weight and length [87].

Clearly, interventions to address zinc deficiency are critical in preventing related childhood mortality and morbidity. The likelihood is great that micronutrient deficiencies do not occur in isolation and multiple deficiencies co-exist [36]; therefore, it is imperative to consider integrating zinc intervention strategies with existing, successful programs. Finally, as with any public health program, monitoring and evaluation is essential to ensure the intervention is appropriate and having the intended public health impact, in this case, improving zinc status.

13.6 Dietary Zinc and the Risk of Cancer: What Is the Evidence?

Globally, there are more than ten million new cancer cases each year, with cancer being the cause of approximately 12% of all deaths [88]. Thus, a large number of epidemiologic studies have been undertaken to identify potential risk factors for cancer, including trace elements. Although many dietary compounds have been suggested to contribute to the prevention of cancer, there is strong evidence to support the fact that zinc may be of particular importance in host defense against the initiation and progression of some cancers [34, 89, 90]. Zinc is known to be an essential component of DNA-binding proteins with zinc fingers, as well as copper/zinc superoxide dismutase and several proteins involved in DNA repair [91]. Thus, zinc plays an important role in transcription factor function and antioxidant defense. Subclinical zinc deficiencies can contribute to single- and double-strand DNA breaks and oxidative modifications to DNA, thus increasing the risk for cancer development [34, 90].

Remarkably, 10% of the US population consumes less than half the recommended dietary allowance for zinc [92] and many more are sub-clinically zinc deficient. The link between zinc deficiency and cancer has been established in cell culture, animal and human studies. Zinc deficiency causes oxidative DNA damage in cells [93], in animals fed a zinc-deficient diet [94] and in healthy men fed a zinc-depleted diet for 6 weeks [95]. In rats, dietary zinc deficiency causes an increased susceptibility to tumor development when exposed to carcinogenic compounds [34], and zinc deficiency has also been suggested to be a contributor to the development of esophageal [96, 97] and testicular [98] tumors in rats. In vitro, cell culture studies have also shown that zinc deficiency can lead to increased oxidative damage to testicular cell DNA [99], lung fibroblasts [100] and in neuronal cells [101].

In recent years, evidence has evolved indicating the involvement and importance of dietary zinc in the development of several cancers. Many potential effects of mild-to-moderate, or subclinical, zinc-deficiencies have been described in relation to different cancers. Mild-to-moderate dietary zinc-deficiencies potentially have systemic effects on the regulation of the immune system as well as

direct cellular effects resulting in dysregulation of gene expression, bioenergetics, metabolic pathways, signal transduction and cell invasion. Many reports have suggested that zinc is involved in cancer development and levels of zinc in serum and malignant tissues of patients with various types of cancer are abnormal [55, 96, 102, 103]. Zinc status is compromised in cancer patients compared with healthy controls [104, 105]. Zinc may directly affect tumor cells by regulating gene expression profiles and/or cell viability, both of which are mediated in part by tumor-induced changes in zinc transporter expression [106]. On the other hand, zinc may indirectly influence tumor cells by affecting processes within the cancer microenvironment, including immune responses – the functions and/or activity levels of immune cells that attack tumor cells are influenced by the intracellular zinc concentrations within those cells [55]. In both cases, zinc contributes to intracellular metal homeostasis and/or signal transduction in tumor and immune cells [107]. Unfortunately, relatively few established and consistent relationships have been identified concerning the role and mechanism of zinc effects in a specific cancer – the exception being prostate cancer.

Zinc appears to play an important role in maintaining prostate health – the prostate contains the highest concentration of zinc of all the soft tissues, but concentrations decrease significantly during prostate cancer [61, 90]. Multiple studies have associated a marked decrease in zinc content with prostate cancer [108–110], and have implicated changes in zinc accumulation in the development and progression of prostate malignancy [102, 111]. There also exists some evidence that increased dietary zinc is associated with a decrease in the incidence of prostate cancer [112]. The possible mechanisms include the effects of zinc on the inhibition of terminal oxidation, induction of mitochondrial apoptosis and suppression of NF κ B activity. Zinc may also play an important role in the maintenance of DNA integrity in normal prostate epithelial cells by modulating DNA repair and damage response proteins, especially p53 [90, 94]. However, high-dose supplementation of zinc may increase prostate cancer risk [113]. Currently, it is unknown why the prostate accumulates high zinc concentrations. However, this phenomenon may render the prostate sensitive to changes in zinc intake. It is possible that dietary zinc deficiency will increase an individual's risk for oxidative DNA damage in the prostate and prostate cancer. Thus, zinc requirements may be enhanced in prostate cancer patients and zinc-supplementation strategies may not only aid in the prevention of cancer, but could also play an important role in limiting its malignancy. In addition, recent findings support the role of zinc transporters as tumor suppressors in the prostate [102, 106]. More *in vivo* studies on the effects of zinc on prostate functions are necessary to more clearly delineate the interaction between zinc and prostate function. However, interpretation of any findings from diet-and-cancer clinical studies in humans is significantly limited by the lack of sensitive and specific zinc biomarkers and should be a priority area of research.

Zinc intakes and/or intracellular levels of zinc have shown a strong inverse correlation to growth and malignancy of prostate cancer. In the PCPT study (Prostate Cancer Prevention Trial), a prospective cohort study examining the 7-year incidence of symptomatic benign prostatic hyperplasia (BPH) in men, the usage of individual zinc supplements was associated with reduced prostate cancer risk and BHP [112]. While in the VITAL Study (VITamins And Lifestyle), long-term average intake of supplemental zinc was not associated with a reduced prostate cancer risk, but supplemental zinc was associated with reduced risk of advanced prostate cancer [114]. Thus, zinc concentration should be taken into account when designing anti-cancer experiments, as zinc is known to exhibit both physiological and pharmacological benefits. Recently, zinc acetate was injected directly into prostate tumors to reduce growth in a xenograft model of prostate cancer [115]. The zinc “treatments” halted the growth of the prostate cancer tumors and substantially extended the survival of the animals, whilst causing no detectable cytotoxicity to nonprostate tissues. These results suggest that both physiological and pharmacological zinc could potentially be used for prostate cancer prevention and therapy.

Overall, the literature highlights that the levels of zinc in sera and malignant tissues are abnormal in patients with various tumors, and that the relationship between tumor development and serum zinc levels appears to be complicated. Indeed, zinc levels are reduced in patients suffering from carcinomas of the liver, gallbladder, digestive tract, or prostate [102, 116], whereas breast cancer patients show decreased and elevated zinc levels in sera and malignant tissues, respectively. Given the fact that worldwide, breast and prostate cancer are common causes of death among women [117] and men [118] respectively, and the high number of zinc-deficient individuals, investigations to decipher the role of dietary zinc in these cancers are vital.

13.7 Could Zinc Fortification Improve Zinc Status?

The three main types of zinc status assessment that are considered include biochemical, dietary, and functional methods. Serum or plasma zinc concentration is considered the best available biomarker of the risk of zinc deficiency in populations [119]. Methods for collecting, processing, and analyzing samples for determining serum zinc concentration have been comprehensively reviewed [45, 120]. The prevalence of zinc deficiency should be expressed as the percentage of the population with serum zinc concentration below the specific lower cutoffs in relation to reference data for age, sex, time of day, and fasting status of the individuals examined [121, 122]. When the prevalence of low serum zinc concentration is greater than 20%, the risk of zinc deficiency is considered to be elevated and should be addressed through public health nutrition interventions to improve zinc status. This same indicator also can be used to assess the impact of an intervention program, by comparing the percentage of individuals with low serum zinc concentrations before and after initiation of the intervention.

Inadequate dietary intake of absorbable zinc is one of the major causes of zinc deficiency. Therefore, assessment of the adequacy of zinc intakes through the use of 24-h recalls, or weighed dietary records, is an important component in evaluating the risk of zinc deficiency in a population [119]. Dietary assessment of zinc status can be used to identify subpopulations that have an elevated risk of zinc deficiency and to characterize dietary patterns that contribute to inadequate zinc intakes, thus informing on the appropriate design of food-based interventions. The prevalence of the population with zinc intakes less than the EAR [45, 123] can be used as the specific indicator of the risk of zinc deficiency in the population. Assessment of the adequacy of zinc intakes should take into account dietary zinc bioavailability, preferably through quantification of the phytate:zinc molar ratio of the diet [124] or by using available equations to predict zinc absorption based on dietary zinc and phytate contents [74]. The risk of zinc deficiency is considered to be elevated and of public health concern when the prevalence of inadequate intakes is greater than 25%, in which case an intervention to increase dietary zinc intakes is recommended [119]. The change in prevalence of inadequate zinc intakes can be used to assess the impact and effective targeting of food-based interventions.

Although there are several adverse functional consequences of inadequate zinc intake, these outcomes are not specific to zinc deficiency. For example, the incidence of some types of infections can be reduced by providing supplemental zinc [120, 125], but the disease rates are more closely linked to the level of exposure to specific pathogens. Thus, a high incidence or prevalence of particular infections, such as diarrhea, may suggest that the population could benefit from interventions including zinc, but the illness rates would not be very useful in quantifying the extent of zinc deficiency in the population. Similarly, low height-for-age is not specific to zinc deficiency and could be attributable in part to maternal short stature, frequent infections, and other nutritional deficiencies. Thus, providing zinc alone should not be expected to fully reverse childhood stunting. Nevertheless, a

previous meta-analysis of randomized, controlled trials among prepubertal children found that the severity of stunting in the study populations predicted the response to zinc supplementation [126]. Thus, the percentage of children under 5 years of age with height-for-age z-score (HAZ) less than -2.0 SD with respect to the reference population [127] has been recommended as the best functional indicator to assess the likely risk of zinc deficiency in a population [119]. This risk is considered to be elevated and of public health concern when the prevalence of low height-for-age is greater than 20%, in which case nutrition intervention strategies should include a means to improve zinc status.

In order to increase zinc intakes, a multipronged approach, involving food fortification, biofortification, zinc fertilizers, and the use of enzymes (e.g., phytase) needs to be adopted. The following section will review these important strategies.

Food *fortification* is increasingly recognized as an effective approach to improve a population's micronutrient status [63]. Food fortification is defined as "the deliberate addition of one or more nutrients to particular foods so as to increase the intake of these micronutrients and correct or prevent a demonstrated deficiency and provide a health benefit" [61]. The WHO's dietary goal of fortification is defined as "the provision of most (97.5%) individuals in the population group(s) at greatest risk of deficiency with an adequate intake of specific micronutrients, without causing a risk of excessive intakes in these or other groups" [61]. Food fortification most often involves the addition of nutrients to food at the point of food processing or production; however, fortification may also occur at the community or household level [63]. The WHO distinguishes three possible approaches to food fortification: mass, targeted, and market driven fortification [61]. Mass fortification is the addition of micronutrients to foods consumed routinely by the general population. Common mass fortification vehicles include cereal flours, vegetable oils and fats, milk, and condiments. Targeted fortification is intended to reach a specific population subgroup that have an identified risk of deficiency, such as complementary foods for young children or rations for internally displaced populations, when normal food distribution channels have been disrupted. Finally, market driven fortification is fortification of processed foods, initiated by a food manufacturer [61, 66].

Food fortification, especially multiple micronutrient fortification, is often considered the most cost-effective approach to address deficiencies if the following conditions exist: appropriate carrier foods are available; the food industry can produce and distribute fortified carrier foods; and those subgroups identified as at risk of micronutrient deficiency have access to adequate amounts of these foods [63, 66]. Fortification may be considered a more appealing option than supplementation as it does not require the population to alter existing food beliefs and practices and therefore may result in less disruption to the health sector. Furthermore, since food fortification costs are supported by industry and the consumer, the cost burden to governments are usually low. Therefore, fortification programs have become more common in lower-income countries [63, 66].

Research indicates that zinc fortification programs can increase dietary zinc intake and total daily zinc absorption [63] with a plateau reached at higher levels of zinc intake. Research conducted in two different adult populations in Denmark and Sweden and in a third study among Peruvian children, it was shown that increasing zinc intakes by adding greater amounts of zinc to food yielded greater net zinc absorption, although the increments in total absorbed zinc decreased relative to the level of zinc fortification [63, 128].

Several zinc compounds are approved for human consumption and may be used as food fortificants, including the sulfate, chloride, gluconate, oxide, and stearate salts [61]. The preferred choices are zinc oxide or zinc sulfate, the two cheapest forms of zinc that are generally recognized as safe for human consumption [61, 63, 76]. Tracer studies of foods fortified with either zinc oxide or sulfate showed that there was no difference in zinc absorption by school children or adults when either compound was used to fortify common cereal staples. Studies conducted in Indonesian schoolchildren reported no differences in zinc absorption from zinc-fortified, refined-wheat

dumplings when the two zinc compounds were compared [129]. Finally, research among Mexican women also reported no differences in zinc absorbed from maize tortillas fortified with either form of zinc [130].

Biofortification refers to the breeding of staple crops for higher levels of vitamins and minerals that are essential for human nutrition and health [131]; this approach contrasts with industrial fortification efforts that focus on processed food items. Biofortification involves breeding staple food crops, such as rice, wheat, maize, and pearl millet both for higher yields and higher nutrient content [131–134]. This method has multiple advantages, including the fact that it capitalizes on the regular daily intake of a consistent amount of food staple by all family members, and, because staple foods predominate in the diets of the poor, this strategy implicitly targets low-income households [135]. Specifically, zinc biofortification could provide both a feasible means of reaching zinc-deficient populations in relatively remote, or rural areas, and it could deliver fortified foods to people with limited access to commercially marketed fortified foods that are more readily available in urban areas [135]. Breeding crops for higher zinc content is a goal of the HarvestPlus Biofortification Program [www.harvestplus.org/]. Research supported by HarvestPlus has determined the potential benefits of a zinc-biofortification program in India [136], where the calculated annual burden of zinc deficiency amounts to 2.8 million DALYs lost (2.7 million from mortality and 140,000 from morbidity), 70% of which occurs among infants. It is estimated that zinc biofortification of rice and wheat may reduce this burden by 20–51% and save 0.6–1.4 million DALYs each year, depending on the scenario. The cost for saving one DALY amounts to US\$0.73–7.31, which is very cost-effective by standards of the World Bank and the WHO, and is lower than that of most other micronutrient interventions. Not only may zinc biofortification save lives and prevent morbidity among millions of people, it may also help accommodate the need to economize and to allocate resources more efficiently. Recently, a zinc-biofortification study, conducted in Mexico [134], reported that absorption of zinc was greater from the zinc biofortified wheat than from control wheat when fed to adult women as their primary source of energy and nutrients. The authors reasoned that higher absorption would be maintained with moderate extraction of the grain. The results of their study confirmed that zinc absorption from the same quantities of wheat flour was greater from the zinc-biofortified wheat than from wheat with a more typical zinc concentration. Though substantial quantities of zinc were lost with moderate extraction (80%), absorption of zinc from the zinc-biofortified wheat remained significantly higher than that from the control wheat. Indeed, the quantity of zinc absorbed from zinc fortified 80%-extracted wheat was similar to that from the 95%-extracted wheat because of the simultaneous reduction in phytate. The findings are of practical interest because it indicates that the benefits of the zinc-biofortified wheat are not lost with a moderate degree of milling. Follow-up long-term feeding studies are needed to verify the efficacy of zinc-biofortified wheat.

Plant scientists recently announced they had built the foundation for a complete “catalog” for corn genes (i.e., the maize genome), with far-reaching implications for the food supply in developing countries [137]. Armed with more-precise genetic information, breeders potentially could now develop new maize varieties that withstand prolonged heat and drought, use nutrients such as nitrogen more efficiently, or pack more nutrition per kernel. And they could do it in far less time than it currently takes to develop new varieties.

Fortification of food grains such as wheat and maize have been subject to numerous studies, however until recently, little was known about biofortification of millet flours. Millets, being less expensive compared to cereals, are the staple mainly for the population below the poverty line. However, this population is also at higher risk for micronutrient deficiencies. In view of this, finger millet (*Eleusine coracana*), widely grown and commonly consumed in six countries (China, Ethiopia, India, the Niger, Nigeria and the former Soviet Union), has been explored as a vehicle for fortification with zinc [138]. Fortified finger millet flour, containing either zinc oxide or zinc stearate so as

to provide 50 mg zinc/kg flour, was examined for the bioaccessibility of the fortified mineral, as measured by an in vitro simulated gastrointestinal digestion procedure and storage stability. Addition of the zinc salts increased the bioaccessible zinc content by up to three times that of the unfortified flour. Inclusion of the chelator EDTA along with the fortified salt significantly enhanced the bioaccessibility of zinc from the fortified flours, the increase being three-fold. Both zinc oxide and zinc stearate were equally effective as fortificants, when used in combination with EDTA as the fortificant. The preparation of either traditional Indian foods like *roti* or dumplings from the fortified flours stored up to 60 days did not result in any significant compromise in the bioaccessible zinc content. Thus, this new study indicates that finger millet flour can also be effectively used as a vehicle for zinc fortification with reasonably good storage stability.

Further research and development activities for zinc-biofortified crops are ongoing [133], and should be available for testing and release as approved varieties within the next 5 years. A complementary tool to the breeding strategy for successful zinc biofortification of grains is the application of *zinc fertilizers* or zinc-enriched NPK fertilizers (nitrogen, phosphorus and potassium). Zinc deficiency in soils and plants is a global micronutrient deficiency problem reported in many countries [139, 140]. The regions with zinc deficient soils are also the regions where zinc deficiency in human beings is widespread, including China, Egypt, India, Iran, Pakistan and Turkey [45, 139-141]. Nearly 50% of the cereal-grown areas in the world have soils with low plant availability of zinc [142, 143]. As cereal crops represent a major source of minerals and protein in developing world, it is essential to have a short term approach to improve zinc concentration in the cereal grains. Convincing evidence about the role of zinc fertilizer strategy in improving grain zinc concentration in wheat has been obtained in field trials in the Middle East. Applying zinc fertilizers to wheat grown in fields in Turkey [144] and Iran [145] improved not only productivity, but also grain zinc concentration. Depending on the application method, zinc fertilizers increased grain zinc concentration three- to fourfold. More recently, scientists at the Indian Agricultural Research Institute in New Delhi, used zinc-enriched urea fertilizers in rice and wheat crops to significantly improve both grain zinc concentration, and grain yield [146]. Thus, in countries where zinc deficiency is both a public health issue and an important soil constraint to crop production, enriching widely applied fertilizers with zinc would be an excellent investment for improving grain zinc while contributing to increased crop production [141].

Modern genetic and molecular technologies provide a number of additional tools that can be utilized for the development of staple foods with a higher *zinc* content and improved bioavailability of this mineral. In cereal grains, most of the phosphate, zinc, iron and calcium are bound in phytate – considered the single most important antinutritional factor for the availability of micronutrients [147]. Phytate (myo-inositol hexakisphosphate) is the primary storage form of phosphorus in many plant tissues such as cereal grains and legumes commonly consumed in diets in the developing world. Phytate is primarily deposited together with protein in aleurone storage vacuoles [148]. In maize, the embryo and the scutellum are the primary depositories for phytate. During germination, inorganic phosphorus and micronutrients are released via the action of the hydrolytic enzyme phytase (myo-inositol hexakisphosphate phosphohydrolase). In the dry seeds and in the digestive tract of nonruminant animals including humans, there is little or no phytase activity [149]. Thus, in farm animals, the undigested phytate excreted in the manure contributes to the environmental phosphate load, a significant ecological concern. This phytate “problem” has attracted substantial interest in animal feed research [150, 151], and more recently, in human studies [152-156]. The depressing effect of phytate on zinc absorption may have impact in some groups, above all in children and women in developing countries who have low zinc intakes [157]. The phosphate groups in phytate are not bioavailable to humans due to lack of the digestive enzyme phytase, which is required to separate phosphorus from the phytate molecule [63]. Thus, there is a rationale for development of foods with improved mineral availability. A third strategy for improving zinc intakes is to improve

the mineral nutrition of seeds by dephytinizing these foods with the addition of microbial *phytase*. Phytases are produced by a number of microorganisms and in most cases are secreted proteins [158]. The phytases produced by *Aspergillus niger* var. *ficuum* are the most intensively studied. The *PhyA* gene encodes a phytase with pH optima between 2.5 and 5.0. Addition of *A. niger* phytase to feed has been shown to enhance the release of phosphate from phytate, to reduce the phosphate excretion, and to improve the bioavailability of zinc bound to phytate [151, 159–161]. Phytase addition to animal feed is currently widely implemented in The Netherlands, India, and the United States. Recently (November 2009), phytase-producing corn was approved for commercial sale in China.

Phytases with varying activity are present in cereals and enzymatic hydrolysis of phytate occurs in food processes such as fermentation, malting and soaking [131]. When the dietary content of inositol phosphates is reduced, absorption of minerals, like zinc, iron and calcium increases [152, 153, 162–164]. Dietary phytase from untreated cereals seems to be an important factor for phytate hydrolysis in humans, whereas intestinal phytases like *Bifidobacterium pseudocatenulatum* appears to play a significant role in phytate hydrolysis in man [165]. Hydrothermal treatment and malting of whole grains to reduce phytate levels are processes that are very well suited to be used industrially – recently, Fredlund and colleagues [166] reported on the influence of different barley products on zinc and calcium absorption. Whole barley kernels were hydrothermally processed in a pilot plant at conditions previously shown to degrade phytate to low levels or malted to increase phytase activity in the product. Single meals based on these barley products, labeled with radionuclides of zinc and calcium, were served to healthy volunteers and whole body retention was measured. The authors report that zinc, but not calcium, absorption was significantly improved in breakfast meals following hydrothermal treatment or malting of the barley. This means that improved zinc bioavailability can occur either by reducing phytate content in the diet, or by increasing dietary phytase activity.

The case for enriching staples such as wheat, millet, or flour with micronutrients like zinc is compelling [36]. But, is the cost of doing so preventative? It is estimated that a woman can receive her entire yearly requirement of zinc through food fortification at an annual cost of US\$0.006–\$0.013 [63]. Providing therapeutic zinc supplements and vitamin A capsules for under 2-year-olds in the developing world would cost a total of US\$60.4 million annually, with benefits worth more than \$1 billion yearly [14]. Adding iron to food costs less than US\$0.10 a head/year, and the economic return (in productivity) is high – for an annual cost of \$286 million, the corresponding benefits are \$2.7 billion. So why, for example, is all flour not fortified with zinc? Partly, for lack of expertise in poor countries [36]. The problem also reflects disarray among donors, aid-agencies and non-governmental organizations (NGOs). The time is now ripe to correct this.

As nutrition scientists, we must recognize that farmers won't adopt biofortified crops because they're high in zinc; they'll adopt them because they're disease-resistant, can withstand drought, and/or because they're more profitable. If available, farmers would plant biofortified millet, or transgenic maize, if they had desirable traits (e.g., they were rust-resistant, or drought-tolerant) thus allowing the zinc to get into the food system much like we put fluoride in the water system. It would be invisible, but it serves to increase zinc intakes.

In summary, the adequate intake of nutritious foods is a prerequisite to achieving and maintaining good health and well-being. Millions of people worldwide, however, are unable to achieve this. In 2007, it was estimated that as many as 852 million people do not eat sufficient food to meet their energy requirements and are consequently undernourished [136]. Many more people suffer from “hidden hunger”: about 2.7 billion are zinc deficient [167], 150 million are vitamin-A-deficient, almost two billion are iodine-deficient, and between four and five billion are iron-deficient [168]. This imbalance between “overt” and “hidden” hunger is underlined in the report of the United Nations Millennium Project's Task Force on Hunger [169], where the authors call for further investments in agriculture and confirm the major role that agricultural research has played in reducing hunger.

Implementation of the multiple approaches described here to increasing zinc intakes would assist in correcting this imbalance.

Depending on the context and the scenario, and subject to the caveats noted above, biofortification appears to be more cost-effective than supplementation, or fortification [30]. In South Asia and sub-Saharan Africa, biofortification enjoys a clear advantage. This is reasonable, given both that the populations in these regions are largely rural, and that seed distribution systems function relatively well in that part of the world. The challenges to implementing biofortification should not be underestimated. Attention needs to be paid to community awareness, dissemination, and behavior change communication, features common to health and nutrition programs, but foreign to most previous agricultural interventions.

It should be noted that strategies to improve micronutrient status, including biofortification and supplementation, have some limitations and should not replace food-based strategies. Moreover, food-based strategies to improve dietary quality in general are consistent with the global need to lower the risk of chronic disease and the “hidden hunger.” The pay-offs from linking agriculture and public health approaches, which often function independently, can be very high [30]. In summary, this review advocates implementation of biofortification programs as a viable strategy, and an important complement to the existing set of interventions to combat specific micronutrient deficiencies, including zinc.

13.8 Conclusions

This paper has assessed recent advances in knowledge of zinc nutrition, human health benefits and the link between moderate zinc deficiency and some cancers. Evidence from randomized controlled trials of zinc supplementation provides a strong basis for the importance of zinc in reducing growth stunting and the prevalence of diarrhea, pneumonia, and childhood mortality [170]. Low dietary zinc intake could also lead to a loss of intracellular zinc levels in the prostate, which could have deleterious effects with respect to prostate cancer development [90]. Potential multipronged approaches available for improving population zinc status include (1) fortification of staple foods, (2) biofortification of crops at the national level or of special foods targeted at specific subpopulations, (3) strategies to modify diets to increase the amount of bioavailable zinc such as the use of zinc fertilizers in nutrient-deficient soils, and (4) the reduction of phytate in cereals [170]. Evidence for the impact of such food based strategies on improving zinc status is still limited; therefore, well-designed and controlled intervention studies are needed to move these strategies forward. Providing supplemental zinc to young children in at-risk populations on a routine basis and/or for the treatment of diarrhea is expected to have a high impact on zinc and health status, particularly among populations with high rates of low-birth-weight or small-for-gestational-age infants, stunting, diarrhea, or lower respiratory tract infections. The WHO/UNICEF recommendation [35] for providing supplemental zinc in conjunction with oral rehydration is advised for the treatment of acute diarrhea. For preventive supplementation, both clinical and operational research is needed to determine optimal doses and dosing schedules (daily vs. weekly supplementation). Currently there are no formal recommendations for preventive programs. All methods should be considered when formulating zinc intervention strategies.

As the fifth top ranking factor contributing to the burden of disease in the developing world, zinc deficiency is increasingly acknowledged as one of the most serious public health challenges [167]. The average global prevalence of zinc deficiency was estimated at 31% with the most severe burden of disease for diarrhea and pneumonia due to zinc deficiency found in South Asia and sub-Saharan Africa [17]. Meta-analysis findings have linked zinc deficiency to the morbidity and mortality of children younger than 5 years through significantly increased risk of diarrhea, pneumonia and malaria.

Public action to remedy and prevent outbreaks of micronutrient deficiency disorders is not only critical in emergencies, it represents the fulfillment of one of Amartya Sen's "moral rights of the hungry" [171]. Entitlements are secured when hungry people establish ownership over an adequate amount of food, or where their moral right to food is translated into a "practical right." Humanitarian action represents precisely that – a practical enforcement of the moral right not to die of a lack of food. The humanitarian imperative demands that relief be provided unconditionally to those who are suffering, whoever and wherever they are [172].

Agronomic approaches such as application of zinc-containing fertilizers appear to be a rapid and simple solution to the zinc-deficiency "problem." Combination of breeding and fertilizer strategies is an excellent complementary approach to alleviate zinc-deficiency related problems in human nutrition. New research programs are needed to develop (or improve) zinc application methods in terms of form, dose, and application time of zinc fertilizers. It is important to highlight that use of zinc-biofortification approach to improve grain zinc concentrations might be limited in various developing countries because resource-poor farmers, especially in sub-Saharan Africa, who cannot afford application of mineral fertilizers, especially micronutrient fertilizers. Under such situations plant breeding becomes a high priority approach to the problem.

That said, enforcing this right to micronutrient-enriched foods in the developing world increasingly means the delivery under extremely difficult circumstances not simply of the right quantity of commodities, but the right quality of foods. Addressing micronutrient and vitamin deficiencies is a core aspect of humanitarian relief and as such represents a commitment by the international community to uphold the moral right of the hungry not just to sustenance but to something farther reaching – nutrition.

13.9 Summary Points

- (a) Zinc supplementation is associated with decreased oxidative stress and improved immune function, which may be among the possible mechanisms for its cancer preventive activity. Preclinical and clinical studies are needed to investigate modulation of genetic and epigenetic pathways of carcinogenesis by dietary zinc.
- (b) Zinc deficiency has been shown to upregulate expression of p53, the tumor suppressor protein. Zinc deficiency also impairs the DNA binding abilities of p53, NF κ B, and AP-1 transcription factors. These studies suggest that a decrease in cellular zinc alone causes DNA damage and impairs DNA damage-response mechanisms, resulting in a loss of DNA integrity and increasing the potential for cancer risk.
- (c) Governments, the food industry and the research community must develop successful programs to increase global zinc intakes through a combination of supplementation, dietary diversification, fortification, biofortification, zinc-fertilizers, phytate reduction and/or utilizing enzymes like phytase. A successful biofortification program requires representatives of these groups for planning, designing, promoting, regulating and supervising biofortification programs.
- (d) The food industry should help to define feasible, affordable fortification strategies, identify appropriate food vehicles and fortificants, develop quality assurance systems and implement educational campaigns to reach target populations.
- (e) Scientific community members should determine the country-specific prevalence of zinc deficiency, the sensory acceptability and efficacy of the chosen zinc compound and food products, develop and implement educational campaigns to reach target populations, and verify the overall effectiveness of zinc-supplementation program(s).

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Chapter 14

Multifaceted Therapeutic Value of Roselle (*Hibiscus sabdariffa* L. – Malvaceae)

Armando González-Stuart

Key Points

- Approximately two-thirds of the world's population rely on a great variety of plants used in various systems of traditional medicine for the treatment of diverse diseases and ailments
- Roselle (*Hibiscus sabdariffa* L.), also known as hibiscus or “sour tea,” is a tropical plant which is used throughout the world as a source of nutritious sustenance to humans, but which can also possess important therapeutic value.
- Roselle calyces are used in the traditional medicine of various countries to treat a wide variety of diseases.
- Roselle extracts are employed in various countries for the treatment of several diseases and ailments, including type 2 diabetes, high blood pressure, hypercholesterolemia, liver diseases, and certain types of cancer.
- The in vitro and in vivo pharmacological actions of Roselle extracts possess strong antioxidant activity which can have various therapeutic applications against chronic and or degenerative diseases.

Keywords Antioxidants • Cancer • Obesity • Plants • Roselle

14.1 Introduction

According to the World Health Organization (WHO), approximately 80% of the world's population relies on a great variety of plants used in various systems of traditional medicine for the treatment of diverse diseases and ailments [1].

A wide variety of plants used throughout the world offer not only nutritious sustenance to humans and animals, but can also possess therapeutic value. Roselle (*H. sabdariffa* L. – Malvaceae), is also known by a variety of names in English, Spanish, and Arabic, such as Hibiscus, African mallow, Jamaica Sorrel, Red Sorrel, Sour tea, *Flor de Jamaica*, *Jamaica*, *Acedera de Guinea*, and *Karkade* [2].

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Roselle is thought to be native to West Africa, but is now grown worldwide in tropical areas [3]. The plant was probably introduced to Jamaica by African slaves and reached Mexico during the Spanish colonial period [4]. Currently, Roselle is cultivated for food, as well as medicine in Asia, Africa, and various countries of tropical America [5, 6].

14.2 Use of Roselle Flowers (Calyces) in Mexican Traditional Medicine

“Flor de Jamaica” (Roselle flower) is a very popular food and medicinal plant in Mexico, as well as among the Mexican American population in the Southwestern United States, and can be found in various markets and grocery stores in both countries [7, 8]. Currently, the largest producers of hibiscus in Mexico are the states of Campeche, Colima Guerrero, and Oaxaca [4].

The flowers can be chopped and added to salads, as well as boiled to make sauces, jams or jellies. The flowers are dried at low temperatures and then boiled to make hot teas, or used as a cold beverage and sweetened with sugar or mix with ginger, rum or wine. It is one of the most popular refreshing drinks consumed in Mexico, especially during the hot summer months [4–7].

Roselle flowers are used in traditional medicine due to its laxative effects, intestinal and uterine muscle antispasmodic activity, hypertensive effects, anthelmintic effects, as well as for the treatment of upper respiratory problems, for dissolving phlegm, as an anti-inflammatory for the gastric mucous membranes, and because of its antibacterial activity in vitro [7, 9, 10].

The calyces (sepals) are used in Mexican and other systems of traditional medicine to lower blood pressure, eliminate kidney stones, as a mild laxative, to treat dysentery and fevers, inflammation of the gums (gingivitis), and as a general tonic to enhance the body’s defense (immune) systems [11].

In the southeastern Mexican state of Chiapas, hibiscus flowers are taken as a tea to treat stomach aches and in the southwestern state of Jalisco, a beverage made from the flowers is taken to relieve kidney problems [4].

In Northwestern Mexico (Sonora), the bark, roots and flowers of the plant are used externally as a wash to treat eye infections, as well as skin sores and wounds [7].

The sepals (calyces) are the parts most used for food and herbal remedies [7, 10], although the roots and seeds also have medicinal properties, as well. The root is considered to have laxative action [6, 11] and the oil extracted from the plant’s seeds has an inhibitory effect on certain fungi and bacteria in vitro [12].

14.3 Therapeutic Value of Roselle’s Bioactive Compounds

The active ingredients in the flowers are antioxidants such as flavonoids and polyphenolic compounds, including proanthocyanidins. These compounds possess antioxidant, antipyretic, analgesic, and spasmolytic activities [13–15]. The flowers also contain polysaccharides and high concentrations of simple organic acids such as citric and malic acids. Nutritionally, the flowers are a good source of minerals, such as calcium and iron, as well as vitamins including niacin, riboflavin, and especially vitamin C [5, 15]. Oil extracted from the plant’s seeds has been shown to have an inhibitory effect on certain bacteria and fungi in vitro [12].

In clinical studies with rats and rabbits, the calyx extracts showed antihypercholesterolaemic, antinociceptive, and antipyretic activities. Surprisingly, no anti-inflammatory activities were noted in this experiment. In both rats and human subjects, a strong antihypertensive action has been

demonstrated. In clinical studies with healthy men, consumption of Roselle extracts has resulted in significant decreases in the urinary concentrations of various compounds, including creatinine, uric acid, sodium, and potassium, among others [12].

A study examined the effect of a Roselle calyx extract (RCE) on the physico-chemical properties, sensory attributes, texture and microbial analysis of a beneficial bacterium (*Lactobacillus casei*) incorporated in probiotic yogurt after manufacturing and during storage. The addition of the RCE into the probiotic yogurt resulted in an improvement of its antioxidant properties, as well as organoleptic qualities, and decreased the exudation of whey proteins (*syneresis*). The results demonstrated that RCE has beneficial effects on the quality of *L. casei* incorporated probiotic yogurt [16].

14.4 Effect on Hematological Parameters

A study evaluated the effects of a Roselle calyx extract on certain hematological parameters in laboratory rats, with the objective of determining its medicinal usefulness in the treatment of anemia. An aqueous extract was orally administered in different doses (200–1,000 mg/kg body wt.) by means of an intraesophageal cannula to four groups (six rats per group), for 2 weeks. After being administered for 14 days, the extract showed significant elevations in hematocrit and hemoglobin in the groups of rats given doses of 200 and 400 mg/kg, respectively, while the groups given high doses revealed significant reductions in the amounts of hematocrit but not in hemoglobin. The researchers suggested that the aqueous extract employed in this experiment had beneficial effects on erythrocytes at low doses (200–400 mg/kg), but these effects may not be present at higher doses. Further studies should be made in order to ascertain the extract's long-term effects, before a recommendation could be made [17].

A study employed an aqueous Roselle extract rich in anthocyanins, hydroxycitric acid, and chlorogenic acids. The researchers found that the extract afforded an effective protection of cultured peripheral blood mononuclear cells from cellular death induced by hydrogen peroxide, as well as played an important role in the production of inflammatory cytokines. This extract promoted the production of IL-6 and IL-8 in vitro and decreased the concentration of MCP-1 in supernatants in a dose-dependent manner. Ingestion of an acute dose of the extract (10 g) was well tolerated by human subjects and decreased plasma MCP-1 concentrations in a significant manner, without further effects on other cytokines. The authors concluded that this effect was not due to a concomitant increase in the antioxidant capacity of plasma. Instead, its probable mechanisms of action may involve a direct inhibition of inflammatory and/or metabolic pathways responsible for MCP-1 production. The results demonstrated that this plant could be considered a valuable option for the treatment of various chronic and inflammatory diseases [18].

14.5 Antioxidant Effects

The antioxidant potential of Roselle extracts was studied, by analyzing different parts of the plant (seeds, stems, leaves, and sepals) with respect to their water-soluble antioxidant capacity, lipid-soluble antioxidant capacity, and content of tocopherols. The results showed that the seeds are a good source of lipid-soluble antioxidants, particularly gamma-tocopherol. Total tocopherols were found to be present at concentrations of 2,000 mg/kg, including alpha-tocopherol (25%), gamma-tocopherol (74.5%), and delta-tocopherol (0.5%). The authors concluded that the seed oil may also have important industrial applications [19].

A study assessed the antioxidant activity of dried Roselle calyces. The preliminary study demonstrated the anthocyanin pigments present in the calyces were able to inactivate the free radicals produced by 1,1-diphenyl-2-picrylhydrazyl. Roselle's antioxidant activity was further assessed using the model of *tert*-butyl hydroperoxide (*t*-BHP)-induced cytotoxicity in primary hepatocytes and hepatotoxicity in rats. A histopathological evaluation of the liver revealed that RA's reduced the incidence of hepatic lesions including inflammation, leucocyte infiltration, and necrosis induced by *t*-BHP. In conclusion, the authors speculated that the RA's could play a role in the prevention of oxidative damage in living systems [20].

A study evaluated the dietary fiber content, the associated polyphenols, as well as the antioxidant capacity of Roselle calyces (RC), as well as the soft drink prepared from them (popularly known as "agua de Jamaica"), with regard to its contribution of fiber to the Mexican diet. RC contained dietary fiber as its major constituent (33.9%) and was also rich in phenolic compounds (6.13%). Soluble dietary fiber and extractable polyphenols contained in RC were also included in the drink, the latter showing important antioxidant activity. The results demonstrated that the RC beverage intake in the Mexican diet may contribute approximately 166 mg of dietary fiber, as well as 165 mg of antioxidant polyphenols per serving, respectively. The researchers concluded that the soft drink made from Roselle possesses very important health benefits [21].

14.6 Hypoglycemic Effects of Roselle Extracts

A study examined Roselle's potential antiatherosclerotic effects and investigated whether the polyphenolic isolate obtained from Roselle calyces (RCI) could protect high-glucose-treated vascular smooth muscle cell and its purported transduction signals. The results showed that RCI dose- and time-dependently reduced the high-glucose-stimulated cell proliferation and migration. RCI suppressed the proliferating cell nuclear antigen (PCNA) level and matrix metalloproteinase (MMP)-2 activation. Additionally, the expressions of connective tissue growth factor (CTGF) and receptor of advanced glycation end product augmented by high glucose were significantly suppressed by RCI. For these reasons, the authors of the study concluded that RCI may have therapeutic value for the treatment of diabetes [22].

A study with laboratory animals assessed the effects of a Roselle polyphenol extract (RPE) on streptozotocin (STZ) induced diabetic nephropathy. The results of the study showed that RPE reduced kidney mass induced by STZ significantly, as well as improved the hydropic change of renal proximal convoluted tubules in rats. Additionally, the RPE also significantly reduced serum triglyceride, total cholesterol, and LDL in STZ induced rats [23].

14.7 Antihypertensive and Antilipidemic Effects

A review of past clinical trials regarding the effectiveness and safety of Roselle for the treatment of hypertension was undertaken by Wahabi et al. (2009), in order to evaluate the evidence. Every randomized controlled trial that had examined Roselle's effectiveness and safety in the treatment of primary hypertension in adults was included. Four trials, with a total of 390 patients, met the reviewers' inclusion criteria. Two studies compared Roselle to black tea; one study compared it to captopril® and the other compared it to lisinopril®. The results of these studies showed that Roselle flowers had greater blood pressure reduction than tea but less than the ACE-inhibitors. However, all

studies, except one, were short term and of poor quality with a Jadad scoring of <3 , which did not meet international standards. The reviewers concluded that the four randomized, controlled studies did not provide reliable evidence to support recommending Roselle for the treatment of adult primary hypertension [24].

A clinical study was undertaken in order to isolate and characterize the constituents responsible of the angiotensin-converting enzyme (ACE) activity of an aqueous extract made from Roselle calyces. Various anthocyanins including delphinidin-3-*O*-sambubioside and cyanidin-3-*O*-sambubioside were isolated by bioassay-guided purification. Kinetic determinations suggested that these natural antioxidant compounds inhibit the enzyme activity by competing with the substrate for the active site. The researchers concluded that the activity of Roselle's antioxidant compounds is concordant with its use as an antihypertensive agent in traditional medicine [25].

A randomized, controlled, and double-blind clinical trial was undertaken to compare the therapeutic effectiveness, tolerability, and safety, as well as the effect on serum electrolytes and the ACE inhibiting effect of a herbal medicinal product obtained from the dried extract of Roselle calyces (RCE) with those of lisinopril®, on patients with hypertension. The study included men and women 25–61 years of age, previously diagnosed with stage I or II hypertension. The subjects were treated daily for a period of 4 weeks with the RCE, 250 mg of total anthocyanins per dose (experimental group), or 10 mg of lisinopril (control group). The experimental group also showed a therapeutic effectiveness of 65.12% as well as a very high level of tolerability and safety (100%). However, BP reductions and therapeutic effectiveness were lower than those obtained with lisinopril ($p < 0.05$). The authors concluded that RCE demonstrated significant antihypertensive effects, along with a wide margin of tolerability and safety. Additionally, RCE significantly reduced plasma ACE activity and demonstrated a tendency to reduce serum sodium concentrations without modifying potassium levels [26].

A clinical study found that Roselle anthocyanins (RAs) could inhibit the serum-stimulated proliferation of smooth muscle cell (SMC) and result in cell apoptosis. The apoptotic effect was dose-dependent. The findings suggest that the mechanisms of the inhibitory effect of RAs on atherosclerosis could be due to inhibition of the proliferation of SMC. The study demonstrated that RAs have a strong potential to induce SMC cell apoptosis via p38 and p53 pathway. Because of this, the rate of atherosclerotic formation is slowed down, and the progress of this degenerative condition is diminished [27].

The antihypertensive and hypolipidemic effects of aqueous extracts made from Roselle (RE) have been demonstrated in both clinical trials and in vivo experiments. For this reason, a study evaluated the effects of a Roselle extract powder (REP) and a recognized preventive treatment (diet) on the lipid profiles of human subjects with and without metabolic syndrome (MeSy). A dose of 100 mg REP capsules was given *per os* daily during 1 month. A preventive diet was given to the control group. Various parameters including total cholesterol, LDL-c, HDL-c, VLDL-c, triglycerides, glucose, urea, creatinine, AST, and ALT levels in the blood were determined in all subjects before and after treatment. The MeSy patients treated with REP showed significantly reduced glucose and total cholesterol levels, increased HDL-c levels, and an improved TAG/HDL-c ratio, a marker of insulin resistance (*t*-test, $p < 0.05$). Additionally, a triglyceride-lowering effect was observed in MeSy patients treated with REP plus diet, as well as in subjects without MeSy, treated with REP. In addition to the well documented hypotensive effects of Roselle, the authors of the study suggested the use of REP in dyslipidemic patients suffering from MeSy [28].

Roselle (RE) has been shown in clinical trials to decrease plasma lipid levels as well as reduce hepatic lesions. A study evaluated a Roselle extract (RE) for its hypolipidemic effect and its putative protective mechanism on hepatic tissue. The RE showed more potency to decrease plasma cholesterol and LDL cholesterol than a RE crude extract. Additionally, it increased HDL cholesterol in a dose dependent manner. It also decreased the lipid content of hepatocytes by means of activating

AMPK and reducing SREBP-1, thus inhibiting the enzymatic expression of fatty acid synthase and HMG-CoA reductase. The authors concluded that RE should be further studied as a potential adjunctive for hepatic lipid control and hypolipidemic therapy [29].

The effect of a Roselle calyx extract (RCE) on fat absorption/excretion and body weight in rats was investigated. The animals were fed with either a basal diet (SDC = Control diet) or the same diet supplemented with RCE at 5%, 10%, and 15%. Only the 5% diet did not show significant increases in weight, food consumption, and efficiency compared to the control. The opposite occurred in RCE at 15% group which showed a significant decrease for these three parameters. The responses for the 10% and 15% RCE diets were similar, except for food intake. In both the control and RCE at 5% groups, no body weight loss was observed, but in the RCE group, a significantly greater amount of fatty acids was found in the feces. This study showed that components of RCE extract at the intermediate and greater concentrations used in this experiment could be considered as potential agents for the treatment of obesity [30].

The antioxidant and antihyperlipidemic activities of extracts obtained from Roselle leaves and calyces were evaluated by assessing their in vitro inhibitory activity on lipid peroxidation and in vivo effects on cholesterol-induced hyperlipidemia in cholesterol-induced hyperlipidemic rats. The most significant antioxidant activity was demonstrated by a dried calyx ethanol extract, followed by the leaf ethanol extract, followed by a hydrous leaf extract. Also, significant antihyperlipidemic activity was demonstrated by the calyx ethanol extract, followed by the leaf ethanol extract. The results of this study showed that rats given the Roselle extracts *per os* showed a decrease in granular degeneration originated by cholesterol feedings. This study suggests that the Roselle ethanol extracts obtained from the plant's calyces and leaves, contain antioxidant compounds, such as polyphenols and flavanols, which also possess important antihyperlipidemic effects [31].

An in vitro study assessed the antioxidant effects of an aqueous extracts from the dried Roselle calyces using rat low-density lipoprotein (LDL). The dried calyx extracts showed strong antioxidant activity. The inhibitory effect of the extracts on LDL oxidation was dose-dependent at concentrations ranging from 0.1 to 5 mg/mL. Additionally, 5 mg/mL of the Roselle extract inhibited TBARS-formation with greater potency than 100 mM of vitamin E. The authors concluded that Roselle extracts possess significant antioxidant properties in vitro [32].

A clinical study evaluated the hypolipidemic effects of Roselle tea in patients with type 2 diabetes and compared them with those of black tea (*Camellia sinensis* – Theaceae). A randomized controlled clinical trial was undertaken with 60 type 2 diabetic patients, who were randomly assigned to two groups: Roselle tea (RT) and black tea (BT). The patients drank RT or BT two times a day for a period of 1 month. Fasting blood samples were taken at the beginning and at the end of the study in order to evaluate levels of lipids, lipoproteins, and apoproteins. In the RT group, the mean of high-density lipoprotein-cholesterol (HDLc) increased significantly at the end of the study, whereas changes in apolipoprotein-A1, and lipoprotein (a) were not found to be significant. Additionally, there was a significant decrease in the mean of total cholesterol, low density lipoprotein-cholesterol, triglycerides, and Apo-B100. In the BT group, only HDLc showed significant change at the end of the study. The researchers concluded that RT had a significant beneficial effect on blood lipid profile in patients with type 2 diabetes [33].

A clinical study examined the antihypertensive effects of Roselle tea (RT) in human subjects. Sixty-five pre- and mildly hypertensive adults, 30–70 years old, and currently not taking blood pressure (BP) lowering medications, participated in a double-blind, placebo-controlled clinical trial. The experimental group drank three 240-mL servings per day of Roselle tea, while the control group drank a placebo beverage during 6 weeks. At 6 weeks, Roselle tea lowered systolic BP (SBP) compared with placebo (-7.2 ± 11.4 vs -1.3 ± 10.0 mmHg). Participants with higher SBP at baseline showed a greater response to the Roselle tea for SBP change. The results of this study showed that daily consumption of RT lowered BP in pre- and mildly hypertensive adults [34].

A randomized controlled clinical trial was undertaken in order to compare the antihypertensive effectiveness and tolerability of a standardized extract made from Roselle calyces with the pharmaceutical known as captopril®. Seventy-five patients 30–80 years old, previously diagnosed with hypertension, but without antihypertensive treatment for at least 1 month before the study were included in the trial. One group was given a tea prepared with 10 g of Roselle dry calyx (RT) in 0.51 water (9.6 mg anthocyanins content), taken daily before breakfast. The other group was given captopril® 25 mg twice a day, for 4 weeks. The results demonstrated that RT was able to decrease the systolic blood pressure (BP) from 139.05 to 123.73 mmHg and the diastolic BP from 90.81 to 79.52 mmHg. Upon terminating the study, no significant differences were seen between BP in both treatment groups. The rates of therapeutic effectiveness were 0.7895 and 0.8438 with RT and captopril®, respectively and both treatments were very well tolerated. The data from this study confirm that the RT extract, standardized on 9.6 mg of total anthocyanins, and captopril® 50 mg/day, did not show significant differences relative to hypotensive effect, antihypertensive effectiveness, or tolerability [35].

A clinical study assessing the effect of Roselle on hypertension was carried out in patients with moderate hypertension, who were randomly assigned to an experimental group taking Roselle and control group, respectively. Systolic and diastolic blood pressures were measured in both groups before and 15 days after the intervention. Statistical findings showed an 11.2% lowering of the systolic blood pressure and a 10.7% decrease of diastolic pressure in the Roselle group 12 days after beginning the treatment, when compared to day one of the treatment. The difference between the systolic blood pressures of the two groups was significant, as was the difference of the diastolic pressures, in favor of the group taking Roselle. The results of this study corroborate those of previous in vitro studies concerning the antihypertensive effects of Roselle [36].

A study was designed to evaluate the efficacy of an aqueous extract of Roselle calyx (RCE) in two forms of experimental hypertension in rats: salt-induced and L-NAME (*N*(omega)-l-arginine methyl ester)-induced and in normotensive controls. The blood pressure and heart rate were lowered in a dose-dependent manner in both the hypertensive and normotensive rats after intravenous injection of 1–125 mg/kg of RCE. These data suggest this plant possesses antihypertensive, hypotensive, as well as negative chronotropic effects [37].

14.8 Effects of Roselle on Weight Loss and Obesity

A clinical study evaluated whether a standardized aqueous Roselle extract (SRE) exerted an effect on body weight in an obese animal model induced by the administration of monosodium glutamate (MSG). The SRE, containing 33.64 mg of total anthocyanins per 120 mg of extract, was given orally at a dose of 120 mg/kg/day for 60 days to healthy and obese mice. The administration of SRE significantly reduced body weight gain in obese mice and increased liquid intake in both healthy and obese mice. No mortality was recorded in the group receiving the SRE. Triglyceride and cholesterol levels showed a nonsignificant reduction in the group treated with SRE. The results of this study validate the popular belief in Mexico that Roselle possesses antiobesity properties [38].

14.9 Potential Chemopreventive Effects Against Cancer

A clinical study in Taiwan examined whether Roselle extracts affected the apoptosis (programmed cell death) of cancer cells. The researchers demonstrated that the Roselle extract induced cytotoxicity and apoptosis of cancerous cells in a concentration-dependent manner. The conclusion

of this study was that Roselle extracts could be developed as a chemopreventive agent for certain types of cancer [39].

According to in vivo and in vitro studies regarding the antioxidant effects of polyphenolic compounds extracted from *H. sabdariffa*, the authors found that the extract possessed significant anti-inflammatory action both in vitro as well as in vivo [40].

A study of the antioxidant effects of anthocyanins extracted from *H. sabdariffa* demonstrated antioxidant activity and liver protection and were evaluated as to their effects upon human cancer cells. The result showed that the antioxidant compounds contained in this plant could cause apoptosis in cancer cells, especially in HL-60 cells [41].

Protocatechuic acid (PCA) is a phenolic compound isolated from dried Roselle flowers, which has demonstrated antioxidant and antitumor promotion effects in various clinical trials. PCA was evaluated for its ability to inhibit the 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-induced promotion in skin tumors of female CD-1 mice. The results of this study demonstrated that PCA possesses potential as a cancer chemopreventive agent against tumor promotion [42].

A study of the effects of PCA demonstrated its protective effects against cytotoxicity and genotoxicity of hepatocytes induced by *tert*-butylhydroperoxide (*t*-BHP). The results showed that PCA demonstrated protective effects against cytotoxicity and genotoxicity of hepatocytes induced by *t*-BHP. The authors proposed that the possible mechanisms of PCA's protective effect could be related to its property of scavenging free radicals [43].

A study was undertaken in order to determine the in vitro effects of phenolic compounds present in Roselle aqueous, ethyl acetate, and chloroform extracts against mutagenicity of 1-nitropyrene (1-NP). Additionally, the antiproliferative effect of these extracts was also assessed. Inhibition of cell proliferation and DNA fragmentation were tested on transformed human HeLa cells. The aqueous extract contained 22.27–2.52 mg of protocatechuic acid (PCA), which were found to inhibit the mutagenicity of 1-NP in a dose-dependent manner, as well as on HeLa cells. The results suggest that Roselle extracts have antimutagenic activity against 1-NP and decrease the proliferation of HeLa cells, possibly due to their content of phenolic compounds [44].

A study found *Hibiscus* PCA inhibited the survival of human promyelocytic leukemia HL-60 cells in a concentration- and time-dependent manner. The study showed that after a 9-h treatment with *Hibiscus* PCA (2 mM), HL-60 cells underwent internucleosomal DNA fragmentation and morphological changes characteristic of apoptosis. The data from this study suggest that *Hibiscus* PCA is an apoptosis inducer in human leukemia cells [45].

14.10 Hepatoprotective Effects

The effect an aqueous extract of the dried calyx of Roselle (RE), as well as of natural antioxidant pigments (anthocyanins) contained in the sepals (calyx), on liver toxicity induced by the drug paracetamol (also known as acetaminophen) in rats. The aqueous extract was given to the rats instead of drinking water for 2–4 consecutive weeks, and the anthocyanins were given orally at doses of 50, 100, and 200 mg/kg for a period of 5 days. Paracetamol was given orally at a dose of 700 mg/kg to induce liver toxicity at the end of the treatments, along with the aqueous extract and anthocyanins. The RE was given from 2 to 4 weeks, but only after 4 weeks did the extract significantly improve some of the liver function tests evaluated. At a dose of 200 mg/kg, the RE restored the hepatic tissue and the biochemical parameters of liver damage to normal levels. Lower doses of the extract were shown to be ineffective. This study concluded that, pending more evaluation for safety and efficacy, the anthocyanin compounds present in the plant can be hepato-protective and reduce paracetamol-induced liver toxicity [46].

Dried Roselle calyx extracts (RE) were evaluated for their potential hepato-protective effects against liver fibrosis induced by carbon tetrachloride (CCl₄) in rats. RE significantly reduced the liver damage including steatosis and fibrosis in a dose dependent manner. These results suggested that RE may protect the liver against CCl₄-induced fibrosis. This protective effect appears to be due to RE's antioxidant properties [47].

14.11 Roselle Extracts May Protect Against Radiation Effects

A study evaluated the radioprotective efficacy of methanol extracts of the leaves obtained from two plants: *Vernonia amygdalina* (VA) and *H. sabdariffa*, commonly known as Roselle (R), and vitamin C (VIT C) against gamma radiation (4 Gy) induced liver damage in male Wistar albino rats. VIT C was given at a dose of 250 mg/kg body weight, while VA and R were given at doses of 200, 400, and 800-mg/kg body weight, *per os*, for a period of 4 weeks prior to radiation and 5 weeks after irradiation. Treatment for 5 weeks after irradiation with VITC, VA, and R significantly decreased the levels of unconjugated bilirubin. Also, treatment with VIT C, VA (800 mg/kg) and R (400 and 800 mg/kg) significantly elevated the levels of reduced glutathione (GSH) by 61%, 56%, 41%, and 44%, respectively, at 5 weeks. The overall results indicate that the extracts of VA and R, and VIT C may augment the antioxidant defense systems in animals and may potentially protect them from radiation-induced liver damage [48].

14.12 Effects of Roselle on Urolithiasis

A clinical study evaluated Roselle's potential uricosuric effect on two groups of human subjects. Group 1 included 9 subjects with no history of kidney stones (nonkidney stone, NKS) and group 2 included nine with a history of kidney stones (KS). Roselle tea containing 1.5 g of dry calyces was administered orally to subjects two times a day (morning and evening) for 2 weeks. Serum and 24-h urinary samples were analyzed for uric acid and other chemical compositions related to urinary stone risk factors. In the KS group, both uric acid excretion and clearance were significantly increased. The results of this study showed that Roselle calyces possess a uricosuric effect, although the specific bioactive ingredients responsible for this effect were not elucidated [49].

Another study evaluated the changes of urine in normal subjects after consuming Roselle juice in different concentrations and durations which may help the treatment and prevention of urolithiasis. Thirty-six male subjects were included in the study. Urinalysis, urine electrolytes, and indices for the measurement of concentration of urine were determined before, during and after drinking Roselle juice. After taking the juice, the subjects' urine showed a decrease of creatinine, uric acid, citrate, tartrate, calcium, sodium, potassium, and phosphate but not oxalate in urinary excretion. The authors of the study concluded that a small dose of Roselle juice (16 g/day) caused a more significant decrease in salt output in the urine compared to a larger dose (24 g/day). The urinary changes were similar to the observations in men with or without kidney stones [50].

14.13 Safety

The plant extracts are characterized by a very low degree of toxicity. The LD₅₀ of a Roselle calyx extract in rats was found to be more than 5,000 mg/kg [51].

Two studies have suggested that very large doses of Roselle water and alcohol extracts of the dried calyx, ingested for relatively long periods of time can have a deleterious effect on testicular function in laboratory rats [52, 53]. The conclusions of these studies may not be applicable to humans, since high doses of an extract, not the whole plant, were given to the animals for prolonged periods of time.

14.14 Conclusion

In view of the reported nutritional and therapeutic properties and relative safety of Roselle, as well as the natural antioxidant compounds isolated from its calyces, especially anthocyanins and protocatechuic acid, this plant may be a source of therapeutically useful products for the treatment of various chronic and/or degenerative diseases including hypertension, type 2 diabetes, hypercholesterolemia, as well as certain types of cancers.

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Chapter 15

The Effectiveness and Economical Benefits of Cosmetic Treatments and Procedures Versus Natural Treatments and Life Style Changes

Pankaj Modi

Key Points

- Skin aging results from the deterioration of the structures in the skin and the slowing of healthy skin functions.
- Anti-aging treatments today consist of both medical as well as natural treatments and therapies.
- The best way to keep our bodies healthy, starting today and lasting a lifetime is to eat a healthy diet, exercise moderately and consider starting a regimen of supplements that include antioxidants, minerals, and vitamins.
- Studies have shown that one can enjoy an increased lifespan with a longer period of mental acuity, learning ability becoming sharper and become more alert by some anti-aging diets and the use of calorie restriction.
- To slow down the biological clock by employing a series of tested effective anti-aging exercises are of great importance for youthful appearance and health.
- In this world of quick fixes, plastic surgery, and a barrage of “miracle” cures, these approaches are not a holistic, long-term approach to keeping the entire body fit, healthy, and young for as long as possible.
- BOTOX® injections continue to be the cosmetic procedure of choice for men and women alike, and offer several benefits for the anti-aging market.
- Growth in this market is driven by a rising demand for BOTOX injections and dermal filler procedures performed primarily to correct facial lines and wrinkles.

Keywords Anti-aging • BOTOX • Cosmetic creams • Cosmetic procedures • Dermal fillers • Exercise • Life style changes • Minerals • Skin laser resurfacing • Skin rejuvenation • Vitamins

15.1 The Aging Process: An Introduction

Most will agree that not growing older is often a secretly held wish. The allure of remaining young and holding on to our looks and physique is a major factor in marketing and media all around us. Yet from the time we are born, we are growing constantly and getting older. During aging cells lose their ability to divide, which can also weaken the immune system.

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Aging symptoms are prolific throughout the stages of life and include puberty, menstruation, genital development, through to menopause, sexual dysfunction such as low sex drive or impotence, hair loss, eye problems and hearing loss. Conventional treatment for aging may include drastic measures such as plastic surgery, which comes with many risks, as well as controversial injections of growth hormone, of which the long-term effects are not known.

15.2 What Causes Aging?

Aging is a rather mysterious process, and no definitive cause has been found. It seems to be a collection of factors within the body working together. One thing we do know is that aging has strong genetic factors. This explains how some cultures seem to age relatively well compared to others. Although we may not realize it, on a cellular level, oxidization occurs and ultimately leads to aging. Most scientists will agree that free radicals often injure cells and lead to aging [1–17]. The chemical process behind aging can be likened to browning a cake in the oven. On a cellular level the “browning” happens between glucose and proteins which causes damage in our genes.

15.2.1 Why Does the Skin Age?

Many factors, both extrinsic and intrinsic, cause the skin to age. Those causes can easily be divided into three main categories: biological or intrinsic aging, environmental aging, and mechanical aging [1–11].

Our skin becomes thinner over time as we age. Its ability to produce certain proteins reduces as we age and as we stretch our facial skin through smiling, frowning, etc., the wrinkles come. The most obvious sign of intrinsic aging is a decrease in the overall thickness of the epidermis as a whole with a reduction in the number of cell layers. The number of cells in the stratum corneum does not diminish with age, however; this is important, because of the vital role of this layer as the skin barrier [13, 15, 17, 20, 21]. On the other hand, the numbers of melanocytes and other cells do decrease with age. So do the numbers of the Langerhans cells, which are involved in the body’s response to allergens. This could be one reason why people tend to experience fewer allergic reactions as they get older. The reticulated dermal fibers become less prominent, and the junction of the dermis and epidermis becomes flattened. This means that the epidermis is not so securely held down, and becomes more vulnerable to damage by friction. Metabolism in the skin (as everywhere else) slows down. So too does the rate at which epidermal cells are produced, which may interfere with wound healing. The time necessary to repair the stratum corneum barrier increases considerably with age. The replacement of skin cells takes about twice as long for people over 75 as for those around 30. Although the sebaceous glands themselves do not change much with increasing age, sebum production declines in many older people, especially after the age of 70, though the glands on the face actually enlarge in people of much older age. With age, the number of active sweat glands falls and their output of sweat decreases too. As a result, perspiration is less in elderly skin. This explains why older people often find it hard to adapt to hot weather.

The second categories of factors that cause the skin to age are all results of extrinsic sources in the environment. Environmental aging occurs because of daily exposure to trillions of free radicals from

a variety of sources: the sun's ultraviolet rays, pollution, smoke, harsh weather, and external stress. These free radicals damage lipids, proteins, and DNA, all of which limit the ability of cells to function and cripple the integrity of overall cell composition. Years of accumulated environmental stress on cellular structures results in the premature aging of the skin [13, 15–21].

Sun exposure is the primary environmental stressor leading to damaged skin. The damage to skin components caused by both prolonged and incidental sun exposure is called photo aging. Although cigarette smoke, exposure to harsh weather conditions and pollution are prolific contributors to environmental aging, UV damage from the sun's rays accounts for 90% of premature skin aging. Photo aging damages collagen, elastin, melanocytes and the moisture barrier resulting in wrinkles, sagging, uneven skin tone, dark spots, and a rough, dry skin texture.

While sun exposure is the environmental stressor that accounts for most premature skin aging, there are others. Pollution damages skin by increasing free radical production and increasing the effects of UV radiation. Harsh weather (dry air, wind, and cold) depletes skin of essential moisture resulting in a rough texture and fine, dry lines. Cigarette smoke increases free radical production and may decrease collagen and elastin production. Cigarettes also significantly decrease the supply of oxygen to skin cells.

The third category of aging is called mechanical aging. Mechanical aging is the result of continually repeated wrinkle causing behaviors, muscle movements repeated day after day and year after year [22–35]. Although it is unrealistic to avoid some wrinkle causing behaviors such as smiling and frowning, the following behaviors should be avoided to help prevent premature signs of mechanical aging:

- Squinting
- The thinker stance (resting chin or cheek in the hand)
- Sleeping on your side or stomach
- Scrubbing with hot water
- Weight fluctuation
- Unbalanced diet and lack of sleep
- Pursing the lips while smoking or drinking from a straw

15.3 Evidence of Aging: Changes in Physiology

A third visible sign of aging is fine lines and deep wrinkles in the skin. The structural protein called collagen, which is found in the dermis, provides a mesh-like framework of support and strength for the skin. As we age, collagen production decreases and collagen fibers degrade at a faster rate than in earlier years. This results in an overall decrease in the amount of collagen in the dermis. Areas with less support begin to cave in and wrinkles begin to form [1–11, 13, 17, 21, 25–27].

Multiple factors lead to decreased collagen levels. First, with age there is a natural decline in messenger molecules that trigger collagen production. There is also an increase in the enzyme collagenase, which breaks the collagen down. Another factor contributing to decreased collagen levels is free radicals from UV exposure. These can damage the collagen strands and stimulate collagenase activity, which leads to the formation of irregular collagen linkages that weaken the skin. In order to avoid UV damage to collagen fibers and fibroblasts, application of a consistent daily sunscreen is necessary. Research also indicates that chemical exfoliation may stimulate collagen production.

The following are factors that decrease collagen levels in the skin:

- UV rays can penetrate the skin and cause damage to collagen-producing fibroblast cells.

- Mechanical stress on the skin caused by repeated wrinkle causing behaviors can also break down collagen.
- With age, the synthesis of glycosaminoglycans (GAGs) decreases, affecting moisture levels in the dermis, collagen becomes brittle and prone to breakage.
- As skin renewal decreases, wounds heal more slowly and the skin thins, becoming more susceptible to environmental stressors; this can lead to damaged fibroblasts and a decrease in collagen levels.

Loss of firmness in the skin is another evidence of aging. All three types of skin aging: biological, environmental, and mechanical contribute to the skin's loss of firmness. Biologically, our body naturally produces more of the hormone DHT as we age. As DHT levels increase, elastin production is inhibited. Elastin is another skin structural protein found in the dermis. This coil-like protein has the ability to snap back into place after stretching, giving the skin its elastic quality. As we age, elastin fibers lose much of their resilience and elastin production within the fibroblasts decreases. This overall decline in healthy elastin levels results in areas of decreased firmness, especially along the jaw line, neck, and around the eyes.

Moisture is also a problem. Over exposure to the sun makes our skin dull and lifeless. That tan might look good short term, but over the long haul the sun cook all the nutrients out of the skin. Another direct result of this is the creation of free radicals, which attack the healthy cells of the skin causing further damage. Free radicals are molecules missing an electron so they attack healthy skin molecules by trying to grab other electrons in order to make them complete again. Older people have a dry skin and therefore have a special need to avoid the over-use of harsh soaps and detergents, in order to prevent problems associated with dryness. Aged skin loses its fundamental ability to control water loss. Many substances will penetrate aged skin more easily than young skin.

15.4 Biological or Intrinsic Skin Aging

Biological or intrinsic aging is the result of changes often genetically determined, that occur naturally within the body. Everyone has a biological clock or chronological age determined by genetic makeup [6–8, 11, 13, 15, 17, 20–22, 26–29, 31–37]. This applies to the skin as well. As our biological clock ticks, our skin gradually loses its ability to function as it once did. Biological aging occurs because of natural changes within the body that manifest themselves in outward signs of aging on the skin.

Frequently, changes associated with biological aging are the result of a gradual shift in the balance of certain hormones and messenger molecules excreted by other glands and organs within the body. Many of these changes are genetically determined and cannot be stopped.

Fortunately, some of the factors contributing to biological aging can be controlled. Scientists are beginning to understand how free radicals (unstable molecules) damage proteins, lipids, and the DNA within cells, and, in turn, accelerate the biological aging process [15, 17, 21–30]. Antioxidants are molecules with the ability to neutralize free radicals in the skin. A healthful diet full of antioxidant-rich fruits and vegetables, along with nutritional supplementation and topical application of key nutrients may help decrease the intensity and delay the onset of many changes that are a result of biological aging.

Skin aging results from the deterioration of the structures in the skin and the slowing of healthy skin functions. Dry skin is a visible sign of skin aging. Healthy, young skin maintains appropriate moisture levels through the sealing properties of the moisture barrier, which is composed of keratin-filled keratinocytes (skin cells) surrounded by and sealed together with interspersed epidermal

lipids (ceramides, lipids, and fatty acids). As we age, the skin produces fewer ceramides, lipids, and fatty acids to seal the moisture barrier resulting in an increase in transepidermal water loss and dryness [21–30].

A natural decline in hormone levels is usually the cause of this decreased production; however, several other preventable factors can also strip epidermal lipids, causing excessive dryness. Consider the following:

- Improper skin care. Using harsh cleansers and neglecting to supplement the skin with rich, nourishing moisturizers.
- Harsh weather conditions. Enduring extreme temperatures and wind without adequate moisturizers and protection.
- UV radiation. Neglecting to protect skin from the sun's UV rays with sunscreen.

A dull, rough complexion is another visible sign of skin aging. Healthy, young skin remains smooth and radiant because fresh, new cells are brought to the surface as older cells are continuously shed. The skin cells in the bottom layer of the epidermis (stratum basale) constantly divide through cell division, forming new keratinocytes. This regenerative process is called skin cell renewal. As we age, the rate of skin cell renewal decreases, causing cells to become stickier and not shed as easily. As a result of cell renewal decreasing, the skin becomes thinner and more susceptible to environmental damage, especially photo damage from the sun's UV rays. Eventually, the skin appears dull and rough in texture.

Several factors contribute to the process of skin cell renewal declining as we age. For example, weakened blood vessels in the dermis and a flattening of dermal papillae decreases the surface area between the dermis and epidermis across which nutrients can diffuse. This process decreases nutrient and oxygen supplies to the basal cells in the lower epidermis. UV exposure can also penetrate the epidermis, damage basal cells, and slow the rate of cell division [31–37, 41–46]. Finally, failure to exfoliate the surface of the skin with physical and chemical exfoliates for the purpose of smoothing the skin and stimulating cell renewal contributes to the decline in renewal.

Environmentally, UV rays can penetrate the skin to damage elastin-producing fibroblast cells. In addition, as skin cell renewal decreases, wounds heal more slowly and the skin thins, becoming more susceptible to environmental damage. This can lead to damaged fibroblasts and decreased elastin levels. Finally, mechanical stress, due to repeated wrinkle causing behaviors, can permanently stretch out elastin fibers.

Enlarged pores are also a sign of aging skin. To a large degree, pore size is determined by genetics; however, as we age, our pores tend to appear larger. The pore's enlarged appearance is due to a buildup of dead cells around the pore. As more collagen breaks down and production slows, the supportive structures surrounding cells decrease and cells can appear stretched. Keeping the skin exfoliated and the pores clear will help reduce the appearance of pore size. In addition, consistently using a sunscreen to protect collagen helps maintain pore size.

Age spots are the last evidence of aging that we are going to discuss. Normal skin pigmentation helps protect healthy skin from the stress of mild UV exposure. Melanin, the skin's photo protective pigment, is produced in specialized melanocyte cells in the lowest layer of the epidermis (stratum basale). As we age, melanocyte activity decreases, making the skin more susceptible to UV damage. With age, melanocytes also tend to cluster together, and this results in patches of pigmentation called age spots.

Many factors contribute to the production of age spots. First, hormone imbalances that occur with advanced age result in fewer melanocytes and can trigger excessive melanin production. Second, UV light rays stimulate melanocytes to produce skin pigment. UV light can also penetrate the skin

and damage melanocyte DNA, which can stimulate melanocytes to enlarge and cluster together. Third, as the cell renewal cycle decreases, wounds heal more slowly and the skin thins, becoming more susceptible to environmental damage. This can lead to damaged melanocytes and abnormal pigmentation. Finally, poor skin care habits can lead to skin irritation, which triggers melanin production.

15.5 Anti-Aging: Where to Begin

Anti-aging is a very popular term that is used daily by many people. Like people have done throughout history, they are looking for a way to prolong their lives [38–40]. Not only do they desire to look younger than they are at this moment, but they also would like to keep hold of their looks for eternity if possible. The object of anti-aging is to improve the current condition, which in turn improves the way that one looks and feels.

15.5.1 Who Benefits from Anti-Aging Treatments?

It can be said, that without doubt, anyone concerned about aging will benefit from anti-aging treatments, procedures, and programs. While physicians and skin care enthusiasts have yet to find the fountain of youth in a bottle, there is no doubt that a healthy lifestyle, a nutritious and balanced diet, daily exercise and skin care helps to reduce signs of aging.

15.5.2 Facial Aesthetic Industry Overview

Anti-aging treatments have been and will continue to be a hot topic among men and women of all generations. Since the times of the ancient Egyptians, Assyrians and Chinese, men and women have sought the fountain of youth and the secrets to anti-aging. These days, products appear and disappear in the blink of an eye, and surgical procedures have advanced to the point where full facelifts are no longer available. Non-invasive surgical treatments, education regarding the nutrients, anti-aging benefits of certain foods as well as attention to the long-term benefits of healthy lifestyles helps to defy the aging process [47–62].

15.6 Popular Anti-Aging Treatments

Anti-aging treatments today consist of both medical as well as natural treatments and therapies. Everything from the latest techniques in thread lift surgical procedures to fat transfers to products that include human growth hormones, sprays and releasers are up for grabs. Natural as well as not-so-natural treatments for skin care and therapies, techniques and procedures to tighten the skin, enhance appearance and reduce unsightly wrinkles encourage a multibillion-dollar industry [63–121]. In addition to the benefits of daily exercise, adequate hydration, a balanced and nutritious diet and “youth in a bottle,” some of the most popular anti-aging treatments include:

- Cosmetic and plastic surgeries
- BOTOX injections
- Fat transfers
- Anti-aging skin care products
- Diets rich in antioxidants
- Anti-aging medications
- Stem cell (rejuvenation and regeneration therapies)
- Human growth hormone products

The popularity of cosmetic and plastic surgery has accelerated in the past few decades. Thread lifts are the most commonly performed technique today that involve fairly noninvasive plastic surgical procedures as opposed to the full facelifts offered in the past. Thread lifts are innovative technologies that rely on the use of strings that are inserted beneath the skin and attached to basic structural facial tissues. Individuals who benefit the most from thread lift techniques are those with mild looseness of the skin around the neck or chin area. If done early enough, the need for more drastic and invasive plastic surgical procedures may be eliminated.

Fat transfers are designed to help “plump” tissues that have lost elasticity and smoothness due to the aging process. Fat transfers are performed by removing fat from other areas of the body and injecting them into areas in the face that help to reduce the signs of sunken skin as well as emphasizing bone structure.

Stem cell treatments may very well be the future of anti-aging treatments. Cell growth and rejuvenation offers BOTOX-like results that reoccur naturally after injections of new, young and healthy skin stem cells. Studies are continuing in this exciting and groundbreaking field of research. Increased demand from aging baby boomers as well as the introduction of numerous technological advances has provided accelerated growth opportunities in the aesthetic and dermatology fields. Growth in this market is driven by a rising demand for BOTOX injections and dermal filler procedures performed primarily to correct facial lines and wrinkles.

Skin care sales grew in 2007 (Millennium Market Research report, 2008) and growth of non-surgical aesthetic procedures is outpacing surgical procedures by a margin of three to one, with dermal fillers injections being only second to BOTOX in this category. Facial moisturizers (anti-wrinkle creams) grew by 38% while cleansers and toners grew by 25% and 14% in the same time period. This demonstrates the consumer shift towards less invasive correction and heavily towards the low non-invasive segment. This trend has been developing for years and shows no signs of decelerating with the dermal fillers market set to continue the growth of recent years. The US dermal filler market is projected to expand at a compound annual rate of more than 25% through 2011 in the USA and 20% throughout the rest of the world, reaching \$1.5 billion in global sales.

15.6.1 Cosmetic Surgery: Highlights from 2007 (Millennium Market Research Report)

- The top non surgical procedure was BOTOX injection
- The top surgical procedure was liposuction
- Americans spent slightly less than \$13.2 billion on cosmetic procedures in 2007
- About \$8.3 billion was spent on surgical cosmetic procedures, with \$4.7 billion on non-surgical procedures
- There was an 8% increase in surgical procedures in 2007, compared to 2006

Table 15.1 2007 top non-surgical cosmetic procedures

Women		Men	
Non-surgical	Number of procedures	Non-surgical	Number of procedures
BOTOX	2,775,176	BOTOX	329,519
Hyaluronic acid (Hylaform, Juvederm, Restylane)	1,448,716	Hyaluronic acid (Hylaform, Juvederm, Restylane)	185,684
Laser hair removal	1,412,657	Laser hair removal	85,910
Microdermabrasion	829,658	Microdermabrasion	84,184
Laser skin resurfacing	647,707	Laser skin resurfacing	63,177

- Men underwent 9% of cosmetic procedures in 2007, an increase of 17% over 2006
- The world skin care market had sales of \$65.7 billion in 2007, up 40% from 2002 (and up 7% from 2006)
- Skin care, the largest cosmetic category, grew faster than the \$291 billion market which saw sales rise by 29% from 2002 (and by 6% from 2006)
- Leading this growth was men's skin care, growing from a very small base of \$ 746 million in 2002 to reach \$1.5 billion in 2007
- Within facial care, nourishers/anti-agers was the fastest growing with 67% growth from 2002 to 2007 reaching \$14.9 billion in 2008 (Table 15.1)

The drivers of this expanding market demand are many: the aging population, expanding media exposure and consumer awareness, new and improved filler technologies, more effective and safer treatment protocols, expanding social acceptance and simple vanity – the reluctance to age gracefully. Additionally, the impact of the arrival of BOTOX cannot be overstated, as this product has become the “gateway” into a cosmetic physician's office for many patients. Many cosmetic physicians are consulted on dermal filler options as a part of the emerging standard of “combined therapies” to create more significant comprehensive aesthetic results.

In regards to filler choices, what is gaining momentum among physicians and patients is the desire for dermal filler products that are safe, increasingly effective, non-animal source, long lasting, quick to perform, comfortable, cost-effective, with excellent, natural appearance and feel.

Nearly 12 million cosmetic procedures were performed in 2007, with breast augmentation, liposuction and nose reshaping procedures ranking in the top ten. Still, many Americans chose a minimally invasive treatment to improve their appearance, turning to BOTOX and micro dermabrasion to fight the signs of aging and restore their youthful looks. According to the American Society of Plastic Surgeons, minimally invasive cosmetic procedures such as laser hair removal and BOTOX accounted for 10 million treatments in 2007 [47–64].

15.6.2 Top Five Minimally Invasive Procedures (Millennium Market Research Report 2008)

15.6.2.1 BOTOX

Procedures performed: 4.6 million

BOTOX injections continue to be the cosmetic procedure of choice for men and women alike, and offer several benefits for the anti-aging market. BOTOX injections can be used to reduce fine lines and wrinkles, and some studies suggest that BOTOX treatments can also help reduce migraines and other pain in the body. BOTOX reduces the nerve impulses linked to certain muscles in the face and body, essentially paralyzing the muscles to reduce contractions.

15.6.2.2 Hyaluronic Acid (Dermal Filler)

Procedures performed: 1,051,000

Hyaluronic acid is the substance found in dermal fillers such as Restylane® and Juvederm®, and can be used for lip augmentation, cheek enhancement and other procedures that imitate a surgical facelift. Since the hyaluronic acid is not absorbed by the body in the same way as collagen, these dermal fillers may provide long-term results.

15.6.2.3 Chemical Peels

Procedures performed: 1,025,000

Chemical peels are readily available at day spas and medispas across the country, but are often a part of a complete skin rejuvenation plan at the dermatologist's office. Chemical peels work by removing the top layer of the skin and stimulating collagen production; the potency of the chemical peel determines the level of results achieved, and options range from lighter AHA peels to intensive phenol peels. Chemical peels can be combined with other skin rejuvenation techniques such as laser skin tightening procedures, laser age spot removal and collagen-boosting treatments such as Thermage and Radiasce.

15.6.2.4 Laser Hair Removal

Procedures performed: 906,000

Laser hair removal makes it easier to manage unwanted facial or body hair so you do not have to resort to shaving and waxing on a regular basis. Laser hair removal procedures do require consistent treatment, but most people can enjoy lasting results after a few weeks or months of appointments.

15.6.2.5 Micro Dermabrasion

Procedures performed: 897,000

Micro dermabrasion offers several benefits for aging skin and can help remove fine lines and wrinkles permanently. The procedure involves “sandblasting” the skin with aluminum oxide crystals to exfoliate the top layer to reveal the fresh layer underneath. This procedure can also be paired with other skin rejuvenation techniques for a complete wrinkle removal treatment program.

15.7 Dermal Fillers

Dermal fillers are made of various kinds of natural or synthetic materials that have been developed over the years for injection into the skin [65–105].

15.7.1 What Are Dermal Fillers and How Do They Work?

As the skin ages, it gradually loses some of its collagen and fat. These are the materials that prevent the skin from becoming saggy. Thus, as we age, our skin can become thinner with more wrinkles and lines.

Dermal fillers help to restore the skin to its former youthful appearance. Material is injected into the skin in areas where it needs to be plumped up again and made to look firmer. This is not a new treatment. As early as the 1890s, doctors took out the fat from patients' arms and inject it into their faces. In fact, fat transplant is still a popular substance used by some practitioners today who can move fatty tissue from an area of the body where it is not required and inject it somewhere else. In the mid-1900s, doctors were using paraffin and then silicone as filler in the skin, with some reported problems regarding the safety that prevented them being used widely.

15.7.2 What Are the Different Types of Dermal Fillers Used?

15.7.2.1 Permanent or Nonresorbable Dermal Fillers

These are newer fillers that can give a longer lasting effect, or even a permanent effect. Dermal fillers tend to be broadly classified as being either non-permanent or permanent in their effect. Practitioners are using these products as non-permanent or resorbable dermal fillers. The leading dermal filler used by most practitioners is a hyaluronic acid based product. This particular brand is manufactured using bacteria. Again, this product comes in different thicknesses and is called Restylane or Perlane® [65–105]. Hyaluronic acid is a naturally occurring substance found in the spaces between the cells of body tissues in all animals. It has already been used widely in general medicine to help eye surgeons perform cataract operations, and for injection into arthritic joints to aid movement. It is estimated that 30 million patients around the world have been treated with some form of hyaluronic acid. Hyaluronic acid has now largely replaced collagen as the favorite filler of cosmetic experts. This is because it is more likely to be compatible with our bodies than collagen, and so people are less likely to be allergic to it and do not require a test prior to use.

Other Hyaluronic Acid Based Products Include: Hylaform® and Hylaform Plus® – Manufactured from cockerel combs. Juvederm ULTRA, Matridur® and Hydrafill are examples of other hyaluronic acid based brands derived from non-animal sources. Newer filler using polylactic acid is promoted under the brand name Sculptra®. According to the manufacturer, Sculptra, as the name suggests, is used more as a sculpting agent rather than just wrinkle filler and larger areas can be treated with a longer lasting result [65–105].

Another product new to the market in 2004 is calcium hydroxyl apatite, the key component of Radiesse™ [90–93]. Calcium hydroxyl apatite has been safely used in the body for many reasons including dental applications where bone build-up is needed for reconstruction and in block form for cosmetic applications such as cheek, jaw, cranial and chin implants. Radiesse is marketed as a long lasting dermal filler and facial sculpting agent where results can last for 2 years or longer. Most of the ingredients of available non-permanent or temporary fillers have been widely used and clinically tested for safety and effectiveness.

15.7.2.2 Collagen-Based Dermal Fillers

In 1981, Collagen was the first filler approved in the USA for soft-tissue filling by injection [93–98]. It is made from bovine (derived from cows' skin) collagen and is currently known as Collagen Instant Therapy. The collagen is taken from the cow and then purified to such a degree that it resembles the collagen that occurs naturally in our own skin. It is necessary to have a skin test before this treatment, however, as some patients may be allergic to bovine collagen. Collagen instant therapy comes in different thicknesses, depending on the depth of the wrinkles or loss of firmness in the skin.

Therapy called by the brand names Zyderm® and Zyplast® by your clinic. Cymetra, a collagen derived from human skin. This is rarely used these days.

According to Statistics from the American Society for Aesthetic Plastic Surgery, (ASAPS) collagen injections were the 13th commonest aesthetic procedure in the USA with more than 58,000 treatments in 2008 alone, (49.6% of these procedures used bovine-derived collagen products and 50.4% used human-derived collagen products). As previously seen when comparing 2006 to 2005 and 2007 to 2006 figures, the 2008 figures also show a decrease in the use of these products by 8.3% compared to 2007 figures. This is mainly due to the increased use of hyaluronic acid based dermal fillers and others (i.e., calcium hydroxylapatite, poly-L-lactic acid and polymethyl methacrylate dermal fillers). The hyaluronic acid based dermal fillers (Hylaform, Restylane & Juvederm) are now beating collagen to 3rd place in the commonest aesthetic procedure in the USA with over 1.26 million treatments in 2008, (a decrease of 12.8% on 2007 figures). With calcium hydroxylapatite (Radiesse) accounting for just under 123,000 dermal filler procedures, (a rise of 3% in its use since 2007), poly-L-lactic acid (Sculptra™) nearly 32,000 (a decrease of 8.7% on 2007), and polymethyl methacrylate (Artecoll®) showing as a new entry in 2007 since US FDA approval with just under 11,000 procedures in 2008, a fall of 10.6% on 2007.

Although similar statistics are not yet available in the UK, there has been tremendous growth in the use of collagen and other dermal fillers in this country. More people than ever are having this treatment because it works, it is not as expensive as a face-lift and it does not involve any surgery. As the use of these products has grown, so has the choice of different filler substances. Since the late 1990s, some manufacturers have been claiming that their products last longer than older fillers, and even that their effects can be permanent.

These products are currently not widely used, but include the following brands:

Artecoll – Rounded PMMA beads in bovine collagen

Aquamid™ – Polyacrylamide

Bio-Alcamid™ – Alkyl-imide

Matridex® – Hyaluronic acid with dextran microspheres

15.7.3 What Skin Problems Can Dermal Fillers Treat?

Collagen treatment has been widely used to increase the size and volume of lips in women for a number of years and this is still the most popular use for most dermal fillers. However, these products are also very effective in both men and women in helping to fill out lines around the lips, the lines from the nose to the corners of the mouth (nasolabial lines), smile lines on the cheeks, as well as crow's feet and forehead wrinkles.

Thicker fillers can also be used to add volume to sunken cheeks and weak chins, reshape the tip of the nose as well as filling out deeper acne or other scars. In addition, fillers can be used to help reduce the appearance of veins and bones in aged hands with thin skin. Some filler can be used to treat larger skin defects in other areas of the body. Depending on the area treated and the depth of wrinkles or scars or sagging of the skin, practitioners may recommend that different combinations of fillers to be used in order to achieve the best results.

15.8 Botulinum Toxin

Botulinum toxin is a type of muscle relaxant originally used to treat muscle spasm. Today, it is also a popular anti-aging product and sold under the brand name BOTOX, Dysport and Myobloc.

Essentially, BOTOX, Dysport and Myobloc work by paralyzing muscles that cause repetitive facial movements such as frowning and smiling. These are said to be effective for treating frown lines, forehead lines, crow's feet and necklines [103–121].

Botulinum Toxin Type A (BOTOX Cosmetic) is a protein complex produced by the bacterium *Clostridium botulinum*, which contains the same toxin that causes food poisoning. When used in a medical setting as an injectable form of sterile, purified botulinum toxin, small doses block the release of a chemical called acetylcholine by nerve cells that signal muscle contraction. By selectively interfering with the underlying muscles' ability to contract, existing frown lines are smoothed out and, in most cases, are nearly invisible in a week.

BOTOX injections are the fastest-growing cosmetic procedure in the industry, according to the American Society for Aesthetic Plastic Surgery (ASAPS). In 2001, more than 1.6 million people received injections, an increase of 46% over the previous year. More popular than breast enhancement surgery and a potential blockbuster, BOTOX is regarded by some as the ultimate fountain of youth.

BOTOX was first approved in 1989 to treat two eye muscle disorders, uncontrollable blinking (blepharospasm) and misaligned eyes (strabismus). In 2000, the toxin was approved to treat a neurological movement disorder that causes severe neck and shoulder contractions, known as cervical dystonia. As an unusual side effect of the eye disorder treatment, doctors observed that BOTOX softened the vertical frown (glabellar) lines between the eyebrows that tend to make people look tired, angry or displeased.

BOTOX treatments accounted for nearly 3 million cosmetic procedures in 2007, and continue to be one of the most popular choices for reducing wrinkles and giving the skin a youthful appearance. For over 10 years, BOTOX has become the cosmetic treatment of choice over the standard facelift, and is primarily used to fill out crows-feet, reduce forehead furrows and even out smile lines.

15.9 Non-invasive Anti-Aging Treatments

15.9.1 How to Eliminate Wrinkles without Surgery

From BOTOX to chemical peels, growing trends in minimally invasive cosmetic procedures indicate more people are turning to elective surgery to improve their appearance [47–63]. Since the quest for the fountain of youth will continue for years to come, cosmetic surgery centers and medispas are developing innovative treatments and lifetime maintenance plans for patients of all ages and backgrounds.

In the past, cosmetic surgery was the best option to eliminate wrinkles. However, there have been significant advancements in non-invasive anti-aging treatments in the past decade. Those with skin renewal in mind now have more options that are less aggressive. Those who wish to have younger looking skin now have more skin renewal options than ever with minimal pain and better results. Many treatments such as botulinum toxin, intense pulsed light, plasma skin resurfacing, thermage and Fraxel laser are non-invasive anti-aging treatments that women as well as men can opt for.

15.9.1.1 Intense Pulsed Light

Intense pulsed light is commonly used for hair removal from the body but has also been successfully used for skin treatments, particularly pigmentation and broken capillaries. During an intense pulsed light treatment, varying wavelengths of light are applied on the problem areas. The treatment may cause mild redness and bruising but these usually subside a few days later.

15.9.1.2 Plasma Skin Resurfacing

Plasma skin resurfacing was developed as an alternative to the classic ablative resurfacing which literally burns off some of the skin. It works by damaging the skin in a controlled manner, resulting in the healing response and collagen production, which in turn allows the skin to remodel and rejuvenate. The damaging agent used is plasma, a high energy ionized gas that does not burn off skin. Instead, the skin will turn bronze and begin to peel 4 days after treatment, taking 2–4 weeks to heal completely. Plasma skin resurfacing is often used for eliminating wrinkles, sun damage, acne scarring and superficial skin lesions.

15.9.1.3 Thermage

Thermage is a non-invasive skin tightening and contouring technique using radio frequency waves. It tightens the skin, smoothes out wrinkles and renews facial contours by causing immediate collagen contraction followed by new collagen production over a period of time. Results are usually visible 4–6 months after treatment. Thermage can also treat moles, warts and small surface blood vessels.

15.9.1.4 Fraxel Laser Treatment

The Fraxel laser has been used to treat various skin conditions such as sun damage, acne scarring, wrinkles and melasma. It works by penetrating fractions of skin spot by spot without breaking the skin's protective outer barrier. The nature of the treatment allows the skin to heal and regenerate much faster than if the entire skin area were treated all at once. A sunburned feeling and appearance may follow the Fraxel laser treatment. The sunburned appearance can be covered by make-up. The skin will naturally bronze, peel and become a little flaky over the next 2 weeks. The use of a moisturizer can help reduce the dry flakes. Several treatments are often required.

Ablative Laser Resurfacing: The Promise, Dangers and Reality

Ablative laser skin resurfacing is a process where the upper layers of aged or damaged skin are vaporized by applying a controlled laser beam. The resulting healing and restructuring of the skin is believed to reduce the appearance of wrinkles. Do not confuse ablative laser resurfacing with non-ablative laser treatments where the skin surface remains largely intact.

Laser resurfacing (a.k.a. laser peel) is one of the most popular invasive procedures in cosmetic surgery. Claims of the benefits of laser resurfacing, depending on the source, range from remarkable to minimal. The dangers of laser skin resurfacing, again, depending the source, range from relatively minor and infrequent to rather significant. The situation is very confusing to a person trying to decide whether to go ahead with laser resurfacing and, if yes, how to best proceed.

Benefits

Most research studies agree that properly performed laser resurfacing can visibly reduce the appearance of fine lines and, in some cases, deeper wrinkles. It is used either on the entire face, or, on more commonly, in the areas around the eyes and mouth. Some surgeons combine laser resurfacing with

a facelift or other procedures to produce maximal effect. The advantages of laser over other resurfacing methods (deeps chemical peels and dermabrasion) include greater precision, less bleeding and discomfort and, possibly, shorter recovery time.

The results of laser resurfacing are particularly noticeable after the initial healing and for about a year thereafter. According to different sources, the results generally last from 1 to 5 years. (The results of lower eyelid resurfacing tend to be less lasting, 1–5 years). Maintenance treatment with topical agents may prolong beneficial effects of laser resurfacing on the skin appearance. Generally, the wrinkles solely due to skin aging respond better than those due to facial movement, such as smiling, frowning or squinting. Even if successfully removed, movement wrinkles tend to recur relatively quickly.

It appears that the results of laser resurfacing vary greatly, depending on the technique, skill of the surgeon and patients unique physiology. Some people experience results exceeding their expectations, while others see little benefit, or even have negative reactions.

Risk

Laser peel or resurfacing, is still an invasive surgical procedure where top layers of the skin are vaporized by a laser-generated energy burst. In most cases, the damage is well controlled and the recovery is smooth. Possible adverse reactions include excessive scarring, infection, loss of normal skin pigmentation, skin redness and dryness, and others. When the procedure is performed skillfully and the patient and technique are properly selected, side effects are relatively infrequent.

15.10 Cosmetic Anti-Aging Solutions: Consider the Cost

One of thing that most worry people is the cost of facial rejuvenation treatments. They are usually not cheap and can cost up to thousands of dollars depending on which treatment they want and even though they are expensive in some cases, they are also risky. Many Americans simply cannot afford the average \$1,000+ treatment plan every so often on average at least twice in a year and are willing to choose a different strategy instead to maximize on the cost and still have their youth preserved up to some extent lot more economically then \$1,000s of expense for dermatologic procedures. Americans typically pay between \$350 and \$1,300 per BOTOX treatment for each area, and the cost has decreased only slightly in the past decade with the onslaught of other facial rejuvenation treatments available.

15.10.1 The Estimated Costs of Facial Rejuvenation Techniques

Collagen injections: \$500–\$750 per treated area

Dermal filler (HA) injections: \$500–\$1,000 per treated area

Radiesse: This is semi-permanent filler. Its results can last from 2 to 3 years. Full results are seen after 2 weeks. It costs from \$500 to \$2,000 per treatment.

FaceLifts: \$5,000–\$10,000

Chemical peels: \$600–\$700

Dermabrasion: \$1,000–\$1,200

Laser skin resurfacing: \$2,300–\$2,500
BOTOX Injections: \$370–\$600
Microdermabrasion: \$200–\$250
Thermage: \$200–\$300
Laser hair removal; \$200–\$500

15.11 The Best Anti-aging Methods?

Is there really a best anti-aging method that exists when applied by any person that will lead to increased vitality and slow the onset of age catalyzed destruction of the body? Moreover, is cheap and economical compared to other cosmetics methods mentioned above? People have searched for the best anti-aging techniques to slow down the biological clock and some have been successful. So, what exactly is the secret of people who effectively achieve extended youth? How can one attempt to thwart the effects of time on the body? It is no myth that through properly applied anti-aging treatment one can enjoy extended health and vitality and perhaps even slow down the hands of time.

People have heard about herbal elixirs, anti-aging creams, and other anti-aging paraphernalia all claiming to be the best anti-aging products available. Is there any truth behind the claims of their manufacturers? There are no real scientific studies backing up the claims of the manufacturers of different anti-aging products, but through the proper conditioning, the body can more effectively ward off the adverse effects of aging through the proper care and maintenance. The body, can take decades of abuses but will remain supple and in good working condition if it is maintained properly. Proper maintenance is the key to the best anti-aging techniques and includes taking care of the three aspects of physical and systemic health, which are flexibility, cardiovascular health and muscular strength. With properly applied training, anyone can benefit from increased health and suppleness and enjoy renewed vigor well into old age.

Flexibility is made up of three basic principals or types of stretching which are commonly employed to increase the elasticity and suppleness of the muscles and joints. The first type is ballistic stretching, which relies on explosive movements to move the limb through its range of motion. The second type of stretch is known as proprioceptive neuromuscular facilitation, or PNF. PNF requires quite a bit of technical knowhow, and although it is suitable for personal trainers and the rehabilitation of athletes, it is too technical to be of use for the average person interested in the best anti-aging methods. The final and most common type of stretching is static stretches. Static stretches rely on holding the muscle in a stretched position for a short period of time to increase local blood flow and slowly increase the range of motion.

Cardiovascular training that is effective as an anti-aging method includes any type of training that increase the heart rate for a given amount of time. The goal of cardiovascular training is to increase the efficiency and strength of the heart, allowing it to deliver more blood to the body with less exertion. Cardiovascular training includes sprints, jogging, rowing, walking, and almost anything that increases the heart rate for a period of time. Good cardiovascular health helps ward off heart disease and stroke, which will pay dividends in terms of long-term health.

The final piece of the best anti-aging method puzzle is strength. Strength training includes progressive resistance exercise meant to increase the tone and strength of muscles. It has been shown that strength training and resistance training helps preserve bone density, and can therefore help prevent diseases like osteoporosis. Strength training also leads to all around increased vitality due to the increased health hormone release associated with it.

15.11.1 All Natural Anti-Aging Solutions

With the growing popularity of all-natural anti-aging products, like all natural anti-aging skin creams for example, there is no reason to believe that person will not be able to find natural solutions to anti-aging products that he or she want. It often pays to take a look at what all natural products may be out there to provide for their specific needs, since nature is often the safest and best and a most economical ways to improve the problems that both the body and the emotions have need of. There are a number of safer routes open and available that can make this happen without risky, painful surgery or the use of chemicals, and lots of money

For starters, some all-natural anti-aging supplements provide the additional antioxidants that the body requires. This provides both the health and wellness that is essential to having healthy looking skin and youthful looks. By using natural supplements along with all natural skin cream, one can gain amazing anti-aging results.

It is important to use all natural products whenever possible because chemicals products are often riddled with side effects that can leave the body with the same problems it had prior to using the chemical laden product, or worse. Luckily, the body knows how to use most natural products which accounts for fewer amount of problems when compared to the products with chemical alternatives. When choosing anti-aging solutions over cosmetic surgery, it is easy to see the potential benefits with far less risks. From anti-aging products to anti-aging therapies, there are a multitude of ways that one can improve the overall well being and health with all natural products. All natural products can even be used as complimentary solutions to the other anti-aging products.

15.12 Anti-Aging Through Lifestyle Changes

It is absolutely ok to age naturally, however, some people, due to their lifestyle and eating habits, begin to show age prematurely [121–157]. There are certain elements that should be included in the everyday diet to help thwart the aging process. These elements include:

- **Watching the Weight** – To really fight the aging process, it is ideal to keep the weight at around 5–10% of what you “should” weigh.
- **Watching the Calories** – Caloric consumption is also important in any anti-aging process.
- **Watching the Fats** – Saturated fat should be decreased or avoided if possible. This one agent will actually help speed up the aging process.
- **Including What Is Important** – The most important anti-aging foods in the daily diet should include fresh vegetables, fresh fruits, oily fish, and whole grains.

Quit Smoking, nothing ages a person’s body and skin more than smoking cigarettes does. Once the smoking is stopped, the body will begin to reverse the damage done to the skin and the organs from years of smoking.

Learn to relax and get more sleep. Along with smoking, stress is a major cause of premature aging. In addition, nothing puts more stress on the human body than lack of sleep, commonly called, sleep deprivation. Sleep deprivation is responsible for depression, heart attacks, memory loss and even death to name a few [123, 124]. The more stress we put on our minds, the more physical damage is done to our bodies. A great way to get relaxation is through Meditation. Another way is to find something to do is to relax. One can try to get a few more hours of uninterrupted restful sleep per day, if they can.

Eating more of the Right Vegetables and Fruits – Vegetables that are rich in colors tend to have more antioxidants in them. Antioxidants are what the body uses to fight free radicals, which clog the cells and often cause diseases like cancer and heart disease as well as aging your skin. Antioxidants help fight them and reverse their damaging effects. Doing these simple lifestyle changes can improve the overall health and well being immensely. An added benefit of doing these simple lifestyle changes are they can reverse the negative effects of aging as well often dramatically without significant costs.

15.13 Anti-Aging Diets: Getting the Facts About an Effective Life Extension Method

No matter what one's age might be or how healthy one feel at the moment, anti-aging diets plays an important part in keeping the body looking great and feeling good. Few good anti-aging diets have recently become very popular as one of the best ways that a person can really beat the aging process [121–157].

One of the first and foremost aspects of anti-aging diets is that of calorie restriction (CR), which is often abbreviated to CR. Essentially, it involves the idea that by limiting the amount of calories that one consumes, and thus by limiting the energy intake, one will be able to slow down the aging process. After some research, it has been shown that calorie restriction has several different, beneficial effects on humans. With calorie restriction, one can see a lowering of the cholesterol level and blood pressure. Because many experts see heightened cholesterol and blood pressure as marks of aging and the breakdown of the body, the improvement of these symptoms is very exciting. Another way to refer to calorie restriction is to refer to as Calorie Restriction with Adequate Nutrition. Rather than just removing foods to lose weight, one must make sure that they are still getting all the important nutrients like vitamins and minerals that body requires. This is an important thing to keep in mind; calorie reduction is not the promotion of starvation. Instead, eating in this fashion encourages one to eat more wisely and to think about what to eat and how much to eat.

How does having a reduced calorie diet fit [128–134] in with what most people are doing? Frequently, people eat about 2–3 lb of food a day. One thing that scientists are beginning to encourage is the viewpoint that food is a drug, one that can be used to slow down the effects of aging. In other words, like a drug, food should be taken only when necessary and taken with care.

If carried out with a view towards nutrition and balance, the use of calorie restriction can help in slowing down the effects of aging without harming the functioning of the body. Calorie reduction should never make one feel weak, dizzy or moody. While there may be some adjustment needed, the signs listed there are indicative of malnutrition. Malnutrition and starvation, though they will bring the weight down, are actually age accelerating. When the body does not get enough fuel and forced to work harder, the body ages more rapidly.

15.13.1 What Are Some of the Benefits of Anti-Aging Diets and the Use of Calorie Restriction?

Studies have shown that one can enjoy an increased lifespan with a longer period of mental acuity, learning ability becoming sharper and become more alert. Significantly, calorie reduction [128–134]

can decrease the chance of heart disease and cancer, along with a decreased loss of bone mass, which can help improve the chances of fighting of osteoporosis.

15.13.1.1 Drink Water

Water is an essential element for all bodies. Without water, the body cannot function and cleanse itself. Drinking a minimum of eight glasses each day can cleanse the body of waste materials and toxins.

15.13.1.2 Healthy Avocados

The avocado is a fruit; many people believe it is a vegetable. This is one of the many great anti-aging foods that should be included in the diet. The avocado contains monounsaturated fat, which is considered one of the healthy fats, as well as Vitamin E and Potassium. Just including avocados into the diet can help lower the cholesterol, keep the skin healthy, stump aging, reduce blood pressure, and reduce fluid retention.

15.13.1.3 Healthy Watermelon

A sweet summer time favorite watermelon from the inside out is extremely healthy and is definitely included in the anti-aging foods category. A watermelon contains necessary essentials such as healthy fats, vitamin E, zinc, selenium, Vitamin A, Vitamin B, and Vitamin C. The seeds and the flesh are both very nutritious and work to fight the aging process.

15.13.1.4 Fight It with Berries

There are many different kinds of berries, however, the blacks and blues are the best when you are looking for anti-aging foods. Berries like black grapes, blackcurrants, blueberries, and blackberries are great aging fighting foods. These berries contain a powerful antioxidant known as phytochemicals. These agents are known to fight the aging process.

15.13.1.5 Whole Grain Cereals

Energy is crucial to life and complex carbs provides with this energy. This is why one should include whole meal rice, cereals and pasta in their diet. The fiber and vitamin B, as well as iron contained in these foods are extremely healthy and contain anti-aging properties.

15.13.1.6 Certain Vegetables Works Better

Looking for a food that not only fights the aging process, but also works to protect against cancers and toxins, include at least 40 oz of a combination or one of the following vegetables:

- Watercress
- Radishes
- Brussels sprouts
- Turnips
- Kale
- Broccoli
- Cauliflower
- Cabbage

It is important to note that in order to get the best properties from the above foods, they should be uncooked and eaten raw.

15.13.1.7 Go Nuts

Nuts have so many different healthy elements and should not avoid them from the diet. They contain selenium, copper, zinc, iron, magnesium, and potassium. These elements can help fight cancer, prevent cancer, and keep the skin looking healthy, as well as the immune and digestive system feeling great. Remember to keep the nuts limited, as they are extremely fatty.

15.13.2 What Should We Eat Daily?

Daily, include a minimum of eight to ten glasses of water as previously stated. The diet should include complex carbohydrates, which may include bulgur, oats, barley, and cereals made with whole grains. Whole fruits, nuts, and green vegetables should be included in daily diet as well. Eggs grown organically are best as well to include in some fashion each day [128–134]. Twice weekly, include fish, cold water and deep sea fish are best, as well as poultry. Once per week limited sweets and red meat (lean cut). Consuming super antioxidant foods like pomegranate juice, acai berry and wheat grass on a daily basis is one of the easiest ways to get maximum anti-aging product benefits with minimum trouble.

15.13.2.1 Anti-aging Nutrients: The Magic of Biochemical Reactions

There are all types of anti-wrinkle creams on the market, but taking anti-aging nutrients [135–146] is one of the healthiest and most efficient ways to slow down the aging process. Aging affects both men and women, and can have both internal and external results that occur when cell production slows down. By taking anti-aging nutrients on a daily basis, both the internal and external results of aging can be slowed down significantly.

Anti-aging nutrients consist of many things already include in the diets, such as dietary minerals, antioxidants, and vitamins [135–146]. Each and every the day human body needs these nutrients to function normally, yet increased amounts can actually work to slow down the aging process. Aging occurs when cell production slows down and changes, but anti-aging nutrients can actually stimulate cell production and help to keep the body in a healthy condition.

Dietary minerals are essential for all living organisms, but are actually ions that are broken down within the body once they are digested. Dietary minerals can come from either food sources or supplements,

where each elemental mineral plays a huge role in how the human body functions. Several dietary minerals are considered anti-aging nutrients, since they directly target the causes of aging and slow down the process.

Manganese, a trace mineral, is one of the essential anti-aging nutrients for all living organisms for processing oxygen. It helps to clear any toxins or contaminants, which can actually speed up aging, such as inhaled cigarette smoke or even dust. It helps to clean out oxygen and ensure a clean supply, which can greatly improve health and slow down the signs of aging.

Individuals consuming diets rich in antioxidants have claimed the anti-aging benefits of such foods for years. Antioxidants help cells in the body to recover from the damage caused by the sun, food toxins, and pollutions in our environment. Antioxidants as well as other food byproducts like omega-3 fatty acids are known to reduce cellular destruction and enhance the reproduction of healthy skin and other tissue and organ cells throughout the body.

Calcium is another essential dietary mineral and can be found in various food items such as milk or cheese. Calcium can improve muscle and digestive health and can be beneficial for anyone with acid reflux or other digestive problems related to increased acid levels. Calcium promotes bone health by adding strength to them and works at clearing the blood stream of any toxins or contaminants that can accumulate over the years.

Selenium is essential for peroxidases, which is a large family of antioxidant proteins. The selenium is a key ingredient in this family, which actually removes toxins within the blood stream and organs in the body. Excessive levels of toxins within the body can lead to faster aging and health problems, yet the selenium helps to clean the body of them to slow down the aging process.

Several enzymes within the body require zinc, another one of the many anti-aging nutrients. Each enzyme group has a different function, such as maturing proteins, carbon dioxide conversion, or to break down alcohol within the body.

Antioxidants are also anti-aging nutrients, and are as essential as the dietary minerals found within the body [135–147]. They are molecules that either slow down or prevent the oxidation of other molecules, in order to prevent the production of free radicals that can damage cells. Lycopene, an antioxidant found in many fruits and vegetables, is a powerful quencher of singlet oxygen, which can actually lead to aging skin when produced during exposure to ultra violet light. It has also been linked to overall improved health, and has shown to decrease the occurrence of cardiovascular disease, cancer, diabetes, and osteoporosis.

Glutathione is another necessary antioxidant, since it directly protects various cell groups from free radicals within the body. By protecting the cells, the free radicals are unable to slow or stop cell production and cause aging to occur. Glutathione cannot be directly used as a supplement, but concentrations can be increased by supplementing cysteine, which can be found in various food products.

Polyphenols are another type of the many beneficial anti-aging nutrients, and have shown to have antioxidant characteristics as well as many health benefits. Polyphenols can reduce the risk of several health conditions, such as cardiovascular disease and certain forms of cancer. They also bind with nonheme iron in the body, and have been shown to reduce the absorption of it by the body.

Even though there are all types of over-the-counter products that can reduce the signs of aging, anti-aging nutrients can actually target the cause of aging and slow it down. Anti-aging nutrients also have many health benefits, and can reduce the risk of serious health conditions in many individuals. They can be found in various food products and vitamin supplements, and are essential for maintaining good health and proper organ functions.

15.14 Anti-Aging Exercise: Rational Method to Slow Down the Clock

To slow down the biological clock [121–147] by employing a series of tested effective training protocols is of great importance for youthful appearance and health and to slow down the process of body aging based on a series of hormonal changes within the body. There are several types of anti-aging exercise. Through proper anti-aging exercise, one can manipulate these hormones declines to enjoy an extended youth. This may sound too good to be true, but it definitely is not. Many people employ proper anti-aging exercises to maximum effect.

15.14.1 The Major Principals Behind Anti-Aging Exercise

To understand how exercise can slow down aging, one must understand what exactly aging means in the common sense of the term. Aging refers to a decrease in vitality within a given system as time passes. The key to maintaining the body is essentially taking care of three essential systems. These three systems are mobility, endurance, and strength. Mobility can be preserved through intelligent scientifically applied stretching programs. Endurance can be preserved through effective cardiovascular training, and strength can be augmented through intelligently applied resistance training. These three things make up the basis of anti-aging exercise.

An effective regime for preserving the mobility is by stretching the muscles and joints through their full range of motion. This is what keeps the body supple throughout life and will make the body less prone to injury because the muscles are able to handle and twist and turn that may be thrown at them. Stretching consists of three basic types. The first is known as ballistic stretching. Ballistic stretching relies on dynamic motion to work a given muscle through its range of motion. Ballistic stretching is geared toward preparing athletes for dynamic movements, like those involved in sprints and jumping, as well as martial arts. Ballistic stretching is a great way to prepare the body for rapid action. The second type of stretching is known as proprioceptive neuromuscular facilitation. Also known as PNF, PNF was developed by physiotherapist for use in rehabilitating sufferers of sports and other injuries. Although it is a supremely effective way to treat the body, it is not commonly used for typical anti-aging exercise. The third type of stretching which is the most common and is the most widely known is static stretching. Static stretching relies on easing a muscle group into a stretched position and then holding that stretch for 15–30 s. When static stretching is employed, the goal is to increase local blood flow to the muscle being stretched as well as slowly increase the range of motion over a period of time. This time period could be anywhere from weeks to months depending on the natural flexibility of the person who is stretching as well as the time it takes for micro trauma from stretching to heal within the muscle. These are the basics to stretching, all of which have their positives and negatives concerning anti-aging exercise.

The second key to anti-aging exercise is to increase the endurance and cardio vascular health through a proper regime of cardio vascular exercise. The goal of cardio vascular exercise is to decrease the resting heart rate, increase metabolism, and decrease fat and cholesterol within the blood. The stronger the heart health, the less likely you are to succumb to high blood pressure, atherosclerosis, and stroke. Most heart disease is due to obesity and high levels of cholesterol within the blood. Through a regular regime of cardio vascular exercise like jogging, swimming, and cycling the body will maintain a low level of body fat and cholesterol.

The third piece of the anti-aging puzzle is strength. The strength training will not only make one stronger and look younger, but will also increase the amount of growth hormone within the body.

Growth hormone has the powerful anti-aging effects of decreasing body fat and increasing lean muscle mass as well as protecting bones from osteoporosis. So, through proper strength training, makes one look better and protects the bones from becoming brittle. This pays huge dividends toward warding off the effects of aging on your body. Proper anti-aging exercise is the key to keeping the heart, mind, and body youthful and vibrant.

15.15 Basic Tips for Choosing the Right Anti-aging Health Products for Unique and Individual Needs

Look at supplements that promote elastic, youthful skin such as vitamin E, vitamin C, and also include a good basic skin care regimen [148–156]. For aches and pains consume anti-aging health products that promotes joint health such as glucosamine chondroitin tablets and various mineral supplements like zinc and magnesium.

Anti-Aging Face Creams – There are all types of anti-aging face creams currently on the market, most of which can be easily purchased at a local drug or beauty store. The only problem is that only a handful of the products on the market actually work, while the others only moisturize the skin. Because of this, it is important to purchase anti-aging creams that contain certain ingredients, to ensure they are actually worth spending money on.

Anti-aging creams can actually stimulate new cell production, with the help of various vitamins and nutrients that promote overall skin health. The most beneficial of such creams and ointments include the ingredients retinol, a vitamin A compound and antioxidant that helps reduce the appearance of wrinkles and neutralizes free radicals. Hydroxy acids, especially alpha hydroxy acids, beta and poly hydroxy acids are known to be nature's own exfoliants. Coenzyme Q10, tea extracts, kinetin and copper peptides are also nutrients, antioxidants and anti-inflammatory ingredients that may be found in cell structures that help reduce the signs of aging. Vitamin A is one of the most popular ingredients contained in anti-aging creams, since the vitamin actually triggers new cell growth when used on a regular basis.

Vitamin C is another must-have for anti-aging benefits, since its bleaching power can actually help to lighten any dark spots or discolorations on the skin. The vitamin C can actually destroy the melanin pigment, which is the substance that gives discolorations and freckles their color. The vitamin C can also help to speed up healing of any acne, and can promote overall healing of damaged or sensitive skin.

15.16 Some Alternative Solutions

Instead of using anti-aging face creams, there are also many options for treating aging skin with raw ingredients. Hazelnut oil can be directly applied to the skin to help slow down the signs of aging, while promoting overall health and improving the look of skin. It works to refine pores, reduce oiliness, and can even moisturize dry and leather like skin. It also firms the skin by promoting cell production, which can help reduce the appearance of wrinkles and saggy skin. Hazelnut oil produces new elastin and collagen fibers, which can help to fill in any defined lines or wrinkles that have occurred from aging. When used in place of anti-aging creams, hazelnut oil can improve the overall appearance of skin.

Aloe Vera is another alternative to anti-aging creams, since the sap inside the plant has many medicinal qualities. When using raw aloe on the skin, it can actually improve the immune system and help heal dry, damaged, or sensitive skin. The aloe sap can also reduce inflammation and help wounds

heal faster, while moisturizing the skin and making it much more radiant. The aloe plant is ideal for slowing down the effects aging has on the skin, and can be used to prevent the signs from occurring when used on a regular basis. Anti-aging face creams and other raw ingredients can easily reduce the signs of aging, especially when used on a regular basis. By promoting cell production and overall health for the skin, maintaining a healthy and youthful appearance can be easily achieved.

15.17 Anti-aging Research

Anti-aging research has recently uncovered two compounds with amazing anti-aging properties: resveratrol and Juvenon [157–168]. Both resveratrol and Juvenon can help to slow the aging process and keep anyone looking and feeling attractive and energetic well into the latest stages of life and both can be effectively taken as daily anti-aging supplements. Anti-aging research has shown that resveratrol is a substance that is produced naturally by some plants when they are attacked by various pathogens [169].

Anti-aging research done on mice and rats revealed that when the research animals were given resveratrol every day, this amazing substance lowered blood-sugar, reduced bodily inflammation of all kinds, increased cardiovascular function, general heart health and caused the animals to age more slowly. Resveratrol is found in the skins of red grapes and is present in most types of red wine, but in order to obtain the anti-aging effects of resveratrol human beings have to take it in the concentrated form of anti-aging supplements. While anti-aging research has not proven the ability of resveratrol to reverse aging in humans, preliminary results are promising, and no major negative effects for taking resveratrol anti-aging supplements have so far been found.

Another compound that has been found to be useful in reversing or slowing the effects of aging by current anti-aging research studies is Juvenon. Juvenon is not a single substance like resveratrol, but rather a popular anti-aging supplement that contains alpha lipoic acid (ALA) and acetyl-L-carnitine (ALCAR), two substances that are essential to healthy cell function. ALA and ALCAR are essential to the normal activities mitochondrial cells; the cells responsible for memory, alertness, healthy mood, and general energy level.

The anti-aging research supporting the use of Juvenon suggests that replacing the levels of ALA and ALCAR in the human blood stream helps the mitochondria to keep functioning at optimal levels and thus slow or reverse the aging process.

Both resveratrol and Juvenon are widely available online and at pharmacies and health food stores in the vitamin and supplement section. In general, both resveratrol and Juvenon are well tolerated by most people and tend to cause few if any problems. So many great anti-aging supplements exist however, that it is always a good idea to stay informed about drug interactions and keep your own doctor in the loop. Anti-aging research continues to open the door to new ways to stay young and vital well into later life. Never before has it been this easy to stay so young for so long.

15.18 Conclusion

The quest for slowing down the aging process and achieving younger looking skin has become a multi-billion dollar business and in 2008, over 15 million cosmetic procedures were performed. The effects of injections are gone in a short amount of time (short-lived effects) and plastic surgery requires updating every 3–6 months depending on the type of treatment. Viable options

are limited-incision facelifts and neck lifts, which can reduce visible aging symptoms by about 5 years. Full facelifts and brow lifts can provide more dramatic, longer-lasting results, enhancing one's overall youthfulness. Rhinoplasty can also rejuvenate an entire facial appearance by reshaping the nasal structure. Facial implants may add instant depth. No matter what equipment or techniques are used, laser resurfacing rarely removes or markedly reduces deep wrinkles or facial sag. If wrinkles are movement related, BOTOX (botulinum toxin) injections are likely to be both safer and more effective. Another alternative for deep wrinkles, whether related to movement or not, are wrinkle fillers, such as Restylane. Injectable fillers and botulinum toxin are suitable for people with busy lifestyles who do not want the inconvenience of a long recovery. Radiofrequency is a procedure that offers an alternative to the traditional facelift. Dermabrasion, laser resurfacing, chemical peeling, micro dermabrasion, and some topical treatments can restore skin, giving it a smoother and refreshed appearance. Facelift remains the procedure of choice to correct marked facial sag. Carbon dioxide and erbium lasers have also been approved to treat sun damage and wrinkles. Use of these lasers is considered minor surgery and is done under anesthesia. These treatments are quite expensive and not everyone can afford them.

Lots of products are out there that claim to reduce and prevent wrinkles. Most of them don't work and most of the claims haven't been scientifically established. Typically, the label will have some complex pseudo-scientific jargon about antioxidants, nutrients and other things that supposedly make the skin look younger. These claims are almost entirely untrue (although some preliminary research shows potential in special formulations that are not yet available over the counter). According to the NIH (National Institutes of Health) and the American Academy of Dermatology, most over-the-counter anti-aging skin care products that target wrinkles merely soothe dry skin. This means they feel very nice going on, but do not reduce those wrinkles at all. By increasing the amount of antioxidants in one's system, one will have less damaging free radicals in the body. The necessary antioxidants can be found in several sources: Multivitamin pills, especially Vitamins C and E.

Fish oil, compounds contains a plethora of important antioxidants, as well as omega-3 and omega-6 fatty acids. It is good for the skin, and good for the entire body. Another fantastic source for antioxidants and important bioflavonoids is grape seed extract. Studies have shown that grape-seed oil is even more potent than vitamin E and vitamin C in the quest for anti-aging. As helpful as sunscreen, exfoliation, and medically based surface treatments are in the fight against aging, it is not realistic to expect noninvasive procedures and products to cure 40 or 50 years' worth of tissue damage. Retinoin cream is created from vitamin A and available with a prescription to treat sun damage and wrinkles as well as age spots and roughness by stimulating the skin to produce collagen.

In this world of quick fixes, plastic surgery, and a barrage of "miracle" cures, one thing is clear: These things don't offer a holistic, long-term approach to keeping the entire body fit, healthy, and young for as long as possible. Frankly, there has been a failure of prescription medicine in the war on degenerative diseases. The best way to keep our bodies healthy – starting today and lasting a lifetime – is to eat a healthy diet, exercise moderately and consider starting a regimen of supplements that include antioxidants, minerals, and vitamins. These important ingredients help keep the cells healthy, inside and out, and remove the danger that the free radicals cause including internal and external damage. Currently, dietary restriction is the only experimental manipulation that has been shown to retard aging of mammals. Although mechanism whereby dietary restriction retards aging is currently unknown, much of the emerging data suggest that the calorie-restricted rodents live longer and age more slowly because they are more resistant to stress and have an enhanced ability to protect cells against damaging agents. Scientific research in the field of anti-aging continues to give rise to new and promising treatment options. A dermatologist can help sort through the numerous options, including the myriad of over-the-counter products.

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Part V
Economic Effects of Dietary Components
in Disease and Prevention Therapy

Chapter 16

Antiviral Potential of Vegetables: Can They be Cost-Effective Agents for Human Disease?

Robert Kelechi Obi

Key Points

- Vegetables are herbaceous plants whose part or parts are eaten as supporting food or main dishes and they may be aromatic, bitter, or tasteless.
- They are the cheapest and most available sources of important proteins, vitamins, minerals, and essential amino acids.
- Many vegetables also contain phytochemicals, which may have antioxidant, antibacterial, anti-fungal, antiviral, and anticarcinogenic properties.
- The recent upsurge in the use of plant-derived materials is driven in part by the high cost of conventional health care, as well as emergence of drug resistant microorganisms and development of drug-related allergies.
- These wonderful herbal sources of cure could be compounded into tablets, injections, and syrups to meet the consumers' taste, whereby control measures as to production regulation would be enforced.
- Given the increasing pressures to control healthcare spending in most countries, there is indeed the need to focus attention on the cost effectiveness of herbal remedies.

Keywords Antioxidant • Antiviral vegetables • Cost effective agents • Fiber • Human disease • Vitamins

16.1 Introduction

For every illness known to man nature has provided an answer in the form of one herb or a combination of herbs. Through the ages, plants have been used as sources of drugs administered empirically for the cure of diseases. The use of plants or herbs came to our ancestors at the dawn of civilization. They observed that sick animals when allowed to eat certain plants and grasses got cured of their illness in the majority of cases. Man then decided to eat the same plants and grasses whenever he was ill. That according to the legend began the use of herbs [1].

Vegetables are those herbaceous plants whose part or parts are eaten as supporting food or main dishes and they may be aromatic, bitter or tasteless [2]. The utilization of leafy vegetables is part

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of Africa's cultural heritage and they play important roles in the customs, traditions, and food culture of the African household [3]. Nigeria is endowed with a variety of traditional vegetables and different types are consumed by the various ethnic groups for different reasons. Vegetables are the cheapest and most available sources of important proteins, vitamins, minerals, and essential amino acids. They are included in meals mainly for their nutritional value; however, some are reserved for the sick and convalescent because of their medicinal properties [4].

The nutritional content of vegetables varies considerably, though generally they contain a small proportion of protein and fat [5, 6], and a relatively high proportion of vitamins, provitamins, dietary minerals, fiber, and carbohydrates. Many vegetables also contain phytochemicals, which may have antioxidant, antibacterial, antifungal, antiviral, and anticarcinogenic properties [7, 8]. The presence of many vitamins and other substance in vegetables provide nutrients that help in protecting the body against cancer, diabetes, and heart disease. Similarly the high levels of fiber in vegetables keep the digestive system healthier and assist in preventing constipation. Vegetables also add wonderful flavors to human diet (www.eFresh.com).

Vegetables are eaten in a variety of ways, as part of main meals and as snacks. While some, such as carrots, bell peppers, and celery are eaten either raw or cooked; others such as spinach, pumpkin, and lettuce are eaten only when cooked [7].

Vegetables have been categorized according to their type and taste. Different varieties include bulb vegetables (e.g., garlic, onion); fruit vegetables (e.g., avocados, cucumber); inflorescent vegetables (e.g., broccoli, cauliflower); leaf vegetables (e.g., spinach, lettuce); root vegetables (e.g., carrot, beets); stalk vegetable (e.g., asparagus, celery); and tuber vegetables (e.g., yam, cassava) (www.eFresh.com). The most powerfully protective domesticated vegetables that are most commonly eaten however are spinach, garlic, broccoli, brussels sprouts, carrots, sweet potato, red pepper, winter squash, and frozen peas (http://www.naturalhub.com/natural_food_guide_vegetables.htm), and *Amaranthus cruentus* L, *Telferia occidentalis* Hook F (fluted pumpkin), *Celosia argentea* L (soko), *Talinum triangulare* (Jacq.) Wild (water leaf), *Vernonia amygdalina* L (bitter leaf), *Gongronema latifolium* L (bush buck), *Cochorus olitorius* L (jute mallow), *Ocimum grattissimum* L (scent leaf), *Gnetum africana* Welw (okazi) and *Piper guineense* Schum and Thonn (Black pepper) among several others [3].

Recently, the use of alternative therapies involving consumption of edible vegetables that promote general well being has become widespread. In particular, there has been resurgence in the public's demand for herbal remedies, despite a lack of high-quality evidence to support the use of many of them [9]. This upsurge in the use of plant-derived materials, as believed by many experts, is driven in part by the high cost of conventional health care, as well as the emergence of drug resistant micro-organisms, and development of drug-related allergies. Given the increasing pressures to control healthcare spending in most countries, it is not surprising that attention is now being focused on the cost effectiveness of herbal remedies.

16.1.1 Health Benefits of Eating Vegetables

There is a growing body of evidence that vegetable consumption has greater health benefits than previously recognized. Vegetables are packed full of antioxidants, fiber, vitamins, minerals, phyto-nutrients, and thousands of other plant chemicals known to provide health benefits. Along with all the many disease-reducing benefits, eating vegetables can also help control weight [10].

Vegetables are low in fat and calories, a good source of dietary fiber and extra energy. All these features help control weight effectively. Being low in calories, a large quantity of vegetables could

be eaten without consuming excess energy while the high fiber content would help to fill the stomach faster, thus limiting the total amount of food consumed. The presence of many vitamins and other chemicals in vegetables supply the body with nutrients necessary to boost energy production within the muscle cells. This, as has been established, provides a natural feeling of vitality and the energy to become more active by helping to burn more energy each day [11].

Vegetables are also low in sodium and this helps to reduce water gain. Sodium is present in virtually all processed foods; it causes the body to hold water within the interstitial areas of the body. It has been estimated that many average people may be holding up to 5 lb of additional water caused from a high intake of sodium. Any reduction in sodium intake will help maintain normal body water content and if enough vegetables are eaten sodium intake naturally lowers blood pressure [12].

Dark green leafy vegetables contain folate, which is essential for normal growth and maintenance of body cells. Folate is found in spinach, dried beans, liver, yeast breads, wheat germ, some fortified cereals, and mustard. Oranges are also a good source of folate. Some dark green leafy vegetables are good sources of calcium too. Vegetables in the cabbage family may be natural cancer fighters. They are called cruciferous vegetables. Experts believe that the nutrients, compounds, and phytochemicals they contain, along with their beta carotene, fiber, and vitamin C, have cancer fighting properties. Vegetables in this group include broccoli, Brussels sprouts, cauliflower, and cabbage [12–14].

Higher consumption of fruit and vegetables also reduces the risk of coronary heart disease and stroke. A recent study found that each increase of one portion of fruit and vegetables a day lowered the risk of coronary heart disease by 4% and the risk of stroke by 6%. Evidence also suggests that an increase in fruit and vegetable intake can help lower blood pressure [14].

Vegetables eliminate excess toxins and wastes from the body, thereby enhancing its good health. Raw vegetables reduce excess cholesterol and balances blood sugar levels. Tomatoes and tomato juices contain lycopene. This has been linked to a lower risk of heart disease and certain cancers, including prostate cancer. Bananas, oranges, apricots, melon, and dried fruits contain potassium, an important mineral for the body [10].

Obi and Nwanebu [15], reported the incurability of a group of transmissible spongiform encephalopathies (TSEs) known to be responsible for some of the brain dementias associated with old age. In a recent study however, it was found that consumption of several vegetables, especially spinach could retard these age-related central nervous system and cognitive behavioral deficits. Similarly, constant consumption of spinach by women (280 g/10 oz of fresh, raw spinach) could push their oxygen radical absorbance capacity score higher than when they took a massive 1.250 g (1,250 mgs) of vitamin C. Oxygen radical absorbance capacity or (ORAC) measures the ability of a given food to scavenge and neutralize damaging free radicals in the body [16] ([//www.naturalhub.com/natural_food_guide_vegetables.htm](http://www.naturalhub.com/natural_food_guide_vegetables.htm)).

16.1.2 Nutrients in Vegetables

16.1.2.1 Useful Antioxidants

Vegetables indeed contain compounds that are valuable antioxidants and protectants. Chief among these are the carotenoids. There are over 600 carotenoids in plants and in some animals (pink salmon is pink because of the carotenoid astaxanthin it contains). Only some – mainly beta-carotenes – are precursors to vitamin A production by the body. The carotenoids not destined to be converted to vitamin A and unconverted beta-carotene is present in human tissues in very small amounts. The main carotenoids contained in human tissues of people consuming western diets include beta-carotene,

Table 16.1 Oxygen radical absorbance capacity of some vegetables, per 100 g in “ORAC units” (approximately rounded to the nearest 50)

Vegetable	Scientific name	ORAC unit
Garlic	<i>Allium sativum</i>	2,000
Kale	<i>Brassica oleracea</i> var. <i>acephala</i>	1,800
Spinach	<i>Spinachia oleracea</i>	1,300
Brussels sprouts	<i>B. oleracea</i> var. <i>gemmifera</i>	1,000
Alfalfa sprouted seeds (sprouts)	<i>Medicago sativa</i>	950
Broccoli	<i>B. oleracea</i> var. <i>italic</i>	900
Beet	<i>Beta vulgaris</i>	850
Red pepper	<i>Capsicum annuum</i>	700
Onion	<i>Allium cepa</i>	500
Sweetcorn	<i>Zea mays</i>	450
Eggplant	<i>Solanum melongena</i>	400
Frozen peas	<i>Pisum sativum</i>	400
Potato	<i>Solanum tuberosum</i>	300
Sweet potato	<i>Ipoemea batatas</i>	300
Cabbage	<i>B. oleracea</i> var. <i>capitata</i>	300
Lettuce, leaf	<i>Latuca sativa</i>	250
Carrot	<i>Daucus carota</i>	200
Green bean	<i>Phaseolus vulgaris</i>	200
Tomato	<i>Lycopersicon lycopersicon</i>	200
Yellow squash	<i>Cucurbita pepo</i>	150
Lettuce	Crisphead	100
Celery	<i>Apium graveolens</i>	100
Cucumber	<i>Cucumis sativus</i>	100

Oxygen radical absorbance capacity or (ORAC) measures the ability of a given food to scavenge and neutralize damaging free radicals in the body. A single serving of fresh or freshly cooked vegetables has, on average, 300–400 ORAC units (From <http://www.ars.usda.gov/is/np/fnr/fnr499.htm#Antioxidant>)

[alpha-carotene, lycopene, lutein, zeaxanthin, and beta-cryptoxanthin. Lycopene contains the greatest antioxidant properties, followed by beta-carotene and cryptoxanthin, then lutein and zeaxanthin [17].

One very useful method adapted to measure the protective antioxidant potential of vegetables or fruits is to measure its ability to absorb damaging oxygen radicals (Table 16.1). These free radicals are implicated in aging, especially memory loss and loss of co-ordination, and degenerative diseases. It does provide a way to measure one element of the relative health usefulness of a vegetable without having to understand which natural plant chemical or combination of chemicals acting together, are responsible for the effect [13].

From the measurements of various vegetables so far, scientists have been able to estimate that a single serving of fresh or freshly cooked vegetables has, on average, 300–400 ORAC units. But some specific vegetables, such as garlic and kale, have particularly high antioxidant levels. A single garlic clove, which weighs around 5 g, has around 100 ORAC units – a massive contribution in a small package. But even a small – 30 g (about 1 oz) – serving of carrots, although much lower on the ORAC scale, is just about equivalent to a clove of garlic for oxygen radical absorbance capacity [18].

Besides, antioxidant activity, some carotenoids, such as lutein, found in dark green leafy vegetables, could also act as an immuno-stimulant, influencing immune cells at the gene level. In addition lutein could increase the density of the macular pigment in the eye and reduce the risk of age related macular degeneration (<http://www.ars.usda.gov/is/np/fnr/fnr499.htm#Antioxidant>).

16.1.2.2 Vitamins and Minerals

Vegetables are important sources of vitamins. They are particularly important as a source of vitamin A, vitamin C, and folate (folic acid, folacin). These three are the major vitamin constituents, but many vegetables are also good sources of thiamine (B1), riboflavin (B2), pantothenic acid (B5), and pyridoxine (B6), which is important in brain function, immune system function, and a precursor to several important hormones. Many vegetables also contain small but useful amounts of vitamin E [19].

Vegetables are generally very good sources of most minerals. Besides the energy derived by eating tubers and roots, it is the protective phytochemicals and the vital vitamin C, vitamin A, and folic acid content that make vegetables essential to human well-being (www.eFresh.com).

Vitamin A

Plants are full of natural pigments called carotenoids, generically referred to as vitamin A; while in animals, vitamin A is referred to as retinol and is obtained from fish liver oils, liver, eggs, and butter and cheese. Very large amounts of retinol are potentially toxic. Vitamin A is concentrated in the liver of all animals, with the highest concentrations found in the livers of carnivorous animals [17].

Carotenes and beta-carotenes are generally obtained from plant foods. Beta-carotene, sometimes called provitamin A, is a precursor of vitamin A. Beta-carotene is converted to vitamin A by the body. Because the rate at which beta-carotene is converted to vitamin A in the body is known, most often, vitamin A content of foods is quoted as actual vitamin A (retinol). It is generally expressed as the number of micrograms per 100 g sample. The micrograms of beta-carotene are usually converted into International Units of vitamin A (by multiplying microgram (mcg) of beta-carotene by 1.6).

Beta-carotene is nontoxic under most circumstances. In fact, the body has a mechanism whereby it can regulate beta-carotene absorption (although absorption is generally rather low and maybe about the range of 15–35%). For raw carrots, for example, only about 1% of the carotene present in the carrot ends up being absorbed. This may rise to maybe 19% when the carrot is cooked. In spite of the fairly low rate of conversion however, carrots alone provide 30% of the vitamin A in diets (http://www.naturalhub.com/natural_food_guide_vegetables.htm).

Fats in meals improve the conversion of beta carotene to the fat soluble vitamin A. The amount of beta carotene converted to vitamin A varies. The more the food is finely chewed or grated, the greater the availability. Moderate cooking increases the availability, as it helps break down the cell walls of the vegetable. Repeated cooking at higher temperatures destroys some of the vitamin A. Vegetables lightly cooked in olive oil, however, are a very good way of maximizing the amount of available beta carotene in diets [20].

There are a number of carotenoids in plants, usually contributing to the yellow, orange, or red coloration of the tissues, among other values. Pumpkin, an outstanding source of carotenoids, is said to have over 500 kinds of carotenoids, and the cooked pulp has as much beta carotene as cooked carrot. Vitamin A is an important antioxidant, vital for healthy skin with good cell membranes, and important for the function of the immune system. But regardless of whether they are converted to vitamin A or not, carotenoids protect cells against oxidative damage. There is indeed a definite correlation between intake of beta carotene derived from vegetables and fruits and lower risk of cancer [21].

Vegetables are one of the most important sources of beta-carotene (the best fruits are mangoes, with 3,894 IU per 100 g serving; melons, with 3,224 IU per 100 g; and apricots with 914 IU per fruit), not least for their inexpensiveness and everyday availability or usage. The recommended daily allowance of beta-carotene for an adult is 3,200 IU, with the optimum intake for well being considered to be 8,000 IU [14] (Table 16.2).

Table 16.2 Vegetables rich in vitamin A

Vegetable	Beta-carotene content (IU)
Pumpkin canned	27,000
Sweet potatoes, baked	20,000
Carrots, cooked	20,000
Spinach, fresh, boiled and drained	7,400
Butternut pumpkin, cooked	7,000
Red sweet pepper, one medium	6,800
Winter squash, “pumpkin,”	6,000
Beet greens, cooked	3,600
Swiss chard, cooked	2,500
Broccoli	1,000
Tomato, one medium	760
Brussels sprouts, cooked	560

Half a cup serving of these vegetables contains these beta-carotene measured in International Units. The number of micrograms per 100 g sample – and the micrograms of beta-carotene are converted into International Units of vitamin A by multiplying mcg of beta-carotene by 1.6. Beta-carotene is non toxic under most circumstances. From http://www.naturalhub.com/natural_food_guide_vegetables.htm

Vitamin C

In temperate climates vitamin C could be stored in the body for up to 3 month especially, during the winter, with small top-ups from tubers and dried fruits. In subtropical and tropical areas, young palatable vegetation is readily available, so storage is not necessary.

Vegetables could be frozen or canned and still remain important sources of vitamins and minerals. A study by the University of Illinois compared the nutrient value of fresh, frozen, and canned produce using both the USDA’s nutrient database and nutrition label claims. According to this study, in most cases the canned vegetables appeared to have nutritional values equivalent to the fresh and frozen forms of the vegetable. Canned and fresh asparagus are comparable for vitamin A and C, and canned spinach, carrots, and pumpkin exceeded the recommended daily intake (RDA) requirement for vitamin A. Canned, fresh, cooked, and frozen carrots have comparable vitamin A. Canned spinach provides anywhere from 50% to 160% of the RDA of vitamin A, depending on the brand, as well as about 15 mg of vitamin C. Canned potatoes also have higher vitamin C than when fresh, possibly, because ascorbic acid may be added as an antioxidant in the canning process (to prevent the peeled potatoes browning when they are exposed to air) (http://www.naturalhub.com/natural_food_guide_vegetables.htm) (Table 16.3).

Folic Acid

The word “folate” is derived from the Latin *folium*, a leaf – a good clue to its high concentration in green leafy vegetables. Deficiency of this natural plant constituent in pregnant women has been linked to particular forms of birth defects. This is because folate is involved in enabling normal cell multiplication for growth and development. Folate deficiency means that the red blood cell production is reduced, resulting in fatigue, and the white blood cell production is slowed, leading to increased susceptibility to infection. In fact, many tissues are affected to a greater or lesser degree when folate is lacking. Though folate could be stored by the body, deficiencies could also arise because folate is water soluble, damaged to some degree by heat (raw cabbage contains 90 µg/100 g of folate while boiled cabbage contains 35 µg/100 g) and reduces in amount in storage (http://www.naturalhub.com/natural_food_guide_vegetables.htm) (Table 16.4).

Table 16.3 Vegetables rich in vitamin C

Vegetable	Mg
Red ripe sweet pepper	226
Broccoli, cooked	58
Brussel sprouts	48
Sweet potato, baked	25
Cabbage, shredded, raw	16
Watercress, chopped	15
Potato, baked, one medium	12
Green pea, frozen, boiled	8
Spinach, boiled	8
Cowpea (<i>Vigna unguiculata</i>) chopped, boiled leaf tips	5
Lettuce, looseleaf, shredded	5
Lettuce, butterhead	3
Carrot, slices, boiled	2

The figures are the contents of Vitamin C in half a cup serving of the vegetables [19]

Table 16.4 Vegetables rich in folic acid [19]

Vegetable	Mcgs/100 g
Wheat germ	330
Raw endive	330
Bran flakes	260
Liver	240
Watercress	200
Spinach	115
Parsley	116
Broccoli	110
Swiss chard/silverbeet	92
Raw cabbage	90
Brussels sprouts	87
(Cooked) frozen peas	78

16.1.2.3 Fiber

This important constituent of vegetables enhances gastrointestinal function, prevents constipation and may reduce the incidence of metabolic diseases like maturity onset, diabetes mellitus, and hypercholesterolemia. Some vegetables rich in fiber include *A. cruentus* L. (Amaranth), *Telferia occidentalis* Hook F. (Fluted pumpkin), *Celosia argentea* L. (Soko), *Talinum triangulare* Jacq. Wild. (Water leaf), *V. amygdalina* L. (Bitter leaf), *G. latifolium* L. (Bush buck), *O. gratissimum* L. (Scent leaf), *Gnetum africana* Welw. (Okazzi), *P. guineense* Schum and Thonn (Black pepper) [3].

16.1.3 Some Vegetables with Antiviral Properties

Viruses are difficult to inactivate chemically and usually require highly toxic agents to do so.

Once a cell is infected it is difficult selectively to inhibit the virus without harming the cell.

Medicinal herbs including edible vegetables contribute to the fight against viral infections through enhancement of immunity [22].

16.1.3.1 *A. viridis* (Linn)

A. viridis is a cosmopolitan species in the botanical family Amaranthaceae. It is commonly known as slender amaranth or green amaranth. It is a monoecious annual herb with erect or occasionally ascending stems 1–8 (-10) dm long, sparingly to densely branched, striate, glabrous and usually becoming pubescent with multicellular hairs above (Fig. 16.1a and b). The leaves are deltate-ovate to narrowly rhombic, with petioles 1–10 cm in length and blades 2–7 cm in length and 1.5–5.5 cm wide. The flowers are green, monoecious (individual flowers are either male or female, but both sexes can be found on the same plant) and are pollinated by wind. The fruit is subglobose and 1.3–1.5 mm long, indehiscent or rupturing irregularly at maturity. The seeds are dark brown to black, more or less shiny, slightly compressed, and 1–1.3 mm long. Propagation is done with the seeds [23] (http://www.pfaf.org/cgi-bin/pfaf/arr_html?Amaranthus+viridis).

Species of *Amaranthus* were widely used by prehistoric and modern Native Americans as food forage for livestock, medicinal plants, and, occasionally, for some other uses, such as face and body paint, ceremonial items, and fuel [24]. The leaves are cooked as spinach to produce a mild flavor. The leafy stems and flower clusters are similarly used. On a zero moisture basis, 100 g of leaves contains

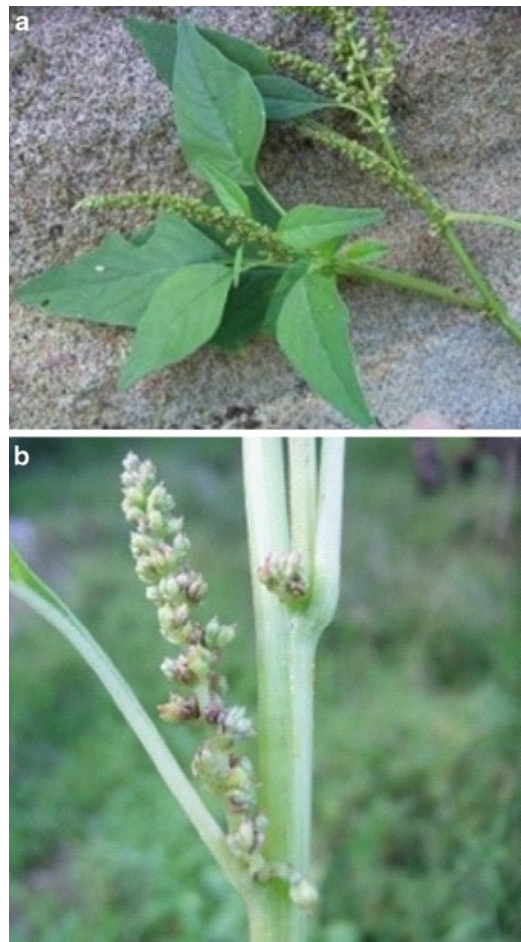


Fig. 16.1 (a) Leaves and inflorescence (b) inflorescence forming

283 cal, 34.2 g protein, 5.3 g fat, 44.1 g carbohydrate, 6.6 g fiber, 16.4 g ash, 2,243 mg calcium, 500 mg phosphorus, 27 mg iron, 336 mg sodium, 2,910 mg potassium, 50 mg vitamin A, 0.07 mg thiamine, 2.43 mg riboflavin, 11.8 mg niacin and 790 mg ascorbic acid. The seeds are similarly cooked. They are very small, easy to harvest and very nutritious. They can be cooked whole to make them gelatinous, but it is rather difficult to crush all of the small seeds in the mouth and thus some of the seed will pass right through the digestive system without being assimilated. The seed contains 14–16% protein and 4.7–7% fat (<http://plantnet.rbgsyd.nsw.gov.au/>).

A. viridis is eaten traditionally as a vegetable in South India, especially in Kerala, where it is known as *Kuppacheera*. It is also eaten as a vegetable in parts of Africa [25]. A traditional food plant in Africa, this little-known vegetable has potential to improve nutrition, boost food security, foster rural development and support sustainable landcare [26]. It is also used as a medicinal herb in traditional Ayurvedic medicine, under the Sanskrit name *Tanduliya* [27]. A decoction of the entire plant is used to stop dysentery and inflammation. The plant is also used as an emollient and a vermifuge (<http://plantnet.rbgsyd.nsw.gov.au/>). Furthermore, Obi et al. [28] in a study in Nigeria, demonstrated that extracts from the leaves of the plant were able to inhibit the measles virus at very low concentrations. According to the study cell cultures were treated with the plant extract before virus stock was added. The observed resistance to the virus stock proved that constant consumption of the plant could prevent initiation of a viral infection.

Spinach is a super source of antioxidants and cancer antagonists, containing extremely high beta-carotene and lutein. It is also rich in fiber that helps lower blood cholesterol. Some of its antioxidants are destroyed by cooking which makes it advisable to eat it raw or lightly cooked (http://www.natural-hub.com/natural_food_guide_vegetables.htm).

In Hawaii, the most common naturalized species of *Amaranthus* occur in low elevation and disturbed habitats [23]. In Fiji, *A. viridis* occur near sea level and waste places as a naturalized weed of cultivation, often locally abundant, common along roadsides and in gardens, plantations and cane-fields [29]. In Africa, it is a common weed around houses and in plantations [30]. In Tonga, it is a weed of plantations and waste areas [31]. In New Zealand, it is a crop of sand dunes [32]. In Papua New Guinea, it occurs as a weed in gardens and waste places as well as in secondary vegetation, at 0–2,000 m altitude [33].

16.1.3.2 *Euphorbia lateriflora* (Schum. and Thonn)

E. lateriflora is a low shrub reaching 1.70 m in height with near-vertical, smooth-glaucous succulent branches belonging to the family Euphorbiaceae (Fig. 16.2). The plant is commonly grown as a hedge and boundary-marker, and produces yellow flowers and leaves which shed, with abundant white latex. It is commonly found in grassy savanna from Sierra Leone to Western Cameroons [34].

The plant has various uses. The latex is used medically as a blood purifier, treatment of venereal diseases, cutaneous fungal infections, subcutaneous parasitic infections, and as a laxative. The phytochemical constituents could be used as repellants for reptiles as well as insecticides, and arachnicides [34]. In addition, Obi et al. [28] reported the antiviral properties of the extracts from the plant, with a similar effect on the measles virus as *A. viridis*.

16.1.3.3 *Lactuca taraxacifolia* (Wild)

Lactuca, commonly known as lettuce, is a genus of flowering plants in the daisy family Asteraceae. The genus includes about 100 species, distributed worldwide, but mainly in temperate Eurasia. *L. taraxacifolia*,

Fig. 16.2 *Euphorbia lateriflora*



Fig. 16.3 *Lactuca taraxacifolia*



one of the species, is an herb with basal rosette of leaves and erect stems up to 1.3 m high from a woody rhizome, originating from Senegal to Southern Nigeria, and dispersed to Sudan and Ethiopia (Fig. 16.3) [34].

The plant is often grown for cropping the leaves, which are sold in markets as cooked or rolled-up balls prepared for use. The leaves are eaten fresh as a salad or cooked in soups and sauces.

Mineral-content of the leaves is relatively high (21.8%), and the plant is burnt to ash in Northern, and Southern Nigeria to prepare a vegetable-salt. Medicinally, the leaves are used to stimulate lactation in nursing mothers and animals, strengthen skeletal structure, and in the treatment of yaws [35]. Furthermore, the plant has also been reported to exhibit antiviral activity against the measles virus [28].

16.1.3.4 *Ceratotheca sesamoides* (Endl)

C. sesamoides also known as false sesame is an annual herb measuring up to 100–120 cm in height, sometimes with woody rootstock, and prostrate, ascending or erect, pubescent stems belonging to the flora family Pedaliaceae. The leaves are opposite or nearly opposite and simple without stipules but with a petiole that measures up to 6 cm in length in lower leaves, and very short in upper leaves; the leaf blade is lanceolate-deltate to ovate-triangular or narrowly ovate, measuring 1.5–8×0.5–4.5 cm (Fig. 16.4) [35].

The flowers are solitary in leaf axils, bisexual, and zygomorphic, with a sparsely pubescent, pink, lilac, mauve or purple funnel-shaped corolla measuring 1.5–4 cm long. The Fruit is an oblong-quadrangular capsule 1–2 cm long, compressed laterally, with slender lateral horns up to 3.5 mm long, bearing many seeds. The seeds are broadly obovate in outline, compressed laterally, 2.5–4×2–2.5 mm, with a smooth, black testa that is radially rugose at the margin [36].



Fig. 16.4 *Ceratotheca sesamoides*

Ceratotheca comprises five species, all of which are native to Africa. *C. sesamoides* shows a wide range of adaptability and environmental flexibility. It occurs as a weed in formerly cultivated fields, particularly on well-drained sandy soils and in localities well exposed to the sun. It tolerates heat and drought well. Under more natural conditions it occurs in open grassland and tree savanna on sandy soils, and rarely in rocky localities [37].

The nutritional composition of fresh leaves of false sesame per 100 g include: water 81 g, energy 226 kJ (54 kcal), protein 4.2 g, fat 0.5 g, carbohydrate 11.0 g, Ca 300 mg, P 86 mg, Fe 3.2 mg, ascorbic acid 28 mg. The nutritional composition of the seed include: water 7.0 g, energy 2,303 kJ (550 kcal), protein 14.2 g, fat 46.5 g, carbohydrate 27.5 g, Ca 887 mg, Fe 38 mg, thiamin 0.75 mg, riboflavin 0.3 mg, and niacin 4.4 mg [38]. The seed oil is similar in composition to sesame oil. It contains the phenylpropanoid lignan sesamin. This compound possesses antioxidant, anti-inflammatory, antihypertensive, cytotoxic (including antitumor), and insecticidal properties [29, 39, 40].

The leaves and flowers of false sesame are consumed as vegetables. The leaves are finely chopped and used in sauces. They are also pounded and mixed with groundnut flour, salt and a little hot water or warm milk and cooked for a few minutes to produce a sauce that is eaten with porridge. Ash may be added to soften the leaves and to reduce bitterness. Onions and tomatoes may also be added. The seeds are crushed to form a paste that is eaten with beans or cassava. They are also crushed for their oil, which is especially suited as salad oil [38].

A decoction of the plant is used against diarrhea. The leaves could be steeped in water and the slimy liquid dropped into the eye to treat conjunctivitis. The mucilage is occasionally used as an emollient and lubricant. In addition the macerated leaves facilitate delivery in humans and animals when eaten in pregnancy. The leaves could also be warmed, ground, mixed with ash, and rubbed on inflamed cervical lymph nodes. The leaves, ground with the rhizome of *Anchomanes difformis* (Blume) Engl. could be applied topically in cases of leprosy. False sesamum is also reported to be used as an aphrodisiac, against jaundice, snakebites, and skin diseases [25, 41]. Besides conjunctivitis (a viral disease), extracts from the leaves of the plant has been shown to exhibit marked antiviral activity against another virus, the measles virus [28].

16.1.4 Some Other Vegetables with Medicinal Properties

16.1.4.1 *O. grattisimum* (Scent Leaf)

This annual plant with characteristic pleasant aroma is believed to be a native of India but presently grows widely in Africa and tropical America where it has several uses ranging from good flavoring for food through mosquito repellent to application in traditional treatment of diseases [42]. Scent leaf is part of a daily diet of Nigerians, particularly the Igbo tribe of Eastern Nigeria where it is used to prepare sauce, a condiment routinely served at restaurants and homes as the first course.

16.1.4.2 *G. latifolium*

Commonly called *utazi* and *arokeke* in South Eastern and South Western parts of Nigeria respectively, is a tropical rainforest plant primarily used as a spice and vegetable in traditional folk medicine. Reports by various authors showed that it contains essential oils, saponins, and pregnanes among others. It has also been reported that aqueous and ethanolic extracts of *G. latifolium* had hypoglycemic,

hypolipidemic, antioxidative and anti-inflammatory properties. In Nigeria *G. latifolium* is widely distributed in thick forests in the Southern parts of the country [43]. The plant thrives well under humid temperature in rich, loamy, and sandy soil all year round. It is cultivated in gardens using the stems or seeds. It is used as a flavoring agent and source of vitamin in foods as well as a good source of natural remedy to relieve cough and stomach ache [44].

16.1.4.3 *V. amygdalina* (Bitter Leaf)

V. amygdalina belongs to the family compositae and is very abundant in grasslands throughout the tropics. The plant, which grows as a soft, wooded shrub in Nigeria, reaches a height of about 6–15 ft with strait, pubescent branchlets that may be glabrous. It is propagated from cuttings and is commonly planted as a hedge (Fig. 16.5). The leaf is very bitter to taste, but the bitterness could be removed by washing in several turns of clean water or by boiling [45].

Bitter leaf is widely used in the Eastern part of Nigeria where the leaf serves as a key ingredient of one of the vegetable soups commonly eaten by the Ibos known as “bitter leaf (or *onugbu*) soup.” Bitter leaf is used in folk medicine for the cure of diverse ailments ranging from eczema, measles, malaria, and ringworm to worm expulsion and diabetes [45].

16.1.4.4 *P. guineense*

Guinea pepper leaves botanically known as *P. guineense* belongs to the Piperaceae family. It is a well known spice in Nigeria. The plant is a climber growing up to 30–40 ft high on trees [46]. Its racemose flowers produce red fruits that later turn brown when dry. These fruits have a peppery taste because they contain piperine. The leaves which also have a peppery taste are pale green when fresh and dark green when frozen dried or ground (www.practicallyedible.com).

P. guineense commonly called *uziza* by the Igbos of Eastern Nigeria is available at strategic periods of the year, namely the dry season, when the conventional vegetables are scarce. It therefore contributes to the food security and nutritional wellbeing of the local people in the southeastern Nigeria as it is normally grown there [46]. *P. guineense* is a good source of minerals including sodium, potassium



Fig. 16.5 *Vernonia amygdalina*

and iron. Chemical analysis of this leafy vegetable shows that it has 78% moisture when fresh, 9.30% oil, and 18.54% protein [47].

Both the leaves and berries (fruits) are consumed. The leaves, whether whole, ground or shredded are added to soups at the last 15 min of cooking to add flavor to the soup. Similarly the fruits are ground when dry and used to prepare important condiments served at restaurants and homes as a first course as well to stabilize the womb after birth (www.practicallyedible.com). Crude extracts of the plant have been found to reduce hyperglycemia, polyphagia, and polydipsia, and inhibition of cancer cells (www.iobbnet.org).

16.1.5 Cost Effectiveness of Use of Vegetables in Disease Management

It takes about \$500 million for one drug to move from the laboratory to the drugstore. Overall, drug companies spend an estimated \$24 billion on research and development, in addition to millions of dollars marketing their products directly to consumers. When compared to the \$100 million allocated by the National Institutes of Health in the US for the study of alternative medicine, it will be observed that most of the infections that people die from as a result of having weakened immune systems (AIDS) are in fact curable and preventable by cost effective means [48].

There are many safe, natural, and cheap remedies available to rid the body of microbial and parasitic infections, including retroviruses and other enemies of the immune system. These natural remedies strongly focus on *prevention* of illness through healthy diet, lifestyle and nutritional and herbal supplements. One such natural food supplement, which forms part of our daily diets, are the vegetables that are readily available and accessible to all including the rich and the poor.

The nutritional value of vegetables varies. As reported by Mensah et al. [3], different classes of vegetables commonly consumed in Nigeria contain varying degrees of minerals ranging from calcium, magnesium, and potassium to sodium, and iron. Calcium is a major factor sustaining strong bones and plays a part in muscle contraction and relaxation, blood clotting, synaptic transmission and absorption of vitamin B₁₂. Potassium and magnesium are known to decrease blood pressure. Potassium plays a role in controlling skeletal muscle contraction and nerve impulse transmission. Patients with soft bone problems are usually placed on high calcium and potassium vegetable meals. Green leafy vegetables also contain iron needed in hemoglobin formation and hence recommended for anemic convalescence [49]. Various minerals are coenzymes in certain biochemical reactions in the body, which underscores the importance of leafy vegetables in metabolic reactions. Constant consumption of green vegetables with such mineral contents will contribute immensely to the general wellbeing of the consumer and assist in preventing disease onset.

As observed in this report, several workers have upheld the invaluable nutritional content of leafy vegetables [50–52]. These nutritional chemicals include proteins, carbohydrates, ascorbic acid (vitamin C), fiber, beta-carotene, moisture, lutein among others. Ascorbic acid as an antioxidant helps to protect the body against cancer and other degenerative diseases such as arthritis and type II diabetes mellitus as well as strengthening of the immune system. Similarly, leaves with high protein values are recommended for patients with protein deficiency diseases while fiber cleanses the digestive tract, by removing potential carcinogens from the body and prevents absorption of excess cholesterol [29]. Leafy vegetables are commonly available and affordable; their nutritional values will improve physical and mental wellbeing, and prevent the onset of diseases.

The phytochemical content of several vegetables have been analyzed by various workers. Qualitatively, a large number of vegetables contain alkaloids, saponins, tannins, cardiac glycosides terpenes, flavonoids, and inulins among others. These phytochemicals are evidence of the various medicinal qualities of the vegetables constantly consumed daily in soups and other food preparations [53–55].

Antiviral vegetables and other routinely consumed vegetables could indeed be cost effective means for the prevention/treatment of human diseases. They are readily available and easily affordable and form part of the daily diet of most rural and urban dwellers. Most of them are obtained free as they grow freely as weeds along road sides, foot paths, and homes. They are incorporated into soups and sauces and promote general wellbeing as well as preventing the onset of diseases.

Since they are consumed as food, there is little danger of development of allergic reactions though there have been few reports of side effects after consumption of edible vegetables. When compared to the severe side effects that develop with treatment of some conventional drugs and the amount spent to treat the side effects, sometimes ending up in debilitations, morbidities, or mortalities, one would still conclude that consumption of edible vegetables is a comfortable, cost effective alternative. Most people are irreversibly deaf, dumb, or crippled today because of one treatment or the other they received at infancy.

There are reports of rising cases of multiple resistance to drugs by microbes such as those causing malaria, tuberculosis etc. But it is on record that most of the herbs used in Asian and African folklore medicine many centuries ago are still effective against many of the conventional drug-resistant pathogens. Resistance develops as a result of constant contact of a pathogen with a conventional drug. As a result, there is need for constant funding of researches in search of new drugs against existing, emerging and re-emerging pathogens. This excessive spending could be avoided if more attention is focused on the natural remedies that microbes have not been able to overcome over the years. The money spent on funding and research could therefore be channeled to other areas of the economy.

The impact of HIV/AIDS is indeed devastating on the economy of countries. Many countries have in fact, lost their best brains to the scourge while many others are still on the awaiting-death list. Not only would the labor force be drastically reduced, the economy of countries would further be weakened by those who have contracted such diseases and could lose many man-hours attending health clinics. In order to stop the dreaded disease from claiming the rest of her citizenry, many countries where the disease is prevalent have resorted to spending a large quantity of their budget importing the antiretroviral drugs [56]. In order to encourage individuals, the drugs are distributed free at clinics and health centers; but is this the best option? All the expenses incurred in the importation and distribution of antiretroviral drugs would be avoided if governments could look inwards at their own natural remedies and educate the patients about good nutrition, based on the consumption of immune-boosting green leafy vegetables and fruits.

16.2 Conclusion

The market is crammed with varieties of vegetables that form an important part of human daily diets. These vegetables are naturally good and contain lots of minerals and vitamins which help in protecting the human body against cancers, diabetes, and heart diseases. Almost all the vegetables are low in fat and calories, with no cholesterol and many of them are great sources of fiber. The high levels of fiber in vegetables keep the digestive system healthier thus, making it possible for constipation to be avoided. Since vegetables are low in calories, large quantities of it could be eaten without consuming excess energy. Furthermore, the presence of many vitamins, essential amino acids and other substances in vegetables provide essential nutrients the body needs to survive.

Some foods contain potent antiviral and anticancer substances called protease inhibitors. They occur in the outer skin of seeds and nuts such as sesame seeds, soya beans, flaxseed, lentils, sunflower seeds and pumpkin pips. These foods are also rich in sterols and sterolins that strengthen the immune system. Eating these seeds is a cheap way of getting more of these vital substances that help ward off

diseases. The body also needs foods that contain antioxidants like citrus fruits and green, orange, or yellow vegetables to prevent damage to genetic materials within the cell.

Nutritional fruit and vegetable supplements containing Vitamin A, C, E, and selenium are also good. In addition adequate supplies of calcium, magnesium and zinc with Vitamin B₆ are vital to immune function. These minerals make the body more alkaline so it can stay free of parasites and respond better to treatments. Similarly, liquid adaptogens containing herbal extracts help to strengthen the immune system and are vital in helping to cope with stress.

Vegetables are indeed safe, natural and cheap remedies available to rid the body of microbial and parasitic infections, including retroviruses and other enemies of the immune system. Toxic drugs and medicines that are very expensive are not the ideal way to treat great numbers of sick people or to keep them healthy. If treatment could include herbal remedies, and food supplements, our future might start looking much brighter. Improved sanitation and hygiene, safe sexual conduct (no sex outside of marriage) can also help to prevent the spread of diseases.

Finally Governments should encourage researches into herbal remedies in order to create awareness to their efficacy. Furthermore these “wonderful” herbal sources of cure could even be compounded into tablets, injections, and syrups to meet consumers’ taste, whereby control measures as to production regulation would be enforced. The sooner this dimension is pursued, the better it will be for health care delivery in this century.

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Chapter 17

Citrus Products and Their Use Against Bacteria: Potential Health and Cost Benefits*

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Key Points

- Citrus pulp and dried peel are by products of juice production.
- Citrus oils can kill bacteria, including pathogenic bacteria.
- Citrus pulp can be used as a high quality feedstuff for animals and are fed currently.
- Research has shown that these products can kill foodborne pathogenic bacteria.
- These products can be used to improve human and animal health at a feasible cost.

Keywords *Escherichia coli* O157:H7 • Orange pulp • Preharvest intervention • Salmonella

17.1 Introduction

Pathogenic bacteria are members of nearly all terrestrial ecosystems, and as such many plants have developed physical as well as chemical resistance methods to infection or colonization. Many plant chemicals demonstrate antimicrobial or antibacterial activities which can alter the microbial ecology of the environment; including the ecology of the gut of animals that consume them [1–5]. This form of interspecies chemical warfare is common in the highly competitive natural environment. Chemicals employed by plants against bacteria to obtain a competitive advantage in their ecosystem include: essential oils [6], organic acids [7, 8] as well as specific toxins [9, 10].

Citrus fruits, including oranges, contain essential oils (e.g., limonene, linalool) in the fruit and peel that are toxic to bacteria [11–13] and also exhibit antioxidant effects in consuming animals or humans [14, 15]. Because of the antioxidant and other health benefits of citrus consumption have been touted for many years by various consumer and medical groups [16, 17]. To date, little research has been performed on how these compounds affect the microbial ecosystem of the gut of humans or food animals, and the subsequent impact human health. In recent years increasing fears about the

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use of medically important antimicrobials (pharmaceuticals) has grown [18, 19], and this has led to a re-examination of alternative antimicrobials that can improve human and animal health and/or productivity [9, 20, 21].

Orange peel and dried orange pulp are byproducts from the production of orange juice. These products have a relative high nutritive value for ruminant animals (e.g., cattle) and nonruminants (e.g., swine). Orange pulp or dried orange peel is available to farmers at low prices in citrus-producing regions (e.g., Florida and California) at very low prices. Some of these byproducts are included in animal diets as least-cost formulation ingredients [1, 9, 22, 23].

Because of the natural antimicrobial effects of this byproduct feedstuff, it has been proposed that this low-cost feed ingredient could decrease pathogenic bacterial populations in food animals. Specifically, it has also been suggested that purified citrus oils could be used as a potential treatment for gastrointestinal infections in humans or animals [3, 24, 25]. Defining specific antimicrobial components in the oils that act against pathogens [26], we can better utilize the components that exhibit optimal suppression of specific pathogens or spoilage organisms in targeted environments. For example, the essential oil most optimal on ground beef or luncheon meats would differ from the most appropriate one for use on lettuce, or to be used in animal feeds to reduce pathogens in the intestinal tract of the live animal [27, 28]. Researchers have also demonstrated that the use of some specific essential oils can reduce pathogen levels on seeds and on salad, and can be used to penetrate biofilms in specific environments [28–30].

17.2 Citrus Essential Oils: Natural Antimicrobials

Many plants and fruits contain compounds that demonstrate antimicrobial activity [7, 9, 31], which can alter the microbial ecology of the surface of a food or any other environment [1, 22, 32, 33]. Essential oils are an important component of the citrus fruit and can act as potent natural antimicrobials [12, 13, 33, 34]. Citrus oils are complex mixtures, comprised of approximately 400 separate organic compounds found in citrus fruits depending on the citrus cultivar, extraction, and separation methods [35–37]. In general, essential citrus oils exert their bactericidal effects at the membrane level [15, 38] where they cause an increase in the permeability of the cell membrane [32, 38, 39]. Disruption of membranes results in bacterial cell death, due to proton-motive force depletion and ion leakage [37, 39]. Thus the oils can be bacteriocidal in high concentrations, but can slow the growth of bacteria at lower concentrations (bacteriostatic). The most well-characterized of the essential oils from citrus products include citrullene and limonene [11, 37, 40], which can exert potent, broad-spectrum antimicrobial activity [41].

Citrus oils are comprised of two primary fractions, the oxygenated compounds and the hydrocarbon fraction. Oxygenated compounds (ester aldehydes, ketones, phenols, alcohols, and oxides) are polar and comprise <5% of the volume; yet these oxygenated compounds give citrus oils their characteristic fragrance and aroma that are used as fragrance and food ingredients [36]. The remaining hydrocarbon fraction is composed of nonpolar compounds [36]. The principal hydrocarbon found in citrus oils is d-limonene [11]. All of the hydrocarbons have low solubility in water, but can be formed into emulsions that can be included into products, or sprayed onto surfaces or onto meat, poultry or vegetable products [42, 43]. Citrus oils are classified as Generally Recognized as Safe (GRAS) by the US Food and Drug Administration (FDA), due to their natural role as flavoring agents in citrus juices.

Essential oils are effective against a broad range of microorganisms, including bacteria and some fungi [13, 34, 37, 44]. The known antimicrobial activity of the essential oils has been shown to encompass *Escherichia coli* strains [4, 5, 15], *Enterococcus* [39], some *Salmonella* spp.

[1, 4, 13, 45, 46], and *Listeria* [47]. In other studies examining the efficacy of essential citrus oils against pathogenic bacteria in and on foods, strains of *Arcobacter butzleri* and *A. cryaerophilus* spp. were inhibited by a specific fraction, while *Campylobacter jejuni* and *C. coli* were strongly inhibited by various other Valencia orange oil fractions and distilled d-limonene [48]. Essential oils also can inhibit the growth of *Helicobacter pylori*, the causative agent of gastric ulcers in humans [24]. Other recent research has indicated that citrus oils can be used to combat Methicillin-resistant *Staphylococcus aureus* (MRSA) infections [49, 50]. MRSA has rapidly risen to be responsible for more than 19,000 deaths per year in the United States [51] and is seen as one of the most potent communicable threats to public health today. Essential oils offer the possibility of combating these antibiotic-resistant organisms because they operate through different physiological inhibitory mechanisms than do most medically-important antibiotics [21, 38, 43, 52]. This means that citrus products (and other essential oil sources) can be viewed as a “green” alternative to reduce antibiotic use [21] or could be used as a surface disinfectant (such as in hospitals to combat nosocomial infections) or in humans [31, 53, 54].

17.3 Foodborne Pathogenic Bacteria and Citrus Oils: A Route to Improve Human and Animal Health

Annually, foodborne pathogenic bacteria cause more than 3.5 million illnesses at a cost to the US economy of more than \$7 billion [55, 56]. Many of the most common foodborne pathogenic bacteria are carried asymptotically in the intestinal tract of food animals [57–59]. Carcass contamination levels with foodborne pathogenic bacteria are reflective of contamination levels in the final products presented to consumers [60, 61]. In recent years, several novel intervention strategies have been implemented in processing plants (e.g., organic acid rinses, steam treatment) to decrease pathogenic bacterial contamination on carcasses [60]. Despite these effective in-plant interventions, too many of the human foodborne bacterial illnesses linked to meat products and large-scale product recalls still occur each year.

Much of the carcass and meat product contamination is a result of the carriage of foodborne pathogenic bacteria in the intestinal tract, often as an undetectable resident or as a transient organism [62]. Foodborne pathogenic bacteria can be introduced into the abattoir in the feces (and transferred to the carcass during processing) or attached to their hide [60, 63, 64], providing a direct entry into the food chain. All of the most common pathogenic bacteria can be found in one or more species of food animals [55, 65, 66]. Furthermore, illnesses caused by foodborne pathogenic bacteria have been carried to humans by other animal vectors, drinking and irrigation water, and by direct animal contact [67, 68].

Thus, as a logical measure to decrease human illnesses directly through food and indirectly through other routes, several strategies have been investigated that decrease foodborne pathogen carriage in food animal species before slaughter [69–72]. Research and industrial focus has begun to shift to developing strategies to reduce foodborne pathogenic bacteria in the gut of animals before they enter the slaughter plant [25, 72]. The end result of reducing foodborne pathogens in live animals will enhance food safety and human health by: (1) reducing the burden entering the plant directly, and (2) allowing in-plant interventions to work against a lower “background” of contamination, allowing these strategies to be more efficacious. The use of antibiotics to decrease the carriage of foodborne pathogenic bacteria has been viewed as a logical extension of the use of antibiotics; but this strategy is not likely to be palatable to the public because of widespread concerns over antibiotic resistance [18, 19, 73–75]. Thus the search for preharvest pathogen reduction strategies have focused on non-antibiotic methods.

The use of essential oils from natural sources to inhibit pathogens in many environments is not a novel concept [6, 12, 15]. However, using these essential oils to improve the growth efficiency of animals [76] or to eliminate certain animal or foodborne pathogens in live animals [1, 3] is a relatively new application that can be utilized to improve food safety and human health. It has been suggested that essential oils be used as feed additives to alter the intestinal fermentation or to decrease pathogenic bacteria from the intestinal ecosystem of humans and food animals [1, 77, 78].

17.4 Animal Feeding and Citrus Products

Ruminant animals, including cattle are unique in their dietary needs because of the large microbial population present in the rumen [79]. This dense symbiotic population allows ruminants to survive in environmental niches unavailable to other mammals by allowing them to digest feedstuffs rich in cellulose. However, this means the diets fed to ruminant animals are often very different from those fed to monogastric animals and are subject to local feedstuff availability constraints. In the United States, cattle are fed to meet their energy and protein needs, but this often must be accomplished on a limited budget. Cattle are fed a wide variety of low-cost byproduct feeds (e.g., bakery and distillers waste) in an effort to obtain a least-cost highly fermentable ration, especially in the dairy industry. In addition, many of these byproduct feeds can be incorporated into swine and broiler rations to provide good nutritive value.

One of the best known byproduct feeds that provides high nutritive value is orange peel or dried orange pulp [23, 80, 81]. Orange peels that are a byproduct of orange juice production can be fed raw or processed into a dried orange pulp pellet; allowing for long-distance shipping and storage as a feedstuff [82]. Research in our laboratory indicated that feeding of the low-cost byproduct feed of orange peels and dried orange pulp exerts effects on the microbial population in ruminal fluid fermentations. Essential oils with anti-microbial properties (e.g., limonene) comprise a significant proportion of the peel of citrus fruits [83]. Thus it is likely that residual essential oils are the active ingredient mediating these microbial ecological changes.

Additionally, feeding essential oils to animals yield benefits that are not directly related to changes in the microbial population. Essential oils have been shown to dramatically improve antioxidant status in rats [14, 84] and act in an oxygen scavenging capacity [16, 85]. The antioxidant activity of essentials found in orange-pulp diet has been linked to decreased tumorigenesis and increased immune responses in rats [84]. Although the level of orange-pulp in the diet that decreased tumors is well above that fed to cattle and swine commercially, the antioxidant and immunostimulatory activity is likely to still be of some benefit to animal producers via improvements in growth efficiency and animal health.

In vitro studies have found that the use of orange peel or pulp does directly decrease pathogenic bacterial populations known to reside within the rumen [5]. Populations of foodborne pathogens (pure cultures of *E. coli* O157:H7 and *Salmonella*) had significantly decreased growth rates, indicating the toxicity of these feedstuffs occurred directly against these pathogenic bacteria. In additional in vitro studies, foodborne pathogenic bacterial populations were decreased significantly by addition of orange peel and pulp in mixed ruminal fluid incubations from animals fed both a pasture- and grain-based diet (Fig. 17.1). When orange peel and dried pulp was fermented in mixed ruminal culture pathogen populations were decreased significantly, but the acetate to propionate ratios (a key measure of fermentation efficiency from a production animal stand point) and total VFA production in these in vitro fermentations were not altered by orange pulp inclusion at levels up to 2% w/v. Continuing in vitro studies examined the antimicrobial activity of seven purified essential oils found in orange peel against a variety of *E. coli* strains, including *E. coli* O157:H7

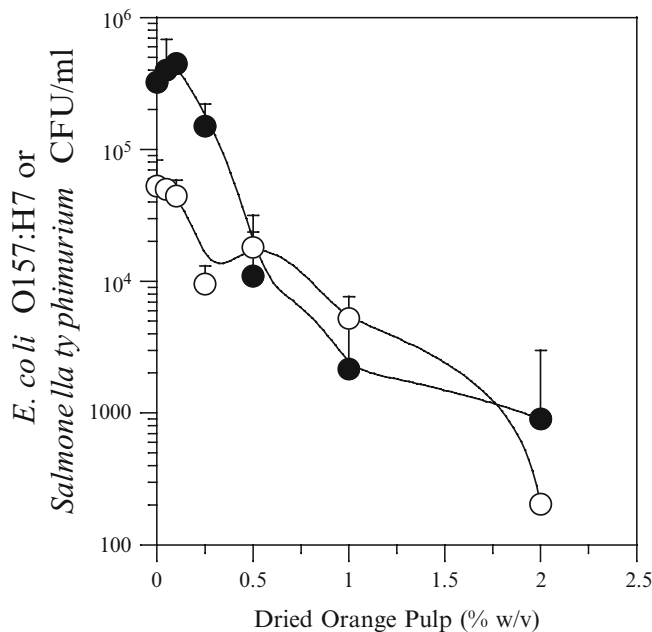


Fig. 17.1 Reduction of *Escherichia coli* O157:H7 and *Salmonella* populations in mixed ruminal bacterial culture in vitro by dried orange pulp addition (Adapted from [16]. With permission)

strains [4]. Only two of the essential oils displayed inhibitory activity in this study, and these were distilled hydrocarbon single fold d-limonene and Orange CP VAL Terpeneless fraction [4]. This result provides a clue to the best specific purified oils capable of controlling pathogens in food animals as a feed additive.

Recently, the concept of feeding citrus pulp as an antipathogen strategy was examined in vivo. Sheep ($n=24$) were placed on a control diet, a diet containing of 10% orange peel or 20% orange peel. After 10 days on the diet, sheep were experimentally infected with *Salmonella typhimurium* via oral gavage. After 5 days, sheep were humanely euthanized and populations of inoculated *S. typhimurium* were determined in compartments of the gastrointestinal tract (Fig. 17.2). There was no significant difference in the *Salmonella* populations in these compartments, but the populations in both the 10% and 20% orange peel diets were reduced numerically. The sheep fed 20% orange peel consumed less diet than did those fed the 10%, probably due to palatability issues and their populations of *Salmonella* were consequently higher (Fig. 17.2).

Swine are often severely affected by *E. coli* diarrhea in the post-weaning phase, often this is caused by the F18-equipped strains [86, 87]. Post-weaning *E. coli* diarrhea is responsible for morbidity and mortality in production swine, and thus represents a significant loss to swine producers [86]. This has led to the development of many probiotic-type products or dietary regimens designed to combat this disease [88–90]. In an unpublished (to date) study, intestinal and fecal populations of experimentally inoculated *E. coli* F-18 in weaned pigs were significantly reduced in swine fed orange-peel (Collier et al., unpublished).

Collectively, our in vitro and in vivo results indicate that orange pulp and/or peel included in ruminant diets decreased ruminal and intestinal populations of food-borne pathogenic bacteria without causing a significant change in the fermentation end-products which could affect animal production efficiency or animal health. Furthermore, the use of orange peel/pulp in monogastric diets can alleviate the effects of post-weaning *E. coli* diarrhea in swine. Overall, these and other

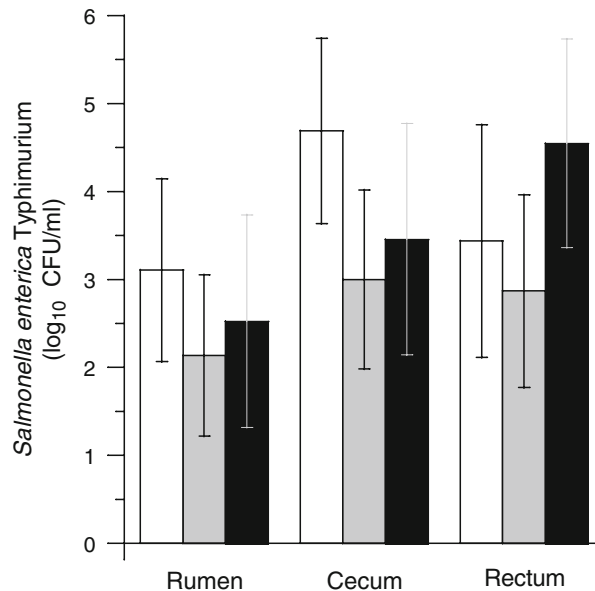


Fig. 17.2 Populations (CFU $\log_{10}$ /mL) of *Salmonella* in the intestinal tract of sheep ($n=24$) fed 0% (open bars), 10% (grey bars) or 20% dried orange peel (black bars) rations. Sheep were fed orange peel diet for 10 days prior to inoculation with *Salmonella typhimurium*. Error bars represent standard deviations of the mean (Unpublished data)

results indicate that orange pulp can be anti-pathogenic on various diets, and that it is likely viable for use in both dairy and beef production systems, as well as swine.

17.5 Conclusions

Anti-microbial compounds are common throughout the plant kingdom and these compounds often make their way in our feed and food supply. Many of these are essential oils that are included in foods as flavor additives (e.g., capsaicin) or in anti-bacterial preparations. The simplicity of this approach has appeal for utilization in many realms of improving animal and human health. Given the ability of these oils to be incorporated into human and animal diets in a cost-effective fashion, it is not surprising that their utilization in animal feedstuffs has increased and been suggested as a possible food safety intervention strategy.

Orange peel and dried orange pulp contains essential oils that are antimicrobials and can be fed to livestock as a nutritious feedstuff. It is currently fed to cattle in certain geographic locations and is amenable to modern production practices across the nation in the cattle and swine industry. In our studies the antimicrobial activities of the essential oils in orange peel was demonstrated in vitro and in vivo against the foodborne pathogenic bacteria *E. coli* and *Salmonella*.

Increasing consumption and utilization of orange peel and pulp to decrease pathogens in food animals can provide synergistic added value to both the animal production and the citrus industry. The inclusion of the essential citrus oils in human foods (and animal feeds) offers a route to impact human health directly and indirectly. Furthermore, the inclusion of orange peel or pulp in animal rations is palatable to an increasingly environmentally concerned consumer as a “green” solution that is available now and is economically feasible. Therefore more research must be performed to determine the antimicrobial activity of citrus products against foodborne and other pathogens in food animals.

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Chapter 18

Potential Chemopreventive Effects of Fruits, Vegetables, and Spices Consumed in Mexico

Armando González-Stuart

Key Points

1. Mexico has a rich tradition in medicinal/food plant utilization among its varied folk healing practices.
2. In spite of widespread use of modern pharmaceuticals, and the availability of “scientific” or mainstream medicine, many people still rely on diverse fruits and vegetables for nutrition, as well as for the treatment of several diseases or ailments.
3. Many food plants used in traditional Mexican cuisine possess not only important nutritional value, but, due to their content of antioxidant or cytotoxic phytochemicals, may also have therapeutic and chemopreventive properties against some forms of cancer.
4. The naturally occurring compounds in food plants could be useful in the treatment of diverse chronic or degenerative diseases, including different manifestations of cancer.
5. Chronic and degenerative diseases not only pose a serious public health risk, but the costs of treatment entail an enormous economic burden to any nation.

Keywords Antioxidants • Cancer chemoprevention • Fruits • Phytochemicals • Vegetables

18.1 Introduction

The incidence of gastric cancer appears to be rising in Mexico, in comparison to other countries, and is currently the second leading cause of death from cancer in Mexico, accounting for more than 5,000 deaths in 2005 [1].

18.2 Importance of Phytochemicals in Cancer Chemoprevention

Chemoprevention can be defined as the prevention of cancer using specific agents, some of which are of natural origin (phytochemicals) that suppress or reverse the carcinogenic process. Recently, much attention has been focused on the anticancer properties of diverse groups of bioactive ingredients normally present as secondary metabolites in a wide array of plants. The chemopreventive effects are

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most probably related to a wide array of specific bioactive ingredients (phytochemicals), such as flavonoids and carotenoids, for example, which are found in a variety of fruits, vegetables, and spices [2].

18.2.1 Selected Fruits, Vegetables, and Spices with Potential Chemopreventive Effects

18.2.1.1 Annatto

Bixa orellana – Bixaceae

Other common names: Achiote, Bija, Anatto, Arnatto, and Roucu

The seed of this plant is used extensively in Mexico and other Latin American countries as a non-toxic source of body paint, as well as a natural food coloring included in a variety of dishes.

Various carotenoid compounds have been extensively studied in some fruits and vegetables (tomato and carrot, for example), but not in annatto. The pericarp of anatto seeds contains various carotenoid phytochemicals that can act as antioxidants. The main carotenoids contained therein are bixin and norbixin. Until recently, little attention has been given to the possible anticancer properties of these compounds.

Bixin is a lipophilic compound, which is currently employed in the food industry as a natural colorant in butter, margarine, corn oil, dairy products, macaroni, sausage, and cheese. In contrast, norbixin is an unusual dicarboxylic water-soluble carotenoid.

A study evaluated bixin obtained from powdered anatto seeds, as well as various other natural pigments, alone or in combination for their relative potencies against cyclooxygenase enzymes and tumor cell growth inhibition by using tumor cell lines from MCF-7 (breast), HCT-116 (colon), AGS (stomach), CNS (central nervous system), and NCI-H460 (lung). The other plant pigments included pure betanin, lycopene, chlorophyll, beta-carotene, and cyanidin-3-O-glucoside. The synergistic effect of the mixtures was evaluated against all the cell lines studied. Bixin, as well as the other pigments, showed COX-1 and COX-2 inhibition and also demonstrated a dose-dependent growth inhibition against breast, colon, stomach, central nervous system, and lung tumor cells [3].

The phytochemicals contained in annatto may serve as potential chemopreventive agents against colon cancer by means of modulating cryptal cell proliferation, but not at the initiation stage of colon carcinogenesis. In general, the data have demonstrated a clear role for these compounds in the prevention of mutation and specific precancerous lesions [4].

A study of male Wistar rats assessed the effect of annatto's bioactive ingredients on DNA damage induced by 1, 2-dimethylhydrazine (DMH). The results of this study suggest that annatto possesses chemopreventive effects via its modulation of the cryptal cell proliferation, but not at the initiation stage of colon carcinogenesis [5].

18.2.1.2 Amaranth

Amaranthus spp. – Amaranthaceae

Other common names: Amaranto, Alegría

Amaranth grain and leaves are nutritious, as well as very high in protein. The plant is grown for its leaves, which can be eaten as a salad vegetable, as well as for its seeds (grain). Amaranth seeds should be rinsed and cooked prior to eating, as they contain substances that may interfere with the absorption of nutrients, which are destroyed by heat.

A trypsin-chymotrypsin inhibitor known as AmI was isolated from amaranth seeds and belongs to a new family of serine protease inhibitors. This compound was found to inhibit the anchorage-independent growth of MCF-7 breast cancer cells, suggesting that AmI may possess anticancer activity [6].

Research in laboratory animals has shown that amaranth oil has an antioxidant effect upon lipid peroxidation. A study evaluated tumor growth in the blood, liver and NK/Ly cells in mice fed with amaranth oil showed various effects on antioxidant activity. The activity of the antioxidant enzymes in hepatocytes from mice fed amaranth oil was applied towards maintenance of antioxidant protection against neoplastic growth. Amaranth's antioxidant effects were due to an important increase in superoxide dismutase (SOD), preserved catalase, as well as a decrease in the activities of glutathione peroxidase. The results showed that the antioxidant activity induced by amaranth oil can potentially inhibit tumor cell proliferation [7].

18.2.1.3 Avocado

Persea gratissima or *P. americana* – Lauraceae

Other common names: Aguacate, Palta, and Alligator pear.

The avocado is a fruit that has long been used as a foodstuff, as well as for medicinal purposes. The leaves, skin, fruit pulp and “seed,” is used throughout Latin America and the Caribbean to treat a variety of ailments, from intestinal worms to hair loss.

The avocado fruit is widely known to be a rich source of monounsaturated fatty acids (omega-9), but it also contains other bioactive substances including carotenoids, which may have anticancer properties similar to those attributed to other fruits and vegetables [8].

Various parts of the avocado plant contain diverse types of phytochemicals, such as flavonoids, alkanols or aliphatic acetogenins, terpenoid glycosides, coumarin, and furan ring-containing derivatives, to name a few. Some bioactive ingredients extracted from the avocado fruit selectively promote cell cycle arrest, suppress growth, and induce apoptosis in precancerous and cancer cell lines, by means of targeting multiple signaling pathways and enhancing intracellular reactive oxygen [9].

Antioxidant phytochemicals extracted from the avocado fruit pulp can selectively induce apoptosis by decreasing reactive oxygen species (ROS) in cancer cells, but not in normal, human oral epithelial cell lines [10].

Persin, a fungitoxic and insecticidal aliphatic ketone found in avocado leaves, has unique effects upon the epithelium of the mammary gland in vivo, as well as cytotoxic effects on human breast cancer cells in vitro. Compounds that have a structural similarity with persin, such as conjugated linoleic acid (CLA), for example, can diminish steroid hormone receptor signaling and modulate the response of breast cancer cells to antiestrogenic compounds. Persin may have similar effects by having a proapoptotic and synergistic actions with the antiestrogenic compound, 4-hydroxytamoxifen. However, although persin transcriptionally down-regulates estrogen receptor (ER) expression, unlike CLA, it also shows efficacy in ER-negative breast cancer cells, both by itself, as well as combined with 4-hydroxytamoxifen, whereas normal breast epithelial cells are unaffected. This suggests that it may act by means of a different ER-independent mechanism. More research is needed, since persin is a new potential anticancer agent. This compound significantly augments the sensitivity of breast cancer cells to the cytotoxic effects of tamoxifen, regardless of their ER status. At the same time, it shows apparent specificity for the cancerous cells [11].

Another avocado bioactive ingredient, persenone A, was evaluated in order to assess its suppressive effects of on lipopolysaccharide- and interferon- γ -induced inducible nitric oxide synthase (iNOS) and cyclooxygenase (COX-2) in a mouse macrophage cell line (RAW 264.7). Persenone A almost totally inhibited both iNOS and COX-2 protein expression. The results showed that persenone A could be a potential agent to prevent certain diseases associated with inflammation, such as cancer [12].

Compared to other commonly eaten fruits, the “Hass” avocado variety contains the highest amount of an antioxidant phytochemical known as lutein. This variety is also a very good source of other carotenoids and vitamin E. An *in vitro* study showed that an acetone extract of avocado containing carotenoids and tocopherols inhibited the growth of both androgen-dependent (LNCaP) and androgen-independent (PC-3) prostate cancer cell lines. Incubation of PC-3 cells using the avocado extract led to cell cycle arrest alongside an increase in the expression of p27 protein. Lutein alone was unable to reproduce the effects of the avocado extract on cancer cell proliferation [8].

18.2.1.4 Aztec Spinach

Chenopodium berlandieri – Chenopodiaceae

Other common names: Guausoncle, Huauzontle, Huazontle, Huauhtli, Pitseed Goosefoot, Southern Huauzontle

The leaves resemble lamb’s quarters (*Chenopodium album*) and can be eaten raw when young. Although the leaves, flowers, and seeds of the plant are edible when cooked, usually only the flower buds are eaten.

This plant contains a small amount of saponins. These steroidal compounds are not well absorbed in the body and are not heat stable. Since saponins are destroyed by exposure to high temperatures, they represent no risk to the consumer if the plant is adequately cooked.

Quinoa (*Chenopodium quinoa*), is high-protein “cousin” of Aztec spinach, which was originally consumed by the Incas and other indigenous groups in South America [13].

18.2.1.5 Beans

Phaseolus spp. – Fabaceae

Other common names: Frijol, Judía, Habichuela, Alubia

The typical Mexican diet has traditionally included a significant amount of a wide variety (more than 200) of different types of beans. Including beans as part of a normal diet has been associated with a decreased risk of gastric cancer, according to a previous study undertaken in Mexico [14].

A study of milled beans was undertaken in order to evaluate the possibility of enhancing phenolic antioxidants, as well as antioxidant activity. Phenolic compounds in beans were concentrated mainly in the seed hull fraction. Methanolic extracts of the bean samples were screened for antioxidant potential. The milled samples showed a correlation of antioxidant activity with phenolic content. These findings suggest a positive correlation between significant free radical scavenging activity and antimutagenic activity [15].

A population-based case–control study was carried out in Mexico City in order to estimate the risk of gastric cancer with regard to the individual and combined consumption of polyphenols from fruits and vegetables, as well as nitrate and nitrite as N-nitroso compounds (NOC) precursors from processed meat sources. Pinto beans are a source of diverse phytochemicals, such as cinnamic acids, secoisolariciresinol, and coumestrol. They also possess high total phenol content similar to that of cranberries and blueberries, one of the most important sources of polyphenols in fruits.

N-nitroso compounds are potent animal carcinogens and are believed to be potential human carcinogens as well. High intakes of various phytochemicals, such as cinnamic acids, secoisolariciresinol and coumestrol, for example, were associated with an estimated 50% reduction in risk for gastrointestinal cancer (GC). In contrast, a high intake of total nitrite as well as nitrate and nitrite from animal sources doubled the GC risk.

A potentially higher risk for GC was observed among individuals who showed a low intake of phytochemicals from fresh fruits and vegetables, and consumed high amounts of animal products containing nitrate or nitrite. The results of this study suggest that nitrate and nitrite compounds used in the processing of cold cuts and other processed meats may increase GC risk through the endogenous formation of potentially carcinogenic NOC, especially in people who normally do not consume sufficient amounts of fruits and vegetables. The authors considered that beans possess significant importance for the potential prevention of gastric cancer. For this reason, the quantification of the polyphenol content of the many varieties of beans existing in Mexico merits further investigation [16].

18.2.1.6 Black Sapote

Diospyros digyna – Ebenaceae

Other common names: Zapote negro

A study of eight fruits and vegetables commonly consumed in Mexico (guava (*Psidium guajava*), avocado (*Persea americana*), black sapote (*D. digyna*), mango (*Mangifera indica*), papaya (*Carica papaya*), prickly pear stems and fruit (*Opuntia* spp.), and strawberry (*Fragaria* spp.)) was undertaken in order to correlate total soluble phenolics, vitamin C, vitamin E, beta-carotene, and total carotenoids, with the total antioxidant capacity of hydrophilic and lipophilic extracts. The hydrophilic extract from guava possessed the highest antioxidant value when evaluated by various assays, but with the ORAC (oxygen radical absorbance capacity) assay, black sapote had the highest value. Since ORAC values are correlated with free radical scavenging activity, black sapote was found to possess important antioxidant properties [17].

18.2.1.7 Chía

Salvia hispanica – Lamiaceae

This plant has been cultivated in Mexico for many centuries and was a very important staple food and medicinal plant for various Mesoamerican civilizations in pre-Columbian times. It is an important source of omega-3 fatty acids, especially alpha-linolenic acid (ALA). Unlike other Mesoamerican pseudocereal crops such as amaranth and quinoa, chía has received scant attention by researchers [13].

A study investigated the effects of certain polyunsaturated fatty acids (PUFAs) and related eicosanoids on the growth and metastasis formation of mammary gland adenocarcinoma in mice. Two vegetable oil sources of omega-3 and -6 fatty acids (Chía and Safflower (*Carthamus tinctorius*)) were used. A commercial diet as was included as control. Neoplastic cells from the Chía groups showed lower levels of arachidonic acid and other eicosanoids compared to both the safflower and oil from the control group. The diet containing Chía diminished the tumor weight and metastasis number, as well as enhanced apoptosis and T-lymphocyte infiltration, while decreasing mitosis, compared to the other diets. The results demonstrated that chía inhibited growth and metastasis in the tumor model used for this study [18].

18.2.1.8 Chickpea

Cicer arietinum – Fabaceae

Other common names: Garbanzo beans, Bengal grams, Egyptian peas

Chickpea seeds are a staple food in many Mediterranean, Asian, and American countries and may reduce serum cholesterol levels and help reduce coronary heart disease and diabetes [19], additionally,

they possess cell growth-regulating properties, which may be useful as natural anticancer agents. Chickpea seed extracts and protein preparations were applied to Caco-2 (epithelial intestinal) and J774 (macrophages) cell lines in order to screen the different chickpea fractions for effects on cell growth. The extracts possessed both cell growth-promoting and cell growth-inhibiting effects. A significant finding was that an ethanol and acetone soluble fraction specifically and almost totally inhibited growth of Caco-2 cells showing a cancerous phenotype. The authors concluded that chickpea seeds are a source of bioactive phytochemicals that deserve further study for their possible antineoplastic effects [20].

Experimental studies have found that legumes, such as soybeans and pinto beans, may have anticancer properties. While chickpeas or garbanzo beans are an important source of various phytochemicals, they have not been sufficiently well researched. A study compared the effects of garbanzo or soybean flour on azoxymethane (AOM)-induced aberrant crypt foci (ACF) in CF-1 mice. Rodent chow was used as a diet for the control group. The results showed that there was a 64% suppression of ACF for mice fed the garbanzo flour versus an inhibition of 58% and 55% for the animals fed the soy and mixed flour diets, respectively. The importance of these findings suggest that garbanzo beans possess bioactive compounds that can inhibit the formation of precancerous lesions in mice and could potentially contribute to a reduction in the incidence of colon cancer in humans who normally consume this plant [21].

18.2.1.9 Chili Peppers

Capsicum spp. – Solanaceae

Other common names: Chile, Ají, Guindilla

Capsaicin, a homovanillic acid derivate, is one of the main phytochemicals contained in chilies [22]. Studies with laboratory animals have shown that capsaicin possesses contradictory effects, such as carcinogenic, cocarcinogenic, anticarcinogenic, antitumorigenic, tumor promoting, and tumor preventing activities.

In spite of the fact that chilies are a source of vitamin C and other antioxidants, some researchers have mentioned that capsaicin may possess carcinogenic activity in humans [23].

A population-based case–control study was undertaken in Mexico City to evaluate the relationship between chili consumption and gastric cancer risk. The study included 220 incident cases and 752 controls randomly selected from the general population. Personal interviews were conducted in order to obtain the information. People who consumed chili peppers had a higher risk for gastric cancer compared with non-consumers. Among the group who consumed chili peppers, there was a highly significant trend of increasing risk with increasing levels (low, medium, and high) of intake. The researchers concluded that chili pepper intake may be an important risk factor for gastric cancer, but further studies are needed to test this hypothesis [24].

A study evaluated the whether the intake of capsaicin could augment the risk of gastrointestinal cancer independently of the presence of the bacteria *Helicobacter pylori*. A 3 year hospital-based case–control study was performed in three different locations in Mexico. Two hundred and thirty-four subjects diagnosed with gastric cancer and 468 matched controls were enrolled in the study, and interviewed regarding their diet as well as other parameters. The risk of this type of cancer increased among those who consumed high-levels of capsaicin (90–250 mg of capsaicin per day, equivalent to 9–25 jalapeños per day), compared to low-level consumers (0–29.9 mg of capsaicin per day, from 0 to less than 3 jalapeños per day). No significant interactions were noted between capsaicin intake and the presence of *H. pylori* regarding the risk of

gastric cancer. The researchers concluded that chili pepper consumption could be an independent determinant of gastric cancer in Mexico [25].

A Chinese study investigated the effects of capsaicin on the proliferation of bladder cancer T24 cells in vitro as well as on xenografts in nude mice in vivo. Capsaicin has been shown to mediate cell death in T24 cells via calcium entry-dependent production of reactive oxygen species and mitochondrial depolarization, but not apoptosis. The authors concluded that capsaicin may have a role in the treatment of bladder cancer [26].

A clinical study by Anandakumar et al. (2009) demonstrated an important chemoprotective role of capsaicin against *benzo(a)pyrene*-induced experimental lung cancer in mice [27].

18.2.1.10 Christophene

Sechium edule – Cucurbitaceae

Other common names: Chayote, Christophine

Christophene was part of the diet consumed by the Aztec civilization in pre-Columbian times. The root, commonly known in Mexico as “chinchayote,” is also edible, if boiled.

A novel ribosome-inactivating protein (RIP), known as sechiumin, was obtained from the seeds of christophene. This compound inhibited the protein synthesis of rabbit reticulocyte lysate strongly with a concentration causing 50% inhibition (IC₅₀) of 0.7 nM, but had a much lower effect on intact HeLa cells, with an IC₅₀ of 5,000 nM. Sechiumin has a highly specific RNA *N*-glycosidase activity towards 28S rRNA, as does the A-chain of abrin, a potent lectin. This study suggests that sechiumin is one of the type-I ribosome-inactivating proteins that could potentially be used for the preparation of immunotoxin as a cancer chemotherapeutic agent [28].

18.2.1.11 Custard Apple

Annona cherimola – Annonaceae

Other common names: Chirimoya, Cherimoya

The Annonaceae are a family that comprise approximately 130 genera and over 2,000 species, which are mostly distributed in tropical and sub-tropical regions. This botanical family is, at present, the only known source of a more than 500 bioactive phytochemicals known as *acetogenins* (ACGs).

Significantly, the ACGs possess a distinctive antineoplastic effect through depletion of ATP levels by means of inhibiting complex I of mitochondria as well as inhibiting the NADH oxidase of plasma membranes of cancerous cells [29, 30].

A clinical study assessed the genotoxic and cytotoxic potential of three isomeric acetogenins (Ace) obtained from the seeds of custard apple in mice. In order to evaluate cytotoxicity, the researchers determined the proportion of polychromatic erythrocytes with regards to the number of normochromatic erythrocytes, and noted an inhibitory effect induced by Ace, which was very similar to the one induced by the chemotherapeutic compound, daunorubicin. Additionally, the authors determined the cytotoxicity of Ace in both a normal fibroblast mouse cell line as well as in a cancerous cell line derived from the human colon. In this study, the strongest decrease in viability was observed in the malignant cell line. This is the first time that these unique phytochemicals have been shown to possess genotoxic capacity in vivo, as well as cytotoxic effects in cultured cells [31].

18.2.1.12 Guava

Psidium guajaba – Myrtaceae

Other common names: Guayaba

A guava aqueous extract inhibited the cancer cell DU-145 in a dose- and time-dependent manner and also showed potential for antimetastasis activity. The authors attributed the guava extract's antineoplastic activity to its significantly high content of flavonoid and polyphenolic compounds. Additionally, the researchers concluded that guava extract could be useful for treatment of brain derived metastatic cancers such as DU-145, since the extract behaves both as a chemopreventive as well as chemotherapeutic agent [32].

The findings of another study showed that guajava extracts were efficacious in preventing tumor development by depressing T regulatory (Tr) cells and subsequently shifting to Th1 cells [33].

Guava leaf essential oil showed very high antiproliferative activity (four times more potent than vincristine) on human mouth epidermal carcinoma (KB) and murine leukemia (P388) cell lines in comparison to 16 other plants used in traditional Thai medicine [34].

18.2.1.13 Ground Cherry

Physalis philadelphica – Solanaceae

Other common names: Tomatillo, *Tomate fresadilla*, Miltomate, *Tomate verde*, Chinese lantern, Winter cherry

Ground cherry, commonly known in Mexico as a “tomatillo,” has been part of Mesoamerican cuisine for centuries. Recent studies have shown that the fruit of this plant may have anticancer potential.

An ethyl acetate-soluble extract and four withanolide compounds were isolated from ground cherry. Research undertaken on Hepa-1c1c7 hepatoma cells showed that withanolides were potent inducers of quinone reductase, suggesting potential chemoprotective activity against cancer. Choi et al. (2006) evaluated the antiproliferative properties of the withanolides in SW480 human colon cancer cells. IxoA, a withanolide compound contained in the edible fruit, was selected for further evaluation. SW480 cells treated with IxoA showed cell cycle arrest in the G2/M phase, up-regulation of hyper-phosphorylated retinoblastoma, and down-regulation of E2F-1 and DP-1. Further, IxoA induces apoptosis in SW480 cells. These findings suggest that phytochemicals contained in ground cherry, such as IxoA, may have potential chemopreventive effects against cancer cells [35].

18.2.1.14 Mamee Apple

Mammea americana – Clusiaceae

Other common names: Mamey, Santo Domingo apricot, Abricó

Three new isoprenylated coumarins isolated from *M. americana* seeds, along with 12 other previously known coumarins were screened for their potential cytotoxicity activity in the SW-480, HT-29, and HCT-116 human colon cancer cell lines. Additionally, their antioxidant capacities were evaluated in the DPPH (1,1-diphenyl-2-picrylhydrazyl) free-radical assay. In the SW-480 cell line, these novel coumarins showed induction of apoptosis [36].

18.2.1.15 Mamey Sapota

Pouteria sapota – Sapotaceae

Other common names: Zapote mamey, Cinnamon Apple, Lucuma

A study was undertaken in order to investigate the cytotoxicity of pouterin in tumorigenic and nontumorigenic mammalian cell lines. HeLa, Hep-2 and HT-29 tumor cells were highly sensitive to pouterin cytotoxicity in a dose-dependent manner, whereas nontumorigenic Vero cells and human lymphocytes were relatively resistant to the vegetable protein. Of the tumor cell lines evaluated, HeLa cells demonstrated the highest susceptibility to pouterin cytotoxicity, showing diverse alterations in morphology, which were consistent with those shown during apoptosis [37].

18.2.1.16 Papaya

Carica papaya – Caricaceae

Other common names: Pawpaw

An evaluation was made regarding the antiproliferative effect of aqueous extracts of 14 fruits and vegetables consumed in Mexico on the MCF-7 breast cancer cell line. The fruits and vegetables employed in the study were avocado (*Persea americana*), black sapote (*Diospyros digyna*), guava (*Psidium guajava*), mango (*Mangifera indica*), prickly pear cactus stems (*Opuntia* spp.) and fruits (commonly known as “tunas”), and papaya (*C. papaya*). Of all the plants studied, only papaya had a significant antiproliferative effect as measured via the methylthiazolydiphenyl-tetrazolium bromide assay [38].

18.2.1.17 Roselle

Hibiscus sabdariffa – Malvaceae

Other common names: Flor de Jamaica, Jamaica, Acedera de Guinea

Roselle or “flor de Jamaica” is an African plant whose flowers are widely used in Mexico to prepare a refreshing cold beverage called “agua de Jamaica.” This plant has been found to possess both antioxidant as well as antiinflammatory properties.

A clinical study in Taiwan examined whether roselle extracts affected the apoptosis of cancer cells. Employing a set of apoptotic detection assays, the researchers demonstrated that the roselle extract induced cytotoxicity and apoptosis of cancerous cells in a concentration-dependent manner. The authors concluded that roselle extracts could be developed as a chemopreventive agent for certain types of cancer [39].

According to an in vivo and in vitro study regarding the antioxidant effects of polyphenolic compounds extracted from *H. sabdariffa*, the authors found that the extract possessed significant antiinflammatory action both in vitro as well as in vivo [40].

Anthocyanins extracted from *H. sabdariffa* demonstrated antioxidant activity and liver protection and were evaluated as to their effects upon human cancer cells. The result showed that roselle’s antioxidant compounds could cause apoptosis in cancer cells, especially in HL-60 cells [41].

18.2.1.18 Sapodilla

Manilkara zapota – Sapotaceae

Other common names: Chico zapote, Naseberry, Sapota

The tropical fruit tree *Manilkara zapota* is native to the Yucatán Peninsula in Mexico and is also found in various countries of Central America. Aside from its nutritional value, the fruit is used to treat diarrhea and pulmonary diseases. The leaves of the tree are also used as a tea in Mexican traditional medicine to treat respiratory problems and diarrhea, while the bark is employed to treat gastrointestinal problems.

Two novel antioxidants, methyl 4-*O*-galloylchlorogenate and 4-*O*-galloylchlorogenic acid, as well as eight previously known polyphenolic compounds with antioxidant activity, were isolated from a methanol extract from the fruit of *M. zapota*. Of the ten polyphenolic compounds evaluated, methyl 4-*O*-galloylchlorogenate showed the highest antioxidant activity and also showed cytotoxic activity in the HCT-116 and SW-480 human colon cancer cell lines. The second compound, 4-*O*-galloylchlorogenic acid, showed significant antioxidant activity, as well as cytotoxic activity in the HCT-116 and SW-480 human colon cancer cell lines [42].

18.2.1.19 Soursop

Annona muricata – Annonaceae

Other common names: Guanábana

Seven new annonaceous acetogenins, as well as five previously known compounds, were isolated from the seeds of *A. muricata*. The acetogenins showed significantly selective in vitro cytotoxicity against human hepatoma cell lines Hep G (2) and 2,2,15 [43].

Three new monotetrahydrofuran annonaceous acetogenins, muricin H, muricin I, and *cis*-annomontacin, along with five known acetogenins, annonacin, annonacinone, annomontacin, murisolin, and xylomaticin, were isolated from the seeds of *A. muricata*. Additionally, two new monotetrahydrofuran annonaceous acetogenins, *cis*-corossolone and annocatalin, together with four previously known compounds, annonacin, annonacinone, solamin, and corossolone, were isolated from soursop leaves. These new acetogenins exhibited significant activity in vitro cytotoxic assays against two human hepatoma cell lines, Hep G(2) and 2,2,15. Xylomaticin demonstrated a significant selectivity toward the Hep 2,2,15 cancer cell line [44].

18.2.1.20 Sweet Potato

Ipomoea batata – Convolvulaceae

Other common names: Camote, Batata

Sweet potatoes are a very important food crop in Mexico, as well as in many other parts of the world. These plants contain appreciable quantities of beta carotene and other antioxidant compounds.

Anthocyanins from sweet potatoes were shown to possess an inhibitory effect on transplantation tumor of mice, and did not show any toxicity or mutagenicity [45].

18.2.1.21 Sweetsop

Annona squamosa – Annonaceae

Two novel acetogenins (ACGs) known as squamostanin-A and squamostanin-B were isolated from a sweetsop seed extract. The cytotoxicity of these two compounds were tested against tumor cell lines of

human colon adenocarcinoma (HCT), human lung carcinoma (A-549), human breast carcinoma (MCF-7), and human prostate adenocarcinoma (PC-3). The results of the cytotoxicity bioassays showed that ACGs have an ample range of cytotoxic activity against certain cancer cell lines and should also be evaluated as potential lead compounds for a future generation of antitumor drugs [46].

Eight new mono-tetrahydrofuran type annonaceous acetogenins, as well as eight previously known compounds were isolated from the seeds of *A. squamosa*. Two compounds known as Squadiolins A and B demonstrated activity against human Hep G2 hepatoma cells as well as significant cytotoxic action against human MDA-MB-231 breast cancer cells. Another related compound, Squafosacin B, also exhibited significant cytotoxic activity against human Hep G2 and 3B hepatoma and MCF-7 breast cancer cells [47].

18.2.1.22 Tree Spinach

Cnidoscolus chayamansa – Euphorbiaceae

Common name on Spanish: Chaya

Chaya has been a significantly important foodstuff since pre-Hispanic times, especially for ancient peoples of the Yucatan Peninsula and parts of Central America. Cooking is essential prior to consumption to inactivate the toxins present in chaya leaves [48].

The antioxidant capacity and total phenolic content of two tree-spinach species (*Cnidoscolus chayamansa* and *C. aconitifolius*) were evaluated in extracts made from raw or cooked leaves. The authors concluded that tree-spinach leaves are a rich food source of natural antioxidants [49].

18.2.1.23 White Sapote

Casimiroa edulis – Rutaceae

Other common names: Zapote blanco, Ice cream fruit, White sapota

The edible fruit of this plant has been used in Mexican traditional medicine for the treatment of hypertension, anxiety, and insomnia. The seeds possess a relaxant and hypnotic effect and can be toxic if ingested in quantity.

Cultured HL-60 promyelocytic cells were employed to monitor differentiation, proliferation and cell death events induced by a set of plant-derived extracts. More than 400 plant extracts were screened, and 34 of them, including white sapote, were discovered to possess potent antiproliferative activity. The flavonoid compound known as zapotin (2',5,6-trimethoxyflavone) was isolated from the seeds of white sapote. Of all the active ingredients studied from various plants, zapotin demonstrated the most favorable biological profile, due to the correlation between induction of differentiation and proliferation arrest, as well as a lack of cytotoxicity [50].

Another study found that zapotin induced cellular differentiation, apoptosis and cell cycle arrest in cultured HL-60 promyelocytic cells. In a two-stage mouse skin carcinogenesis model, topical application of zapotin significantly inhibited 7,12-dimethylbenz(a)anthracene/12-*O*-tetradecanoylphorbol-13-acetate-induced mouse skin tumorigenesis demonstrating the potential chemopreventive activity of this flavonoid compound [51].

Zapotin was also found to induce both cell differentiation and apoptosis with cultured human promyelocytic leukemia cells (HL-60 cells). Additionally, this compound inhibited 12-*O*-tetradecanoylphorbol 13-acetate (TPA)-induced ornithine decarboxylase (ODC) activity in human bladder carcinoma cells (T24 cells), as well as in TPA-induced nuclear factor-kappa B (NF-kappaB) activity with human hepatocellular liver carcinoma cells (HepG2 cells). More research is needed in order to elucidate the chemopreventive capacity of zapotin [52].

Murillo et al. (2007) reported the potent anticancer activity of zapotin and suggested it could potentially have both chemopreventive and a chemotherapeutic activities against colon cancer [53].

An in vitro study examined the effects of natural zapotin extracted from white sapote seeds and synthetic zapotin in SW480, SW620, and HT-29 colon cancer cell lines and also on the generation of aberrant crypt foci (ACF) in laboratory mice. The zapotin treatment showed a significant suppression of cell proliferation in the HT-29 cells and increased apoptosis in the totality of the colon cancer cell lines studied [54].

18.3 Conclusions

Cancer is an important disease in various industrialized and developing countries, including Mexico. Some expressions of this disease, especially gastrointestinal cancer, could theoretically be prevented by changes in certain lifestyle habits, such as avoiding fried foods and decreasing the intake of processed meats that contain *N*-nitroso compounds as colorants or preservatives, along with an increase in the intake of various fresh fruits, vegetables, and spices. Various food plants contain important phytochemicals with potential antioxidant and anticancer properties, which should be included in the diet on a daily basis.

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Chapter 19

Bioactive Nutritional Supplements for Chronic Kidney Disease: Potential Cost Benefits

Glenda C. Gobe, Robert G. Fassett, and Jeff S. Coombes

Key Points

1. Chronic kidney disease (CKD) affects approximately 10–15% of the adult population in industrialized countries and the incidence of CKD, and its associated end stage kidney disease, are increasing each year.
2. Renal replacement therapies are already a significant cost to health systems internationally, and this is expected to increase.
3. There could be significant benefits through sensible use of bioactive nutritional supplements as either prophylactic treatment against development or progression of CKD, or as single or co-therapies, along with established conventional medicines, for CKD.
4. Although efficacy trials with antioxidants have been generally disappointing in non-CKD patients with cardiovascular disease, the increased oxidative stress in CKD may provide an environment for antioxidants to be protective.
5. It is imperative that use of dietary supplements be monitored closely in all patients, and that health care practitioners take an active role in identifying patients who are using such supplements and be able to provide appropriate patient education.

Keywords Chronic kidney disease • Fish oil • Inflammation • Omega-3 fatty acids • Oxidative stress • Vitamin E

19.1 Introduction

The costs of renal replacement therapies to health systems internationally are substantial and are increasing in association with the increasing incidence of chronic kidney disease (CKD), which is also exacerbated by an increasingly aging population in developed countries. CKD, involving replacement of functioning renal mass with fibrosis and scarring, is a predisposing factor to the development of end stage kidney disease (ESKD) [1]. The ESKD population requires dialysis for maintenance therapy or needs renal transplantation to remain alive. The CKD and ESKD populations are also vulnerable to complications and co-morbid conditions that adversely affect quality

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of life and longevity [2]. Among these are diabetes and the metabolic syndrome, hypertension, anemia and its complications, dialysis and its complications, uremia-related diseases, and high mortality rates from cardiovascular disease.

Screening and treatment strategies introduced over the past decade have had limited success in improving outcomes through early detection of CKD. The current prevention or treatment strategies rely heavily on conventional medicines. Those therapies involving the use of bioactive nutritional supplements, or nutraceuticals, either singly or in conjunction with other conventional medicines, have received only moderate attention. There are also few robust trials of their usage. The potential cost benefits of these strategies, if they are successful, highlights the need for further research to identify the bioactive components of nutritional supplementation that may be used as complementary or alternative treatments to reduce the incidence and cost of CKD and ESKD.

When the costs associated with cardiovascular disease and other co-morbid complications and the burden on families and communities who care for CKD patients are considered, it becomes evident that new treatments that can alleviate these costs will improve public health and save expenditure in health budgets. To understand how bioactive nutritional supplements might benefit treating CKD, it is necessary to know something about the pathogenesis of CKD. The following chapter therefore describes (1) how CKD develops and what might be targeted with use of new therapies; (2) current treatments for CKD; (3) the critical importance of rigorous scientific analysis and reporting of new therapies that modulate CKD, using an example of oxidative stress and the use of antioxidants in CKD; and (4) the bioactive components of some nutritional supplements that are known to ameliorate some of the causal mechanisms of CKD and its associated co-morbid conditions. The final segment describes some current and predicted costs of renal replacement therapies and the potential social and financial benefits that may accrue through sensible use of some alternative therapies for CKD, such as bioactive nutritional supplements.

19.2 Development and Outcomes of Chronic Kidney Disease

CKD affects approximately 10–15% of the adult population in industrialized countries and the incidence of CKD, and its associated ESKD, is increasing [3]. The costs of providing dialysis and kidney transplantation to affected individuals are expected to grow several-fold over the next decade [4]. No matter the cause of CKD or the longer term outcome of ESKD, people with CKD have a greater burden of cardiovascular or metabolic disease, have unacceptably high mortality and poor quality of life, and are often from minority groups such as black and native Americans, and aboriginal and Pacific Islanders [5–7]. At least 10% will die directly or indirectly from CKD.

The kidney is very adaptive to injury. Following early injury and loss of function, there is an adaptive response by healthy portions of the kidney to take over the structure and function of lost nephrons. In this process, there is stimulation of the renin–angiotensin–aldosterone system (RAAS), which then initiates local glomerular afferent arteriolar dilatation, efferent arteriolar vasoconstriction, and an increase in blood volume via aldosterone stimulation [8, 9]. The result is increased glomerular perfusion, and thus enhanced filtration by remaining functional nephrons. A major side effect of RAAS induction is glomerular hyperperfusion and hypertrophy, and sometimes hypertension, which further damages remaining functional renal tissues, causing inflammation, sclerosis and scarring [8]. The tubules and the interstitium may also be affected by ischemia and hypoxia, with injury of tubular epithelium stimulating activation of interstitial and immune cells (inflammation) and then replacement of the tubular epithelium. Renal injury may originate in the glomeruli and progress to the tubulointerstitium, or may start within the tubulointerstitium followed by altered glomerular filtration, perfusion and autoregulation. No matter the initiating anatomy, loss of functioning renal mass may be significant [1].

Table 19.1 Classification of chronic kidney disease. Glomerular filtration rate (GFR) decreases with progressive chronic kidney disease (CKD). The filtration rate has been classified to allow staging of CKD

Stage	Clinical features	GFR (mL/min/1.73 m ²) ^a
1	Evidence of kidney disease in urine, blood, or imaging with normal or increased GFR	90
2	Mildly decreased GFR	60–89
3	Moderately decreased GFR	30–59
4	Severely decreased GFR	15–29
5	Renal failure	15 or renal replacement therapy

^aMeasured using the MDRD formula (*MDRD* modification of diet in renal disease)

Eventually the adapting glomeruli and the repairing tubulointerstitium become irreversibly injured and non-functional, and a vicious cycle of progressive injury, repair and loss of function can ensue. Sustained low-level injury and/or failure of the kidney to recognize the successful end point of repair after significant acute kidney injury are important in the development of CKD. The consequence of developing CKD is a reduction in glomerular filtration rate (GFR). Table 19.1 demonstrates the classification of stages of CKD using GFR.

Renal fibrosis is a precursor of CKD and ESKD. As stated previously, it develops progressively. Key contributing factors are excessive accumulation of extracellular matrix (ECM) and defective degradation of ECM [6, 10]. Chronic inflammatory cells, like macrophages and activated myofibroblasts, and damaged tubular epithelium and glomeruli, secrete ECM proteins. Their subsequent build-up distorts the normal renal architecture, and increases tubular atrophy and apoptosis or programmed cell death (Fig. 19.1). In general, there is also development of glomerulosclerosis and vascular ablation. The discovery of apoptosis in CKD is potentially one of the most exciting outcomes of nephropathologic research. This mode of cell death is controlled by expression or activation of the cell's own genes, and so its identification means there may be multiple targets that can be modulated for the benefit of renal health. Such modulation may be with use of dietary supplements or alternative therapies, as well as by conventional medicine [11].

Figure 19.2 demonstrates some of the many causes or predisposing factors for development of CKD, and its progression to ESKD. Cardiovascular disease such as atherosclerosis and hypertension, metabolic disease such as diabetes, bacterial infections especially those that are continual and low level, nephrotoxins, and the burden of reduced nephron number through premature birth, maternal nutritional deprivation, or faulty fetal development of multiple causes are only some of the factors that contribute to development of CKD in the adult. Many of the pro-fibrotic mechanisms activated by these causes may be preventable by use of bioactive dietary supplements either in the mature adult, in the developing neonate and child, or in the mother during development of the fetus.

19.2.1 Factors That Exacerbate Development of Chronic Kidney Disease

Obesity, increasing age and smoking exacerbate the development of CKD. This is a concern because of the upward trend in the prevalence of obesity in Western societies, the increasingly aging population in many countries [3], and an increase in smoking especially in females [12].

Obesity: Similar co-morbidities for obesity and CKD include insulin resistance (Type 2 diabetes), hyperlipidemia, and endothelial or vascular dysfunction (hypertension). Visceral obesity appears to be the key factor in the pathogenesis of CKD [13]. Hyper-triglyceridemia and low levels of high-density lipoprotein (HDL) cholesterol are produced through metabolism of visceral adipocytes, increasing the

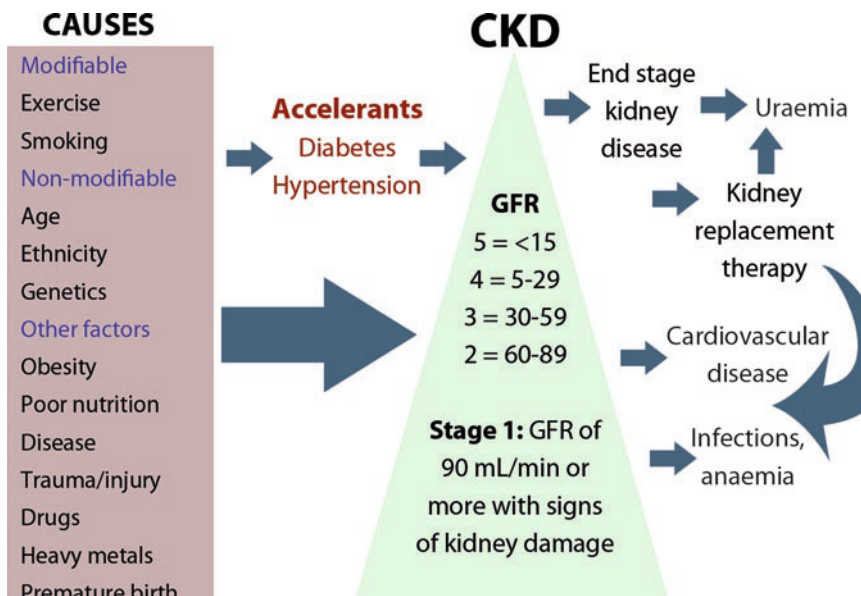


Fig. 19.1 Grading of chronic kidney disease. Chronic kidney disease (*CKD*) is graded in stages from 1 to 5, according to an estimated glomerular filtration rate (*GFR*). *CKD* is caused by many modifiable, non-modifiable and other factors. Type 2 diabetes and hypertension, known to increase with aging, accelerate progression of *CKD*, as do cardiovascular disease, infections and anemia, all known outcomes of *CKD*. The final stage, end stage kidney disease, is treatable only with kidney replacement therapies such as dialysis or transplantation

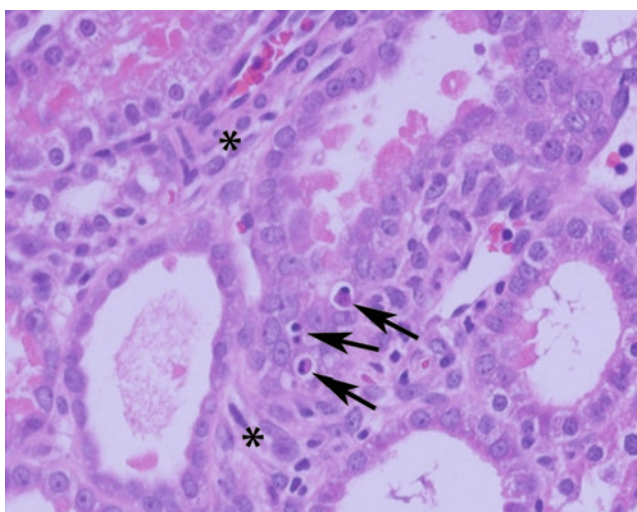


Fig. 19.2 Morphological changes of chronic kidney disease. As chronic kidney disease progresses, there is loss of functioning kidney tissue and a buildup of interstitial tissue and extracellular matrix proteins. In this photo of the cortex of the kidney, there is loss of brush border and flattening of epithelial cells, apoptosis of tubular epithelium (arrows) and an expansion and cellular activation of the interstitial space (asterisks)

relative risk of progression of *CKD*. Vascular inflammation and atherosclerosis are promoted by hyper-homocysteinemia and oxidation of low-density lipoprotein (LDL) [14]. Oxidative stress may be a key driving mechanism for development of obesity-related *CKD*. Oxidative stress stimulates synthesis of angiotensin II, which in turn increases secretion of transforming growth factor-beta (TGF- β)

and plasminogen activator inhibitor-1, thereby propagating renal fibrosis. Renal fibrogenesis involves many pro-fibrotic factors, but the main one is likely TGF- β [6], and antioxidant treatments often target this factor. Local synthesis of angiotensinogen by adipocytes, activation of the profibrotic hormone leptin, and hyperinsulinemia contribute to the development of hypertension in obesity and CKD [15].

Aging: Even in the absence of obesity, hypertension and Type 2 diabetes, the kidneys are adversely affected by increasing age [3]. Renal function in aging may be able to predict how long we would live, barring accident or cancer. Altered gene regulation from renal aging and cell senescence mediates oxidative stress, inflammation, hypoxia, altered metabolism, fibrogenesis and increasing programmed cell death or apoptosis. The cells of the kidney that are most susceptible to age-related oxidant-induced apoptosis are those of the proximal tubule as these cells that contain large numbers of mitochondria and are the most reliant on oxidative phosphorylation. Mitochondrial dysfunction in aging is one of the up and coming therapy targets [16].

Drugs, smoking and other environmental toxins: These are known to exacerbate the development of CKD through, at times, overlapping events: the cytotoxic effect, inflammation and induction of pro-fibrotic molecules. Many drugs are filtered through the kidney and may be nephrotoxic [17]. An example is the commonly used chemotherapeutic drug *cis*-diammine-dichloroplatinum (II) (cisplatin) which is known to induce long term renal dysfunction. Smoking is the largest single preventable cause of death and disease in general, and has close links with development of CKD, most likely via vascular damage. Environmental toxins, like heavy metals, are often nephrotoxic and cumulative. For example, cadmium is present at low, seemingly acceptable, levels in cigarettes. It is also found in areas where mining, particularly for zinc, has disturbed the surroundings. Cadmium is said to have a half-life in the body of around 20 years, and it accumulates in the proximal tubular epithelium [18]. Oxidative stress is again a key mechanism in the pathogenesis of CKD from these agents. For example, advanced oxidation protein products and the plasma oxidative stress marker myeloperoxidase were increased in all groups exposed to nephrotoxins, with an additive effect on CKD when both smoking and the nephrotoxins are involved. Surprisingly, inflammatory cytokines do not appear to have such an influence in smoking and environmental toxin-induced CKD, indicating pathways to CKD need to be defined for most effective development of any new treatments.

19.3 Established Strategies for Treatment of Chronic Kidney Disease

19.3.1 Pharmacological Blockade of the Renin–Angiotensin–Aldosterone System

Since the introduction of angiotensin-converting enzyme inhibitors (ACEI) in the early 1980s and angiotensin-II (ANG-II) receptor blockers (ARB) in the mid-1990s as antihypertensive therapies, pharmacologic blockade of the RAAS has become one of the most effective and widespread therapeutic approaches in the management of CKD and associated cardiovascular disease [8, 9, 19]. Blockade of the RAAS lowers blood pressure, decreases proteinuria and slows the rate of decline in GFR in patients with CKD [8]. Blockade of the RAAS with ACEI and/or ARB may be incomplete because both classes of compounds interrupt the normal feedback inhibition of renin release, leading to a reactivation of the downstream effects of ANG-II, including aldosterone release. Renin has also long been regarded as a logical point to inhibit the RAAS because it is the first and rate-limiting step in the cascade and is highly selective for its substrate, angiotensinogen [20]. Direct renin inhibition, by drugs like Aliskiren, is currently approved for the treatment of hypertension. Because Aliskiren

directly inhibits the catalytic activity of renin, the production of ANG-I, ANG-II, and aldosterone are also modulated.

The classical epithelial effects of aldosterone on salt retention and volume expansion adversely affect blood pressure and, consequently, cardiac and renal function. In addition, aldosterone has a profibrotic, pro-inflammatory effect at nonepithelial mineralocorticoid receptors, promoting progression of CKD. Thus, over time significant numbers of patients suffer progressive CKD despite use of ACEI, ARB or renin inhibition. This suggests additional supplemental therapies are needed. Dietary therapies with bioactive products aimed at the RAAS may be beneficial either as single treatments or as supplements to the conventional therapies.

19.3.2 Modulation of Glucose

Diabetic nephropathy remains the leading cause of CKD and ESKD in developed countries. High blood glucose is in itself toxic to the kidney, but in addition, it acts via various other mechanisms such as increased production of oxidative stress and advanced glycation end products (AGEs), and activation of the RAAS and protein kinase C [21]. It also induces vascular inflammation and alters gene expression of growth factors and cytokines. CKD associated with Type 2 diabetes may be treated with intensive glucose control, and blockade of the RAAS is another important treatment for both metabolic and hemodynamic derangements in diabetic nephropathy. However, new therapeutic interventions that may prevent this devastating disorder, even in the presence of hyperglycemia, are needed. For example, the effect of dietary intake of omega-3 poly-unsaturated fatty acids has been tested on insulin-sensitizing actions in adipose tissue and improved insulin tolerance [22]. Although this investigation concentrated on hepatic steatosis, which was reduced in conjunction with the omega-3 treatment, similar effects might have been found in diabetes-associated CKD.

19.3.3 Lipid Modulation

High serum cholesterol is closely linked with cardiovascular risk including diminished endothelial function, inflammation and oxidative stress [23]. In patients with CKD, the relationship between high levels of cholesterol and cardiovascular risk is confounded and the underlying mechanisms are complex [24]. Lipid lowering drugs have been in use for some time now for cardiovascular disease per se, but until recently not specifically for CKD. Statins are widely used. There is now evidence from large trials of statins in cardiovascular disease that patients in the early stages of CKD (CKD 2 or 3) also benefit from statins. There was small but significant slowing of progression of CKD. In patients with ESKD and after transplantation, the evidence was not so compelling. One observational study showed improved survival in hemodialyzed patients put on statins [25], but an Australian study compared the effect of lipid lowering on carotid intimal-medial thickness. Aggressive lowering of low-density lipoprotein cholesterol reduced the maximum intimal-medial thickness in cardiac patients without CKD but remained unchanged in patients with CKD [26]. As with other CKD treatments, however, other lipid lowering nutritional supplements deserve trialing.

Omega-3 dietary supplementation in dialysis patients may be beneficial. Leaf et al. [27] investigated the benefits of omega-3 fish oils and found positive results against sudden cardiac death, a co-morbidity in dialysis patients. Although studies in dialysis patients that have measured the susceptibility of LDL to oxidation have not supported omega-3 supplementation, other studies have

found that omega-3 fatty acids seem to increase the antioxidant capacity of LDL particles. Ando et al. [28] directly measured the effects of 12 weeks of 1.8 g/day eicosapentaenoic acid (EPA) supplementation on plasma oxidized LDL particles. Compliance was confirmed by fatty acid plasma measurements. Levels of oxidized LDL were significantly lower (by 38%) by 12 weeks of treatment compared with baseline in the placebo group. EPA may protect LDL against peroxidation or improve the body's ability to scavenge oxidative species. More clinical trials are needed to assess the outcome of omega-3 dietary supplementation.

19.3.4 Antioxidants

Reactive oxygen and nitrogen species are continuously produced in the human body and are normally controlled by endogenous antioxidant enzymes such as superoxide dismutase, glutathione peroxidase and catalase (Fig. 19.3). These reactive species are essential for energy supply, detoxification, chemical signaling, and immune function. Their overproduction, via exposure to external oxidant

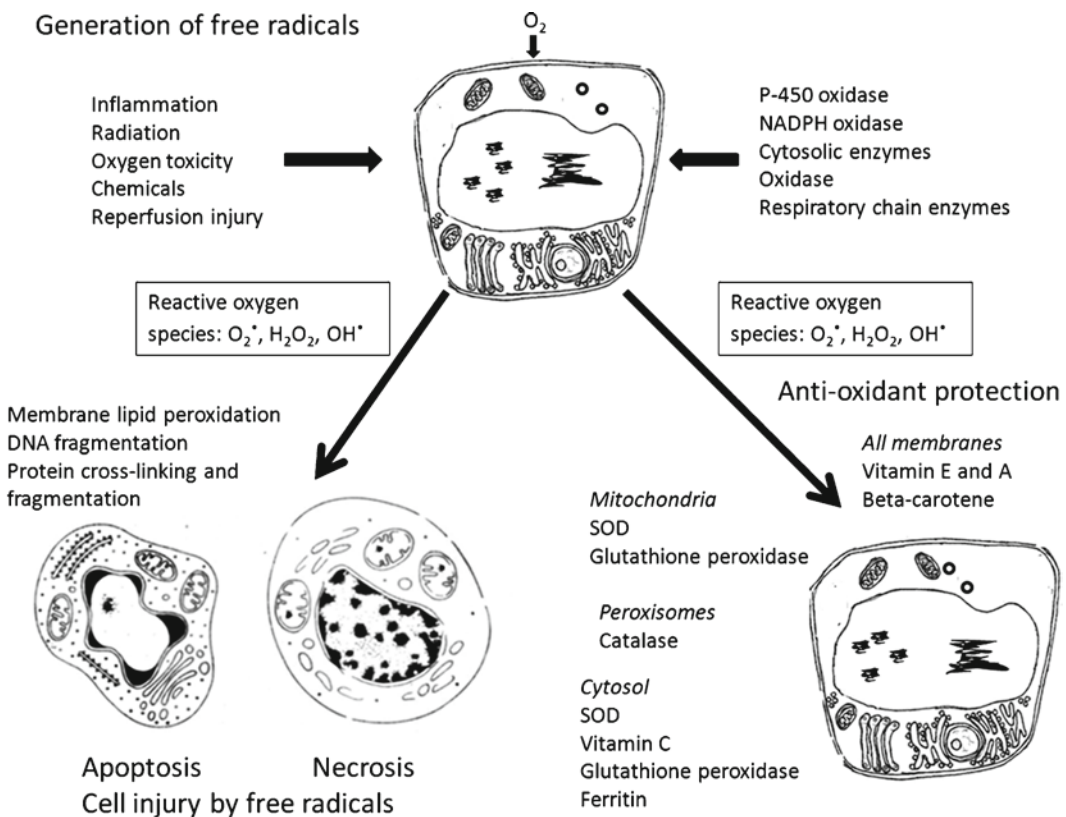


Fig. 19.3 Oxidative stress in cells, cell injury, and protection by antioxidants. Cells are constantly bombarded with damaging stimuli that cause the build-up of free radicals, most often reactive oxygen species. Depending on the natural antioxidant protection, the effects of these free radicals are neutralized and the cells maintain their health. If there is an imbalance in the levels of oxidative stress and antioxidant protection, the cells may die by either apoptosis (programmed cell death) or necrosis (Adapted from Robbins Pathological Basis of Disease, 7th Ed., Saunders Publishing. With permission)

substances or a failure in the antioxidant defence mechanisms, damages essential biomolecules like DNA, RNA, proteins, and lipids. This damage has been associated with an increased risk of CKD [29]. The reactive species are generated by the metabolism of arachidonic acid, platelets, macrophages, and normal functioning cells in the kidney like the tubular epithelium and the endothelium. Therefore, by increasing levels of scavengers of free radicals, the kidney may be protected from oxidative damage. Surprisingly, however, the use of antioxidants has demonstrated conflicting results. One success story is with *N*-acetyl-cysteine (NAC), a proven antioxidant. NAC was used against placebo in ESKD patients on hemodialysis where it decreased the incidence and fatal outcome of acute myocardial infarction and stroke in these patients [30]. Although efficacy trials with antioxidants have been generally disappointing in non-CKD patients with cardiovascular disease, the increased oxidative stress in CKD may provide the environment for antioxidants to be protective. Clearly more investigations and controlled trials are required before specific antioxidants can be recommended and a detailed discussion on the use of Vitamin E is provided below.

Vitamin E (alpha-(α) tocopherol) is receiving attention as an antioxidant in CKD patients, although its use is not without controversy [31]. People with diabetes, likely to have CKD, have a higher than usual need for vitamin E, which improves insulin activity and acts as an antioxidant and a blood oxygenator, often in association with some of the B group vitamins, and at quite high doses. A rapid increase in plasma tocopherol levels occurs up until 6 weeks, followed by a slow but continuous increase for the duration of the trial and no adverse reactions were reported [32, 33]. In humans, 1,600 mg/day of α -tocopherol over 21 days found substantial plasma tocopherol increases with no reported adverse events [34]. Furthermore, in dialysis patients a number of studies have trialed α -tocopherol supplementation using doses of 600–800 mg/day over 12–52 weeks with no reported adverse events [35–37]. A meta-analysis questioned the safety of α -tocopherol supplementation [38, 39]. Miller et al. (2005) concluded that doses of greater than 400 mg/day of α -tocopherol may increase all-cause mortality and should be avoided [38]. The paper was subsequently severely criticized with numerous letters to the editor in the next issue by leading oxidative stress scientists [40–50]. Major concerns included a bias in the data analysis and numerous methodological flaws [40]. There has also been speculation that α -tocopherol may displace gamma-(γ) tocopherol in the body leading to potential problems. Reduced serum concentrations of γ -tocopherol were recorded when α -tocopherol was supplemented [51]. One of the final concerns is that high doses of α -tocopherol may affect coagulation and cause an increase in bleeding. This has occurred in normal healthy humans [52, 53] due to adverse interactions between α -tocopherol and vitamin K-dependent carboxylase [54].

19.3.5 Anti-inflammatory Effects

Protein-energy wasting and chronic inflammation are important co-morbid conditions that contribute to, and predict poor clinical outcome in, patients with advanced CKD [55]. The exact mechanisms leading to these unfavorable conditions are most likely multifactorial. Nonetheless, nutritional anti-inflammatory interventions may provide potential treatment options to conventional medicine to decrease the high mortality and morbidity in patients with advanced CKD.

Several pilot studies indicate that anti-inflammatory intervention can improve the metabolic and nutritional profiles of CKD patients. The effects of omega-3 fatty acids on clinical benefits for inflammation-mediated diseases such as rheumatoid arthritis, inflammatory bowel disease, some skin disorders, sepsis, and some kidney diseases have been reported [56–60] and the same may occur in CKD and ESKD [61, 62]. Parenteral nutrition enriched with omega-3 polyunsaturated fatty acids

again has been reported as having beneficial effects [63, 64]. The mechanism of action of omega-3 polyunsaturated fatty acids may include suppression of the pro-inflammatory cytokine tumor necrosis factor- α and inhibition of activation of the transcription factor nuclear factor kappa-B. In addition, it appears that the common pathway for metabolic derangements in CKD is related to exaggerated protein degradation relative to protein synthesis. Several studies suggest that chronic inflammation can predispose advanced CKD patients to a catabolic state leading to worsening of protein-energy wasting by both increasing protein breakdown and decreasing protein synthesis. Chronic administration of nutritional supplementation, both parenterally and orally, may improve nutritional status even in inflamed states in hemodialysis patients.

19.4 Standardization of the Analysis of Dietary Supplements: An Example with Antioxidants

The increased intake of antioxidants from dietary supplements may reduce the risk of development of CKD. There is, therefore, an increasing interest in natural antioxidants as the bioactive components of dietary supplements. A dietary antioxidant is a substance that significantly decreases the harmful effects of reactive species such as reactive oxygen and nitrogen molecules that disrupt normal physiological function of cells [65, 66]. For scientific publication of those benefits, the analyses of antioxidant properties must be standardized, rigorous, repeatable, and tested in humans.

Assays are needed to standardize measurement of oxidative stress and the effects of antioxidants. The normal levels of the antioxidants or their metabolites must be known and these are usually at the limits of detection in most assays. In addition, measurement methods for antioxidant capacity are not standardized and results appear to be inconsistent among laboratories. While it is useful to confirm that there is oxidative stress evident when a subject already has a clinically diagnosed disease, it is of little value as a predictive tool. Assays in common usage are the oxygen radical absorbance capacity (ORAC) assay, the Folin-Ciocalteu method, and the Trolox equivalent antioxidant capacity (TEAC) assay [67, 68]. ORAC represents a hydrogen atom transfer reaction mechanism. The Folin-Ciocalteu method is an electron transfer-based assay and gives reducing capacity normally expressed as phenolic contents. The TEAC assay represents a second electron transfer-based method. Measurement of oxidative stress biomarkers (for example, lipid peroxides, malondialdehyde and isoprostanes) is also used [69, 70]. The gold standard is now the measurement of markers of lipid peroxidation, like the 8-isoprostanes, which are formed by non-enzymatic peroxidation of arachidonyl lipids only after endogenous antioxidants are exhausted. Measurement of 8-isoprostanes is therefore an effective means of assessing antioxidant status. The selection of the appropriate assay is the key to information on free radical sources, their importance to human pathology and biology, and their modulation by the bioactive antioxidant components of new treatments.

19.5 Bioactive Dietary Supplements: Ameliorating Factors that Contribute to Chronic Kidney Disease

The number of nutritional supplements, and their bioactive components, that have been reported as beneficial in kidney disease is extensive. Many are reported in non-English journals and so are not readily available for representation in this review. Undoubtedly, however, the benefits of bioactive components of nutritional or dietary supplements such as vitamins C, E, and D, omega-3 fatty acids,

or olive leaf extracts, are known to be antioxidant, hypoglycemic, anti-hypertensive, anti-microbial, anti-inflammatory, and/or anti-atherosclerotic [71, 72]. These benefits, if suitably analyzed and published, must amount to a cost-effective way of reducing the social and financial burden of CKD. In the following paragraphs, the effects of bioactive dietary supplements will be discussed, and specifically, those of plant phenols which have proven antioxidant effects [66].

Bioactive plant phenols are now being developed commercially. Production methods for antioxidant plant phenols include genetically modifying for increased phenolic compound contents in plants, enzymatically modifying the structure of the phenolic compounds for improved pharmacological characteristics with a lower hydrophilic action, and quantitating structure – activity relationships of various phenol classes. One such potent antioxidant is oleuropein, a major constituent of the secoiridoid compounds in the olive leaf [73]. Olive phenols may exhibit synergistic behavior in their radical scavenging capacity when mixed, as occurs in the olive leaf extract with a high content of oleuropein and some other active polyphenols. Oleuropein is capable of preventing the generation of reactive oxygen species because it possesses a catechol group that is needed for optimal antioxidant and/or scavenging activity of the superoxide anion, the hydroxyl radical and hydrogen peroxide. The effect of olive leaf extract on the glycemic responses has been investigated in humans. For example, Sato et al. [74] reported an anti-hyperglycemic activity of a TGR5 agonist isolated from olive leaf. In addition, Zhong et al. [75] found an extract of teas containing olive leaf caused malabsorption of carbohydrate but not of triacylglycerol in healthy volunteers, suggesting a use against obesity and therefore against diabetes type 2. In contrast, Kamgar et al. [76] reported that antioxidants did not reduce oxidative stress or inflammatory markers in patients with ESKD, so it appears more research needs to be carried out.

Although there are undoubted advantages to taking these dietary supplements in ameliorating factors that contribute to the pathogenesis of CKD and some of the associated diseases and co-morbid conditions, human trials still need to be carried out in a more targeted, carefully constructed manner to fully assess the potential benefits of dietary supplementation in patients with CKD. It was obvious from the review of the literature, limiting our review only to omega-3 and olive leaf extracts, that many of the published studies were characterized by suboptimal study design, small sample sizes, supra-physiologic doses of the dietary supplements, and little to no discussion of adverse effects or adequate long-term follow-up. In the human trials, there was little evidence of confirmation of compliance.

19.6 Potential Cost Benefits of Dietary Nutritional Supplements to Chronic Kidney Disease

Complementary and alternative medicine, including dietary supplements, is a multibillion-dollar industry, but rigorous testing of these treatments is often lacking. When it is done, researchers often find it difficult to have the research reports accepted in reputable scientific journals. It is also very unfortunate that manufacturers are not required to rigorously prove safety and efficacy, because of the lack of regulation by Food and Drug Administration bodies. In the USA, dietary supplement-induced adverse events are regularly reported to Poison Control Centers. However, with regard to CKD and its co-morbid conditions, apportioning blame of any serious adverse event like myocardial infarction to the treatment of CKD with dietary supplements should be considered simplistic and incorrect. A typical medical history of a CKD patient 50 years or older might be many years of smoking, developing visceral adiposity and an increasing body mass

index, several years of Type 2 diabetes mellitus and its side effects on the kidney and the vasculature, a history of hypertension, and anemia. Thus, should this person be treated with conventional medicines like ACEI and/or ARB, or be on dialysis, plus have a dietary supplement such as omega-3 fatty acids, it is difficult to tease out the exact cause of any serious adverse event that might occur to this patient.

There is now an emphasis on regular assessment of renal health in patients over 50 years of age. It would therefore be a simple task, during the early stages of disease, to include treatments that might slow CKD progression and significantly reduce associated cardiovascular disease. This has been occurring with use of lipid lowering drugs like the statins, but a simple dietary supplementation of something proven to have positive outcome in minimizing progression of CKD through modulation of many of the causative mechanisms of the disease may be more cost effective. There are, however, few data that allow determination of actual cost benefits of use of dietary supplements in CKD.

In order to determine the impact on costs and health outcomes of changes in the clinical management of CKD and ESKD with use of dietary supplements, current costs and benefits of conventional treatments must be defined and estimated. The existing patterns and costs of renal replacement therapy may be used to predict future health care costs and benefits of treating new and existing end-stage kidney disease patients. ESKD management in developed countries has strongly stimulated the concept of “nephroprotection” aimed at the early detection and subsequent prevention of progression of CKD, mainly through lifestyle adjustment and the use of new pharmacological or nutraceutical agents. Costs associated with lost earnings and productivity, and other out-of-pocket costs of patients and families such as the cost of carers, travel, over-the-counter medications as well as other consumables are also very large.

19.6.1 The Costs of Adverse Effects from Using Dietary Supplements in Chronic Kidney Disease

The costs of adverse effects of treatments with dietary supplementation go way beyond the actual incident of toxicity. Doctors using conventional medicines need little reason to steer away from any use of alternative therapies. A potential “cost” of use of the dietary supplements is their possible exacerbation of acute and chronic renal disease conditions [77]. Recently, Gabardi et al. [78] explored the impact of complementary and alternative medicine on renal function in human subjects, both adult and pediatric. Their review focused on 17 dietary supplements that have been associated with direct renal injury, immune-mediated nephrotoxicity, nephrolithiasis, rhabdomyolysis with acute kidney injury, and hepatorenal syndrome. These authors concluded that it was imperative that use of dietary supplements be monitored closely in all patients, and that health care practitioners take an active role in identifying patients who are using such supplements and be able to provide appropriate patient education.

Once again using omega-3 supplementation as an example, the risk of its use possibly receives greater press than the benefits of its use. Increased bleeding times have been reported, primarily with >3 g/day fish oil, although findings are equivocal. Increases in serum glucose and LDL levels have also been seen with large fish oil doses (e.g., >4.5 g/day). Gastrointestinal complaints, like a fishy after taste, nausea and stomach upset, have been commonly reported. Methylmercury and organochlorine concentrations can vary widely in fish oil supplements, depending on the quality of the refining process.

19.7 Conclusion

Cost-effective care for CKD should encompass a strategy which includes early detection of CKD in patients at risk, organization of a sustained medical follow-up of CKD-detected patients; provision of all validated measures of optimal renal care, and referral to a qualified nephrological team, working in close coordination with general practitioners and other specialists. It is the latter factor, the “alternative specialist,” that needs greater involvement, because at present there is likely underutilization of specialists who could recommend rigorously tested beneficial dietary supplementation in CKD. The lack of involvement of these specialists may relate to physician concern regarding worsening of renal function, lack of evidence for use of certain therapies, associated co-morbidities, and generally worsened outcomes in CKD patients. None-the-less, official policies designed to reduce the social and financial burden of CKD must go beyond support for the testing of conventional therapies and increasing eligibility for health insurance, because of the probability of benefits from use of the dietary supplements in reducing the burden of disease.

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Chapter 20

Preoperative Immunonutrition: Cost–Benefit Analysis

Marco Braga and Simona Rocchetti

Key Points

- Standard enteral preparations have been modified by adding specific nutrients: arginine, omega-3 fatty acids, and nucleotides.
- These up-regulate host immune response, to control inflammatory response, and to improve nitrogen balance and protein synthesis after injury.
- The majority of randomized trials focused on clinical outcome have been carried out in GI cancer elective surgical patients.
- When immunonutrition was limited to postoperative period the results were conflicting.
- Better results on outcome were obtained when the provision of the immunoenhancing diet was anticipated before surgery.
- This allowed to significantly reduce postoperative infection rate either in malnourished or in well nourished patients.
- Cost–benefit analyses showed that immunonutrition resulted in a positive cost-effectiveness ratio compared to conventional treatment.

Keywords Cost–benefit analysis • GI cancer • Immunonutrition • Postoperative infections • surgery

20.1 Introduction

Postoperative infectious complications remain common, adding to length of hospital stay, healthcare costs and potential excess mortality. Furthermore, rates of nosocomial infections are rising in surgical and intensive care units and the apparent increase in both Gram-positive and Gram-negative resistant bacteria is of particular concern, making the prevention of infection a major surgical issue [1]. The causes of infectious surgical complications are multi-factorial and dependent to an extent on the primary surgical pathology, and the type and magnitude of operation. Nevertheless, there is growing evidence that traumatic and surgical insult is associated with a period of relative immune suppression, which may expose patients to subsequent risk of infection.

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In addition, surgeons are increasingly under pressure to reduce healthcare costs. In many countries healthcare payers and providers encourage medical and surgical staff to reduce patients' length of hospital stay, particularly for elective surgery. Therefore, there is an imperative to reduce the potential for postoperative infectious complications [2].

Among the proposed strategies to reduce postoperative morbidity and its related costs, artificial nutrition is recognized as an important part of the patient care, particularly for patients undergoing major surgery for cancer of the GI tract. In recent years, major advances have been made in the field of clinical nutrition. Improvements in patient outcome have been obtained with early enteral nutrition in both malnourished cancer patients undergoing elective major surgery and intensive care unit patients [3, 4]. A further interesting field of research is the possible modulation of post-injury metabolic response by using new formulas supplemented with specific nutrients (immunonutrition).

20.2 Results of Clinical Trials with Immunonutrition

Recently, the main focus of clinical nutrition has moved from the issue of energy and nitrogen requirement to the pharmacological effects of specific key nutrients. Standard nutritional feeds have been modified by adding specific substrates such as arginine, omega-3 fatty acids, and nucleotides. The main target of this new diet is not solely to provide energy and nitrogen, but to modulate inflammatory post-injury response and to counteract postoperative immune impairment, which may per se increase patient susceptibility to infectious complications. Most of the randomized controlled trials have been carried out in GI cancer elective surgical patients. When the administration of Impact was limited to the postoperative period, immunonutrition enhanced the host defense mechanisms and helped to overcome the postsurgical immune depression more rapidly than the standard diet. However, this improvement occurred with some delay [5]. In fact, in the first days after surgery, the impairment of phagocytosis and lymphocyte mitogenesis, the alteration of cytokine profiles, the reduction of immunoglobulin levels and number of activated T and B cells were similar in patients fed with either immunonutrition or standard diet.

The delayed recovery in immune response might explain why the supplemented diet given solely in the postoperative course led to variable improvements in outcome [5–9]. Heslin et al. who studied 195 patients undergoing elective cancer surgery did not find any difference in postoperative infectious and noninfectious complications by comparing groups treated with either an early postoperative immuno-enhancing diet or simple crystalloid fluid replacement [6]. However, in the immunonutrition group the average postoperative energy intake was 60% of the nutritional goal and only 30% was given with the immuno-enhancing diet. When the amount of immunonutrients given early after surgery was higher a significant reduction of postoperative infections was reported by Daly et al. [7], whereas a not statistically significant reduction of overall postoperative complications by immunonutrition was found in a multicentre study from Germany [5] and in a large single-center study from Italy [8]. These contrasting data supported the hypothesis that the amount of substrates given in the first days after surgery was not sufficient to reach adequate tissue and plasma concentration promptly enough to be active. In fact, it takes around 5 days for immune-enhancing nutrients to become incorporated into the host tissues and to alter inflammatory mediators and fatty acid profiles. Since the impairment of the host defense mechanisms occurs immediately after surgery, immunonutrients should be given prior to surgery to obtain adequate levels at the time of surgical stress.

When immunonutrition was given orally for 7 days before surgery better metabolic effects were obtained in comparison with standard diets. In particular, modulation of inflammatory response, enhancement of cell-mediated immune response, and up-regulation of gut microperfusion and oxygenation

have been found early after surgery [10, 11]. These results suggested the concept that the key point in elective surgical cancer patients is to anticipate the provision of immunonutrients before operation.

Two prospective, randomized, double-blind clinical trials demonstrated that cancer patients fed before and after surgery with the diet supplemented with arginine, omega-3 fatty acids, and RNA had a significant reduction of both postoperative infections and length of hospital stay when compared to patients fed with a standard enteral formula [12, 13]. It could be speculated that the reduction of postoperative infections found in the supplemented group in both studies is the translation of the immunologic and metabolic advantages previously reported in patients receiving perioperative supplementation with immunonutrition [10, 11]. It has been also reported that perioperative immunonutrition is efficacious regardless of the baseline nutritional status of the patients (Table 20.1). In fact, preoperative administration of the immune enhancing diet reduced postoperative infection rate not only in malnourished patients, but also in the subgroup of well nourished patients in whom an impairment of the host defence mechanisms has been reported after surgery [12].

A post hoc analysis showed that clinical outcome was improved also in a subgroup of patients who received solely the preoperative supplementation because they did not tolerate early postoperative jejunal infusion. This is the reason why we designed a randomized clinical trial in well-nourished patients with gastrointestinal cancer comparing oral administration of immunonutrition for 5 days before surgery, perioperative immunonutrition, and conventional treatment (no feeding). Preoperative supplementation was as effective as the perioperative treatment in reducing postoperative morbidity and both approaches were significantly superior when compared with conventional treatment [14]. In other words, prolonging infusion of immunonutrients via the jejunal route postoperatively did not further improve clinical outcome. Another randomized clinical trial showed the same result by preoperative supplementation of key nutrients in well nourished patients undergoing elective colorectal resection for neoplasm [15]. This further supported the concept that the mechanism of action of these key substrates is more pharmacological than nutritional. A post-hoc analysis suggested that in the general cohort of so called well nourished patients the risk to develop postoperative complications was progressively higher with the increasing of body mass index value. In particular, postoperative morbidity rate was significantly higher in obese patients (55%) compared to patients with normal body mass index value ($p=0.04$). Preoperative administration of immunonutrition reduced postoperative infection rate in all three subgroups (normal, overweight, and obese) with a similar pattern [14]. These results fully confirmed that obesity is a major negative predictive variable on surgical outcome and suggested obese patients as potential target in future randomized clinical trials to evaluate the possibility to reduce postoperative morbidity rate by using immune-enhancing substrates.

Different results were obtained in malnourished patients in whom perioperative immunonutrition was superior to the simple preoperative approach. In fact, prolonging immunonutrition in the postoperative period allowed a further reduction of postoperative infection rate [16]. This could be explained by the fact that malnourished patients have both a greater impairment of immune response and higher energy and nitrogen requirements compared to well-nourished patients.

Table 20.1 Effects of preoperative immunonutrition on infection rate in GI cancer elective surgical patients

Author	Blinding	Control group	Pts #	Nutritional status	Infection rate treatment vs control	P
Braga [13]	Yes	Standard EN	206	Mixed	13% vs 29%	0.02
Senkal [14]	Yes	Standard EN	154	Mixed	13% vs 24%	0.08
Gianotti [15]	Not	Fluids	305	Welln.	14% vs 30%	0.006
Braga [16]	Not	Fluids	200	Welln.	12% vs 30%	0.04
Braga [17]	Not	Standard EN	150	Maln.	10% vs 24%	0.06

20.3 Cost–Benefit Analysis of Immunonutrition

Despite promising results from randomized clinical trials, the high cost of these new nutritional products could be considered a major drawback for their routine use. In view of the world-wide increasing concerns over exploding costs in medical care, the decision process for adopting the use of new products for routine treatment should not only weigh clinical benefits and risks, but also consider whether these benefits are worth the health care resources used. This decision making process should be informed by cost-effectiveness analyses of clinical trials in which the following costs have to be calculated: the mean in-hospital-related costs of routine surgical care per patient, the costs of treating postoperative infectious and non-infectious complications, the costs of nutrition, and the overall costs for all patients.

From a methodological point of view an economic analysis should be performed by a blind economist on data gathered from a prospective randomized clinical trial. For resource assessment, a specific electronic record form should be used to enable a detailed assessment of the amount of health care goods and resources that each patient with postoperative complication received for the treatment of the same complication. To simplify and standardize the recording, resources have to be previously defined including the following items: complication type and duration in days; laboratory and microbiology analyses; medical, technical, and diagnostic services; surgical and therapeutic interventions; medications; and outpatient follow-up consultations. For patients who developed more than one complication, resources used should be separately recorded for each complication. The additional length of hospital stay due to postoperative morbidity has to be valued at a daily rate, which covers the cost of board, lodging, routine medical supervision, and nursing.

Three cost-effectiveness analyses evaluated whether the use of preoperative immunonutrition led to a saving in health care resources consumed (Table 20.2). The cost of nutritional formula was approximately threefold higher in the group receiving the supplemented diet compared to the control group receiving standard diet. In all three studies it has been found that the saving due to significant reduction in postoperative morbidity by preoperative immunonutrition more than offsets the higher cost of the supplemented diet [13, 17, 18]. This translated into a substantial cost saving and in a positive cost-effectiveness when compared to a standard diet. Looking in detail, this overall net saving in the cost-effectiveness ratio is largely due to the differences observed for infectious complications, whereas a much smaller or no effect was observed for noninfectious complications or anastomotic leaks. Moreover, the mean cost to treat an infectious complication was significantly lower in the supplemented group, because of the shorter time needed to recover from the complication and less resources used. Although speculative, this could be due to a more efficient immune response observed in the patients who received immunonutrition.

Interesting findings were obtained by correlating the actual costs to diagnosis-related group (DRG) reimbursement rates [18]. In patients without complications, the specific DRG reimbursement rate covered the costs in both groups. When postoperative complications occurred, only the preoperative approach demonstrated consistent profitability in all three types of operation. In fact, the percentages

Table 20.2 Cost-effectiveness analysis of preoperative immunonutrition

Author	Cost of nutrition ^a		Cost of complication ^a		Cost-effectiveness ^a	
	Treatment	Control	Treatment	Control	Treatment	Control
Senkal [14]	347	49	964	2,688	1,504	3,587
Gianotti [18]	347	103	768	2,345	1,339	3,725
Braga [19]	144	33	1,728	3,089	2,985	6,244

^aPer patient randomized

Costs are in Euro

of DRG reimbursement consumed by costs of complications were 71% in colorectal surgery, 69% in gastrointestinal surgery, and 97% in pancreatic surgery. Conversely, DRG reimbursement did not cover the costs of complications for gastroesophageal and pancreatic surgeries in the conventional group, despite the higher DRG reimbursement rates applicable to complicated cases.

These results should stimulate the transition of preoperative oral immunonutrition into routine practice [19]. In fact, patients can be easily prepared for surgery at home in a short period of time (5 days) and no postoperative prolongation of immunonutrition is required in well nourished subjects, thus avoiding any potential side effects of early jejunal feeding.

Some general limitations of economic analyses should be noticed on the transferability of the present clinical and economic data, which may influence also their reproducibility. Comparable cost saving by the routine use of preoperative immunonutrition might be achieved in hospitals where the same type of operations are performed on a similar volume and complication rate. Moreover, the economic parameters may differ from country to country based on the type of health care system and reimbursement rates.

The cost-analyses are usually based only on calculation of hospital resources spent. The assessment of community associated costs, including sick leave, rehabilitation, full recovery of physical and social performance would probably even magnify the advantage of immunonutrition even more.

20.4 Conclusion

To administer immuno enhancing diet before surgery seems to be the key point to improve outcome in elective GI cancer patients. In these subjects, preoperative immunonutrition improved metabolic postoperative response and significantly reduced postoperative infection rate and length of hospital stay. Cost-benefit analyses suggested that preoperative immunonutrition could be the dominant nutritional support strategy in patients candidate to major GI surgery for cancer, as reported in recent guidelines.

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Part VI
Cost Effectiveness of Dietary Intervention
in Cardiovascular Disease and Diabetes

Chapter 21

Nutritional Management of Hypertension: Cost Versus Benefit

Angelique Mavrodaris and Saverio Stranges

Key Points

- The incidence of cardiovascular disease (CVD) and hypertension is increasing in both developed and developing countries with major impacts on morbidity and mortality.
- Nutritional management of high blood pressure is an important intervention that is safe, sustainable and cost-effective.
- Dietary modifications that decrease BP include: reduced sodium and increased potassium intake; increased fruit and vegetable intake; low-moderate dark chocolate intake; moderation in alcohol intake and specific dietary patterns including DASH, Mediterranean and vegetarian diets as well as weight management.
- The role of dietary supplements with vitamins and minerals for the management of hypertension is currently under review but benefits have yet to be shown.
- Dietary factors that manage and prevent hypertension on both individual and population levels across the lifespan form the basis of a healthy lifestyle that will reduce morbidity and mortality and lead to healthier aging.

Keywords Cardiovascular disease (CVD) • Cost–benefit • Cost-effective • Dietary factors • Hypertension (high blood pressure) • Non-pharmacological management • Nutritional management

21.1 Introduction

Cardiovascular disease (CVD), comprising coronary heart disease (CHD), stroke and heart failure, continues to be an increasingly important cause of mortality and morbidity [1]. Worldwide, urbanization and aging have led to a drastic demographic shift and a subsequent change in the pattern of diseases and mortality causes. Chronic disease, CVD in particular, have replaced communicable diseases as the greatest cause of mortality and morbidity. Among the different risk factors leading to CVD (i.e., smoking and cholesterol) abnormal levels of blood pressure (BP) is the number one factor in terms of impact on the burden of disease in both developed and developing countries [2].

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Hypertension (systolic BP ≥ 140 mmHg, diastolic BP ≥ 90 mmHg, or use of antihypertensive medication) affects approximately one billion people worldwide. This figure is anticipated to increase by 60% to 1.56 billion people by 2025, emphasizing the magnitude of the impact that hypertension and related effects have on humankind [3]. Currently contributing to 4.5% of the disease burden, hypertension is estimated to be the cause of 7.6 million premature deaths (13.5% of total deaths) throughout the world [1].

Data analyzed from the Framingham Heart Study confirmed that elevated BP is directly related to a decrease in life expectancy and increase in years of life lived with cardiovascular disease. Normotensive men and women were found to have increased total life expectancies of 5.1 and 4.9 years respectively, in contrast to people affected with hypertension [4]. Current research has shown that a reduction in blood pressure by 10 mmHg systolic or 5 mmHg diastolic results in a potential decrease of CHD events by 22% and a decrease in stroke by 41% [5]. Thus, the prevention and control of blood pressure is an essential public health priority.

A complex interplay between genetic, environmental and pathological factors leads to increased BP. Environmental factors, and in particular modifiable lifestyle factors, are the main targets for primary prevention and management of increased blood pressure. Lifestyle modifications that have a significant impact on BP management include dietary modifications, weight management and physical activity. The importance of dietary factors in BP management is well-documented and far-reaching with the potential to prevent hypertension, function as initial treatment and augment management with concurrent anti-hypertensive use [6, 7]. The cost-effective, non-pharmacological and safety implications of dietary modifications accentuate the importance of this strategy [8].

Dietary modifications that have been suggested to decrease BP include: sodium reduction; increased potassium intake; increased fruit and vegetable intake; low-moderate dark chocolate intake; moderation in alcohol intake; specific dietary patterns including vegetarian, Mediterranean and DASH (Dietary Approaches to Stop Hypertension) diets as well as weight management.

We will review the current literature and evidence and discuss the importance of nutritional modifications with regard to their efficacy in blood pressure control and prevention of hypertension. We will also evaluate the cost of nutritional prevention and management of hypertension against the benefit of these measures in order to identify effective and sustainable strategies to maintain dietary modifications and improved blood pressure control. It is clear that improved adult health based on healthier lifestyles is necessary for reduction of mortality and morbidity in the future in both developed and developing countries for which cost-effective solutions are essential.

21.2 Sodium and Potassium

Evidence has highlighted the interaction of sodium and potassium, rather than their effects individually, as a principal factor causing hypertension and contributing to cardiovascular disease. This concept was defined in previous years when the balance of sodium, potassium and magnesium was viewed as a main regulator of arterial homeostasis and BP yet subsequent study focused separately on each factor's contribution placing more emphasis on the role sodium played in the pathogenesis of hypertension [9].

Primary hypertension is caused by an interaction of external environmental factors (diet) and ionic disturbances originating in the kidney. Human kidneys normally function to preserve sodium and release potassium as pre-historic human diets were rich in potassium and low in sodium. Modern Western diets however include many processed foods and are high in sodium and low in potassium, thus inducing a sodium excess and potassium deficiency in the body through kidney-mediated

mechanisms. Eighty percent of dietary sodium in fact, arises from food processing with only 12% occurring naturally in foods and the rest added during cooking or dining [10]. These modifications cause an increase in peripheral vascular resistance and result in higher blood pressure levels. Sodium, the principal extracellular cation, has received most concentration as the main environmental (dietary) agent contributing to higher BP levels but more recently the importance of potassium, the main intracellular cation, and potassium deficiency has been studied and now accepted as an important contributor to the development of hypertension and cardiovascular disease [11].

Studies are once again drawing attention to the joint effects of sodium and potassium with important findings such as an observational trial conducted by Cook et al., using data from the Trials of Hypertension Prevention (TOHP) which showed that higher sodium to potassium excretion ratio is associated with increased risk of subsequent CVD, with a more powerful effect than that of sodium or potassium alone [12]. Current thought regards the interaction of sodium and potassium (and magnesium) as a single dominant dietary environmental factor involved in BP regulation leading to the development of hypertension and associated cardiovascular implications [13].

21.3 Dietary Salt (Sodium) Reduction

“Therefore if large amounts of salt are taken, the pulse will stiffen and harden (Huang Ti Nei Ching Su Wein – Chinese physician, 1700 BC).”

The important regulatory effect of dietary salt (sodium chloride) on blood pressure has been established through key epidemiological and clinical research [14], and observed in populations worldwide [15, 16]. Studies have also demonstrated a significant decrease in BP in both hypertensive and normotensive individuals after a reduction in dietary sodium intake [17]. Recently, observational follow-up studies of the trials of hypertension prevention (TOHP) have reported that a reduction in dietary sodium also decreases cardiovascular risk and prevents cardiovascular disease [18]. Population-wide reduction of dietary sodium intake is thus one of the most effective dietary modifications to decrease BP and prevent hypertension and CVD.

Studies utilizing 24-h urinary collection to ascertain an estimate of urinary sodium excretion and reflect the dynamics of dietary sodium intake have been performed [19]. The first such epidemiological study to assess the effect of dietary sodium intake on BP across populations was completed in 1960. The study included five populations with a moderate sodium intake and although certain details and definitions were inconsistent, the results showed a linear relationship between dietary sodium intake and BP across all five populations [20]. A second study analyzing the effect of salt intake on BP in 50–55 year old men, spanning 27 populations followed 10 years later again showing a linear distribution [21]. Thirdly, a large international, epidemiological study performed in 52 centers across 32 countries and termed the INTERSALT study was initiated in 1981. Standard methods along with the large sample size (10,079 men and women between from 20 to 59 years of age) improved on previous studies and observed both the within- and cross-population correlation between 24-h urinary sodium and BP [22]. Within centers, a significant linear correlation between 24-h urinary sodium and BP was shown. These within-center results concluded that a 100 mmol/day higher sodium intake (2.3 g/day) would result in a 3–6 mmHg higher systolic and 3 mmHg higher diastolic BP.

Salt reduction has been recommended and confirmed by study groups worldwide including The China Salt Substitute Study Collaborative Group who documented sustained systolic blood pressure reduction after salt substitution (reduced-sodium, high-potassium salt substitute) in 608 rural Chinese randomized participants, averaging 60 years of age (64% had a history of vascular disease and 61% were taking one or more blood pressure-lowering drugs at entry). The difference between randomized

groups receiving salt substitute and normal salt intake was 3.7 mmHg systolic BP (95% CI 1.6–5.9, $P<0.001$). Maximum reduction 5.4 mmHg of occurred at 12 months (CI 2.3–8.5) and results indicated that further reductions in systolic BP could be expected over time ($P<0.001$) [23].

Randomized-controlled trials assessing the effects of dietary salt restriction on BP showed that a reduction of six grams a day of dietary salt would reduce systolic/diastolic BP by 7/4 mmHg in individuals with hypertension and 4/2 mmHg in individuals without hypertension.

It was concluded in a meta-analysis analyzing the results of the randomized-controlled trials that these effects could potentially lower the rate of stroke by 24% and coronary heart disease by 18% [24]. Of course, confirmation of these findings in a further randomized-controlled trial assessing cardiovascular mortality and morbidity with relation to dietary salt restriction would be ethically unacceptable, but a recent meta-analysis of prospective cohort studies conducted by Strazzullo et al., the relationship between the level of dietary salt intake and the development of cardiovascular disease and stroke was performed. Nineteen cohort samples from 13 studies averaging a follow-up period of 3.5–19 years were analyzed. Higher salt intake was significantly associated with greater risk of stroke (pooled RR=1.23, 95% CI 1.06–1.43; $P=0.007$) and cardiovascular disease (pooled RR=1.14, 95% CI 0.99–1.32; $P=0.07$) with greater associations documented the longer the follow-up and the larger the difference in sodium intake [25].

Restriction of dietary salt intake on a population level therefore, should be actively promoted and applied in an effort to prevent cardiovascular disease.

21.4 Dietary Potassium Increase

Decreased potassium levels directly affect blood pressure and have been shown to contribute significantly to the development of hypertension and cardiovascular disease [26, 27]. Numerous studies have documented the inverse relationship of potassium levels on blood pressure and although findings have not always been consistent, the interaction between sodium, potassium and blood pressure has been established [11].

One of the first epidemiological studies to document the effect of potassium intake on blood pressure was the INTERSALT. As with sodium, this study reported 24/h urinary sodium, potassium, and sodium/potassium ratio values, both within- and cross-population, in order to analyze relationship between dietary intake of potassium and blood pressure levels. Findings indicated that a potassium intake of 50 mmol/day led to a significant decrease of 3.4 mmHg in systolic blood pressure (SBP) and 1.9 mmHg in diastolic blood pressure (DBP) within centers. This relationship was observed amongst both men and women and became more prominent with increasing age [22].

Initial studies realized the potential of potassium supplementation and recommended an increased potassium intake to treat and prevent hypertension nearly 25 years ago [28]. A significant average decrease of 3.1 mmHg in SBP and 2.0 mmHg in DBP was reported by a pooled meta-analysis of 33 randomized controlled trials assessing the effect of potassium supplementation (75 mmol/day) on blood pressure in both normotensives and hypertensives. The more marked reductions in blood pressure were observed among patients with diagnosed hypertension in comparison to normotensive participants.

In a recent review however, extracted from the Cochrane Database of Systematic Reviews, the effects of oral potassium supplementation were assessed only to conclude that on taking potassium supplements, overall no significant reduction in blood pressure was observed in patients with high blood pressure [29]. The review analyzed five randomized controlled trials (RCT) ($n=425$) and documented large but statistically non-significant reductions in SBP (mean difference: -11.2 , 95%

CI: -25.2 to 2.7) and DBP (mean difference: -5.0 , 95% CI: -12.5 to 2.4) in participants receiving potassium supplementation compared to control groups. Unfortunately, the evidence examining the association between potassium supplementation and blood pressure remains inconclusive. In this review, several factors such as small participant numbers, short duration of follow-up and unexplained heterogeneity between studies could contribute to discordant findings. It was concluded that additional high quality RCTs with larger sample sizes and sufficient follow-up time are essential to establish the effects of potassium supplementation on blood pressure and whether this intervention does in fact lower blood pressure and can be of significant use in the treatment and prevention of hypertension.

21.5 Recommendations

Current recommendations for general population groups, excluding special groups (certain chronic renal disease and medication, athletes, environmental factors) adapted from The American Institute of Medicine increase the dietary potassium : sodium ratio by a factor of 10 (0.2–2.0), bringing levels closer to what pre-historic human diets included and what our renal systems had adapted to. The Institute suggested an intake of no more than 3.8 g of sodium/day in adults less than 50 years of age, 3.2 g of sodium/day in adults between 50 and 70 years of age and 2.9 g of sodium/day in adults over 70 years. At least 4.7 g of potassium/day is recommended for adults (National Academies Press).

This major public health initiative can only be achieved through effective cooperation of all stakeholders including health care professionals and organizations, political parties, food industries and the general public. Through clear communication and education, this can be accomplished and changes in food industry processing practices made. The importance and benefits of this drive cannot be over-emphasized – this cost-effective intervention has the potential to greatly reduce the burden of hypertension worldwide.

21.6 Specific Dietary Patterns

21.6.1 Dietary Approach to Stop Hypertension (Dash)

The Dietary Approach to Stop Hypertension (DASH) diet is a unique dietary plan characterized by a combination of nutrients that together generate targeted lowering effects on blood pressure and is used in both the treatment and prevention of hypertension [30, 31]. The DASH dietary plan consists of an increased intake of fruit and vegetables, low-fat dairy products, fish and poultry as well as whole grains and nuts. Red meat, sweets, and sugar-containing beverages are consumed only in very limited quantities. Comprising these components, the DASH dietary plan results in high levels of potassium, magnesium, calcium, and fiber consumed along with moderately high protein consumption and low levels of total, saturated fat and cholesterol [32].

The first study to report the effects of a combined dietary plan was a randomized controlled trial, the DASH trial, which included 459 adults with ($n=133$) and without hypertension ($n=326$) who were followed up for 11 weeks [33]. Initially, participants followed a control diet that resembled the average Western diet, in terms of fat content, and was low in fruit, vegetables, and dairy products. After 3 weeks, participants were randomly assigned to three groups and each group to a different dietary plan. The first

group continued with the control diet, the second group consumed a diet similar to the control diet but with a higher intake of fruit and vegetables and the third group followed the DASH diet. Other modifying factors such as sodium and alcohol as well as body weight were maintained at constant, pre-intervention levels throughout the study to limit confounding. Final results showed that in comparison with the control diet group the DASH dietary plan significantly reduced systolic blood pressure (SBP) by 5.5 mmHg and diastolic blood pressure (DBP) by 3.0 mmHg within 2 weeks while the second group dietary plan, comprising a higher intake of fruit and vegetables, significantly reduced SBP by 2.8 mmHg and DBP by 1.1 mmHg. Interestingly, in participants with established hypertension, even greater blood pressure reductions in the DASH dietary plan group (11.4 mmHg reduction in SBP and 5.5 mmHg reduction in DBP) were documented in comparison with the control diet group.

21.6.2 Mediterranean

The potential beneficial effects of the Mediterranean dietary pattern have become a source of much interest and study in recent years. Research has shown reductions in mortality from diseases such as cardiovascular disease (CVD) and cancer as well as morbidity while following a Mediterranean diet [34, 35].

The Mediterranean diet has been defined and includes the following dietary factors: a high intake of plant foods comprising mainly fruit and vegetables, cereals and wholegrain breads, beans, nuts and seeds; locally grown, fresh and seasonal, unprocessed foods; desserts comprising high doses of fresh fruit consumed daily where as concentrated sugars or honey consumed a few times per week in smaller quantities; olive oil as a main cooking ingredient and source of fat; low to moderate amounts of cheese and yogurt; low quantities of red meat and higher quantities of fish and low to moderate amounts of red wine often accompanying main meals [34].

A decreased prevalence of cardiovascular disease risk factors in association with a Mediterranean dietary pattern was documented in a cohort study of 3,204 asymptomatic high-risk patients adhering to Mediterranean dietary patterns in varying degrees [36]. Recent studies have also documented a decreased incidence of both metabolic syndrome and diabetes mellitus [37]. A study conducted among 2,730 participants of the Framingham Heart Study Offspring Cohort without type 2 diabetes analyzed the longitudinal association between Mediterranean dietary pattern and metabolic syndrome traits over a mean follow-up time of 7 years [38]. Results showed participants in the top 20% following Mediterranean dietary patterns had a decreased incidence of metabolic syndrome (30.1%) compared to participants in the lower 20% weakly following Mediterranean dietary patterns (38.5%).

Regarding effects on hypertension specifically, a prospective Spanish cohort performed evaluated 9,408 men and women for adherence to Mediterranean dietary pattern and the incidence of hypertension [39]. Reductions in mean levels of both systolic (moderate adherence: -2.4 mmHg; high adherence: -3.1 mmHg) and diastolic blood pressure (moderate adherence: -1.3 mmHg; high adherence: -1.9 mmHg) were reported after 6 years of follow-up, suggesting that a Mediterranean dietary pattern could prevent the development of hypertension. A previous study had documented similar associations although cereal intake as part of the diet was positively associated with arterial blood pressure [40].

21.6.3 Vegetarian

Aside from fruits and vegetables or plant-based foods, vegetarian dietary patterns are characterized by higher intakes of foods containing fiber, potassium, polyunsaturated and monounsaturated fatty

acids. Individuals maintaining this dietary pattern also consume less alcohol, animal proteins and saturated fats, which individually have effects on mean blood pressure levels. This dietary pattern is in contrast to western and industrialized habits as made evident by a greater number of non-vegetarians among the adult US population [41].

It is well established that vegetarians have lower blood pressures than do non-vegetarians [42]. Observational studies, primarily, have documented the association between a vegetarian dietary plan and blood pressure as well as the increase in blood pressure upon the introduction of red meat to a vegetarian diet [43].

The Coronary Artery Risk Development in Young Adults (CARDIA) Study is a population-based, prospective study of cardiovascular disease risk factor development in both black and white men and women conducted in four clinical centers across the USA. This study was used to analyze associations of vegetarian diet, dairy products and non-vegetarian diet with a 15 year incidence of increased blood pressure and the development of hypertension among black and white men and women [44]. 4,303 study participants were included in the study and over 15 years of follow-up the following results were obtained: 23.2% (997/4,304) of participants were found to have increased blood pressure; 591 (13.7%) were diagnosed with defined hypertension and 406 (9.4%) with high-normal blood pressure values. Over the 15 years of follow-up, results showed that 64% of participants with increased blood pressure values (997) were black men and women. Vegetarian dietary pattern was thus inversely related to an increased blood pressure.

The study also showed that after adjustment for race, sex and various other possible confounders, the greatest intake of fruit and vegetables and other plant-based foods per day was among adult white women and those with higher educational backgrounds. Although adjustment for clinical center was also made, the study does not take into account socio-economic backgrounds and deprivation scores. An issue of great importance, which was also highlighted in the study, is that often those who consume more fruit and vegetables, plant-based foods and less or no meat are more likely to be maintaining other healthy lifestyle patterns such as increased physical activity, moderation of alcohol consumption, no cigarette smoking and following diets with fewer calories, saturated fats and less salt.

A cross-sectional analysis on a large cohort of 34,192 California Seventh-day Adventists (for religious reasons follow a vegetarian diet including milk and eggs and do not smoke or drink alcohol) documented that prevalence of hypertension was nearly double among Adventists who did not follow a vegetarian diet in comparison to those who did [45]. Studies have also shown that Adventists following vegetarian dietary patterns have decreased mortality due to cardiovascular disease compared to individuals living in the same community not following vegetarian dietary plans. Furthermore, the age-dependent rise in blood pressure levels, typically experienced by individuals living in industrialized countries, may be largely attenuated by a long-term adherence to a vegetarian dietary regimen [46].

Collectively, results from observational studies performed have shown that individuals following a vegetarian dietary pattern have lower systolic (3–14 mmHg) and diastolic (5–6 mmHg) blood pressure values as well as a lower prevalence and risk of development of hypertension (2–40%) than those not adhering to a vegetarian dietary pattern (8–60%) [46].

A vegetarian dietary pattern has been shown to be associated with decreased blood pressure values in both normotensive and hypertensives [42]. It must be kept in mind that decreased blood pressure values associated with vegetarian dietary patterns may also be in part due to non-dietary factors that are closely linked with a vegetarian lifestyle. In light of recent focus placed on climate change – following vegetarian dietary patterns has both health and environmental benefits. By eating more vegetables and fewer or no animal products, less methane (which contributes to global warming) is produced.

21.6.4 Increased Fruit and Vegetable Intake

As addressed in combination with vegetarian dietary patterns, increased consumption of fruit and vegetables alone has been postulated to reduce blood pressure. A recent study in Japan has shown that high-level consumptions of fruits and vegetables are associated with a significantly lower risk of hypertension [47].

21.6.5 Carbohydrate

Research into this field was initiated by the observation that populations that eat carbohydrate-rich, low-fat diets that have low BP levels as compared with Western countries. Proposals that both the type and amount of carbohydrate could reduce BP were made and although challenging to specifically address the association of carbohydrate-based foods only, a number of studies exist. The results of these observational studies conducted however, remain to date inconclusive [44].

21.6.6 Fiber

More than 40 randomized trials of dietary fiber supplementation have been conducted. Still, most did not have BP as their primary outcome, and many had a multi-component intervention. A meta-analysis of these trials, 73 restricted to the 20 trials that increased just fiber intake, documented that supplemental fiber (average increase, 14 g/day) was associated with net systolic and diastolic BP reductions of 1.6 and 2.0 mmHg, respectively. Subsequently, in a large randomized trial, 74 supplemental fiber products did not lower BP. Overall; data are insufficient to recommend an increased intake of fiber alone as a means to lower BP.

21.6.7 Additional Dietary Factors

21.6.7.1 Moderation in Alcohol Intake

Alcohol intake has increasingly become an important lifestyle factor contributing to a raised blood pressure levels [48]. Both cross-sectional and prospective epidemiologic studies have consistently reported associations between heavy alcohol intake (at least three standard-sized drinks per day) and raised blood pressure, increasing the risk and prevalence of hypertension [48–50]. The alcohol hypertension relationship has been studied intently and although to date no firm biological mechanisms have been uncovered to explain the resultant effects on blood pressure, the contributory role of alcohol is evident [51]. Research has led to the conclusions that an increased risk of hypertension occurs at levels of intake of more than two drinks per day in men and more than one drink per day in women and lighter-weight individuals [2, 6]. Other factors such as drinking pattern and choice of drink may also play a role and will be discussed further.

From another perspective, light to moderate drinking has been shown to reduce the risk of Coronary Vascular Disease (CVD) and overall mortality in several recent studies [52]. These studies have documented up to a 35% decrease in CVD risk [53, 54]. The resultant J-shaped associations reported by more and more studies examining alcohol and the secondary effects on blood pressure and CVD

lend to the complexity of this lifestyle factor and ongoing debate as an equal number of studies report linear findings and no cardio-protective effects of light to moderate alcohol intake [55]. Nevertheless, research progresses and evidence continues to highlight the importance of alcohol intake in both the management and prevention of hypertension as well as CVD [56].

21.6.7.2 Epidemiology

Over 80 cross-sectional studies completed worldwide have demonstrated increased mean blood pressure levels and an increased prevalence of hypertension in individuals with high alcohol intake while normal blood pressure levels were found amongst individuals with a light to moderate alcohol intake [51]. Furthermore randomized controlled trials, in addition to the blood-pressure raising effect of alcohol, have demonstrated the reversibility of this effect in both normotensive and hypertensive individuals. Results from the Kaiser Permanente Study found similar blood pressure levels amongst individuals who abstained from alcohol and individuals who were no longer consuming alcohol as well as a return to normal blood pressure levels within 1 week once alcohol consumption was halted [57] while Parker et al., confirmed significant reductions in blood pressure levels of hypertensives within weeks of decreased alcohol intake [58]. Subsequent randomized controlled trials have also documented a dose-dependent decrease in blood pressure levels. Data from a meta-analysis, reviewing 15 randomized controlled trials, concluded that a 76% reduction in alcohol intake (from three to six drinks per day) resulted in a systolic decrease of 3.3 mmHg and diastolic decrease of 2.0 mmHg [59]. These findings were confirmed by an additional systematic review of alcohol intervention studies recently published [60]. The decrease in blood pressure was maintained with sustained alcohol reduction, emphasizing the magnitude of this lifestyle modification.

A recent study analyzed the association between alcohol intake and the risk of developing hypertension using data from two large cohorts, the Women's Health Study (WHS) and the Physician's Health Study (PHS) [61]. The study confirmed an increased risk of developing hypertension with heavy alcohol intake but found that associations with light to moderate alcohol intake differed between men and women. The relationship between light to moderate intake of alcohol and hypertension corresponded to a J-shaped curve in women, where light alcohol intake slightly lowered hypertension risk and heavy alcohol intake an increased risk, while in men a strong linear relationship correlating increasing alcohol intake with increased risk of hypertension was documented. These findings were replicated in Japanese male cohort studies [62] while findings from the Nurses' Health Study II also showed a J-shaped association between alcohol consumption and risk of developing hypertension [63].

Various studies showed no difference in the hypertension-related hospitalization rates between non-drinkers and light to moderate drinkers, suggesting a threshold effect [57] while a non-significant 12% decrease in hypertension among white males was found in the Atherosclerosis Risk in Communities cohort and a continuous relationship between alcohol intake and blood pressure in men (weaker relation at levels below 300 mL/week) in the INTERSALT study [49].

21.6.7.3 Alcohol Drinking Pattern

As made evident by the differing associations among men and women and observed alcohol–blood pressure interactions, factors other than quantity of alcohol are involved in the resultant effects of alcohol including drinking pattern, drinking in relation to diet and lifestyle and beverage choice.

Alcohol drinking pattern, including frequency and intensity of intake, has been associated with a significant increased risk of cardiovascular disease and hypertension in relation to episodic-heavy drinking. For example, findings from a study on the health consequences of binge drinking in 1,154

men and women showed that consumption of eight or more drinks on one occasion was associated with a significant increase in blood pressure compared to a regular pattern of drinking. Similar results were found in the INTERSALT study.

A population-based cross-sectional study of 2,609 white male and female individuals free from other cardiovascular disease from the Western New York Health Study analyzed the association between drinking pattern in relation to food consumption and hypertension [50]. After adjustments for the amount of alcohol consumed in the previous 30 days were made, the risk of developing hypertension increased to 64% in individuals who consumed alcohol without food. These results re-enforced findings documented in an earlier cross-sectional study of a large sample of wine-drinkers from the Italian Nine Communities Study which showed drinking alcohol outside of meals was associated with higher risk of hypertension and death from cardiovascular disease and myocardial infarct [64, 65]. In addition, even light to moderate alcohol intake without food was associated with a significantly (45%) higher prevalence of hypertension. If light to moderate alcohol intake is indeed associated with a decreased risk of cardiovascular disease, this finding could suggest that alcohol intake without food may counteract these benefits, pending further study.

Alcoholic beverage choice continues to inspire study, after the French Paradox of relative low rates of cardiovascular disease possibly explained by red wine intake, yet results from the fore-mentioned observational studies found no consistent beverage-specific associations with hypertension risk in individuals drinking beer, wine, or spirits [50, 64], and a recent randomized controlled trial found no beverage-specific association with hypertension risk [66]. Studies conducted in China [67], and Japan [68], reporting higher blood pressures amongst individuals consuming liquor and spirits were attributed to general increased alcohol intake among individuals drinking liquor and spirits. Varying effects of specific beverages are more likely to be explained by differences in lifestyle [69].

21.7 Summary and Recommendations

Prospective studies are needed to support these findings and clarify the role of drinking pattern in the relationship between alcohol consumption and blood pressure.

Currently guidelines recommend two or fewer alcoholic drinks per day in men and one or less per day in women and lighter-weight persons [2, 6]. As heavy alcohol intake is significantly associated with an increased risk of hypertension and has been described as a reversible cause of hypertension, the reduction of alcohol intake is thus one of the most important lifestyle modifications impacting on the management and prevention of hypertension.

The questions regarding light to moderate alcohol intake and associated benefits remain under review. Perhaps, even after countless studies addressing this matter, the conclusion reached will remain as the ancient Greek philosopher Cleobulus taught thousands of years ago: “Τί ν Μ τρὸν πῖστον” – Everything good in moderation.

21.7.1 Low to Moderate Chocolate Intake

Epidemiological research has shown that regular dietary consumption of plant-derived foods and beverages rich in antioxidant vitamins and flavonoids reduce the risk of cardiovascular disease (CVD) [70]. Certain chocolates have been identified as having a high polyphenolic flavonoid content; along with fruit, vegetables and black and green teas. In recent research cocoa has been associated with

beneficial effects on blood pressure, insulin resistance and vascular and platelet function. By increasing nitric oxide bioavailability and protecting vascular endothelium flavanols are documented to reduce the risk of CVD. Findings have suggested that flavanol-rich, low-energy cocoa food products may be involved in the reduction of CVD risk [71]. Many mechanisms through which flavonoids and cocoa may affect the cardiovascular system, such as activation of nitric oxide and antioxidant and anti-inflammatory effects have been proposed but not yet confirmed [72].

Cocoa and chocolate is composed of lipids and sterols, fiber, minerals and flavanoids. The predominant fatty acids in cocoa butter are saturated fatty acids but because higher levels of stearic acid are present which does not elevate serum cholesterol levels as other saturated fatty acids do. Small amounts of plant sterols present in cocoa are also thought to competitively inhibit cholesterol absorption in the body during digestion. The unprocessed cocoa bean's coat is made up of bran, which is both an insoluble and soluble source of fiber and leads to decreases in serum lipid levels, but unfortunately, cocoa powder contains very little fiber. High quantities of minerals are also present in chocolate, especially those with higher quantities of cocoa bean solids such as dark chocolate. Magnesium, copper, potassium and calcium are all present in cocoa beans and are associated with BP regulation and reduction in CVD risk. As mentioned previously, an inverse association between potassium intake, BP, and CVD-related mortality exists, thus the potassium content in a serving of dark chocolate (161 mg, comparable with the level found in an apple) could also in part explain the proposed potential health benefits of cocoa [70].

Cocoa contains high levels of polyphenolic compounds, in particular monomeric (epicatechin and catechin) and oligomeric (procyanidin) flavonoids which are known to have antioxidant properties and function as free radical scavengers and in this way possibly are involved in maintaining plasma oxidant defense mechanisms, preserving vascular wall tone and decreasing platelet reactivity the risk of clot formation and thrombosis [70]. Much research has been directed toward the flavanol content of chocolate as flavanols to increase the bioavailability of nitric oxide (NO) in endothelial cells via their antioxidant actions and so activate vascular endothelial NO synthase which is involved in endothelium-dependent vasorelaxation [73].

Recent observational data a cohort of 470 elderly men free of chronic disease at baseline participating in the Zutphen Elderly Study, the Dutch contribution to the Seven Countries Study [74], showed that habitual intake of cocoa-containing foods was inversely associated with BP and 15 year CVD and all-cause mortality. Results documented a 3.7 mmHg lower mean SBP (95% confidence interval (CI) of -7.1 to -0.3 mmHg and p -value=0.03) and 2.1 mmHg lower mean DBP (95% CI of -4.0 to -0.2 mmHg and p -value = 0.03) in the highest tertile of cocoa intake compared with the lowest tertile. The adjusted relative risk for men in the highest tertile was 0.50 (95% CI of 0.32–0.78 and p -value=0.004) for cardiovascular mortality and 0.53 (95% CI of 0.39–0.72 and p -value=0.001) for all-cause mortality in comparison with mortality data in participants with the lowest tertile of cocoa intake [75].

Studies have reported reductions in systolic blood pressure (SBP) in healthy and both young and elderly hypertensive patients after the consumption of dark chocolate for 15 days [76, 77].

In a recent randomized controlled trial 19 hypertensives with impaired glucose tolerance were randomized to receive flavanol-rich dark (FRDC) or flavanol-free white chocolate (FFWC) at 100 g/day for 15 days. The effects of flavanol containing chocolate on endothelial function, insulin sensitivity, b-cell function and blood pressure were assessed and results showed an improvement in insulin sensitivity and b-cell function and a reduction in BP in the study population after consumption of FRDC. After 15 days reductions (p -value $\leq$ 0.0001) in both clinical SBP (-3.82 ± 2.40 mmHg) and 24-h SBP (-4.52 ± 3.94 mmHg) compared with baseline were reported in the FRDC group but not in the FFWC group, as well as reductions in clinical DBP (-3.92 ± 1.98 mmHg) and 24-h DBP (-4.17 ± 3.29 mmHg). Thus, the FRDC group displayed both lower 24-h, daytime, and nighttime

systolic and diastolic BP in comparison to baseline values which were not present in the FFWC group [71].

An additional study conducted on a larger sample of participants with longer follow-up time by Taubert et al., made use of a lower dose of FRDC and reported that only 6 g/day FRDC (not FFWC) significantly reduced mean SBP (22.9 mmHg) and DBP (21.9 mmHg) after 12–18 week consumption of in pre-hypertensive and grade 1 hypertensive patients [78].

In conclusion, Grassi et al. document a beneficial effect on BP as well as vascular function and insulin sensitivity after a short-term consumption of 100 g (2,347 kJ) of FRDC but also warn that any energy-dense food should be added with caution not to adversely affect body weight. In the study conducted by Taubert et al., however longer-term, daily intakes of only 6.3 g (126 kJ) FRDC was reported to effectively reduce BP and propose the reasonable incorporation of cocoa products (FRDC) into a dietary approach to lower BP and CVD risk.

Research has draw attention to the potential value of developing flavanol-rich, low-energy cocoa foods, beverages, and supplements but further studies are necessary to confirm results and association of FRDC with BP. Studies performed to date are based on small participant numbers and short follow-up periods. It is also difficult to limit confounding factors in these studies and taking into consideration the many mechanisms of action of flavanols proposed and other factors and substrates that can also be involved in BP regulation.

21.8 Nutritional Supplementation

The evolving field of nutritional supplementation is gaining increasing awareness as observational trials identify beneficial health effects and apparent reductions in blood pressure (BP) and prevention of hypertension [6]. Results from studies assessing the effects of nutritional supplementation must be interpreted with caution as the micronutrients from daily diet cannot be accurately accounted for and this leads to confounding of results and incorrect associations made. Dietary supplements currently under review for potential beneficial effects will briefly be discussed below.

21.8.1 Vitamins

21.8.1.1 Vitamin B and Folate

Folate supplementation is already known as a major public health triumph with many beneficial effects, especially during pregnancy and the subsequent prevention of neural tube defects. A few small randomized-controlled trials have recently supported the role of folate as a BP-reducing agent [79]. More recently, a large prospective cohort study recruiting participants from both the Nurses' Health Study I and II to include older and younger populations prospectively examined the association between folate intake and risk of incident hypertension after a follow-up period of 8 years. Higher total folate intake (dietary and supplemental) was associated with a decreased risk of incident hypertension, particularly in younger women who consumed 1,000 µg/day or more of total folate compared with those who consumed less than 200 µg/day (RR = 0.54; 95% CI 0.45–0.66; $P < 0.001$) [80].

The effects of folate in BP regulation and potential to prevent hypertension require further study and could very well prove to be an important cost-effective intervention to reduce the burden of hypertension associated cardiovascular disease.

21.8.1.2 Vitamin C

Vitamin C is thought to play a role in regulation of production and action of endothelium-derived nitric oxide, which performs a major function in vascular tone maintenance and response [81]. Authors assessing the DASH diet have also hypothesized that high levels of vitamin C in the diet could attenuate the observed BP effect [82].

In a recent cross-sectional analysis, including 242 women aged 18–21 years from the cohort of the National Heart, Lung and Blood Institute Growth and Health Study Block et al., analyzed the associations of vitamin C levels with BP after 10 years and with change in BP during the previous year. The study revealed promising results and concluded that vitamin C was inversely associated with BP and change in BP. This study was conducted among young people who tend to have naturally lower BP's and further high-powered evidence is necessary to confirm this association [83].

The role of antioxidative vitamins in cardiovascular disease and associated complications has received much attention after experimental studies reported findings of slowed atherogenesis due to antioxidants. Plasma vitamin C has been under investigation as a risk factor for increased BP and cardiovascular disease. A 10.4-year prospective cohort study conducted among 2,419 middle-aged men from Eastern Finland in fact found low plasma vitamin C was associated with an increased risk of stroke. This association was more pronounced among hypertensive and overweight men and needs to be confirmed in randomized trials as vitamin C supplementation could prove to be an important public health intervention to decrease the risks of developing cardiovascular disease in both developing and developed countries [84].

As research continues to uncover associations between plasma levels of vitamin C the role of vitamin C supplementation is also under investigation. Data analyzed from three prospective cohorts (Nurses' Health Study I ($n=88,540$), Nurses' Health Study II ($n=97,315$), and the Health Professionals Follow-up Study ($n=37,375$)) aimed to ascertain whether higher uric acid levels (as a result of higher intake of fructose) are associated with an increased risk for developing hypertension and lower uric acid levels (as a result of higher intake of vitamin C) decreased BP or prevented hypertension. Using multivariable Cox proportional hazards regression relative risks and 95% confidence intervals for incident hypertension were established for both fructose and vitamin C intake. Fructose intake did not increase the risk for developing hypertension and vitamin C supplementation data revealed no significant differences between individuals who consumed $>1,500$ mg/day and those who consumed <250 mg/day was observed. Relative risk among the two Vitamin C groups and (CI) were as follows: Nurses' Health Study I $RR=0.89$ (0.83–0.96), Nurses' Health Study II $RR=1.02$ (0.91–1.14) and Health Professionals Follow-up Study $RR=1.06$ (0.97–1.15) [80].

Unfortunately, few randomized controlled trials exist and a recent trial administering 500 mg of vitamin C with assessment of effects on BP also proved inconclusive with no reduction in BP with moderate doses (500 mg/day) of vitamin C supplementation. In this study 244 Japanese participants with atrophic gastritis, initially taking both vitamin C and Beta Carotene supplements to prevent gastric Cancer were recruited and randomly assigned 50 or 500 mg daily doses of vitamin C supplementation for a period of 5 years [85].

21.8.1.3 Vitamin E

Prospective cohort studies have described associations of vitamin E supplementation with prevention of cardiovascular disease. Recent evidence however has to date not confirmed any such association [86].

21.8.1.4 Vitamin D

Some epidemiological and clinical studies have shown that increased dairy consumption or calcium or vitamin D supplementation can have a beneficial effect on blood pressure, as well as lipid and lipoprotein concentrations. Supplementation with reduced-fat calcium-vitamin D3 fortified milk did not have a beneficial (nor detrimental) effect on blood pressure, lipid or lipoprotein concentrations in healthy community-dwelling older men [87].

A recent systematic review article examining the results of clinical studies corroborates the hypothesis that vitamin D sufficiency induces lowering of arterial blood pressure [88]. Randomized trials are greatly needed to clarify and definitively prove the role of vitamin D in the prevention and management of hypertension.

21.8.2 Minerals

A recent Cochrane review did not find sufficient evidence to advocate the use of any combination of potassium, magnesium or calcium supplementation to reduce mortality, morbidity or BP in adults [89]. Minerals implicated in the regulation of BP will be expanded on below and recent research regarding supplementation discussed.

21.8.2.1 Calcium

Decreased concentrations of intracellular calcium is thought to result in a number of physiological effects including lipolysis and inhibition of lipogenesis as well as the suppression of vascular smooth muscle tone. Vitamin D and calcium are linked through a number of metabolic pathways and Vitamin D is essential for calcium homeostasis and absorption [90]. An increased calcium intake results in reduced levels of parathyroid hormone and $1,25(\text{OH})_2$ vitamin D and by a negative feedback mechanism leads to a lowered calcium influx from outside the cell membrane [91]. Calcium is present in dairy products and a number of epidemiological and clinical studies have revealed a beneficial association between the intake of dairy products or calcium supplementation with blood pressure and cardiovascular disease [92].

Randomized-controlled trials conducted in the last decade have failed to confirm this association. A subsequent trial conducted by Bostick et al., analyzed the effects of two doses of calcium supplementation on blood pressure (BP) (the study also evaluated serum cholesterol levels) in 193 normotensive men and women. No statistically significant effects of supplemental calcium intake on BP were reported and only a weak association with a reduction in systolic BP of 1 mmHg was documented. The study was limited by a small sample size and authors concluded that perhaps a larger study utilizing a higher dose of calcium might offer greater reductions in total cholesterol levels and in this way potentially minimizing the risk of developing cardiovascular [92]. In a further study conducted among normal, postmenopausal women over 30 months, calcium supplementation of 1 g/day and placebo were randomized among two groups and effects on body weight and BP measured. The effect on BP replicated findings from a prior meta-analysis and various observational trials with a small and transient decrease in systolic BP of 1 mmHg but no effect on diastolic BP [93]. The trial was one of the largest, and for the longest duration, conducted and revealed the short-term decrease in BP, which seemed to occur only until 6 months. The routine use of this micronutrient for the management of hypertension was not recommended [94].

The most recent Cochrane review completed in 2006 included 13 randomized controlled trials ($n = 485$) between 8 and 15 weeks follow-up. The analysis revealed participants receiving calcium supplementation as compared to control had a statistically significant reduction in systolic BP (mean difference: -2.5 mmHg, 95% CI: -4.5 to -0.6) but not diastolic BP and concluded that the apparent causal association between calcium supplementation and BP reduction is weak and more likely to be due to bias. Authors recommended the undertaking of larger, longer duration and better quality double-blind placebo controlled trials to further analyze the effect of calcium supplementation on BP and the development of cardiovascular disease [95].

A more recent randomized controlled trial conducted among 323 healthy men over 2 years evaluated the effect of calcium supplementation (placebo, 600 mg Ca/day, or 1,200 mg Ca/day) on the change in the ratio of HDL to LDL cholesterol and other cholesterol fractions, triglycerides, body composition and BP. No significant effects on serum lipids or body composition were observed and the only sustained treatment effects on BP over the whole trial period were documented in participants with baseline calcium intakes below the median value in which BP values showed borderline treatment effects ($p = 0.05$ – 0.06 while receiving 1,200 mg Ca/day compared with placebo). The authors concluded that calcium supplementation in those with low dietary intakes may benefit blood pressure control [94]. Ongoing research with larger study populations and longer follow-up times are necessary to accurately confirm the effects of calcium supplementation on BP.

Some epidemiological and clinical studies have assessed the effects of increased dairy (of which calcium is a major constituent) consumption or calcium and/or vitamin D supplementation on BP. A sub study of a 2 year randomized controlled trial documented the effect of 400 mL/day of reduced fat milk fortified with 1,000 mg of calcium and 800 IU of vitamin D3 or control in 167 healthy men over 50 years of age. No beneficial effects on BP were observed after supplementation with reduced-fat calcium–vitamin D3 fortified milk [87].

Baseline calcium levels have also recently been a source of interest in the prevention of hypertensive disease. A prospective cohort by Wang et al., analyzed the associations of dairy product intake, calcium and vitamin D with the incidence of hypertension in 28,886 women aged 45 years using semi-quantitative food frequency questionnaires. After 10 years of follow-up, the study documented an inverse association between low-fat dairy products, calcium, and vitamin D intake with risk of hypertension in the study population. This decreased risk was not observed in participants taking additional calcium or vitamin D supplements. This study draws attention to the potential roles of dairy products and dietary calcium and vitamin D in the primary prevention of hypertension and development of cardiovascular disease and it will be interesting to follow what subsequent studies will uncover [96].

Calcium supplementation during pregnancy has also been a topic of recent study in which a number of trials have documented reductions in the incidence of hypertension in the mother [97]. Bergel et al. recently assessed the effect of calcium supplementation during pregnancy on BP levels in children and young adults and reported an association between maternal calcium intake during pregnancy and offspring BP. This line of research evaluating factors during fetal life is an increasingly important field requiring further study and could potentially lead to advances in the prevention of hypertension in both children and adults with important public health benefits as calcium supplementation during pregnancy is both a simple and cost-effective intervention [98].

21.8.2.2 Magnesium

Mineral supplementation with magnesium has been reported by a number of observational trials to reduce blood pressure. In meta-analyses including randomized controlled trials conducted however,

these results could not be replicated and at present, there is insufficient data to support the use of supplemental calcium or magnesium as a mode of BP control [99].

A number of experimental studies have supported the association between magnesium and the regulation of BP, although unable to confirm the exact mechanism by which a deficiency of magnesium may lead to higher BP levels and hypertension [100]. Magnesium is involved in the permeability and regulation of calcium and sodium channels directly involved in the development of hypertension. Disturbances of calcium and sodium regulation is thought to also result in increased levels of intracellular calcium and reduced levels of intracellular magnesium which in turn affects sodium homeostasis. All these mechanisms are thought to raise BP levels [101].

Although a recent Cochrane review of 12 combined randomized-control trials from 8 to 26 weeks follow-up found that participants receiving magnesium supplements as compared to control did not significantly reduce systolic BP levels, but did statistically significantly reduce diastolic BP (mean difference: -2.2 mmHg, 95% CI: -3.4 to -0.9) the review did not find convincing evidence to support the use of oral magnesium supplementation to treat high BP in adults. This was due to the unexplained heterogeneity between trials poor quality of the included trials. As with calcium supplementation, longer duration with larger study populations and improved quality double-blind placebo controlled trials are needed to accurately assess and confirm the role, if any, of magnesium supplementation on blood pressure management and prevention of cardiovascular disease outcomes [102].

21.8.2.3 Selenium

Recently, attention has been drawn to this micronutrient with antioxidant properties and potential cardio-protective effects. Selenium facilitates the synthesis of selenoproteins that are present in the endothelium and are involved in inflammatory mechanisms and studies have attempted to clarify the association of this micronutrient with cardiovascular disease.

Few observational studies have evaluated the association between selenium and blood pressure (BP) and their findings are inconsistent. In the Flemish Study on Environment Genes and Health Outcomes (FLEMENGHO), higher blood selenium concentration was associated with lower systolic and diastolic BP at baseline and with a lower risk of hypertension over 5.2 years of follow-up among men, though not among women [103]. In a cross-sectional study conducted in Finland, a population with low selenium status at that time, serum selenium was also inversely related to systolic BP levels in 722 middle-aged men [104]. However, in another Finnish study in 1,100 elderly men, no relationship was found between BP and serum selenium concentration [105], as was also the case in a cohort of 364 southern Italian men [106]. Likewise, in the EVA study, plasma selenium was not associated with baseline systolic BP levels. Moreover, men with hypertension had higher plasma selenium than men without major cardiovascular risk factors [107]. Finally, in a recent cross-sectional analysis of serum selenium and hypertension in the US NHANES 2003–2004, high selenium was associated with a higher prevalence of hypertension [108]. The odds ratio for hypertension comparing the highest (≥ 150 $\mu\text{g/L}$) to the lowest (< 122 $\mu\text{g/L}$) quintile of serum selenium was 1.73 (1.18–2.53).

Unfortunately, no data are available on the effect of selenium supplementation on BP endpoints in randomized controlled trials using single selenium supplements. In the HDL-Atherosclerosis Treatment Study (HATS) trial, selenium (100 $\mu\text{g/day}$) was administered along with vitamin E (800 IU/day), vitamin C (1,000 mg/day), and β -carotene (25 mg/day), with no effect on BP [109]. In China, antioxidant supplementation (selenium 50 $\mu\text{g/day}$, β -carotene 15 mg/day, and vitamin E 60 mg/day) of a nutritionally deficient population was linked to increased isolated diastolic hypertension, but other BP endpoints were not significantly different between treatment groups [110].

Few studies have examined the potential efficacy of selenium supplementation in cardiovascular disease prevention in humans. A randomized, placebo-controlled trial to assess whether selenium

supplementation affects endothelial function in healthy men was conducted over 48 weeks. The study however failed to confirm the association and concluded that selenium supplementation is not likely to improve endothelial function or protect against cardiovascular disease [111]. Likewise, results from few randomized trials of selenium supplementation do not support beneficial effects of selenium in cardiovascular prevention. For example, in *post-hoc* analyses from the NPC trial, selenium supplementation (200 µg/day) was not significantly associated with any of the cardiovascular disease (CVD) endpoints after 7.6 years of follow-up [all CVD: hazard ratio (HR) = 1.03, 95% confidence interval (CI): 0.78, 1.37; myocardial infarction: HR=0.94, 95% CI: 0.61, 1.44; stroke: HR=1.02, 95% CI: 0.63, 1.65; all CVD mortality: HR=1.22, 95% CI: 0.76, 1.95] [112]. Conflicting results from research highlight a need for further study and understanding of the association of selenium with hypertension and cardiovascular disease.

21.8.3 Multivitamins and Minerals

With reference to multivitamin and mineral supplements, few studies have been performed evaluating effects on blood pressure (BP).

A recent randomized, double-blind, placebo-controlled trial conducted over a 26 week period in China among 128 obese women, between the ages of 18–55 years, with increased cardiovascular disease risk (hypertension, hyperglycemia, hyperlipidemia) assessing the effect of multivitamin and mineral supplementation (MMS) on BP and C-reactive protein (CRP) supported the hypothesis that MMS could lower BP. Participants were randomized to four groups, and received daily doses of either one tablet of high-dose MMS, or one tablet of low-dose MMS, or one calcium tablet (162 mg) or identical placebo for 26 weeks. Diastolic and systolic BP (DBP and SBP) measured at baseline and at the end of the trial was significantly lower in the MMS group compared to the placebo group ($p < 0.05$). A non-significant reduction in DBP was also reported in the MMS and calcium groups compared to baseline ($p < 0.08$). The trial is limited by several factors and confounders such as increased dietary awareness of participants from a specific study population potentially exposed to alternative management [113].

21.8.4 Fish and Fish Oils

A limited number of small clinical trials have documented the BP lowering effect of fish oil supplements. The effect however is dose dependent and a large dose (more than 3 g/day) is required to decrease SBP by 4.0 mmHg and DBP by 2.5 mmHg in hypertensive patients. Due to this high dose, unwanted side effects, high costs and limited data, fish oil supplementation is currently not routinely recommended [114].

21.9 Weight Management

The strong association between obesity, hypertension and cardiovascular disease (CVD) is well-documented [115], and evidence has shown obesity to be the most important risk factor predisposing to both hypertension and CVD [116], and associated with increased mortality and morbidity [117].

Urbanization and changes in dietary habits have led to a significant increase in the prevalence and burden of overweight and obesity not only in developed countries as was previously described, but

even more so in developing countries. The WHO estimated that approximately 1.6 billion adults (aged 15 or older) were overweight (BMI [weight in kilograms/height² in meters] ≥ 25) and at least 400 million adults were obese (BMI ≥ 30) in 2005 [1]. It is important to note that although BMI ≥ 25 defines overweight, mounting evidence has documented an increase in risk of chronic disease beginning from a BMI ≥ 21 .

21.10 Weight Reduction and Hypertension

Evidence has shown that weight loss results in significant reductions in risk of developing hypertension and CVD. A recent review of 25 randomized controlled trials including trials based on weight reduction through energy restriction, increased physical activity or both, reported average reductions of 4.4/3.6 mmHg for systolic and diastolic blood pressure respectively after a 5 kg loss of weight. A 0.92 mm Hg reduction of diastolic blood pressure per kilogram of weight loss was shown [118]. The majority of the studies included in this review used short follow-up periods of 1 year. A second systematic review analyzed studies assessing the effects of weight loss on blood pressure and hypertension over more than 2 years [119]. Results of this study showed a 6.0 mm Hg systolic and 4.6 mm Hg diastolic decrease in blood pressure after a 10 kg weight loss; a significantly reduced effect than that observed in short-term follow-up studies. Initial blood pressure, length of follow-up, medication changes and physiological restrictions may have confounded results in long-term studies.

21.11 Summary

In general, current support strongly supports weight loss and the ideally the attainment of a BMI of 25 kg/m², as an effective approach to prevent and manage high blood pressure. It is also important to advocate the prevention of weight gain in those who have normal body weight and the value of constant health education is evident [6].

The relationship between weight, hypertension and cardiovascular disease is complex involves many other variables including other lifestyle factors [119]. Inconsistent results evident among studies highlight the need for further research in this important area. The effects of weight loss on blood pressure in both long and short-term studies may have yielded conflicting outcomes but the prominent effect of pre-weight loss blood pressure was mutual. The importance of preventing hypertension and weight gain cannot be over-emphasized.

21.12 Cost Versus Benefit

High blood pressure (BP) is one of the leading causes of global burden of disease in both developed and developing countries and accounts for 64 million disability adjusted life years (DALY) or 4.4% of the global burden of disease [120]. Overall, 26.4% (95% CI 26.0–26.8%) of the adult population in 2000 had hypertension (26.6% of men [26.0–27.2%] and 26.1% of women [25.5–26.6%]), and 29.2% (28.8–29.7%) were projected to have this condition by 2025 (29.0% of men [28.6–29.4%] and 29.5% of women [29.1–29.9%]). The estimated total number of adults with hypertension in 2000 was 972 million (957–987 million); 333 million (329–336 million) in developed countries and

639 million (625–654 million) in developing countries. The number of adults with hypertension in 2025 is predicted to increase by about 60% to a total of 1.56 billion (1.54–1.58 billion) [3].

Hypertension is also the leading risk factor for chronic disease worldwide and despite much research and progress over the years, the prevalence of this disease is still high and suboptimal BP management reflects a continuing need for effective health policy and practice [121]. Awareness of the burden of disease caused by this risk factor reinforces why assessment of the costs and effects of the available interventions to reduce the prevalence of this risk is essential [122].

To further illustrate the necessity of an accurate cost-effective and cost-benefit analysis the growing burden of hypertension can be considered. More than 65 million US adults had hypertension in 1999–2000. This number is significantly higher than the 50 million estimated for the 1988–1994 period. The total US hypertension burden and prevalence rate estimated, in the study conducted by Fields et al., values of 9% and 11% higher compared with a recent NHANES based report. This difference is very significant. In addition to hypertensive complications and co-morbid conditions, greater numbers of adults with hypertension will result in greater healthcare and societal costs as well as direct and indirect costs regarding length and quality of life influenced by hypertension and health and resource use. If the burden-based strategic cost estimate was \$110 billion for US residents with hypertension alone or with hypertensive complications and co-morbidities, a 10% underestimation of the total hypertension burden could result in a strategic under-allocation of \$11 billion in necessary resources [121].

Risk analysis identifies cost-effective measures that can be employed to reduce the risk of mortality. This approach provides decision-makers with information on which interventions are low-cost ways of improving population health and which improve health at a much higher cost. There are few studies assessing the cost-benefit effects of nutritional modifications on blood pressure regulation as this task is naturally challenging. Smaller, individual dietary intervention studies report cost-effective results but these are often difficult to apply to a larger general population group with the goal of hypertension prevention on a large-scale [123].

In a cost-effectiveness analysis by Murray et al., interventions to lower systolic blood pressure, such as nutritional management and salt reduction, in association with CVD risk reduction was discussed using a standard multi-state modeling tool, PopMod and information from The Commission on Macroeconomics and Health which recently defined interventions that have a cost-effectiveness ratio of less than three times gross domestic product per head as cost effective. Interventions of interest (non-personal) included strategies to reduce salt-consumption in the general population and nutritional education. These nonpersonal interventions were found to be cost-effective with several far-reaching implications in particular, reductions in population-level CVD risk.

The non-personal interventions considered were more cost effective than the personal interventions, such as pharmacological management of hypertension (β -blockers) but had a lower overall effect on population health. It is also important to note that the non-personal dietary interventions assessed in this study are only a selection of those possible and the qualitative assessment of effects associated with each intervention is difficult to determine. However, when assessing dietary intervention such as strategies to achieve moderate but widespread changes in manufactured food (e.g., in overall fat content), it is important to take into consideration the wider applications of the intervention and the major dietary components involved in the etiology of most major chronic diseases.

With reference to under-developed countries who cannot afford the \$14 per year per patient to provide β -blockers, a more cost-effective solution such as salt-reduction and dietary education would prove more beneficial.

As mentioned previously cost-effectiveness analysis is an essential tool for public health decision and policy making but should not be used as a definitive guide to resource allocation and intervention choice. The intervention that has the lowest cost-effectiveness ratio may not address other goals of

health policy and the improvement of general population health must be considered in context with all health priorities and associated factors of each country such as poverty and inequalities [122].

21.13 Conclusions

Cardiovascular disease (CVD) is a major cause of morbidity and mortality worldwide, thus emphasizing the significance of hypertension as a risk factor.

An important final consideration, now in both developed and developing countries, is the implications that a growing aging population will bring to management of hypertension worldwide. Approximately 81% of all US adults with hypertension were at least 45 years of age, even though this group comprised only 46% of the US population, in 2000 illustrating how aging adults are also disproportionately impacted by hypertension [121]. The size of this group is expected to continue to increase and age-dependency of hypertension prevalence will become increasingly more important. Hypertension-focused primary prevention interventions are likely to be most beneficial when applied to individuals before 45 years of age [123]. Naturally, healthy behavior and dietary regulation across the lifespan is important on both an individual and population level.

Population-wide dietary interventions such as incremental reduction in sodium content of processed foods, combined with strategies to mitigate a counterbalancing increase in sodium added to foods by individual consumers, have proven to positively impact primary prevention of hypertension and BP control rates over a wide range of age in a cost-effective manner [124, 125].

The fact that hypertension continues to be a major attributable cause of stroke, coronary heart disease, heart failure, atrial fibrillation, and end-stage renal disease predicts an added future negative impact of the growing hypertension burden. The importance of cost-effective health policy, medical care, and public health solutions and actions that improve hypertension prevention and management, such as nutritional management, are unquestionable [121].

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Chapter 22

Cost-Effectiveness Analysis of the Mediterranean Diet for Persons after a Heart Attack

Kim Dalziel and Leonie Segal

Key Points

- Economic evaluation of the Mediterranean diet for patients following first AMI (acute myocardial infarction).
- A cost utility analysis was conducted, using a Markov model to describe health status, costs, quality of life and deaths to compare the Mediterranean diet to a prudent Western diet.
- Program effectiveness was based on the Lyon Diet Heart Study.
- Costs were estimated in \$AU, (and converted to \$US and €Euros) based on reported resource use.
- Performance was measured as cost per quality adjusted life year (QALY) gained.
- Extensive one-way sensitivity analyses were performed.
- The Mediterranean diet was estimated to cost less and be more effective (dominant) compared with a prudent Western diet.
- There was a mean gain in life years of 0.56 per person and a gain in quality adjusted life years of 0.61 per person.
- Based on the published results from the Lyon Diet Heart Study, and conservative assumptions, the Mediterranean diet is cost saving for persons following first AMI when modeled over 10 years.
- Policy makers and clinicians should strongly consider application of results to their own setting.

Keywords Cost-effectiveness • Economic analysis • Mediterranean diet • Myocardial infarction • Nutrition

22.1 Introduction

Heart disease is the leading cause of death globally leading to around one-third of global deaths in 2004 [1]. Around 80% of cardiovascular deaths took place in low to middle income countries [1]. It has been estimated that more than half of deaths and disability from heart disease and stroke could be prevented by modifications to lifestyle such as adopting a healthier diet, increased physical activity and quitting smoking [1]. In addition to the 17.1 million people who died from heart attacks and

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strokes in 2004 more people survived with on-going disability and with a significant portion requiring costly ongoing clinical care [1]. In 2009, the cost of heart disease and stroke (including health care costs and lost production) in the USA was projected to exceed \$475 billion [2].

Lifestyle changes related to diet have the potential to modify disease outcomes and costs of management. Lifestyle interventions have been successfully trialed in several populations [3–6], including in patients surviving an initial heart attack. The Mediterranean diet is one such lifestyle option found to be protective [3]. Key elements of the Mediterranean diet are high quantities of fruit and green vegetables, grains, beans, nuts, seeds, several servings of oily fish per week, low consumption of red meat and offal, no butter or cream, and oils/spreads restricted to olive oil or other unsaturated fats. Moderate alcohol consumption (wine) is usually permitted.

Advice to adopt a Mediterranean diet has been shown to induce behavior change in patients following a first myocardial infarction [7] confirmed by a change in nutrient intake [3] consistent with the dietary recommendations. The diet has also been shown to be effective in preventing further cardiac events [3] and reducing mortality. The assessment of the economic performance of the Mediterranean diet is timely given the interest by policy makers in cost-effectiveness, and the dearth of published economic evaluation studies on lifestyle interventions and the continuing burden of heart disease.

The aim of our study was to assess the economic performance of the Mediterranean diet after myocardial infarction, in terms of cost per quality adjusted life year (QALY). By expressing performance as cost per QALY [4] it is possible to compare this nutrition intervention with other approaches to prevention and management of disease. Cost-effectiveness analyses are a critical input to ensuring the best use of scarce health care resources and are increasingly relied on by policy makers, health care managers and clinicians.

22.2 Methods

22.2.1 Perspective

The economic evaluation took a societal perspective with the core analysis focused on patient outcomes and the health system. The comparator was a “prudent” Western diet control group who were advised to follow recommendations of the American Heart Association as per “usual care.”

22.2.2 The Intervention

A search was conducted for high quality studies (RCTs or meta-analyses) evaluating the effect of a Mediterranean diet in persons with a previous AMI on clinical outcomes, compared to a typically recommended diet. Person with previous AMI have a high risk of future cardiovascular events creating opportunity for substantial absolute benefit in the medium term from an effective intervention. Medline (OVID 1966 to current) and the *Cochrane Database of Systematic Reviews* (including ACP Journal Club, DARE and CCTR) were searched in December 2009 using key words and subject headings for “myocardial infarction” and key words for “Mediterranean diet.” A total of 71 studies were identified, 4 of which were RCTs assessing effectiveness of the Mediterranean diet in patients with previous heart disease [3, 8–10]. Note the serious concerns regarding the validity of the study

by Sing et al. [9] published by the Lancet (Horton R. Expression of concern: Indo-Mediterranean Diet Heart Study. *Lancet* 2005;366;354–6). The Lyon Diet Heart Study [3] was chosen as the primary source of effectiveness data for this economic evaluation due to the high quality trial design involving long follow up period of 4 plus years, comparison with a randomized “usual care” control group, large sample size ($n=605$), low loss to follow-up ($<8\%$ after 4 years), and comprehensive measures of outcome. Whilst the study by Tuttle et al. [10] was a similar design, only 102 participants were randomized (to a Mediterranean diet or low fat American Heart Association diet) with both receiving an extensive program of dietary consultations; plus “matched” usual care controls. In the study by Sondergaard et al. [8] only 131 patients were randomized to a Mediterranean or usual care diet plus statins and were followed up at 12 months. The study by Singh et al. [9] has had serious questions regarding its validity.

The Lyon Diet Heart Study was conducted in six health services within Lyon, France between March 1988 and March 1992. The trial design and outcomes have been described in detail in a number of key papers [3, 7, 11, 12]. A total of 605 patients aged less than 70 years were recruited into the study. Participants all had survived a myocardial infarction within 6 months of enrolment. Recruitment took place in hospital and patients were randomized at an outpatient clinic 2 weeks following discharge, to the Mediterranean diet ($n=303$) or Western American Heart Association diet ($n=302$) group. Participants’ mean age was 54 years (SD 10 years) and 91% were male (549/56). The baseline characteristics of the two study groups were similar.

The intervention group received dietary advice during a 1 h consult with the research cardiologist and dietician, “to adopt a Mediterranean-type diet” as described in the introduction (for full diet composition refer to [7]). In addition, intervention participants were supplied with rapeseed oil margarine, as a butter replacement [7]. Intervention patients attended at 8 weeks, then annually for up to 4 years for further counseling by the research dietician and completion of a dietary survey, and for data collection and counseling by the research cardiologist.

Control group participants received usual advice for cardiac patients from the hospital dietician or attending physician (for full diet compositions refer to [7]). They also saw the cardiologist for data collection at 8 weeks, then annually for up to 4 years.

22.2.3 Effectiveness

Results were analyzed on an intention to treat basis (except for 21 randomized patients who refused follow up shortly after the start of the study) [3]. The majority (92.4% and 93.4%) of the original 302 intervention group and 303 control group participants randomized, who were still alive and not censored, attended the final study visit. Of the 15 control and 19 intervention patients who did not attend the final visit, vital status was known for all except 4.

At 4 year follow up the Mediterranean diet group had six cardiac deaths compared with 19 in the control group (RR 0.35, 95% CI 0.15–0.83, $P=0.01$) and there were 14 combined cardiac deaths or nonfatal AMIs in the Mediterranean diet group compared with 44 in the control group (RR 0.28, 95% CI 0.15–0.53, $P=0.0001$). There were 14 deaths from all causes in the Mediterranean diet group compared to 24 in the control group (RR 0.44, 95%CI 0.21–0.94, $P=0.03$). There were 68 minor events (for example stable angina, revascularisation or restenosis) in the Mediterranean diet group compared with 90 in the control, 13 major events excluding stroke (for example unstable angina, heart failure or pulmonary embolism) in the Mediterranean diet group compared with 42 in the control group, and four strokes in the control group with none in the Mediterranean diet group. Results have been used to inform the economic model and are reported in full in [3].

22.2.4 Measurement of Economic Performance

The primary measure of economic performance was the cost per QALY gained, a measure combining impact on quality of life and mortality. The QALY gain (or loss) is a commonly adopted health outcome measure. It is derived by combining length of time in a health state with the “change in utility” of that health state, and adding this to life years gained (or lost). Utility is measured on a scaled from 0 to 1 (using specified techniques [13, 14]) where 0 corresponds to a health state equivalent to death and 1 represents full health. Thus for example, an extra year spent in full health would contribute +1 QALY, as would 4 years in better health involving a change in “utility score” from 0.45 to 0.7.

Utilities were applied to the five distinct health states. They were obtained from the published literature as follows; 0.93 for event free [15], 0.89 for minor events [15], 0.88 for AMI [16], 0.78 for major events [15], and 0.54 for stroke [17].

The cost per additional cardiac death or AMI averted (the major primary endpoint for the trial), was also calculated for the Mediterranean diet compared to the Western diet.

22.2.5 Cost

The cost of the intervention was based on the incremental resource use for the Mediterranean diet group compared to the Western diet group described in the reports of the clinical trial [7], to which Australian published unit costs were applied and converted into US\$ and Euros € using published exchange rates (as at 1 June 2009).

The additional costs were composed of an initial consult with a cardiologist and a dietician, and a follow up visit with a dietician at 8 weeks, and again annually for years 2–4 (Table 22.1). Unit costs were derived from the Australian Medicare Benefits Schedule [18].

Differential food costs incurred by patients adhering to the Mediterranean diet have been estimated by applying food unit costs obtained from a major Australian retailer [20] to the mean differences in

Table 22.1 Incremental cost of Mediterranean diet intervention based on described resource inputs [7]

Item	Mean incremental increase in cost per person AU\$	Reference for unit cost
Year 1		
Initial consult with cardiologist ^a	142.65	[17] ^a
Initial consult with dietician ^b	58.85	[17] ^b
Follow up visit at 8 weeks with dietician	58.85	[17] ^b
Written instructions	1.27	[18]
Food costs ^c	153.39	[19]
Total year 1	414.74 (US\$336, €237)	
Years 2–4		
Follow up visit with dietician	58.85	[17]
Food costs ^c	153.39	[19]
Total years 2–4 (annual cost)	212.24	
Total cost over 4 years	1051.46 (US\$852, €600)	

^aItem number 110

^bItem number 10,954

^cSee Table 22.2

grams per day for each major food group reported in the Lyon Heart Study [7]. The food basket was chosen to provide an upper limit on the possible cost difference (see Table 22.2).

The total cost of the intervention was estimated at \$415AU (\$336US, €237) for year one plus an additional \$212AU (\$172US, €121) per year for years 2–4, or \$1051AU (\$851US, €600) in total (Table 22.1).

Table 22.2 Estimation of the incremental food cost of adhering to a Mediterranean type diet (I) compared to a Western diet (C) (2009 costs)

	Mean difference between I & C groups [7] (g/week)	<i>P</i> value	Cost/kg [19] (AU\$)	Adopted cost/kg for food group (AU\$)	Increased cost/week (AU\$)
Bread	154	0.01		\$5.80	\$0.89
Tip top Sunblest white sandwich bread			\$5.80		
Tip top Sunblest multigrain sandwich bread			\$5.80		
Cereal	–38	0.22		\$4.34	–\$0.16
Vetta spaghetti No. 1			\$4.34		
Legume	70	0.07		\$7.98	\$0.56
Sanitarium brown lentils			\$7.98		
Vegetables	196	0.07		\$5.32	\$1.04
Potatoes farmland washed 3 kg pre-pack			\$3.00		
Broccoli-loose			\$4.99		
Tomatoes truss premium 500 g pre-pack			\$7.98		
Fruit	336	0.007		\$3.48	\$1.17
Apples – Granny Smith			\$3.98		
Bananas – loose			\$2.98		
Delicatessen	–49	0.01		\$16.86	–\$0.83
Coles boneless Virginian leg ham portion			\$15.50		
Coles BBQ thin sausages – 500 g			\$7.86		
Tibaldi beef salami			\$27.23		
Meat	–137	0.009		\$18.75	–\$2.57
Savings budget beef sirloin porterhouse steak			\$28.00		
Coles beef mince regular			\$9.50		
Poultry	35	0.42		\$14.17	\$0.50
Chicken breast fillets skin off			\$14.17		

(continued)

Table 22.2 (continued)

	Mean difference between I & C groups [7] (g/week)	<i>P</i> value	Cost/kg [19] (AU\$)	Adopted cost/kg for food group (AU\$)	Increased cost/week (AU\$)
Cheese	16	0.25		\$29.82	\$0.48
Farmland tasty cheese 250 g			\$18.28		
Tasmanian heritage brie cheese			\$41.36		
Butter and cream	−97	<0.001		\$8.90	−\$0.86
Western star spread- able Traditional blend – butter			\$9.80		
Farmland thickened cream 300 mL			\$8.00		
Margarine	97	<0.001		\$7.60	\$0.74
Flora canola dairy spread 500 g			\$7.60		
Fish	49	0.16		\$22.02	\$1.08
Flake gummy filet approximately 500 g			\$25.82		
Coles tuna chunk in olive oil 95 g			\$18.21		
Oil					
Crisco vegetable oil 2 L	−115.5		\$5.10	\$5.10	−\$0.59
Bertolli extra Virgin olive oil 1 L	109.9		\$13.60	\$13.60	\$1.49
Total cost difference/week – all			\$2.94 (US\$2.38, €1.68)		
Total cost difference/week – only for food groups with significant difference			−\$0.55 (US\$−0.45, €−0.31)		
Total cost difference/year – all			\$153.39(US\$124.23, €87.55)		
Total cost difference/year – only for food groups with significant difference			−\$28.90(US\$−23.41, €−16.50)		

Downstream costs of clinical management were captured in “transition costs” which were incurred each time a person experienced an event, regardless of study group (see modeling section below). Mean per patient costs of clinical management associated with each event category and data sources are described in Table 22.3. Clinical management costs were largely limited to hospital costs, except for stroke, which also included community-based costs for 1 year providing a lower bound estimate of the “potential cost saving” of the Mediterranean diet, given its lower event rate. In the sensitivity analysis, costs for stroke were also assigned to each patient each cycle to reflect the on-going cost of management.

22.2.6 Modeling

A state transition model (Markov) was developed in TreeAge Pro (2009) in order to estimate impacts on disease, mortality and quality of life for the Mediterranean diet and usual care group during the

Table 22.3 Event costs applied to the cohort as it transitions between health states

Event ^a	Cost per person AU\$	Reference
Minor event (e.g., stable angina, revascularisation, or restenosis)	1,516 (US\$1,228, €865)	[20] ^b
Non-fatal AMI	5,624 (US\$4,555, €3,210)	[20] ^c
Major event (e.g., unstable angina, heart failure or pulmonary embolism)	4,740 (US\$3,839, €2,705)	[20] ^d
Stroke – new event	31,839 (US\$25,787, €18,173)	[21] ^e
Stroke – ongoing management	7,220 (US\$5,848, €4,121)	[22]

^aEvents are all subsequent to a first AMI (the primary entry criteria for entry into the trial)

^bAustralian refined diagnosis related groups (see Table S11.19) AR-DRG F74Z

^cWeighted mean for AR-DRG F41A, F41B, F60A, F60B

^dWeighted mean for AR-DRG F62A, F62B, F72A, F72B

^eWeighted average using number of Australian cases for ischemic stroke and intracerebral hemorrhagic stroke

4 years of the trial and beyond (for the 10 year model duration). In accordance with the trial data, the economic model assumed the cohort was 91% male (549/56) with a mean age of 54 years.

Individuals were allocated into one of five discrete health states: alive free of further events, alive following minor events (e.g., stable angina, revascularisation or restenosis), alive following AMI, alive following major event (e.g., unstable angina, heart failure or pulmonary embolism), alive following stroke, and death (Fig. 22.1). The cohort progressed annually (cycle length 1 year) between these health states according to transition probabilities derived from the trial and from the published literature (Table 22.4). Each year the cohort for each intervention group accumulated costs and quality adjusted length of life. Results were summed over the period of the model and total costs and total QALY's compared for control and intervention groups. Rates were transformed into transition probabilities using the generally accepted approach [23]. The model commenced with all people in “alive free of events.” The model presumed a one-way progression in health state (from least severe to most severe). The model assumed that the intervention group transitions from “alive free of events” reverted to the control probabilities after year 4.

22.2.7 Analysis

The base case model was applied over 10 years; that is 6 years beyond trial end point. Estimated costs, utilities and life years for the intervention and control cohort were summed over the model period and compared. A half cycle correction was applied to costs and benefits. Costs and benefits were discounted at 5% per annum according to current Australian guidelines [29]. Extensive univariate sensitivity analyses were performed and involved varying estimates of effect size, cost, utility, time horizon and discount rate.

22.3 Results

The cost-effectiveness results of the Mediterranean diet advice compared to usual care (involving a prudent Western diet), based purely on the 4 year trial results was a cost per cardiac death or AMI averted of at “worst” \$10,626AU (\$8,606US, €6,065) excluding cost savings from events averted, to

Markov model diagram showing health states and permitted transitions

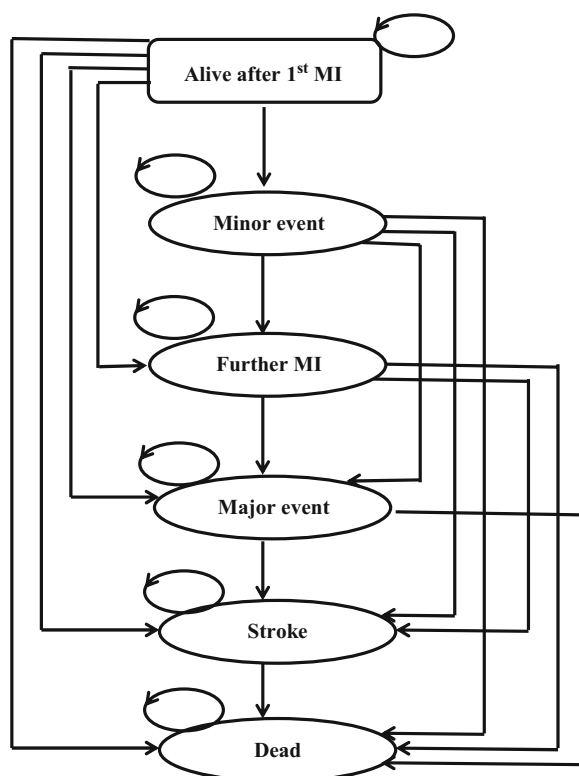


Fig. 22.1 Markov model diagram showing health states and permitted transitions

\$10AU (\$8US, €6) per cardiac death or AMI averted when the costs of cardiac events were also incorporated (Table 22.5).

When the cost utility of the Mediterranean diet was modeled over 10 years, it was cheaper and more effective (dominant) than usual care (to adopt a prudent Western diet). A net saving of \$179AU (\$145, €102) per person was estimated whilst achieving a mean gain of 0.56 life years per person or 0.61 QALYs per person.

22.3.1 Sensitivity Analyses

One-way sensitivity analyses showed that the Mediterranean diet remained either dominant (cheaper and more effective) or highly cost-effective (less than \$1,500AU (\$1,215US, €856) per QALY) under all scenarios (Table 22.6). The model was most sensitive to the cardiac event rates (effectiveness estimates) which resulted in a cost per QALY of \$1,460AU when the lower estimate of effectiveness (i.e., more cardiac events) was used drawing on the 95% CI from the original Lyon Diet Heart Study. The most favorable result for the Mediterranean diet is when a cost per annum of \$7,220AU (\$5,848US, €4,121) is added for those having a stroke (leading to a cost saving per person of \$853AU (\$691US, €487)).

Table 22.4 Transition probabilities after first AMI

Time <i>t</i>	Time <i>t</i> + 1					
	Event free	Minor event	Non fatal AMI	Major cardiac event	Non fatal stroke	Dead
Event free						
Intervention group [3]	# ^a	0.063 [0.048–0.086] ^b	0.007 [0.003–0.016] ^b	0.011 [0.006–0.021] ^b	0.000	0.012 [0.006–0.024] ^b
Control group [3]	#	0.090	0.023	0.039	0.004	0.022
Minor event	–	#	0.014 [23]	0.030 ^c	0.011 ^d [24]	0.033 ^c
Non fatal AMI	–	–	#	0.183 [23]	0.055 [23]	0.159 [25]
Other major cardiac event	–	–	–	#	0.015 [23]	0.170 [26]
Non fatal stroke	–	–	–	–	#	0.225

^aResidual value (1-the rest of the probabilities in the row) as each row must sum to one

^bRanges represent upper and lower limits derived from the 95% CIs of the risk ratios calculated from the original study report [3] Table 1, p.780. All differential variation is attributed to intervention arm. Unable to calculate a risk ratio for stroke with zero events.

^cResearcher judgement

^dThe 5 year probability of survival following stroke was multiplied by the RR of already having CHF (2.28, [27]) adjusted for the prevalence of CHF in the original population (16.74% [28])

^eThis transition is assumed to be the same as alive free of events to dead

Table 22.5 Cost-effectiveness and cost utility

	Mediterranean diet	Western diet	Difference
Cost effectiveness ^a over 4 years AU\$			
Costs/person:			
Program costs ^b	438	0	438
Food costs ^b	1,611	1,048	683
Cardiac event costs ^c	467	1,518	−1,051
Outcomes:			
Cardiac death and non fatal AMI events ^d	14/302 (4.6%)	44/303 (14.5%)	9.9 percentage points
Cost per cardiac death or AMI averted			
Incl. program costs only			4424 (US\$3,583, €2,525)
Incl. program and food costs			10,626 (US\$8,606, €6,065)
Incl. program, food and event costs			10 (US\$8, €6)
Cost utility ^e modeled over 10 years AU\$			
Total costs/person	4,985	5,164	−179 (US\$−145, €−102)
Mean life years/person	7.09	6.53	0.56
Mean QALYs/ person ^f	6.43	5.82	0.61
Discounted cost per QALY gained/person			Western diet dominated by Mediterranean diet

^aDerived from the events reported by the trial and described resource use

^bSee Table 22.1

^cCosts from Table 22.2 and event rates from [3] Table 1, p. 780

^dThis is the major primary endpoint (composite outcome 1) from the clinical trial [3], assuming each AMI and death within the 4 years affects a separate person

^eModeled using assumptions and parameters outlined in Table 22.3 and methods section

^fMean QALYs are less than mean LYs, as this incorporates the negative impact on quality of life of the cardiovascular events

22.4 Discussion

Economic evaluation of the Mediterranean diet in those with a previous AMI, when compared with usual care, was found to be the dominant strategy (less expensive and more effective). The estimated saving was a mean \$179AU (\$145US, €102) per person, with estimated performance remaining dominant or highly cost-effective under all scenarios considered in sensitivity analyses.

We note that the research by Tuttle et al. [10] in which an extensive dietary consultation regimen was offered for both the “Mediterranean diet” group and “Low fat” diet group found no statistically significant difference between the two groups in CVD events over a 46 month median follow-up period. Tuttle however found a large and significantly lower relative risk for CVD events in the diet groups combined compared to a matched “usual care” control (who should be receiving advice re adoption of the American Heart Association “low fat” diet) of RR=0.33. This is consistent with the de Lorgeril study findings of RR=0.28–0.44 depending on outcome.

We also note that a finding of no difference between the Mediterranean diet and low fat diet groups in the Tuttle study is not surprising. The dietary consultation protocol was identical, the

Table 22.6 Sensitivity analysis assumptions and results

Scenario	Inc cost (Mediterranean diet MD compared to Western diet WD) per person AU\$	Inc QALYs (MD compared to WD) per person	Cost/QALY AU\$
Base case	−179 (US\$−145, €−102) ^a	0.61	MD dominates
Upper estimate of intervention effect (less cardiac events) ^b	−458 (US\$−371, €−261)	0.85	MD dominates
Lower estimate of intervention effect (more cardiac events) ^b	283 (US\$229, €162)	0.19	1460 (US\$, €)
Utilities all decreased by 0.05	−179 (US\$−145, €−102)	0.58	MD dominates
Utilities all increased by 0.05	−179 (US\$−145, €−102)	0.64	MD dominates
Discount rate 3%	−139 (US\$−113, €−79)	0.68	MD dominates
Discount rate 0%	−73 (US\$−59, €−42)	0.82	MD dominates
Time horizon 20 years	488 (US\$395, €279)	1.05	467 (US\$, €)
Time horizon 15 years	212 (US\$172, €121)	0.89	239 (US\$, €)
Time horizon 5 years	−514 (US\$−416, €−293)	0.21	MD dominates
Number of consults doubled	352 (US\$285, €201)	0.61	578 (US\$, €)
Number of consults halved	−444 (US\$−360, €−253)	0.61	MD dominates
Addition of state costs for stroke of AU\$7220 ^c	−853 (US\$−691, €−487)	0.61	MD dominates
Food costs doubled	415 (US\$336, €237)	0.61	727 (US\$, €)
No additional food costs	−799 (US\$−647, €−456)	0.61	MD dominates

MD Mediterranean diet, WD Western diet, LF low fat diet, QALY quality adjusted life year

^aA negative value indicates that the Mediterranean diet is cost saving

^bCalculated using the range presented in Table 22.4

^cState costs are assigned to each patient for each cycle they spend in the stroke health state, they reflect the ongoing costs associated with living in this condition

dietary advice given to both groups was similar and the diet composition of the two groups based on food diaries was almost identical.

Taken together the two RCTs plus the recently published cohort and other epidemiological studies [30–33] strongly suggest that a high quality dietary intervention modeled on the Mediterranean diet (or the American Heart Association low fat diet) is highly effective and highly cost-effective (and possibly dominant) compared with “usual care” for persons after a first AMI. It is also clear that despite dietary advice being identified in clinical practice guidelines as a core component of usual care post AMI, dietary advice under usual care is not achieving anywhere near the benefits that are possible; suggesting widespread failure of delivery of best practice care.

We contend that the policy conclusions are certain and robust given that under a range of plausible and valid assumptions; provision of advice to adopt a Mediterranean-style diet in persons following AMI is cost saving or cost-effective. The results of this economic evaluation support access to high quality dietetic advice to support the adoption of a Mediterranean diet in similar patient cohorts.

22.4.1 *Strengths and Limitations*

One area of uncertainty is the generalizability of effectiveness results to populations outside France and to the current day. Issues that might affect the generalizability include baseline prevalence of AMI's in the community, as any substantial departure from the study experience will affect absolute risks, even if relative risks are unchanged. Secondly the typical current management of heart disease; and thirdly the cultural acceptance of the intervention, usual dietary patterns in the community and usual dietary advice in this cohort including effectiveness of delivery.

There is an argument that some 15 years on from the Lyon Heart Study the prevalence and management of heart disease and AMI have changed; such that there is now less scope for potential benefit. We suggest this argument is weak. First; France (the setting of the original study) had and still has very low rates of heart disease compared to most other countries. In 1997 there were 10.46 female AMI deaths/100,000 people in France compared to 33.89 in Australia, and 28.45 in the USA. Likewise there were 29.35 male AMI deaths/100,000 people in France in 1997 compared to 64.45 in Australia, and 56.40 in the USA (age standardized to world population [34]). Thus while countries like Australia have seen a decreasing rate of fatal AMI's over the last two decades, down from 203.9/100,000 people in 1980, 145.8 in 1990, to 78.2 in 2000 (age standardized to Australian population [35]), current rates are still higher than France in the early 1990s when the Lyon Diet Heart Study was conducted. This is consistent with the results of the more recent Tuttle study which found the relative risk between the diet and control groups almost identical to the results of the Lyon Heart Study.

In relation to estimated costs, generalizability is more problematic as management patterns and cost of hospitalization vary across health systems; and others may wish to re-do the calculations using our model. Estimating costs and cost-effectiveness in America and Europe, using currency conversion is less robust than directly deriving unit costs for those health systems. We note, however, that the generally lower inpatient costs in Australia for CVD events avoided compared with USA or most of the EU means that the possible cost savings likely to be realized in other countries are greater, so our reported cost-effectiveness estimates should therefore be conservative. We recognize that food costs may also vary across countries depending on local availability of products and local cost of living. Our evaluation has provided differential food costs based on Australian data for a subset of foods that make up each typical diet. The food basket was chosen to provide a high estimate of the differential cost of the Mediterranean diet. Furthermore, sensitivity analysis shows that even if food costs were doubled the intervention would still be highly cost effective at \$727AU (\$589US, €415) per QALY gained. Recent evidence has broadly confirmed that high adherence to a Mediterranean diet will be more costly for individuals [36, 37].

We also note that estimated cost effectiveness is likely to be conservative for the following reasons: First, we have included only transition or event costs in our estimate of potential downstream cost savings and not also on-going differentials in costs of management. A more comprehensive costing analysis would increase the cost saving of the Mediterranean diet compared with usual care. Second, the analysis used an intention to treat approach which will bias results towards the null, and thirdly, the Mediterranean diet may significantly reduce other disease such as cancer, Parkinson's and Alzheimer's even in the short term (such probable benefits are included only to the extent that they are captured in all-cause mortality [32, 38]).

The preparedness and capacity of a particular patient group to adopt a Mediterranean-style diet is also important. According to other studies, the uptake of a Mediterranean diet is theoretically possible in other countries such as Germany based on the availability of food [39], but also trial experience [10]. Nutrition is not just about food availability, it is also about lifestyle, culture and social structure. It would seem that the Mediterranean diet or the key protective elements of the diet are transferable to people not living in the region for example as evidenced by the fact that the original

population in the Lyon Diet Heart Study did not normally consume the traditional Mediterranean diet. [40]. It seems that although the diet is theoretically transferable, this will not be automatic. Further research into implementation of the Mediterranean diet in other regions of the world is warranted. The adoption of the diet is aided in that it is attractive for its “famous palatability” [41].

Important changes in current management of heart disease may affect generalizability, but this is uncertain. At the time of the Lyon Diet Heart Study ASA therapy, ACE inhibitors and beta-blockers were used in a similar way to current management, but the use of statins has since increased substantially. However, a recent trial in which patients were randomized to the Mediterranean diet plus statin treatment or statin treatment alone found that the addition of the diet substantially and significantly improved clinical outcomes [8]. There is an inherent contradiction in study design, with a lengthy follow up desirable for assessment of longer term impacts, but with increased likelihood that management will have changed since study commencement.

Whilst, ideally utility data would be based on directly collected utility/quality of life scores for the original patient cohort, quality of life was not measured in the Lyon Diet Heart Study. We have thus relied on published utilities chosen to closely match the reported health states, generated using the preferred time trade off technique [13, 14]. Any potential error is small as the vast majority of QALY gain is driven by a reduction in events observed directly from the trial rather than the assigned utilities.

22.4.2 Relation to Previous Research

To our knowledge this is the first cost-effectiveness study of the Mediterranean diet for any patient group (aside from our own previous work [42]), and we have only been able to locate one other cost utility study of any nutrition intervention in cardiology [43]. The results can be compared with other interventions for persons with established heart disease. For example, another study [44] reported a cost per life year saved of \$3,600US for beta-blocker therapy, from \$20,200US to \$2,024,800US for lovastatin, from \$9,200US to \$1,142,00US for coronary artery bypass grafting, from \$1,300US to \$3,900US for physician counseling to stop smoking, and \$124,400US for exercise electrocardiogram. The WHO defines very cost effective interventions as costing less than mean gross domestic product (GDP) per head which equates to approximately \$30,000 for Europe, \$40,000 for the USA and \$31,000 for Australia in 2005 international dollars [45]. The Mediterranean diet is more cost saving compared to the “usual care” reflecting the large reduction in cardiac event rates achieved, through a relatively low cost intervention.

22.5 Conclusions

Based on the published results from the Lyon Diet Heart Study, and conservative assumptions, the Mediterranean diet was cost saving for persons following first AMI. Replicating the Mediterranean diet intervention in other countries and health settings could substantially improve health outcomes and reduce the use of health care resources. With risk factors related to coronary heart disease continuing to rise across the world, this represents an important opportunity for cost-effective preventative care.

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Chapter 23

Nutrition and the Benefits of Early Interventions in Diabetes, Cardiovascular and Noncommunicable Diseases

Ian Darnton-Hill, I. Caterson, and S. Colagiuri

Key Points

- Changing nutrition and dietary patterns are contributing to the current global epidemic of the noncommunicable diseases that includes increasing rates of obesity, cardiovascular diseases and hypertension, and diabetes, as well as some cancers.
- Other factors include changing activity patterns, genetic and early developmental factors, and an increasingly global obesogenic environment.
- The burden of these diseases are increasingly shifting to poor- and emerging-economy countries so that by 2020, noncommunicable diseases will cause seven out of every ten deaths, and account for 80% of the global burden of disease in these countries while in affluent countries the burden will increasingly be borne by the socio-economically less well-off.
- Many countries will therefore suffer from a double burden of malnutrition with both undernutrition and noncommunicable diseases coexisting, further straining already overtaxed health systems with often poor capacity.
- Modifying diets is an essential part of combating these diseases – the benefits of early dietary interventions, continued throughout the life-course have a strong scientific underpinning and were recently re-enforced by WHO again for immediate national action to supplement other lifestyle changes and modifications of the obesogenic environment.
- Facilitative changes in behaviors, policy and programs are needed at individual, national and global levels.

Keywords Cardiovascular diseases • Diabetes • Diet • Noncommunicable diseases • Nutrition • Obesity • Prevention • Public health

23.1 Introduction and Background

Nutrition, along with changing activity patterns, genetic and early developmental factors, and an obesogenic environment, are all playing critical roles in the current global epidemic of the noncommunicable diseases. Rates of obesity, cardiovascular diseases and hypertension, and diabetes, as well as some cancers, sleep apnea, joint problems, and some others, are all escalating globally. The World

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Health Organization (WHO), amongst others, has been monitoring the growing and changing dimensions of the noncommunicable diseases epidemic (used here synonymously with chronic diseases, and with the understanding that this chapter refers to the nutrition-related chronic diseases). In the early 1950s the extent of the emerging epidemic was largely seen in the more affluent countries, but was already expanding to other economies. At a World Health Assembly (WHA) in 2000, the World Health Organization (WHO) sought to bring attention to the emerging problem in the transitional and emerging economies and to the fact that the global burden would soon be predominantly in the low- and middle-income countries (“Developing Countries”), which has now happened. It is predicted that by 2020, noncommunicable diseases will cause seven out of every ten deaths in low to middle income countries, compared to less than half in 2006, and account for 80% of the global burden of disease [1]. As many of the poorer countries still have a high burden of infectious disease, including the recently emerging ones such as TB and HIV/AIDS, the demographic and socio-economic transitions are already imposing constraints on addressing this double burden of infectious and chronic diseases, especially as the health systems are already under-resourced and of often low capacity [2, 3].

At present these noncommunicable diseases are responsible for about 35 million deaths each year (60% of all deaths worldwide) [4]. The most recent report from WHO on the global burden of disease and attributable risk noted that the leading global risks for mortality in the world are high blood pressure (13% of deaths globally), tobacco use (9%), high blood glucose (6%), physical inactivity (6%), and overweight and obesity (5%) [5], along with socio-economic inequalities and food politics as important larger determinants [6]. The eight risk factors that account for 61% of cardiovascular deaths (or >75% of all ischemic heart disease worldwide) are alcohol use, tobacco use, high blood pressure, high body mass index, high cholesterol, high blood glucose, low fruit and vegetable intake, and physical inactivity. Over 84% of the total global burden of disease these risk factors occur in low and middle-income countries [5].

At the same time, the global epidemic is changing in other ways besides shifting the biggest impact to transitional economies. Many middle and poor income countries have seen, for example, levels of obesity that are now higher than in the USA as in the women of poor countries like Mauritania and the poorer areas of urban South Africa. The example of the Pacific Islands, in particular Nauru, is well-known and often quoted – some of the highest levels of obesity and the highest rates, and along with the Pima Indians in south-western North America, and some other ethnic groups, of diabetes in the world. The latter ethnic group is particularly interesting in terms of prevention as their genetically similar relatives, the Pima in Mexico, who have a more traditional diet do not have anything like the same levels of diabetes. It is also interesting to note that as the income of Nauru has declined, so has the prevalence of obesity and diabetes.

South Asian populations appear to be particularly affected and at younger ages [7]. Besides the many social, environmental and resource differences among emerging economies, it seems likely there is also a different relationship between Body Mass Index (BMI) and percentage body fat depending on ethnicity [8, 9], so for example Asian Indians consistently have up to 5% higher body fat at any BMI compared with Caucasians, as well as increased risk of type 2 diabetes and cardiovascular disease (CVD) at a lower BMI [10]. In contrast to Asians, there is good evidence that Pacific Island populations, specifically those of Polynesian ancestry, have lower body fat and more muscle mass [11] but confusingly, although Pacific Islanders and Asian Indians are at the opposite extremes of the BMI-body fat relationship, both suffer from very high rates of diabetes [10]. Similarly, the prevalence of type 2 diabetes in China has gone from being virtually unknown to at least 5% of the population currently [12]. In countries such as Australia, New Zealand, the UK and others, cardiovascular disease rates are worse in marginal and ethnic minorities [13] and in larger minority populations such as African-Americans in the USA [14]. These variations are thought to be due to differences

in lifestyle, diet, physical activity, environments, and genetics. Nevertheless, a recent review showed that the proportional effects of the major risk factors are similar across “Western” and “Asian” populations, at least in the USA [15].

WHO has predicted that percentage increases in mortality from noncommunicable diseases will reach double digits in the coming years, underlining the urgent need to act. In the next 10 years, it estimates, the world will see an overall 17% increase in mortality from these groups of diseases, but the greatest increase will be seen in developing countries: about 27% in the African region, 25% in the Middle East, and 20–21% in Asia and the Pacific [4]. It is particularly worrying that young children continue to have rises in prevalence of obesity as weight problems in childhood are likely to track into adulthood [16]. These are worldwide trends [4, 17]. It is also being increasingly recognized by Governments that, whereas the treatment of these diseases is at a high cost because of their chronic nature, and so usually require lifelong, expensive management and treatment, they would be more cost-effectively addressed through a preventive and public health approach [18]. However, despite some successes with coronary heart disease (CHD) prevalence [19], such population-level preventive approaches have so far proven a challenge (2008).

The chapter will look at trends in the global burden of the nutrition-related chronic diseases, the epidemiology of those diseases, the burden and economic costs of these diseases, the prevention, especially through nutritional approaches, including the role of nutraceuticals, existing recommendations and their impact, public health approaches, and concludes with a summary of the benefits of early nutritional interventions in the prevention of these diseases at a national, and global, level. As the topic is on nutrition and the benefits of early intervention, other interventions will not be addressed, except briefly, physical activity and the broader social environment.

23.2 Diet and the Noncommunicable Diseases

The chronic diseases of the nutritionally related noncommunicable diseases are often both a clinical outcome as well as a further risk factor to other chronic diseases [16]. This means for example that obesity, with adverse clinical outcomes of its own, also predisposes to type 2 diabetes, hypertension and likely cardiovascular disease as well as other nutritional chronic diseases such as joint problems, mobility, and sleep apnoea. Diabetes is similar, having adverse consequences of its own such as blindness, and peripheral neuropathies but posing also a greater risk of both causing and worsening cardiovascular disease [20]. Dietary factors such as the intake of too much saturated fat, salt and alcohol, a lack of physical activity, and a genetic predisposition to the condition, raise blood pressure, serum cholesterol, and lead to an increase in obesity levels, and other risk factors in the development of noncommunicable diseases [5, 17, 21].

In the report of the Joint WHO/FAO Expert Consultation on “Diet, Nutrition and the Prevention of Chronic Disease,” it is noted that there have been profound changes in diets and lifestyles with industrialization, urbanization, economic development and market globalization and these have been perhaps even more rapid in the last few decades [17]. Food and food products have become both cheaper and more like commodities to be produced and traded in global markets, expanding greatly from what was essentially a local base [17]. Recent trends towards globalization appear to be lessening many traditional dietary cultural differences, often with adverse effects on the diets of children and adolescents. A recent study in four countries in Europe found many similarities across diverse, albeit European, cuisines and dietary patterns [22]. These changes in the world food economy have been reflected in changing dietary patterns of increased consumption of energy-dense diets high in fat, particularly saturated fat, salt, and low in unrefined carbohydrates. At the same time nutrition is

being identified as a “major, modifiable determinant of chronic disease,” with scientific evidence increasingly demonstrating that such alterations in the global dietary patterns, have strong effects, both positive and negative on health throughout life [16, 17, 23].

Early studies such as the transgenerational Japanese populations from Japan to Hawaiian populations to those in western USA, acculturating to different lifestyles and diets, all the while increasing their risk of noncommunicable diseases, including cancers, and other observational studies, helped formulate the concept of the nutrition transition following the existing demographic and epidemiological transitions occurring globally [24]. Populations shifted from diets high in unrefined carbohydrates, low in fat, low salt and high fiber (often monotonous and challenging to ensure nutrition security) to one of high fat, especially saturated fat, refined carbohydrates, high salt and high refined sugar content (the latter a combination initially attractive to virtually all, it appears). These transitions occurred slowly (over a couple of hundred years in Europe, North America and Australia) but have happened in less than 50 years in countries in East Asia [25].

Even within the affluent country populations, dietary patterns continue to change [17]. There have been changes not only in energy expenditure patterns with increasing mechanization and ubiquitous transport, but also of increasing amounts and ubiquity of food available, increasing energy density, and a marked increase in consumption of empty calorie foods such as sweetened soft/carbonated drinks, and increases in serving sizes [26]. At the same time, the amount of advertising of more energy-dense foods, including to children, has increased, as well as some evidence that adolescents drink more soft drinks when the television is on [27]. The increasing amount of time spent in front of a computer, at least in children, is also associated with increased risk of obesity and in young adults, all-cause and cardiovascular mortality [28]. The average North American consumes about 250 more calories per day than a few decades ago; with roughly half that increase coming from soda/soft drinks and other sugar sweetened beverages [29]. Evidence is growing that the body handles energy in liquid and solid foods differently with the suggested consequence that if one has say, a confectionary bar before dinner, this will affect appetite, whereas a soft drink before dinner is less likely to. The report of a 21-year follow-up in Finnish children, now adults, found that it was the increase in the consumption of sugar-sweetened soft drinks that was directly associated with BMI in adulthood [30].

There has subsequently been a further, if insufficient, shift in richer countries, usually by the more affluent, better educated groups, back to healthier diets and increasing voluntary physical activity. In the USA, this has contributed to antioxidant intakes differing by socio-demographic subgroups (older adults, Caucasians and those with higher incomes and exercise levels as well as women and non-“smokers” and non-“users of alcohol”) [31]. But these are proportionally small groups, generally privileged and having small impact on the following epidemics.

The obesity epidemic is global: in 2005, 400 million adults were obese and it is anticipated this will double by 2015 [32]. In countries like the UK it is anticipated that by 2050, unless something changes, 60% of men, 50% of women, and 25% of children will be classified as obese – a dramatic increase from 25% for men and women currently, already a shocking figure, and 10% of children [33]. An Australian survey [34] found a significant increase in the proportion of obese children, from 5.2% in 1995 to 7.8% in 2007–2008 and the rise was almost entirely amongst boys where almost 10% were obese, compared with 4.5% a decade ago. In Australian adults, 68% of men and 55% of women are currently overweight or obese, as measured by Body Mass Index (BMI), an increase from 64% and 49% respectively a decade ago. The link between diet and obesity is self-evident but extremely complex while in essence remaining a matter of energy intake exceeding energy output and activity levels [35]. However, there are other components involved such as genetic factors, familial and cultural influences, environmental milieu, and processed food availability. While numerous very large cohort studies have firmly established obesity as a strong predictor of both overall and cardiovascular mortality in both men and women, there appears to be particular increased risk with abdominal obesity [36].

At the same time, the prevalence of diabetes is increasing in all parts of the world, both types 1 and 2, but especially the latter [5, 37]. It continues to be relatively frequently undiagnosed, especially in under-resourced areas and poorer countries [37]. About 28 million Africans are reported to be estimated to die in the next 20 years of NCDs. Ten million currently have diabetes and this will increase to 19 million by 2025 if nothing is done and yet probably only about one in four are actually diagnosed and treated [38]. Even in cities such as New York, it has been reported to be often under-diagnosed, especially in minority populations. The International Diabetes Federation estimates that 285 million adults worldwide have diabetes [39]. The levels of type 2 diabetes are increasing rapidly and are estimated to reach 439 million by 2030 [39]. It is paralleling the obesity epidemic; in 2005, 400 million adults were obese and it is anticipated this will double by 2015 [40].

Diabetes accounts for 6% of total global mortality, with half of diabetes-associated deaths being attributed to cardiovascular disease. Diet is an integral factor in both the development and management of type 2 diabetes and has been shown to be a critical factor in prevention. The types of foods also play a role and the glycemic index appears to be important in both development of the disease and the management [41, 42]. Various aspects of diet such as fat, carbohydrate, fiber, whole grains, magnesium, glycemic index and load have all been related to insulin resistance [43]. The predisposition to develop diabetes and the course of the disease varies by ethnicity [40] and individuals of South Asian origins present earlier and have higher morbidity and mortality in the UK and in their countries of origin. These South Asian populations, besides being prone to develop insulin resistance and the metabolic syndrome, have low intakes of monosaturated fatty acids (MUFA), *n*-3 polyunsaturated fatty acids (PUFA) and fiber, and high intakes of total fats, saturated fats, carbohydrates and trans-fatty acids and it has been suggested that dietary factors are likely to be more important than genetic factors in the observed high rates of obesity, metabolic syndrome and diabetes [44]. In the USA, Hispanics and African-Americans are disproportionately affected by diabetes and experience more complications and higher mortality than non-African-Americans [40]. The prevalence of overweight in Chinese adults was 22.8% in a 2002 survey and the prevalence of obesity 7.1%, while the prevalence of diabetes was 5.2% (12.7 million) among men and 5.8% (13.3 million) in women (35–74 years), with another 20 million with intermediate hyperglycemia (IHG) or “prediabetes” [12].

At the same time as the marked increase in risk factors globally of overweight and obesity and reduced physical activity, it is likely low birthweight in countries such as India, followed by adult, or younger, weight gain, has been another factor [16, 45]. Younger age groups are being affected, and the increase in diabetes is contributing to increased incidence and increased mortality due to cardiovascular diseases [20, 46]. The estimated 22 million children worldwide who are now obese or overweight are also at much increased risk of type 2 diabetes that was not seen in these age groups in the past. It has been suggested that it may be a more aggressive phenotype than that of the adult onset type and could foretell a later increased problem at a younger age of cardiovascular disease than at present [40] and again suggests the need for early intervention [16]. This is especially true as the risk for children can begin *in utero* with offspring of women with gestational diabetes likely to be more at risk of developing glucose intolerance and diabetes in later life. The incidence of gestational diabetes is also increasing and now affects around 5% of pregnancies [40].

Diet is again fundamental in both the development of the cardiovascular diseases such as coronary heart disease and hypertension, and in their management with dietary interventions being the “cornerstone to treat metabolic syndrome and insulin resistance...” [47]. Adiposity is a major risk factor for cardiovascular disease, especially when this excess is located in visceral depots [48]. Changes in population levels of known risk factors, including diet and reductions in smoking prevalence, have led to the impressive declines in mortality from coronary heart disease in recent decades [19, 49]. Some recent evidence from Canada [50] and Scotland from 1986 to 2006 [49] suggests that this trend may be flattening in younger adults in the most socially deprived groups. However, at

present, most deaths caused by the recognized risk factors are from cardiovascular diseases and the largest risk factor (in the USA) is high blood pressure, which is responsible for 45% of all cardiovascular deaths, followed by overweight/obesity, physical inactivity, high LDL cholesterol, smoking, high dietary salt, high dietary trans fatty acids, and low dietary ω -3 fatty acids [15].

Elevated blood pressure was previously presumed to naturally increase with age until it was discovered that in older tribesmen in the highlands of Papua New Guinea blood pressure levels tended to drop with age. This is presumed to be because of lessening BMI with age but also because of a traditionally low intake of sodium, conditions that were, and are, not occurring in ageing, male populations in affluent and emerging economy countries. Annually, 15 million people worldwide suffer from a stroke, of whom five million die and another five million are left permanently disabled. The stroke burden is projected to rise from about 38 million DALYS in 1990 to around 61 million in 2020 [51]. This makes prevention an important public health priority even allowing for the fact that better diagnosis and treatment and reduced smoking prevalence have contributed to a reduction in some developed countries.

The authors of a recent meta-analysis confirmed that a higher salt intake was associated with an increased risk of stroke and probably cardiovascular disease [52]. Clinically important cardiovascular events were reduced by 21–41% in people who received an intervention to reduce sodium intake. A recent editorial comment on the meta-analysis of cohort studies confirming the benefits of reducing salt (sodium chloride) intakes suggested that this means public health authorities should promote more actively that individuals consume less salt as a preventive measure [52]. As raised blood pressure accounts for 62% of strokes and 49% of coronary disease events [1], the projected benefits of salt reduction are substantial although the goal of 5 g/day remains a real dietary challenge, in a public health sense, especially in Asia and Eastern Europe. Adherence to a healthy (traditionally intakes of low saturated fatty acids and high in polyunsaturated fatty acids) but reduced salt Japanese diet was associated with a 20% lower rate of all-cause and cardiovascular mortality [53]. Of two meta-analyses showing clear protective effects of fruits and vegetables: one compared highest with lowest intake [54], and the other the risk of stroke was reduced by 11% for each additional serving per day of fruit and by a nonsignificant 3% for each additional serving per day of vegetables [55]. Consequently diet remains an important part of the prevention of hypertension, and as an important part of the overall prevention of the noncommunicable diseases.

Other noncommunicable diseases are also clearly associated with dietary factors [56]. More than 70,000 new cases of cancer a year in Europe can be attributed to excess body weight, with the most common types of cancer attributable to obesity being endometrial, postmenopausal breast, and colorectal cancers. In the next decade, as smoking prevalence decreases in some countries, it is predicted that obesity will become the biggest attributable cause of cancer in women. Cancers, while clearly having strong links to diet, e.g., colon cancer, breast cancer, prostate, renal, pancreatic and probably other cancers, will not be further considered here (as about cardiovascular disease and diabetes) but are amply reviewed by the extensive WCRF/AICR review [56].

23.3 Costs Associated with the Noncommunicable Diseases

The cost of the noncommunicable diseases has been calculated for a number of affluent countries, and although the figures vary because the challenges of costing depend on the assumptions made, the cost is undoubtedly high. Other chapters in this volume examine this in more detail with the emphasis here being on the benefits of early intervention.

Being obese or overweight is associated with a substantial health burden with increased risks of cardiovascular disease, type 2 diabetes, stroke, and some cancers [1, 57]. The economic cost of this health burden has been estimated to be as high as US\$147 billion per year [57]. The direct medical costs of treating obesity have been estimated to have risen to nearly 10% of all spending on health care in the USA [29]. The prevalence of obesity rose by 37% between 1998 and 2006 while over the same period, expenditure related to obesity doubled, from \$74bn (£44bn; (51bn)) to \$147bn (with both numbers adjusted for inflation to 2008 dollars) with prescription drug expenditures being a large part of that cost [29]. The average expenditure per obese person rose by only 11%, while the increase in prevalence accounted for 89% of the doubling in expenditure. It was noted that if obesity prevalence had remained steady at 1998 numbers, annual medical expenditures would have been reduced by \$US40 billion in the USA.

A recent re-evaluation of the cost of overweight and obesity in Australia suggested a figure of \$AU19 billion, a figure substantially higher than previous estimates [58]. Using data from the longitudinal component of the Australian Diabetes, Obesity and Lifestyle study on over 6,000 participants ≥ 25 years at baseline, the authors found that annual direct costs per person increased from \$AU1,479 for normal weight to \$AU2,788 for the obese. In 2005, direct costs were \$AU10.7 million more in the overweight and obese than in normal weight people (and in addition these same individuals received a further \$AU36 billion in Government subsidies). Importantly they also found that costs were lower in overweight or obese people who lost weight or reduced waist circumference compared with those who progressed to, or remained, obese. They concluded that there are financial incentives at both individual and societal levels for those who are overweight or obese to lose weight and/or reduce their waist circumference [58].

An editorial on salt reduction in the *British Medical Journal* described the substantial projected benefits of salt reduction and that in the USA, if sodium could be reduced to the upper limit recommended in the USA of 5.8 g/day (c.f. 5 g in WHO recommendations), then it should reduce the prevalence of hypertension by 11 million and save \$US18 billion in healthcare costs and gain 312,000 QALYs [59]. Another estimate calculated that if salt intake could be reduced by 3 g a day it would save between \$US10 to 24 billion a year in health care costs, including through reductions in rates of coronary heart disease and strokes [60].

The burden of noncommunicable disease has a major effect on socioeconomic development in poor nations. WHO health analysts estimate that in developing nations that are experiencing rapid economic growth, heart disease, stroke, and diabetes alone reduce gross domestic product (GDP) by between 1% and 5% each year. In rich nations only 7% of deaths caused by high blood pressure occur under age 60, whereas in the Africa region this rises to 25%; over 83% of all deaths globally (3.4 million) caused by high blood glucose occur in poor and middle income countries [4, 61]. Adults are being affected at younger ages than in more affluent countries, and often it is the more educated, with considerable economic costs to these countries. A report from Australia (the National Preventative Health Taskforce) made 74 recommendations and noted that Australia, as in many other countries, is spending 70% of its health budget on treating chronic disease and only 2% on prevention [62] and that diseases due to alcohol, tobacco and obesity collectively cost \$AU6 billion.

23.4 Evidence of Impact of Diet on Noncommunicable Diseases

The WHO Technical Report 916, “Diet, nutrition and the prevention of chronic diseases” ably reviewed the strength of the evidence of associations between diet, and nutrients in the diets and the development and management of noncommunicable chronic diseases [17]. The Expert Consultation

concluded there were clear relationships such as saturated fats, trans-saturated fatty acids, polyunsaturated fatty acids, fruits and vegetables, and salt, and others likely but less certain such as simple carbohydrates [17, 63]. Although the role of dietary therapy has been integral for both primary and secondary prevention of CVD, the evidence for dietary modification and its reduction of all-cause mortality is limited [64] as it is all but impossible to sift out the specific contributions of diet from other lifestyle changes usually occurring at the same time. However changes in risk factor levels with dietary change have been clearly shown [17, 65]. As seen in Table 23.1, the consultation found strong enough evidence for recommendations on 15 dietary factors [17, 63].

Table 23.1 Ranges of population nutrient intake goals (% of total energy unless otherwise stated) for diets appropriate for prevention of the diet-related noncommunicable diseases from the WHO/FAO Techn Rep No. 916 (2003) (Nishida et al. 2004)

Dietary constituent	1989 WHO study group recommendations	2002 joint WHO/FAO expert consultation recommendations	Rationale for WHO/FAO expert consultation recommendations
Total fat as percent energy	15–30%	15–30%	Obesity/CVD/diabetes
Saturated fatty acids (SFA)	0–10%	<10%	Diabetes/CVD
Polyunsaturated fatty acids (PUFA)	3–7%	6–10%	CVD
ω-6 PUFAs		5–8%	CVD
ω-3 PUFAs		1–2%	CVD
<i>Trans</i> Fatty acids%E		<1%	CVD
Monosaturated FAs (MUFAs)		By difference ^a	
Total carbohydrate as%E	55–75%	55–75% ^b	
Free sugars ^c	0–10%	<10%	Obesity/dental disease
Complex CHOs	50–70%	No recommendation	
Protein	10–15%	10–15% ^d	
Cholesterol	0–300 mg/day	<300 mg/day	CVD
Salt ^e (sodium chloride) intake g/day	<6 g/day	<5 g/day (sodium <2 g/day)	CVD/hypertension
Vegetables and fruits g/day	≥400 g/day	≥400 g/day	CVD/cancer
Pulses, nuts, and seeds	≥30 ^f		
Total dietary fiber	27–40 g/day	From foods	
NSP	16–24 g/day	From foods	Obesity/diabetes/CVD/cancer

NSP nonstarch polysaccharides

^aThis was calculated as: total fat-(SFAs + PUFAs + TransFAs)

^bThe percentage of total energy available after taking into account that consumed as protein and fat, hence the wide range

^cThe term “free sugars” refers to all monosaccharides and disaccharides added to foods by the manufacturer, cook or consumer, plus sugars naturally present in honey, syrups and fruit juices

^dThe suggested range should be seen in the light of the Joint WHO/FAO/UNU Expert Consultation on Protein and Amino Acid Requirements in Human Nutrition, held in Geneva from 6 to 16 April 2002

^eSalt should be iodized appropriately

^fAs part of the 400 g/day of fruit and vegetables

Assessing single nutrients or food groups in relation to the occurrence of disease has recognized limitations because food components of diet can have both synergistic and antagonistic interactions and because people eat a complex diet of nutrients [66, 67]. Nevertheless, much of the scientific investigation into a relationship between diet and noncommunicable diseases has been on single nutrients or classes of nutrients (and not surprisingly many of the public health recommendations are similarly focused). Similarly, it has been noted that much of the earlier research was on male Caucasian populations living on “western” diets [16, 68], although there are increasing large studies from middle-income countries such as China and India. The fact that whole diets may have a different impact from isolated nutrients on risk factors led to WHO and FAO encouraging countries to develop national policies using food-based dietary guidelines [63]. Similarly WHO considered there was enough evidence available to recommend a life-course approach to prevention [16].

23.4.1 *Macronutrients*

The role of lipids, e.g., has been documented at least since Keys et al. in the early 1950s [69], and dietary constituents have been increasingly disaggregated into smaller and smaller subunits and becoming increasingly complex. The 2003 WHO Report broke down recommendations for total fat into saturated, polyunsaturated, monosaturated, and trans fatty acids in recognition of the available evidence at the time and which has only become stronger, while at the same time more nuanced in terms of the contribution of the qualitative composition of fats in the diet in modifying the risk of cardiovascular diseases [63]. Current evidence suggests saturated fat adversely affects vascular function whereas polyunsaturated fats (mainly linoleic [18:2*n*-6] and *n*-3 PUFA) are beneficial. EPA (20:5*n*-3) and DHA (22:6*n*-3) can reduce blood pressure, improve arterial compliance in people with type 2 diabetes and dyslipidemias, and augment endothelium-dependent vasodilation [70]. Despite limited evidence of any effect on weight [71, 72], dietary fat remains one of the major modifiable factors for coronary heart disease because of the well-documented influence of dietary fatty acid chain length, degree of unsaturation and geometry of double bonds (*cis* and *trans*) on the atherosclerotic and thrombotic pathways leading to coronary heart disease [73]. A recent Joint FAO/WHO Expert Consultation on fats and fatty acids was unable to reach agreement on the upper-value macronutrient distribution range for percent energy (%E) to come from fat [74]. The roles of the omega fatty acids are increasingly recognized as important and the current proportions of ω -3 and ω -6 fatty acids is a reversal of the patterns humankind consumed for millennia [75]. The role of ω -3 fatty acids and, more specifically, fish oil through diet or supplementation, in secondary prevention of CVD seems to be supported by cohort studies, randomized clinical trials, meta-analysis, and systematic review [76]. WHO considers there is sufficient evidence to recommend dietary intake levels for both ω -3 and ω -6 fatty acids (WHO 2003). The Mediterranean diet and (omega) ω -3 fatty acids have been “unambiguously” shown to be effective in reducing the complications of coronary heart disease in European studies [77].

Trans fats, formed during the partial hydrogenation of vegetable oils, are associated with cardiovascular diseases [78] but because the process converts vegetable oil into semisolid fats for margarine and commercial and manufacturing processes, these partially hydrogenated fatty acids have been attractive to the food industry because of their long shelf-life, stability during deep-frying and the semisolidity that enhances baked goods and sweets [78], especially in low income countries where because of the low-cost of hydrogenated fat, they are frequently consumed [63], not least because such margarines do not require refrigeration.

The recommendations on total carbohydrates suggest that total dietary fiber and nonstarch polysaccharides come adequately from varied diets. To some controversy, free sugars were recommended

to be <10% of total carbohydrates as the consultation felt that at any given level higher intakes of free sugars threaten the nutrient quality of diets by providing significant amounts of energy without supplying specific nutrients [63]. They also agreed that restriction of free sugars was likely to contribute to reducing the risk of unhealthy weight gain [17]. Although this has been disputed, especially by the soft drink industry, there appears to be an increasing scientific consensus, and public acceptance that the current obesity epidemic, especially in the USA, is contributed to by the high intakes of sweetened soft drinks. WHO is currently reviewing the evidence on the effects of sugar consumption on health and in particular on obesity and other related noncommunicable diseases (following the new WHO guidelines process) [79].

23.4.2 Micronutrients

A beneficial role for vitamins in cardiovascular disease (CVD) is still unclear, for although being supported by observational studies, randomized controlled studies have not yet supported a role in either primary or secondary prevention of CVD [80]. Some have even suggested increased mortality in limited cases such as beta-carotene in those with pre-existing late-stage atherosclerosis. A recent review concluded that carotenoids through their retinoid and retinoid metabolites may have roles in the metabolic syndrome [81]. Vitamins may be beneficial to individuals who are antioxidant deficient or exposed to increased levels of oxidative stress such as smokers, people with diabetes and the elderly [80], suggesting a possible prevention role through subgroup targeting, which would have public health programming implications. Reactive oxygen species and free radicals have been implicated in the pathophysiology of CVD [82], with vitamins E and C and beta-carotene suggested as the fundamental protective components, possibly along with high fiber and flavanoids. Vitamins E and C in combination have shown long-term antiatherogenic effects although their effect on clinical endpoints has been inconsistent [80]. Low serum vitamin D in US adolescents is strongly associated with hypertension, hyperglycaemia, and metabolic syndrome, independent of adiposity (from NHANES 2001–2004) [83]. A recent study suggested that disparities in vitamin D status may partly explain increased cardiovascular mortality in African-Americans [84].

There is suggestive evidence that zinc deficiency may contribute to a reduced life expectancy in people with heart disease [85]. The programmatic implication of this is that recent evidence suggests zinc supplementation may reduce mortality [85]. The relationship between iron intake and blood pressure is unclear with one cross-sectional study suggesting an inverse relationship, but there does appear to be an association with a greater risk of hypertension and low total and nonheme iron intakes [86].

A recent review concluded that currently the available evidence is insufficient to recommend the routine use of B vitamins, vitamin E and vitamin C for the prevention of strokes [87]. In Nepal, maternal micronutrient supplementation was associated with lower offspring systolic blood pressure at 2 years of age but there is little evidence of an effect of maternal calcium on offspring blood pressure [88]. What has been clear is the consistent finding that individuals with a high dietary intake of fruit and vegetables, and likely adequate micronutrient intakes and other components of a varied diet, have a clear reduction in the incidence of coronary heart disease, stroke and cardiovascular mortality [80].

23.4.3 Components of Whole Diets

As noted in the previous section, many dietary constituents have been identified as playing a role in either the development or management of the diet-related chronic diseases. A longitudinal cohort

study of elderly men in three European countries and 20-year mortality, found not only that the dietary intake varied greatly between the three countries (which would make the framing of broad public health nutrition recommendations therefore more of a challenge) but nevertheless, after adjusting for age, smoking, and alcohol consumption, the healthiest diet compared with the least healthy had a RR of 0.87 (95% CI 0.77–0.96) in reducing 20-year mortality and this magnitude of effect was similar in each country. One of the authors' conclusions was that studying the dietary pattern as a whole is more important than specific dietary components, at least with respect to the survival of older people, probably because it takes into account intercorrelations of nutrients in the diet [89].

It is amazing the number of foods and drinks, which if consumed is said would have an impact on the incidence and prevalence of the nutrition-related chronic diseases. These range from cranberries, green tea and phytosterols in margarine to skim milk, and just about everything in between, however exotic. Antioxidant activity is a common factor in many. A recent review of berries and noncommunicable diseases found that because they contain a wide variety of phytochemicals, such as phenolic acids, flavonoids, tannins and various sterols, they are a rich source of antioxidants [90]. Two of the most predominant of those antioxidants are the anthocyanins (flavonoids) and the ellagitannins. As well, berries are generally good sources of fiber and potassium and even ω -3 fatty acids [90]. These phenolic compounds have the potential to protect against lipid peroxidation, and this has been seen in a couple of human studies in which drinking cranberry juice for 2 or 4 weeks resulted in a significant fall in oxidized LDL levels [91]. Studies reviewed included one showing consuming strawberries resulted in reductions in LDL and LDL:HDL ratio and to a significant reduction in LDL oxidative damage [92] and a Finnish study with various berries showed significant improvements in platelet function, HDL cholesterol and blood pressure [93].

Because the burden of chronic degenerative diseases, especially cardiovascular disease, is increasingly high all over the globe, and especially in India [7], it is important to observe dietary effects in other cultures besides northern European, Australasian and North American populations. A recent study in India found independent and interactive effects of plant sterols and fish oil *n*-3 long-chain polyunsaturated fatty acids on the plasma lipid profiles of mildly hyperlipidemic Indian adults and noted that this potent hypo-triacylglycerolemic effect of plant sterols in this population warrants additional investigation [94]. Khandelwal et al. [94] found that 2 g of plant sterols/day in a yoghurt drink format lowered plasma LDL-C by about 5% and TAG by 15% and suggest that plant-sterol enriched foods are a promising addition to interventions aimed at lowering heart disease risk in Indian populations. In a study in south India, Radhika et al. [95] found a strong inverse correlation between the fruit and vegetable consumption and cardiovascular disease risk factors, which is encouragingly similar to those of affluent country studies given the very different dietary and lifestyles in this population. That lifestyle and diet do make a difference in cardiovascular outcomes is true in all societies, e.g., in China in different ethnic groups, there were observed differences in blood pressure levels and the prevalence of hypertension because of different dietary habits, lifestyles, education level, and geographical surroundings [96].

Many epidemiological studies have shown inverse relationships between the consumption of diets rich in polyphenols and cardiovascular risk [97]. Many demonstrations of the effects of dietary polyphenols have concentrated on the most abundant flavanoids but there are many other dietary compounds that may also exert significant antioxidant effects such as indoles including serotonin, melatonin, tryptophan, indole-3-carbinol, and pyridoindoles, including an extract of safflower seed as one of the richest dietary sources of indolic polyphenols [97]. The regular consumption of tea (*Camellia sinensis*) probably contributes to the prevention of type 2 diabetes [98] and both oolong tea and green tea have positive effects on plasma glucose levels, and possibly coffee. Regular intake of the green tea polyphenol (epigallocatechin-3-gallate) had no effect on insulin resistance in a randomized controlled trial but did result in a modest reduction in diastolic blood pressure [98].

The WHO report of 2003 [17] was very clear, as was subsequently the report on food, nutrition, physical activity, and the prevention of cancer [56] that a diet high in fruits and vegetables has an evidence-based positive relationship to the prevention of noncommunicable diseases. Fruit and vegetable intake take is usually associated with lower levels of serum cholesterol [99] and lower blood pressure [100] and the increase in cardiovascular risk factors with ageing tends to be slower in fruit and vegetable consumers, and results in less coronary and cerebrovascular events [101].

Two meta-analyses of fruit or vegetable consumption have shown clear protective effects of fruits and vegetables against stroke when comparing highest with lowest intake [54], and in the other, the risk of stroke was reduced by 11% for each additional serving per day of fruit and by a nonsignificant 3% for each additional serving per day of vegetables [55]. The protection of fruit has been also found in Japanese, Chinese in Shanghai, and in the Mediterranean region [51]. Protective effects of plant-based foods against cardiovascular diseases have been shown by prospective studies; in particular fruit and vegetable intakes have been associated with reduced risks of stroke and coronary heart disease and nut intake with reduced risk of coronary heart disease and total mortality [102]. Fruit juice consumption has increased markedly over the last decade and makes an important contribution to vitamin C intakes, especially in older teenagers [33], and a review by Ruxton et al. [103] found convincing evidence from epidemiological and clinical studies that pure fruit juice reduces CHD risk via a number of probable mechanisms, although the effect on cancer was less convincing [33, 103].

Cholesterol concentrations are lower in vegetarians than meat eaters and vegans also have lower intakes of saturated fatty acids than do vegetarians [104]. An analysis of five prospective studies showed reduced mortality from ischemic heart diseases (IHD) by 24% (95% CI 6–38%) in vegetarian rather than meat-eaters [104, 105]. Differences in low density lipoprotein cholesterol, BMI and blood pressure seem to account for much of the protective effects seen in nonmeat-eaters, although it is thought to be not so much the absence of meat itself as low intakes of saturated animal fats and dietary cholesterol. Mann [104] also points out that vegetarian diets almost invariably include relatively high amounts of nuts, whole grains, unsaturated oils, fruits, and vegetables – all of which may be cardioprotective. Vegetarians also have lower rates of type 2 diabetes and hypertension [104]. While there are also important ecological benefits of vegetarian diets [104, 106], in terms of prevention of the nutrition-related chronic diseases, they may be no better than Mediterranean, Asian or “modified conventional Western” dietary patterns. A study by Mizrahi et al. [107] in Finland tried to further tease out the actual specific roles for different plant foods and found substantial protection against all types of stroke from a higher consumption of total fruits, but not for total vegetables, although there was for the subgroup of cruciferous vegetables that have high levels of vitamin C, sinapine, and glucosinolates (which can be converted to isothiocyanates). The fruit group effect was largely caused by citrus fruits, which have levels of vitamin C and also flavanones (naringenin and hesperetin) [51]. Suggested mechanisms include reductions in oxidative stress, inflammation or cytokine production, preservation of endothelial-unmediated vasodilation, inhibition of plaque formation, improvements in adipose tissue and kidney functions, reductions in thrombotic tendency, or amelioration of lipid levels, among others [51].

23.4.4 Mediterranean Diet

The traditional Mediterranean style of diet is credited as the reason for relatively good cardiovascular health in southern Europe and around the Mediterranean Sea [108], particularly compared with northern European countries – although public health interventions and public policies have helped to reduce the negative impact of diets in countries such as Finland [109]. A wide range of

epidemiological studies and RCT trials have confirmed that a Mediterranean-style diet has beneficial effect on glucose handling and diabetes prevention [110]. A study showing positive effects of the Mediterranean diet of fish, fruit vegetables, and olive oil reduced the need for treatment even after being adjusted for the weight loss, suggesting there was more to the overall diet than just the constituents and the weight loss [111], which is an intriguing possibility. A meta-analysis demonstrated that adherence is associated with a significant decrease in overall mortality (9%), morbidity from cardiovascular disease (9%), incidence of, or mortality from cancer (6%) and reduced incidence of Parkinson's disease and Alzheimer's disease [67]. The most likely reasons for this is the MUFA content along with high fiber, omega-3 fatty acid content, and drinking of moderate amounts of alcohol with diets that may also be relevant [110]. It has also been recently shown that the Mediterranean diet appears to reduce waist circumference in a high-risk cardiovascular population, reversing the negative effect that the 12Ala allele has, and even better that the beneficial effect of this dietary pattern seemed to be higher among subjects with type 2 diabetes [112]. A Mediterranean-style diet has been shown to have its beneficial effects on the occurrence of diseases in both industrialized and less-industrialized countries [67].

23.5 Role of Dietary Supplements and Nutraceuticals

As noted, high levels of vitamin C, sinapine, and glucosinolates (which can be converted to isothiocyanates) in cruciferous vegetables and the high levels of vitamin C and flavonones (naringenin and hesperetin) in fruits, especially citrus fruits, are thought to be largely responsible for the likely cardio-protective effects seen with fruit and vegetable intake [51]. However, it has been suggested that such effects are likely to be different when such constituents are given in a pill because some of the above (or other) compounds are not present and some of their mutual interactions are lost. The positive impact of omega-3 fatty acids along with the relative unpalatability of fish oils have led to extensive use of fish-oil capsules, along with capsules for promoting fiber intake and so on. In the same way, multiple micronutrients may not have the effects that could be expected, except for some micronutrients in the elderly. The success of organic foods has stimulated multinational food industry giants to accelerate investments in "functional foods" that are intentionally modified to make them healthier or more nutritious. PriceWaterhouseCoopers expects the global market for functional foods to increase from \$US78 billion in 2007 to \$US128 billion in 2013 with examples such as enriching eggs with omega-3 fatty acids to combat hypertension and sterols in margarines to impede the absorption of cholesterol [113]. More nutraceuticals, such as spreads and margarine with cholesterol properties, are appearing on supermarket shelves and are seen as a promising area for profit-making by the food industry. Nevertheless, their impact at a population level has yet to be demonstrated. At the same time, national authorities, especially in Europe, are examining, and sometimes questioning, many of the health claims being made.

23.6 Genetic Components

However, it is not only the sort of diets and nutrient content that leads to differing dietary and health outcomes. Genetic, environmental and behavioral factors are all important. For example, eating a large proportion of intake in the morning has been associated with lower overall intake, while eating a high proportion of intake in the evening has been associated with higher overall intake [114].

The associations between the time of day and total impact appear to be macronutrient specific, i.e., morning carbohydrate (CHO) intake is associated with reduced daily CHO intake and similarly for fat and protein. Recent work on the developmental origins of adult disease indicate that epigenetic mechanisms modulate structure and function at both the cellular and tissue levels, and reflect the food and nutrients available to the body as a whole and within the wider society and thus the potential for the growth and development of individuals [115].

As noted by others, given the short timeframe, the cause of the increase in obesity rates in the USA and globally is not due to an overall change in human genetics but rather to a change in environmental factors [29]. The typical (especially western but increasingly global) diet has changed greatly over the last 200 years or so – too quickly to be accompanied by a commensurate evolutionary adaptation – and this imbalance has resulted in associations between certain genetic polymorphisms and diet and increased CVD risk becoming more apparent [116]. But even a simple model of benefit and risk is difficult to interpret in terms of dietary advice to carriers of the many alleles associated with NCDs that are being identified, because of conflicting interactions between different genes, for example in the case of *n*-3 family of polyunsaturated fatty acids that are under-represented in the modern diet [116]. Similarly, although the extreme case of leptin not being produced because of a genetic fault has been known for a decade, it is only responsible for a very small number of cases, whereas for most overweight and obese people it is the result of a combination of many genetic variations with small effects [117].

It has been noted that the cardiovascular diseases (CVD) are a good example of complex and multifactorial disease caused by genetic, environmental factors and their interactions [116]. Currently the prevention of CVD is directed at modifiable factors such as waist circumference. However there are at-risk sub-populations genetically, e.g., the Pro12 Ala polymorphism of the PPAR γ gene that regulates insulin sensitivity and adipogenesis, and such populations may not respond to some such existing interventions. In the case for example of the leptin receptor (LEPR) associated with insulin resistance, diets low in plasma *n*-3 and high *n*-6 PUFAs status exacerbated the genetic risk of one of the polymorphic forms, but the associations were abolished by changing the diet to one of high *n*-3 and low *n*-6 [118].

23.7 Public Health Responses

Although the rise in the noncommunicable diseases, especially obesity and diabetes, seems to be inexorable, there have already been public health successes in addressing some aspects. Since the late 1970s, age-adjusted CHD mortality rates have been halved in most affluent countries (but not in the Middle East) although this decrease diminished in the 1990s [16, 19, 109, 119, 120] and nearly ceased in younger age groups [120]. This has been seen in young people in at least Australia, Canada, UK and USA, and particularly in low socio-economic populations [50, 121, 122]. While this has been attributed mainly to a reduction in smoking levels, it seems likely that dietary changes contributed, e.g., the reduction of saturated fats. Changing or modifying the environment in which these diseases develop, e.g., Mauritius and Poland, where changes in tariffs and taxes on foods high in saturated fats had the unplanned effect of lowering cardiovascular disease risk [17]. In countries in which dietary changes have largely not been made, such as Scotland, the prevalence has change little. Similarly in the countries of the previous Soviet Union have shown, if anything, a marked increase in the incidence of noncommunicable diseases, leading to actual decreases in life expectancy (although excessive alcohol is thought to play a large role in these countries).

Public health responses to the global epidemic of other nutrition-related noncommunicable diseases, apart from these early successes with coronary heart disease risk starting in the 1960s [19], have had relatively limited success, especially with obesity and diabetes in constraining the global rises in prevalence. Not all CVD risk factors are modifiable such as age, sex, and family history (genotype) whereas diet and alcohol intake, along with smoking, physical activity, and the intermediate risk factors of hypertension, blood lipid profile, glucose intolerance, and overweight and obesity can be modified by lifestyle or pharmaceutical intervention [116]. Children are a relatively new target population but efforts to prevent overweight and obesity in this group build on a poor record of success with adults, especially in sustained weight loss or changes in behavioral patterns. Singapore has some success with a national program against obesity in children but which would not necessarily be applicable in cultures more concerned with free trade and personal freedoms than public health [123]. The on-going discussion has been between the relative importance of individual behavior and unhealthy environments although it is probably an unnecessary argument, as it would seem self-evidently not to be a matter of either/or but requiring modifications to both, as well as societal change. As has been briefly discussed, in both affluent and poorer countries, any reductions in incidence are certain to be cost-effective given the growing dimensions of the problem, and the lifelong negative impacts. This is especially true when symptoms and signs appear in childhood as increasingly is happening with obesity, diabetes, and hypertension. There are also considerable psychosocial and cultural impacts. So far, it has not proven possible to quantify the size of the role of dietary changes alone in reducing NCD risk [124]. However, extensive changes in people's attitudes and beliefs, and marked shifts in the more affluent sections of most societies, and significant changes in foods available in supermarkets such as high fiber, low fat, and low glycemic foods, have been documented.

The background paper for WHO clearly identified the evidence for public health interventions and recommended that the evidence suggested this should be done throughout life, including maternal health and nutrition, in a life-course approach [16]. The background paper concluded that the evidence showed, even at that time, that the risk of disease is influenced by factors at all stages of the life course; that life course influences are disease specific, but that there is considerable overlap of risk factors, outcomes and influences; and that life course impacts on disease are population specific – reflecting social, economic, cultural, nutritional, and probably ethnic differences [16]. The range of interventions available are broadly: (1) individual behavior change programmes; (2) dietary change – therapeutic, national and cultural and nutraceuticals; (3) unhealthy environments and society, including the role of inequalities; (4) role of the food and soft drink industries, as well as legal issues and the role of recent food price rises and agriculture; and (5) global issues.

Individual behavior change, including dietary restrictions and modifications can clearly work on an individual level but it is not always clear why it works for some, and not for others – the majority. Even when weight loss is successful, sustained weight loss is poor, except for some highly motivated individuals [125]. As a public health approach, it has not been successful. In relation to the promotion of physical activity Cobiac, Vos, and Baredregt [126] make the statement “...substantial variability in quantity and quality of evidence on intervention effectiveness, and uncertainty about the long-term sustainability of behavioral changes...” and this would seem to have wider applicability from the experience for dietary change so far. Treatment of childhood obesity by retraining with a feedback device has shown significant improvement in reducing body fat and HDL cholesterol in a randomized controlled trial as an adjunct to standard lifestyle modification [127]. Despite an enormous industry around weight loss and diet foods, and a recent spate of “reality television weight loss” shows, the prevalence of overweight and obesity continues to grow in all countries (with the possible exception of some very resource-poor countries in Asia and sub-Saharan Africa) and especially in poorer communities in transitional and more affluent countries.

The food industry has consistently emphasized the individual's need to change their behavior while high energy, foods have become increasingly cheaper, more ubiquitous, and in ever larger helping sizes, which makes such change increasingly difficult. One reason to tackle the problem early in the life course, or even during maternal care, is demonstrated by the experience of New York City when it introduced calorie (dietary energy) information in fast food restaurants; about half of those surveyed reported noticing the information but in only a quarter of these consumers did it actually affect their choice- and even those who said it did, they did not actually purchase foods with lower energy content, and most reported being more interested in getting cheap, fast food [128]. Another study in the same city found that only 0.1% actually looked at the available calorie information at the various popular "fast food" food chains targeted [129]. An Australian survey [34] found that only 6% of children were eating the recommended five or more servings of vegetables a day and more than a third of the population had had no exercise at all in the fortnight before the survey. In the UK, Lobstein [130] has noted a consensus exists on what a healthy diet should look like, but that the last national dietary survey, conducted in the UK in 2001, showed that only less than 1% of adults were meeting all five dietary targets at once of the government's dietary guidelines for fat, saturated fats, sugar, salt, and fruit and vegetables. A British Heart Foundation survey found that nine out of ten mothers misunderstood the nutrition information on children's food packaging and in a socio-economically deprived community in the USA, misunderstandings leading to inappropriate diets were common [131].

Much of the above suggests that relying simply on individual behavior change will be insufficient, especially for obesity, and that factors beyond the individual must be addressed [132]. Consequently there have been many calls for changes in the "obesogenic environment" [26, 36, 132, 133]. Global analysis has identified that it is a relatively modest number of risk factors that are responsible for a substantial portion of mortality and disease burden [15]. The authors concluded that targeting a handful of dietary, lifestyle, and metabolic risk factors has a large potential for impact but that the distribution of risks did vary across global regions as did risk factor levels in relation to economic development and urbanization and that there is therefore "a need for national, and even subnational, analysis of the health consequences" [15] and therefore tailored interventions [15, 18]. They go on to suggest that combinations of food industry regulation, pricing and better information (although this last does not seem to be supported with experience thus far) can be effective in reducing exposure to dietary salt and trans fatty acids, especially in prepared meals and packaged foods and snacks [15]. While fiscal measures, such as taxing unhealthy foods, have so far proved unpopular, especially in the USA, an alternative that has been suggested would be to subsidize production or sale of food according to public health benefits. It has been repeatedly noted, including by Lock et al. [134] that healthier food crops such as fruit and vegetables receive little government support in either the EU or USA [135, 136].

Risk can be reduced by targeting high-risk people and by targeting risk in the entire population [5] and WHO recommends a preventive strategy that blends synergistically an approach aimed at reducing risk factor levels in the population as a whole with one directed at individuals at high risk [18]. Social and political issues then become important, as well as issues of access. An example is the effect of public health insurance for the poor in Mexico which led to increased access to health and better blood glucose control and some indication that also improved management of some other chronic diseases although long-term effects are not yet known [137]. Other suggested recommendations have included those from the CDC (Centers for Disease Control and Prevention in the USA) proposed strategy and others, is to increase the availability of supermarkets in underserved areas because of the evidence that the availability of healthy foods is better and cheaper in supermarkets than in small stores [57], improving access to public transport, requiring physical

education to be part of the school timetable, and increasing the availability of affordable, healthy, and small-portion-sized food and drinks in public venues. A report from Australia by the National Preventative Health Taskforce suggests, among 74 other recommendations, phasing out the promotion of energy-dense, nutrient-poor food on television before 9 p.m. over the following 4 years and that healthy foods could be taxed less to make them more affordable [62]. The most recent WHO Executive Board in 2010 proposed guidelines for marketing to children, partly because voluntary measures have failed to satisfy many.

Because weight gain in both children and adults is associated with sugared beverage intake [138, 139], decreasing sugar-sweetened beverages has been found to significantly decrease BMI among overweight children, especially girls in Brazil, the UK, and USA and can be done through schools [140]. Nevertheless it is difficult to achieve changes in dietary habits of children and adolescents, although helped when there is increased availability of fruits and vegetables, as well as nutritional information [141]. It has also been noted that environmental factors in food and beverage intake and choices differs between adolescents and adults [27], with implications for public health interventions in terms of targeting.

Price has been found to be an important factor in shaping people's diet. Over the past few decades, highly sugared and carbonated products have become relatively less expensive, while fresh fruits and vegetables have become relatively more expensive [29]. It has been frequently suggested that a substantial soda tax would probably be the single most effective way we could reduce obesity but has been actively resisted by the industry. In the USA, one company analysis showed that "a 12% increase in price led to a 15% reduction in consumption" of its product [29]. A review of 160 studies found price elasticities for foods and nonalcoholic beverages ranged from 0.27 to 0.81, with food away from home, sweetened soft beverages, juices and meat being most responsive to price changes, for example a 10% increase in soft drink prices should reduce consumption by 8–10% [142]. Furthermore, a tax on soda drinks of 1 cent a liquid ounce has been estimated by the CDC in the USA to generate \$US100 to \$US200 billion over the next 10 years. In the UK, nearly every food item has been affected, although to different extents. Food prices have followed the investment process, the real price, after adjusting for general inflation, of fruits, vegetables, and fish has increased steeply over the past 2 decades whereas the price of soft drinks, snacks, and take-away food has fallen. Vegetable oils, starches, and sugar have remained relatively cheap on global markets, even as overall food prices have risen [143]. As Lock and colleagues [134] show the trends are towards greater provision of less healthy foodstuffs, which they suggest means "that the most nutritious foods may soon sit only on the tables of the rich."

Nevertheless, many, especially in the USA believe the food industry needs to be an essential part of any public health effort against obesity because unlike tobacco, food is necessary, while also arguing for a public policy role by Government [136]. Also, most of the food that most people eat, now that over half the World's population is urbanized, comes through the private sector. However, this does not mean many of the same public health measures used in the attempted control of the tobacco industry cannot be effective [144]. There are already moves within the food manufacturing and the fast food industry to offer healthier alternatives, smaller portions, and products that do not include trans-fatty acids. A recent review of the effect of rising food prices on diets found that generally, prices of energy dense foods, such as soft drinks and snack foods, where most of the value is introduced in processing and marketing, have been more resistant to rapid rises in commodity prices than unprocessed foods (and that these price increases of basic foods have usually been passed on rapidly to consumers through higher retail prices) [135, 143, 145].

If only individual behaviors are considered as suitable for interventions, then other opportunities will be lost. With the increasing globalization of food and eating habits, individual behavior change

needs to be supported by national promotive activities and legislation, and global measures. On a larger scale than public health as generally considered, Lock et al. [135] have described how agricultural subsidies, while generally not large enough to influence consumer demand directly (as their effect is diluted by costs of manufacture, distribution, and marketing), they do have significant effects at producer level [146]. Case studies from Brazil, Chile, and Colombia show that changes in agricultural policies and production were linked to shifting consumption patterns of soya bean oil, meat, and fruit that influenced risks of noncommunicable disease [147]. Agricultural subsidies have affected diet quality worldwide through promoting production of high fat, energy dense foods. Support for corn and soya bean has made ingredients such as high fructose corn syrup and partially hydrogenated oils ubiquitous in industrial food production. They have little nutritional value and are used only for flavoring or extending shelf life. Although this may lead to cheaper processed foods, ingredients such as trans-fatty acids significantly increase cardiovascular disease risk [78].

WHO has built on the increasing number of national experiences and the vast amount of new research, especially since the late 1990s, to develop policy with its Member States. Partly as a result of policy recommendations, many countries now have national policies on noncommunicable diseases prevention and control and on diet, physical activity, and chronic disease [4, 18]. Because of perceptions that global food policy was the outcome of dealings between highly financed food and trade corporations on the one side and the intergovernmental agencies such as the United Nations Food and Agriculture Organization, the World Health Organization, and the World Trade Organization on the other [143], increased transparency and documentation allowing exposure to challenge and accountability has been increased [63]. But as WHO found after the release of the 2003 Report, this process can also be used to hinder adoption of evidence-based recommendations [63]. The challenges in making changes at the local, state, or national levels are clearly both political and operational. It was the concreteness of the recommendations (compared with those of the 1989 Study Group) as much as the actual values and ranges that caused the response (Table 23.1) [17, 63].

Since then, largely through the mechanism of the annual WHA (and the Executive Board that proceeds it), the report has been the background evidence base for the Development of a Global Strategy on Diet, Physical Activity and Health in 2004 with a series of recommendations. In 2007, the World Health Assembly asked that the Prevention of the Global Strategy for the Prevention and Control of NCDs be put into more concrete action. In 2008, the WHA endorsed the Action Plan for 2008–2013 [18] with its six objectives, performance indicators and with a particular focus on low- and middle-income countries and vulnerable populations. The Action Plan for the global strategy for the prevention and control of noncommunicable diseases has suggested that all member states implement the actions, plus others as appropriate, recommended in the Global Strategy on diet, physical activity, and health by developing national policies and action plans – implementing the food-based dietary guidelines report and in particular reducing salt levels, ensuring optimal feeding for infants and young children, including exclusive breast-feeding for first 6 months of life, eliminating industrially produced trans-fatty acids, decreasing saturated fatty acid intakes and limiting free sugars [18]. They also suggest all countries develop frameworks and mechanisms to promote responsible marketing of foods and beverages to children on the assumption this will reduce the impact of foods high in saturated fats, trans-fatty acids, free sugars, or salt [18]. The strategy also promotes increased physical activity, reducing the harmful effects of alcohol and promotes tobacco use control. Surprisingly it does not mention the nutrition of women likely to become pregnant or the diet and health of pregnant and lactating women. This strategy and action plan is intended to complement the Global Strategy on Diet, Physical Activity, and Health which now has at least 30 countries (Member States) implementing policy options recommended by the Global strategy, with other countries with policies that are consistent with much of it [4]. Objective three of the NCD Action Plan, e.g., is: “to

promote interventions to reduce the main shared modifiable risk factors for noncommunicable diseases: tobacco use, unhealthy diets, physical inactivity and harmful use of alcohol” [4].

23.8 Benefits of Early Nutrition Interventions in Preventing and Managing Noncommunicable Diseases

The effect of diet on human health has been reported in many epidemiological, population-based and randomized clinical trials, and while difficult to quantify the specific impact there appears now ample evidence that a dietary pattern rich in some beneficial food groups such as fruit and vegetables, whole grains and fish is associated with a reduced incidence of cardiovascular and neoplastic disease [72]. There are many scientifically valid reasons why interventions should be early and intense, addressing all ages and at a personal and clinical level, as well as nationally and probably globally. The reasons why this might be so, emerge from the review above. The strands that weave together include influences of genetics and nutrigenomics, impact of maternal nutrition and health, foetal environment, impact of weight gain throughout childhood and especially in the first 2 years of life, tracking of noncommunicable disease measures throughout life, ability to affect outcomes throughout the life course and increasing longevity [148]. As a Lancet editorial has pointed out, a century ago, 1 in 20 people worldwide was over 65 years of age whereas today it is one in six and by 2051 expected to be one in four [40] – these figures have enormous implications for prevention that must be done throughout the life-cycle and also addressed to the new elderly as a group who will also live longer in most societies, than ever before [16, 149]. It also notes that half the world’s over-65 population lives in Asia, which given the high levels of noncommunicable diseases in these countries, especially South Asia, will also have worldwide repercussions. Increasingly, the preponderance of older people will be living in poor and middle-income countries [149].

The earlier review for WHO, noted that interventions should be early (prenatal) and consistent over the life-course [16]. The actual interventions will depend on age, social circumstances, culture and resources, at the very least. Among others are that NCD outcomes can be influenced in early childhood, foetal development, and given the role of gestational diabetes, even before that in the development of overweight in potential mothers. Findings of a relationship between prenatal growth and risk-specific cancers, metabolic disease, and CVD suggest that early life environment is a causal component in the etiology of these conditions [150, 151] and so important implications for a life course approach [16, 152]. Risk of specific diseases may reflect the nature and/or magnitude of the environmental exposure during early life and it is suggested that the magnitude of a maternal nutritional challenge and the relative amount of specific nutrients in the maternal diet induce directionally opposite changes in the physiology and epigenotype of the off-spring [150].

Another reason is that whereas dietary patterns do change, they are heavily influenced by socio-economic status, including within populations. In a investigation of trends in dietary patterns and compliance with WHO recommendations in OECD and low to middle income (including 43 “least-developed”) countries, it was found that whereas there has been significant improvements in adherence to WHO goals for both developing and especially OECD countries, there has been no improvement for the least developed countries [22]. This re-enforces findings on the double burden of malnutrition as the distribution of the rising burden of diet-related chronic diseases is occurring globally, and more rapidly in poorer countries but also in rich countries – food insecurity associated with chronic disease has been described in low-income NHANES participants in the USA [153]. The findings also suggest that socio-economic drivers are more relevant than socio-cultural factors in

determining healthiness of diets [22], not to mention availability and accessibility to adequate and healthy foods. Within countries, the observed levelling of mortality decrease from CHD in young adults, and the rise in other NCDs in the poorer socio-economic groups cannot be addressed without improving social inequalities [154].

The WHO background paper concluded with seven conclusions [16]; to which should now be added, the increasingly evident role of the genotype, the difficulty of having an impact on obesity, and the bewildering amount of new information on all sorts of dietary constituents and their specific impacts. Another major factor will be the increasing commercial opportunities, such as weight loss clinics and nutraceutical foods by the private sector, and the increasing realization by Governments of potential savings to stretched health budgets by early intervention. The earlier conclusions were:

- Unhealthy diets, physical inactivity and smoking are confirmed risk factors.
- The biological risk factors of hypertension, obesity and dyslipidaemias are firmly established as risk factors for coronary heart disease, stroke and diabetes.
- Globally risk factor trends are rising, especially obesity, and in the low and middle-income countries especially, smoking.
- The major biological risk factors emerge and act early in life, and continue to have a negative impact throughout the life course.
- They can continue to affect the health of the next generation.
- An adequate and appropriate postnatal nutritional environment is important.
- Interventions are effective but must extend beyond the individual risk factors and continue throughout the life course.

23.9 Conclusions

The evidence supports a dietary approach along with attention to physical activity and other lifestyle changes. However the extent to which diet alone contributes to demonstrated national impact of noncommunicable diseases prevention programming, on a population basis, is less clear [124] although it seems clear that the consumption of fruits, vegetables, whole grains, and reduced fat dairy products protects against noncommunicable diseases risk factors, including insulin-resistant phenotypes [43].

What has emerged in the 7 years since the WHO report on diet, physical activity and chronic disease is that: The evidence for most known risk factors gets stronger, although somewhat modified in the case of fats; that public health programs can work, although with little evidence that this is true for obesity, and maybe diabetes; and, that public health programming around diet and the prevention of noncommunicable diseases is increasingly complex. The role of genetics and nutrigenomics has further complicated the picture suggesting that over time, there may be a need for more nuanced, and targeted, interventions according to genotype. Nevertheless, environmental actions to allow for increased physical activity and increased consumption of fruits and vegetables remain universal recommendations. The environmental considerations of some of the recommendations, on the global fish catch, e.g., have been touched upon by FAO in the 2003 report, but in nothing like the detail needed. McMichael and others continue to point out the impact of environmental change on health [106]. The commerciogenic and globalization aspects remain to be addressed satisfactorily, although there is some evidence of a greater perception of need for individual, private sector and public sector behavior change. However, it has also become clear this is more difficult than presumed, not least in children, and especially with obesity.

At the very least, reductions along the lines of the WHO recommendations should be strongly promoted, and including strong emphasis on a dietary or food-based approach seems the most useful, e.g., the Mediterranean-type diet [67] and some traditional Asian diets. An important consideration is that the more equally wealth is distributed, the better the health of that society [155]. Deliberate interventions to reduce inequalities in health through modification of major risk factors have had limited success to date for the poorer proportions of most societies. The alternative is to tackle both the social inequalities themselves and to shift lifestyle choices by promoting changes away from the current obesogenic environments of most countries. At the same time, policies that promote good nutrition and healthy diets as early interventions in diabetes, cardiovascular and other noncommunicable disease, based on the increasing evidence, will save both lives and money, if pursued at the national level.

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Chapter 24

Cost-Effectiveness of Glycemic Control

Economic Considerations with Lifestyle Modification Versus Pharmacologic Therapy in Achieving Glycemic Targets in Type 2 Diabetes Mellitus

Emily Knezevich, Jennifer Campbell, and Daniel Hilleman

Key Points

- Diabetes mellitus affects approximately 24 million people in America.
- Analysis of the economic cost of diabetes in the USA are an estimated \$174 billion.
- Type 2 diabetes results from numerous causes and most highly associated causative factors being lifestyle choices.
- Dietary and exercise practices can increase or decrease one's chance of developing type 2 diabetes.
- The cornerstones of preventing and treating type 2 diabetes, lifestyle modification and medication therapy, are aimed at maintaining optimal blood glucose levels.
- There is clear evidence of benefit that tight glycemic control decreases diabetes related complications and costs.
- Lifestyle modification is considered first line therapy for treatment and prevention of type 2 diabetes.
- The progressive nature of diabetes often requires the use of drug therapy to achieve glycemic targets.
- Tight glycemic control provides a cost effective means of reducing unnecessary health care expenses.
- Identifying ways to contain health care costs and obtain high value for our health care investments continues to be a priority.

Keywords Diabetes mellitus • Economic cost • Exercise • Glycemic • Lifestyle modification • Type 2 diabetes

24.1 Introduction and Background

Diabetes mellitus affects approximately 24 million people in America today with 90% or more of those being diagnosed with type 2 diabetes [1]. In its 2007 analysis of the economic cost of diabetes in the USA, the ADA reported that diabetes expenditures, both direct and indirect, were an

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estimated \$174 billion [2]. Type 2 diabetes results from numerous causes, with one of the most highly associated causative factors being lifestyle choices. Dietary and exercise practices can increase or decrease one's chance of developing type 2 diabetes. According to the American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists (AACE), the cornerstones of preventing and treating type 2 diabetes, lifestyle modification and medication therapy, are aimed at maintaining optimal blood glucose levels. There is clear evidence of benefit that tight glycemic control decreases diabetes related complications and costs. Lifestyle modification is considered first line therapy for treatment and prevention of type 2 diabetes. However, the progressive nature of diabetes often requires the use of drug therapy to achieve glycemic targets. With the growing epidemic of type 2 diabetes, tight glycemic control provides a cost effective means of reducing unnecessary health care expenses.

24.2 Introduction to Cost Effectiveness

Health care expenditures in the USA were approximately \$1.9 trillion in 2004 [3]. This figure is more than two and a half times greater than the \$717 billion spent in 1990 and more than seven times the \$255 billion spent in 1980. The USA spends a larger share of its gross domestic product (GDP) on health care than any other major industrialized country [4]. Expenditures for health care represent nearly one-seventh of the nation's GDP and continues to be one of the fastest growing components of the Federal budget. In 1960, health care expenditures accounted for about 5% of the GDP which had grown to 16% in 2004. Thus, identifying ways to contain health care costs and obtain high value for our health care investments continues to be a priority.

In its 2007 analysis of the economic cost of diabetes in the USA, the ADA reported that diabetes expenditures, both direct and indirect, were an estimated \$174 billion [2]. \$116 billion alone was spent on direct medical costs including hospital care and medications [2]. The ADA estimates that productivity lost due to diabetes cost the US \$58 billion [2]. The actual cost of diabetes, however, is believed to be much higher because some costs could not be accurately estimated, such as the services of unpaid caregivers. In addition, there was insufficient data available to evaluate whether people with diabetes had more dental and eye care services [2].

Given the current health care economic environment, studies designed to evaluate the economic impact of glycemic control in diabetic patients are important. The results of these studies should be used to guide the selection of the most cost-efficient means of achieving glycemic targets in diabetic patients. The purpose of this review is to briefly describe the pharmacoeconomic methods that can be used in these studies and to summarize the results of published economic analyses of diabetic treatments.

24.3 Pharmacoeconomic Principles

The discipline of pharmacoeconomics has been developed and refined over the past two decades. Pharmacoeconomics is a process in which the costs, risks, and benefits of medical therapies are identified, measured, and compared [5]. The primary goal of pharmacoeconomics is to determine which therapy produces the best health outcome for the resource invested.

The most commonly used pharmacoeconomic study methodologies are summarized in Table 24.1. Cost of illness studies identify and measure the overall cost of a disease in a specific population.

Table 24.1 Pharmacoeconomic study methodologies

Methodology	Description
Cost of illness	Costs of a disease in a specific population is determined; assessment of treatment effectiveness not made
Cost minimization	Determines the least costly treatment for a specific condition; assumption is that the treatments produce identical outcomes
Cost-effectiveness	Determines cost per unit of effectiveness; cost per life year gained is a benchmark
Cost-utility	Adjusts life-years gained by a utility factor (quality of life assessment); determines cost per quality-adjusted life year gained
Cost-benefit	Health outcomes measured in monetary units

Cost, as discussed later, can include both medical and non-medical costs. Effectiveness or outcomes of treatment interventions are not determined in a cost of illness study. Cost-minimization studies are performed when comparing two or more treatments that are assumed to produce equivalent outcomes. The costs of delivering the treatments to patients are compared with the lowest cost treatment being preferred as efficacy and safety (by definition) are not different among the treatments. This type of methodology is infrequently used as it is often difficult to assume or demonstrate that two treatments will produce an identical outcome in terms of efficacy and safety.

Cost-effectiveness studies determine a cost per unit of therapeutic outcome. When mortality is evaluated, cost-effectiveness studies report the cost per life year gained. Cost-effectiveness is determined using the following equation:

$$\text{Cost – effectiveness} = \frac{\text{Cost (\$) Treatment A} - \text{Cost (\$) Treatment B}}{\text{Mortality (\%) with Treatment A} - \text{Mortality (\%) with Treatment B}}$$

By convention, interventions with cost-effectiveness ratios of \$35,000 per life year gained or less are considered to be cost-effective [6]. Any unit of effectiveness can be used in a cost-effectiveness analysis (i.e., cost per mg/dL reduction in blood glucose, cost per successfully treated patient, etc.). Cost-utility analyses take cost-effectiveness studies one step further by adjusting life-years gained according to changes in quality-of-life. Patient perceptions about their quality-of-life are measured using survey instruments. The quality of life determination is referred to as a “utility.” In utility assessments, quality of life is scored as a single number from two extremes of health, 0.0 for death and 1.0 for perfect health. Hence, a utility is expressed as a percentage of perfect health. For example, if a treatment extends life by 5 years and the utility associated with the treatment is 0.8 (80% of perfect health), the quality adjusted life years gained is 5×0.8 or a quality adjusted life year (QALY) gained of 4.

Cost–benefit analyses assign dollar values to health-outcomes. In this type of analysis, health benefits are reported in monetary units. If mortality is assessed, a dollar value has to be assigned to a human life. The most common method of assigning value to a human life is the human-capital method which values life based on the individual’s contribution to society in terms of income or income minus consumption. Although used in insurance and legal arenas, there are obvious ethical concerns about using this approach to assist in making health-care related decisions. Cost-benefit analysis has been used to evaluate the benefit of vaccination programs such as the use of an influenza vaccine in a healthy population [7]. The costs of the vaccine, the lost productivity associated with the clinic visit to administer the vaccine, and the occurrence of side effects associated with the vaccine are determined. These treatment costs are then compared with the cost associated with lost productivity in the population due to lost work days secondary to the occurrence of influenza. If the costs of lost productivity are greater than the cost of treatment, the vaccination program would be considered cost-beneficial. Using a cost-benefit method makes sense in this situation as the mortality rate for influenza in an otherwise healthy population is generally quite low.

Table 24.2 Types of health care costs

Types of cost	Examples of costs
Direct medical	Medications; laboratory tests; clinic, emergency room, and hospital visits; professional fees
Direct non-medical	Transportation to health-care facilities; hotel stays near hospital for family members; meals for family members staying near hospital; family care (babysitter) while in hospital
Indirect non-medical	Lost wages of patient; lost wages of family members caring for a sick family member; loss of future income due to premature death
Intangible	Pain; suffering; grief

Cost determination may be the most challenging aspect of pharamcoeconomic studies. Costs are typically categorized as direct medical, indirect medical, indirect nonmedical, and intangible (Table 24.2) [5]. Direct medical costs are those that can be directly measured and result specifically from resources used to prevent, treat, or diagnosis disease. Direct nonmedical costs result from disease, but are not used to purchase medical services. Examples of these types of costs include transportation to hospitals or clinics, costs of hotels for family members staying near a hospital, etc. Indirect nonmedical costs are related to lost productivity (lost wages) due to illness. Intangible costs are also a direct result of disease, but cannot be easily converted into monetary units. These include pain, suffering, and grief. Attempts to quantify these are carried out in quality of life assessments.

Determining costs of health-care resources is challenging as charges for medical services are inflated and do not reflect the actual costs of such resources. For some health care resources such as medications and supplies, the actual costs of purchasing these items can be directly determined either at the institutional level or by using national pricing databases [8]. For other health care resources such as laboratory tests, diagnostic tests, and therapeutic procedures, multiple costs may be involved in providing these services which would include the personnel needed to carry out the test or procedure, reusable (capital intensive) equipment, and disposable supplies. Estimates of the costs for these types of resources, as well as for the costs of clinic and emergency room visits, can be derived from Current Procedural Terminology (CPT) codes and Medicare's Resource Based Relative Value Scale (RBRVS) reimbursement schedule [9]. Although the resultant values are in fact not costs, they do represent what is considered fair market value for these services.

For determination of hospitalization costs, two approaches are most commonly used. Hospital charges for a specific patient stay can be directly identified from the Universal Billing Form (UB) 82/92. These charges can be converted to costs using institutional or departmental Medicare cost-to-charge ratios [10]. The other common approach for determining costs of hospitalization is to use the Healthcare Cost and Utilization Project (HCUP) nationwide inpatient sample (NIS) database [11]. Diagnosis related groups (DRGs) can be identified in the HCUP NIS and charges for patients with a specific DRG can be identified. Those charges are converted to costs using the Medicare cost-to-charge ratio. The HCUP NIS data does not include professional fees. The use of the HCUP NIS is less accurate in determining a specific institution's cost of hospitalization compared to the use of the UB 82/92 approach, but it may be a more accurate reflection of national or regional hospitalization costs for a specific DRG. In addition, the use of UB 82/92 data can be cumbersome as large numbers of patients would be needed to determine an overall average cost for a specific disease state. This is not a concern when the HCUP database is used.

24.4 Lifestyle Modifications

The most recent consensus algorithm from the ADA and European Association for the Study of Diabetes (EASD) reports that "effective weight loss, with its pleiotropic benefits, safety profile, and

low cost, should be the most cost-effective means of controlling diabetes – if it could be achieved and maintained over the long term [12].” A significant trial that compared lifestyle modification against drug therapy in the prevention of diabetes was the Diabetes Prevention Program (DPP) [13]. The DPP study overwhelmingly demonstrated that making changes in lifestyle habits greatly outweighs the benefits seen with standard medication therapy including the commonly prescribed first-line agent metformin.

There is widespread agreement that lifestyle modification is a necessary component of any therapeutic plan for patients with type 2 diabetes. However, some variance has been seen in the type and extent of lifestyle changes required for a substantial reduction in risk of developing diabetes. In the DPP trial, lifestyle modifications consisted of both an exercise and diet prescription. Patients had to partake in 16 counseling sessions with their case-manager in the first 24 weeks of the study. These sessions included instruction in diet, exercise, and behavior modification. Changes were recommended based on goals developed for each patient enrolled in the study. Patients were expected to lose at least 7% of their body weight through reduction of fat intake by 25% and an increase in physical activity to more than 150 min weekly. These changes resulted in a 58% relative risk reduction (RRR) compared to “usual care.” Patients receiving drug therapy alone had a substantial decrease in risk (31%), but that reduction in risk was not greater than that achieved by lifestyle modification. Similar reductions in relative risk have been observed in other trials evaluating similar endpoints [14].

The mechanism of why lifestyle modifications producing weight loss reduces the development of diabetes and its complications is best understood through a review of the pathophysiology of diabetes itself. Type 2 diabetes has multiple mechanisms explaining the resultant rise in blood glucose including reduced insulin secretion, decreased insulin utilization (or insulin resistance), and increased glucose production [15]. Weight gain, particularly visceral, is often seen with type 2 diabetes. This can decrease the body’s ability to effectively utilize insulin to move glucose from the bloodstream into cells to use for energy. This process results in a hyperinsulinemic state which ultimately leads to insulin deficiency after pancreatic beta cells are exhausted and resultant elevations in postprandial blood sugar due to an inability to control hepatic glucose production. The exact mechanism of why obesity worsens insulin resistance is unclear. It is believed that an increased adipocyte mass may result in increased circulation of free fatty acids and other modulators of insulin sensitivity. Elevations in free fatty acids may also impair glucose utilization in skeletal muscle, worsen beta cell function, and increase hepatic glucose production [15, 16].

Excessive adipocyte mass being the major known cause of insulin insensitivity leading to type 2 diabetes has led practitioners to encourage patients at risk for developing or who have currently developed diabetes to seek the expertise of a registered dietician (RD) to help educate them in the principles of medical nutrition therapy (MNT). Most insurers, including Medicare, cite MNT sessions as a covered benefit for patients with type 2 diabetes. Knowledge of MNT is a key to the prevention and progression of long term complications associated with the disease. According to the American Association of Diabetes Educators (AADE), a MNT session performed by a RD has the following goals: (1) encourage regular physical activity and weight loss in the overweight population to reduce risk of type 2 diabetes and cardiovascular disease; (2) prevent and treat chronic complications through attainment of metabolic goals (blood glucose, A1c, lipid levels, blood pressure, and body weight); and (3) enhance knowledge and ability of patient to make healthy dietary and physical activity choices [17]. Intervention by an RD using MNT demonstrates not only an improvement in glucose control (1–2% improvement in hemoglobin A1c levels), but also an improvement in lipid profiles, weight management, adjustment in medications, and lower rates of progression of comorbidities [18].

MNT has no standard requirements regarding the design of each session. Each session should be tailored specifically to the individual patient’s need. There are, however, recommendations for general topics that patients should be made aware of. These include, but are not limited to weight

loss through an increase in physical activity or reduction in high calorie, fat, and carbohydrate containing foods and a discussion of social habits (alcohol and tobacco) and nutritional supplements taken [19]. Diets high in total and saturated fat have been proven to decrease insulin sensitivity and are consequently recommended to be removed from the diet. Conversely, an inverse association between consumption of polyunsaturated fat and the development of diabetes has been reported resulting in the recommendation to incorporate these fats into the diet instead of saturated fats [20]. Increasing fiber in the diet is a common recommendation for dietary prevention of many metabolic conditions, including type 2 diabetes. It has been established that increased levels of dietary fiber delay absorption of carbohydrate following a meal, likely resulting in a more efficient ability of the body to process glucose from food. Foods high in fiber and low in saturated fats such as whole grains, certain cereals, fruits, vegetables, and low-fat dairy have been shown to cause less of an increase in blood glucose than those that may be considered a “simple sugar” lacking nutritional value. These types of foods are recommended as optimal carbohydrate sources for people with type 2 diabetes [19].

Both aerobic and resistance training have been tested as lifestyle modifications in patients with type 2 diabetes. Current recommendations describe a need for at least 150 min/week for aerobic exercise and encourage resistance training at least three times weekly if the patient is capable. Properly conducted exercise regimens have been shown to result in up to a 0.7% reduction in hemoglobin A1c independent of body mass index (BMI). Exercise should only be recommended after evaluation of a patient’s ability to safely perform prescribed exercise activities [19].

In addition to nutrition therapy, patients with type 2 diabetes should be provided with Diabetes Self Management Education (DSME) to supplement their dietary plan. DSME is also a covered benefit as determined by the Centers for Medicare and Medicaid (CMS) and can be provided by a number of health professionals including dietitians, nurses, pharmacists, physician’s assistants and others as long as they are qualified and have a background in diabetes education and management. DSME has been proven in numerous clinical trials to have similar improvements to MNT when comparing metabolic outcomes (lipid levels, blood pressure, A1c) [19]. The AADE has developed seven self-care behaviors that are reviewed during a typical DSME session (Table 24.3). They include: being active, healthy eating, taking medication, monitoring, problem solving with blood glucose levels, reducing risks of diabetes complications, and healthy coping for psychosocial adaptation to the disease. Each session, similar to MNT, must be individualized to each patient receiving counseling to maximize their efficacy. Goals regarding the patients’ abilities to achieve self care habits should be identified and assessed in a timely manner.

In addition to MNT and DSME, oral hypoglycemic therapy initiated early in the treatment of type 2 diabetes has more recently been recommended. A consensus statement from the ADA and EASD recommends early initiation of metformin after diagnosis of type 2 diabetes in conjunction with lifestyle modification [12]. This consensus statement reports failure of lifestyle interventions within the first year of treatment due to nonadherence and inability to maintain recommended behaviors,

Table 24.3 AADE 7 self-care behaviors

Healthy eating	Follow ADA recommended diet to maintain BMI < 25 kg/m ²
Increased physical activity	150 min aerobic activity/week 3 days of resistance training
Monitoring	Monitor food, activity and blood glucose as needed
Taking medication	As recommended by health care provider
Problem solving	To deal with barriers in reaching weight loss, activity, and glycemic goals
Healthy coping	To deal with stress and other emotions related to diabetes management
Reducing risks	To prevent long term complications through adhering to recommendations and follow up appointments

indicating a need for early adoption of pharmacotherapy to avoid target organ damage that may occur if glycemic goals are not obtained and maintained early in the course of disease progression. In addition, the consensus statement emphasizes the benefits seen with metformin, not only in A1c reduction, but also in reducing microvascular and macrovascular complications inherent to long standing disease as demonstrated in the United Kingdom Prospective Diabetes Study (UKPDS) [21, 22]. With any drug therapy, however, common adverse effects likely to be experienced must be anticipated. Contrary to lifestyle modification, drug therapy recommended in the current therapeutic algorithms have many potential adverse effects which may result in serious complications leading to hospitalization or even death if used inappropriately.

Despite the demonstrated efficacy and safety of lifestyle modification including a healthy diet and physical activity to promote weight loss, medication therapy is often necessary to obtain optimal glycemic levels in patients with type 2 diabetes. There are a multitude of barriers to the maintenance of lifestyle recommendations. In a survey received of 365 patients with type 2 diabetes, some of the most common causes for discontinuation of recommended lifestyle therapy were cost, portion size, family support, quality of life, confusion, emotional aspects, and difficulty during holidays or special occasions [23]. This survey concluded that patients felt even minor dietary changes were far more difficult to implement than initiation of oral pharmacotherapy [23]. This is not unexpected as taking oral medication often requires minimal changes in lifestyle to achieve glycemic targets while adherence to prescribed lifestyle modifications (diet and activity) are difficult to maintain. However, survey results did demonstrate that a weight loss diet was associated with a similar degree of difficulty compared to taking twice daily insulin injections which is one of the more difficult therapeutic methods for patients with type 2 diabetes to agree to initiate. The most common complaint of those surveyed was that diets often prescribed by educators tended to be unaffordable [23]. This represents the importance of individualizing MNT and DSME to each patient educated. In addition to cost barriers, weight loss attained to achieve glycemic lowering superior to that achieved with oral medications, required at least a 5% reduction in body weight which can be difficult for many people to achieve. Smaller weight losses are associated with less glucose lowering when compared to common pharmacotherapeutic treatments [23].

24.5 Cost Effectiveness of Glycemic Control

The cost effectiveness of glycemic control has been evaluated in several studies. The strongest evidence for the cost effectiveness of glycemic control comes from two prospective studies and a retrospective study. The DPP and the UKPDS evaluated the cost effectiveness of glycemic control in terms of clinical outcomes in their respective prospective studies [24–26]. Gilmer et al. performed a retrospective study which evaluated the cost effectiveness of glycemic control by comparing changes in percent A1c to health care expenditure [27]. Several additional studies provide further evidence of the cost effectiveness of tighter glycemic control through retrospective analyses of health care costs by level of glycemic control or through use of models to predict costs and cost savings of different treatments.

As discussed previously, the DPP study demonstrated that treatment with either lifestyle modification or metformin delayed or prevented the progression to type 2 diabetes compared to placebo. In addition, the study performed within-trial cost analyses which looked at costs of both treatments from a health system perspective, societal perspective, and in terms of QALYs gained compared to placebo. From the health system perspective, to prevent or delay one case of diabetes cost US\$15,700 and US\$31,300 for lifestyle modification and metformin respectively, compared to placebo [24].

From society's perspective the same treatments cost US\$24,000 and US\$34,500 for lifestyle intervention and metformin respectively, compared to placebo [24]. For each QALY gained, the lifestyle modification cost US\$51,600 and metformin treatment cost US\$99,200 [24]. An analysis of studies that included diabetes self management training and programs by Boren et al. found that as the DPP study suggests lifestyle modification may be affordable in clinical practice when group education and generic medications are used [28].

The UKPDS compared intensive glucose control with sulfonylureas or insulin to conventional treatment which was primarily based on diet [21]. The within trial economic analysis found that intensive glucose control with sulfonylureas or insulin was cost effective compared to conventional treatment [25]. In the economic analysis of the trial, time to first event was the primary measure of effectiveness. The incremental cost per event-free year gained was the primary measure of cost effectiveness [25]. The analysis found that the net trial costs per patient were not statistically significantly different between the intensive glucose control group and the conventional treatment group (£9,608 vs £9,869, respectively) reflecting the reduced cost of complications in the intensive glucose control group [25]. This reduced cost of complications balanced the cost of intensive glucose therapy. In addition, analyses found that in real world conditions, the cost difference between conventional and intensive glucose control therapies would not be significantly different (£7,871 vs £8,349, respectively) [25]. No statistically significant difference in cost was found in comparisons of separate analyses of costs per patient for conventional treatment versus treatment with insulin or sulfonylurea [25].

A substudy of the UKPDS compared intensive glucose control with metformin in overweight patients to conventional treatment, primarily diet [22]. This substudy also performed a cost analysis of metformin treatment compared to conventional therapy in overweight subjects [26]. Results of the analysis showed that glycemic control with metformin had a net savings of £258 per patient [26]. This was due to a reduction in complication associated costs as well as an increase in life expectancy [26]. The study found that much of the cost of complications was due to the cost of hospital stays. The conventional treatment group had a mean cost per patient per hospital stay of £4,632 compared with £3,317 for the metformin group. This was due primarily to shorter hospital stay per admission in the metformin group (8.0 vs 9.6 days for conventional therapy; 95% confidence intervals 0.2, 3.0). The metformin group also had fewer hospital admissions but the difference was not statistically significant [26].

Additional studies using models to predict costs and costs savings of different treatments provide further evidence of the cost effectiveness of tighter glycemic control. Using data from the DPP, Herman et al. simulated the lifetime costs and health outcomes to estimate the future cost effectiveness of lifestyle modification or treatment with metformin compared to placebo [29]. Their model demonstrated that compared to placebo both lifestyle modification and treatment with metformin decreased the absolute and relative risk of developing diabetes (20% vs 8%, respectively; and 24% vs 10%, respectively) [29]. In addition, compared to placebo, the cost per QALY was US\$1,100 and US\$31,300 for lifestyle modification and metformin treatment respectively [29]. The modeling demonstrated that both lifestyle modification and treatment with metformin continued to be cost effective.

Palmer et al. also used data from DPP to forecast cost effectiveness of lifestyle modification and metformin treatment in three European countries, the UK, and Australia. Their model found that both interventions increased the number of disease-free years and life expectancy. Lifestyle modification was more cost effective than metformin [30]. Cost savings per patient was €380 for lifestyle modification and €358 for metformin. Both treatments had an incremental cost effectiveness ratio of €17,900 per life year gained compared to placebo [30].

Jacobs van der Bruggen et al. found that lifestyle interventions were cost effective in preventing the onset of diabetes in subjects at low to moderate risk for developing diabetes [31]. The study modeled intervention costs using a chronic disease model developed by the Netherlands' National

Institute for Public Health and the Environment. Using the model, researchers can simulate how disease and disease risk develop over time in the Dutch population. Jacobs van der Bruggen et al. used two Dutch studies to capture intervention costs. The first study, Hartsлаг Limburg (Heart Health Limburg), was a community program designed to prevent cardiovascular disease in the overall population by focusing on nutrition and physical activity [31]. The second program was the Study on Lifestyle Intervention and Impaired Glucose Tolerance Maasricht which observed the effects of a 3 year dietary and exercise intervention program in subjects who had impaired glucose tolerance and were also overweight. The model found that both types of treatments decreased diabetes related lifetime medical costs. The community program was more cost effective in preventing one new case of diabetes (€1,800–9,000) compared to the intensive lifestyle program (€4,000–21,000) [31]. The cost effectiveness of the intensive intervention improves when unrelated health care costs (due to increased lifespan) are included [31]. Costs per QALY, with unrelated health care costs factored in, were €3,100–3,900 and €3,900–5,500 for the community program and intensive lifestyle modification respectively [31].

Furthermore, the study by Gilmer et al. also found strong evidence that glycemic control is cost effective. The study looked at the glycemic control and associated health care costs of 3,017 individuals with type 2 diabetes in a large health maintenance organization (HMO) [27]. The relationship between glycemic control and health care costs were estimated through regression analysis. The study found that higher A1c levels were associated with progressively higher medical costs [27]. Increases of 1% in A1c correlated with a 7% increase in expected health care costs [27]. In addition, complications such as heart disease significantly increased health care expenses. The analysis found that the mean 3 year cost for health care for a patient with only type 2 diabetes was \$10,439 [27]. If the patient also had hypertension and heart disease, the 3 year mean cost was \$44,417 [27]. The study also found that the cost reduction was statistically significant as the A1c fell from 10% to 7% [27]. Although the analysis did detect a reduction in cost when the A1c fell from 7% to 6%, it was not statistically significant [27].

Several additional studies provide further evidence of the cost effectiveness of tighter glycemic control through retrospective analyses of health care costs by level of glycemic control. Several studies have found that tighter glycemic control reduces diabetes related health care costs [27, 32–34]. A study by Testa et al. found that there were significant health economic benefits associated with improved glycemic control among patients with type 2 diabetes [32]. The study randomized 569 subjects with type 2 diabetes to treatment with placebo or glipizide for 12 weeks. The primary end points included changes in A1c and glucose levels from baseline, quality of life, and health economic indicators such as higher retained employment, productivity, absenteeism, bed days, and restricted activity days. The study found that the glipizide treatment group had significantly better outcomes in all areas. The glipizide treatment group had 97% retained employment versus 85% in the placebo group ($p < 0.001$) [32]. Economic losses due to absenteeism were significantly lower in the glipizide group (US\$24 per worker per month lost versus US\$115 per worker per month in the placebo group; $p < 0.001$) [32]. In addition, the interventional group compared to placebo also had fewer subjects who stayed home due to a diabetes related symptom (5.5% vs 8.4%, respectively; $p = 0.06$) which resulted in decreased economic losses (US\$1,539 lost per 1,000 person days vs \$1,843, respectively; $p = 0.05$), and fewer restricted activity days (28% vs 45%, respectively; $p = 0.01$) [32].

Two additional studies looked at the cost effectiveness of improved glycemic control [33, 34]. Shetty et al. did a retrospective analysis evaluating whether lower A1c levels were associated with lower health care costs in the short term, by comparing the health care costs of patients whose A1c levels were consistently $\leq 7\%$ to patients whose A1c levels were consistently $> 7\%$ over 1 year [33]. Using data from a large USA managed care organization (MCO) which provided physician, hospital, and pharmacy services, the study identified 6,780 patients with type 2 diabetes who had at least one

prescription for an oral antidiabetic medication or insulin and at least one A1c value. Patients with a claim for type 1 diabetes were excluded as were patients who had A1c levels that were both $\leq 7\%$ and $> 7\%$ during the study time period [33]. Forty-six percent (3,121) of the patients had A1c levels $\leq 7\%$ and 54% (3,659) had A1c levels $> 7\%$ throughout the study period. The study found that patients who maintained their A1c $\leq 7\%$ during the study period had higher baseline costs during the 6 months preceding the study period (US\$2,419 vs US\$1,911 for the above target group; $p < 0.001$) [32]. However, the total diabetes costs were significantly decreased in the A1c $\leq 7\%$ group compared to the A1c $> 7\%$ group during the study period (US\$1,171 per patient versus US\$1,540 per patient, respectively; $p < 0.001$) [33].

A study by Wagner et al. also found that stable improvement in glycemic control led to significant cost savings within 2 years of the improvement. The study looked at the health care costs and utilization over a 5 year period (1992–1997) of diabetic patients in an HMO [34]. The patients were divided into two groups based on their ability to sustain improvement in glycemic control (defined as a reduction in baseline A1c by $\geq 1\%$ that was maintained through the study period) [34]. The study found that while mean total health care costs decreased with improved glycemic control, the cost savings were only statistically significant for patients with improved glycemic control who had baseline A1c levels $\geq 10\%$ [34]. However, health care utilization by the patients with improved A1c decreased consistently over the study period with a statistically significant decrease in primary care visits starting in 1994 ($p = 0.001$) that was maintained throughout the study (1995, $p < 0.001$; 1996, $p = 0.005$; and 1997, $p = 0.004$) [34]. Additionally, the improved cohort significantly decreased health care visits to specialists by the end of the study (1997, $p = 0.02$) [34]. A limitation of the study, was that while the two study cohorts were similar demographically, the patients with sustained improvement in their A1c had significantly higher baseline A1c levels than patients who did not improve their A1c (10.0% vs 7.7%, respectively; $p < 0.001$) [34].

As the studies above demonstrate regardless of specific treatment followed compelling evidence exists for the cost effectiveness of glycemic control. Two prospective studies, the DPP and the UKPDS found glycemic control to be cost effective in terms of delaying or preventing clinical outcomes [24–26]. Several studies demonstrated that more intensive glycemic control decreased health care expenditure and utilization [26, 32–34]. Modeling studies predicting costs and cost savings of different treatments provide further evidence of the cost effectiveness of tighter glycemic.

24.6 Conclusion

Although lifestyle modification has been found to be both effective in preventing and treating type 2 diabetes, patients rarely maintain glycemic control with lifestyle modification alone. In addition to the numerous barriers patients face in sustaining lifestyle modifications, type 2 diabetes is a chronic progressive disorder that causes continuing worsening of glycemic control [12]. Over time, patients will require more intensive interventions (medications, higher doses, additional medications) to meet target glycemic goals [12]. The UKPDS found that only 56% of subjects randomized to conventional treatment (1,35) were still being treated with diet alone at the end of the study [21, 22]. It also demonstrated that 44% required additional medication to treat protocol defined hyperglycemia [21, 22]. The 10 year follow-up to the UKPDS found that after 5 years only 5% of the conventional treatment subjects were controlled on diet alone [35]. Once diabetes has been diagnosed, lifestyle modification and medication are both necessary to maintain target glycemic control and prevent morbidity and mortality.

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Chapter 25

Benefits of Low Glycemic and High Satiety Index Foods for Obesity and Diabetes Control and Management

Pankaj Modi

Key Points

- Cardiovascular disease risk may be reduced by consuming a low glycemic index diet.
- Studies have shown clients can successfully incorporate the glycemic index in their dietary routine with positive outcomes.
- Weight loss may be another benefit found with choosing low glycemic index foods.
- Diets with high glycemic impact have been postulated to increase risk of obesity, insulin resistance, diabetes and cardiovascular disease.
- A reduction in the glycemic impact of the diet has been proposed as a means of assisting body weight management, improving blood glucose control and reducing diabetes, cardiovascular and related risks.
- Safe choices for weight-loss regimens include energy restricted diets calculated according to the Therapeutic Lifestyle Change Diet recommended by the National Cholesterol Education Program, the diet recommended by the Heart Association.
- There is accumulating evidence that diets containing a lower level of fat and carbohydrates that elicit low glycemic responses (low GI foods or diets) cause important health benefits such as lowering total cholesterol and improving the metabolic control of diabetes.
- Long-term multicentre randomized intervention trials are needed to improve knowledge on these issues and to determine the contribution of diet, exercise, and metabolic and psychosocial factors to weight loss and weight-loss maintenance.

Keywords Cardiovascular disease • Diabetes • Fullness factor • Glycemic index (GI) • Glycemic load (GL) obesity • Insulin resistance • Satiety index

25.1 Introduction

America is so fat... two-thirds of US adults are officially overweight and about half of those have graduated to full blown obesity, according to data from the National Health and Nutrition Examination Survey (NHANES). New info from the Centers for Disease Control and Prevention (CDC) found in

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2007, only four states had a prevalence of obesity less than 20%. Twenty-two states had prevalence equal to or greater than 25%, in Mississippi and West Virginia, the prevalence of obesity was equal to or greater than 30% [1–20]. In the North America amongst kids 6–19 years old, one in six is overweight, and another 15% are headed that way [5, 6]. The studies have found overweight children and adolescents are more likely to become obese as adults, further weighing down the health care system with concomitant concerns with Type-2 diabetes, hypertension, hypercholesterolemia and more [11–14]. Even our pets need Jenny Craig! The National Academy of Science estimates one in four pets is overweight or obese (Figs. 25.1 and 25.2).

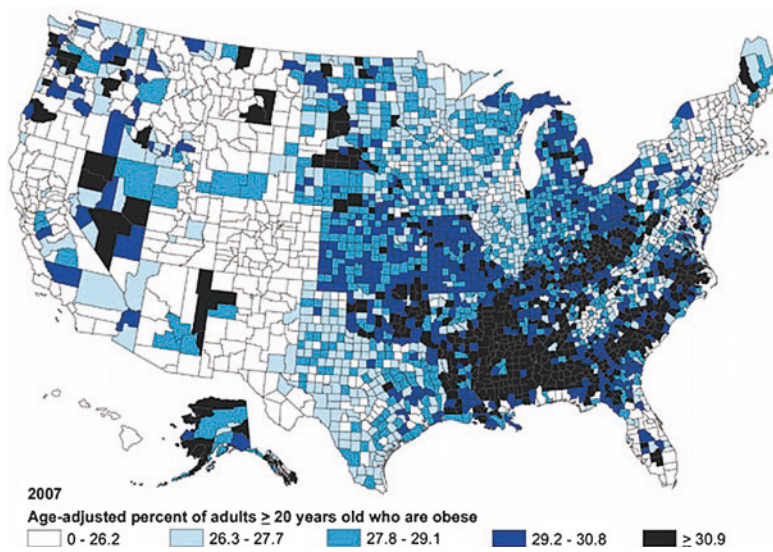


Fig. 25.1 Percent of obese adults (BMI less than 30) in United States

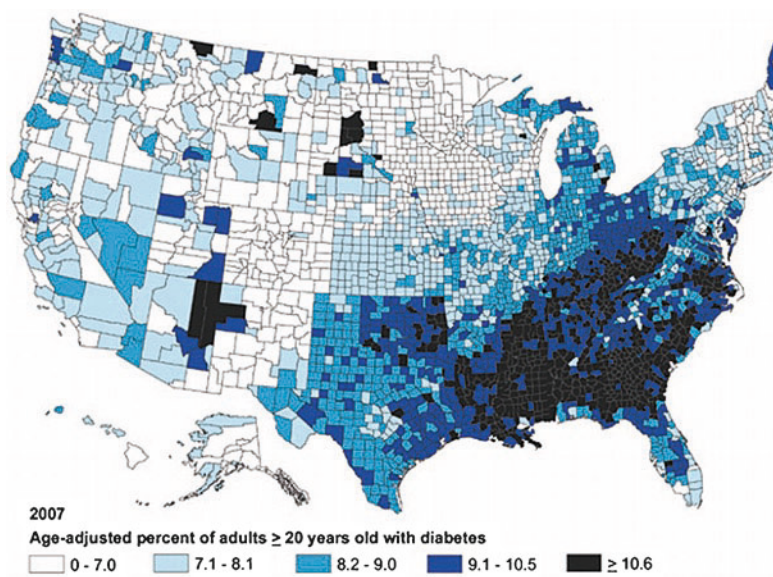


Fig. 25.2 Percent of adults in United States who are diabetics

Overweight and obesity are becoming epidemic worldwide, and the US ranks high among the developed nations for prevalence of these conditions. Approximately 300,000 adult deaths in the USA each year are attributable to unhealthy diet habits and physical inactivity. Nearly two-thirds of US adults are overweight ($\text{BMI} > 25 \text{ mg/kg}^2$) or obese ($\text{BMI} > 30 \text{ mg/kg}^2$). From 1960 to 2000, the prevalence of obesity has more than doubled, with most of the increase occurring in the past 20 years. Obesity is the major environmental risk factor for developing type-2 diabetes; an estimated 70% of diabetes risk in the USA can be attributed to excess weight. Individuals who are overweight or obese also have higher rates of hypertension and dyslipidemia [14–19]. Obesity is associated with a 50–100% increased risk of death from all causes. Most of the increased risk is from cardiovascular disease (CVD). The life expectancy of a moderately obese person may be shortened by 2–5 years. As the prevalence of overweight and obesity has increased in the USA, so have related health care costs, both direct and indirect. The estimated total health care cost of diabetes in 2007 was \$222.9 billion, and that attributable to excess weight was \$150 billion.

The global trend in rising levels of obesity, diabetes and cardiovascular disease has re-fuelled consumer and research interest in the dietary intake of fat, protein and carbohydrates necessary to maintain good health. The World Health Organization (WHO) and Food and Agriculture Office (FAO) of the United Nations stated that globally, overweight populations are a bigger problem than under nourishment, and recommend people in industrialized countries base diets on low glycemic index (GI) foods to prevent most common diseases of affluence. According to the World Health Organization (WHO), an estimated 177 million people had diabetes in the year 2000 and by 2025; this figure will rise to over 300 million. The costs of diabetes include reduced quality of life and the increased risk of developing micro vascular and macro vascular complications such as retinopathy and cardiovascular disease (CVD) [12–22].

Nutrition therapy plays a vital role in the treatment and management of both types of diabetes. The basic guidelines for the management of diabetes includes controlling portions (particularly carbohydrates), decreasing obesity, increasing fiber, reducing saturated and trans fat to <10% of energy, and choosing low glycemic index foods more often. Dietary carbohydrates are generally found in starches, fruits and vegetables, milk products and sugars and should provide 50–60% of our energy requirements.

25.2 What Is the Glycemic Index?

The glycemic index originated as a research tool [23–42]. It assigns a numerical value to a food indicating how much and how rapidly 50 g of its carbohydrate content will raise blood-sugar levels, compared to 50 g of a reference food (glucose or white bread). Glycemic index (GI) is a numerical Index, a carbohydrate-containing food classification system first proposed in 1981 [27]. Thus, the glycemic index refers to the blood glucose raising potential of carbohydrate (CHO) foods and allows a classification of foods based on the postprandial (post meal) blood glucose response compared to a reference food, (i.e., their conversion to glucose within the human body). It compares carbohydrates in foods as eaten, on a gram per gram basis. The glycemic index (GI) is often classified into three categories: low (<55), medium (55–70), and high (>70) GI foods. The glycemic index has been recognized by WHO and diabetes associations in Canada, Europe, Australia, and South Africa as a useful tool in the management of diabetes. Only recently has the American Diabetes Association acknowledged that the use of the glycemic index can provide

additional benefits to that observed when total carbohydrate is considered alone as stated in the ADA 2004 position statement on dietary carbohydrates. However, many questions still surround the practical use and clinical significance of the glycemic index. The GI cannot be applied to foods containing no carbohydrate (i.e., cheese, eggs, meats, etc.). High GI foods produce a greater increase in blood glucose levels than low GI foods. Examples of high GI foods are white bread, crackers and corn flakes. Low GI foods include many vegetables, most fruits, dairy products, pulses and some sugars. Many things contribute to the GI of a given food, including its fat and fiber content and how much it’s been processed.

25.3 The Glycemic Index Yields Some Surprises

Nutritionists used to believe that all simple sugars digested quickly and caused a rapid rise in blood sugar, and that the opposite was true for “complex carbohydrates.” But that’s not always the case. While many sweet and sugary foods do have high GI’s, some starchy foods like potatoes or white bread score even higher than honey or table sugar (sucrose).

The GI was created by analyzing, over time, the blood of healthy volunteers after they had ingested a variety of carbohydrates [25–33, 35–39]. Then, using a scale from 0 to 100, with 100 representing simple sugar, those foods were listed in the index according to how they affected the blood sugar levels of the volunteers (Table 25.1). Highly processed foods like white bread and starchy food like potatoes earned a high number while foods such as whole grains, unsweetened yogurt and apples earned a low number, thus the terms high-glycemic and low-glycemic. Foods that rank at 70 or higher are high GI, while foods ranked below 55 are low GI. There is also a mid-range from 56 to 69 that includes syrups, pomegranate juice, muesli and some bread.

Table 25.1 Evaluating GI and GL

		Low	Medium		High
Glycemic index (GI)		≤55	56–69		≥70
Glycemic load (GL)		≤10	11–19		≥20
GI and GL for selected foods					
			Serving size		
Food group	Food	GI	oz	g	GL
Breads	White bread	73	1.06	30	10
	Whole wheat bread	71	1.06	30	9
	Pumpernickel bread	50	1.06	30	6
Cereal/grains	White rice	79	5.29	150	40
	Brown rice	55	5.29	150	18
	Spaghetti	42	6.35	180	20
	Cornflakes	92	1.06	30	24
	Shredded wheat	75	1.06	30	15
	Oatmeal (rolled)	54	0.88	25	9
Fruit	Watermelon	72	4.23	120	4
	Raisins	64	2.12	60	28
	Bananas	51	4.23	120	13
	Oranges	48	4.23	120	5
	Grapes	43	4.23	120	7
	Strawberries	40	4.23	120	2
	Apples	40	4.23	120	6
	Grapefruit	25	4.23	120	3

(continued)

Table 25.1 (continued)

GI and GL for selected foods

Food group	Food	GI	Serving size		GL
			oz	g	
Vegetables	Baked potato	85	5.29	150	26
	Corn	53	5.29	150	17
	Sweet potato	61	5.29	150	17
	Peas	48	2.82	80	3
	Carrots	47	2.82	80	3
Legumes	Lima beans	32	5.29	150	10
	Garbanzo beans	33	5.29	150	10
	Red lentils	26	5.29	150	5
	Peanuts	14	1.76	50	1
Dairy	Milk (nonfat)	32	8.82	250	4
	Low fat fruit yogurt	33	7.05	200	10
	Ice cream	61	1.76	50	8
Sugar	Sucrose (table sugar)	68	0.35	10	7
	Honey	55	0.88	25	10
Snacks	Pretzels	83	1.06	30	16
	Popcorn (plain)	72	0.71	20	8
	Potato chips	54	1.76	50	11

The glycemic index of a certain food also takes into account its type of sugar or starch, the amount of protein, fiber and fat that it contains, how highly processed it is, the way it has been cooked, cooking time, its acid content and ripeness. There are several different GI scales and testing methodologies available, some with differing values for the same food.

25.4 ...and Why It's Important

Simply put, high-glycemic foods cause “spikes” a rapid rise and fall in blood sugar and insulin levels because the body digests and absorbs them so quickly. These episodes have been linked to greater sensations of hunger and higher stress hormone levels. Experts believe that diets filled with high GI foods may lead to overeating, obesity and adult onset diabetes.

By contrast, low-glycemic foods takes much longer to digest, providing the body with a slow, steady supply of energy that prolongs a feeling of fullness and helps prevent overeating, promotes healthy cholesterol levels and decreases the risk of diabetes. If used intelligently as part of a broader balanced diet, the glycemic index is a good general reference for choosing healthy food. Some of the benefits gleaned from eating low-glycemic foods and maintaining stable blood sugar levels include:

- Weight control
- An increase in insulin sensitivity
- A lower risk of heart disease
- Healthy blood cholesterol levels
- An increase in satiety improved physical endurance
- Faster recovery from exercise

25.5 What It's Not...

The glycemic index is not a cure-all for diabetes or other diseases, nor should it be used as the sole reference for a balanced diet, since it applies to only one aspect of nutrition carbohydrates. Our bodies require three types of nutrients: carbohydrates, fats, and proteins. Of the three, carbohydrates are the major source of energy in the diet, providing us with the immediate fuel we need to solve a math problem, climb the stairs or run a marathon. Carbohydrates are broken down into simple sugars by the body, transported in the blood, and then moved into the cells with the help of insulin. The glycemic index does not measure fats or proteins and both of those nutrients affect the body's response to carbohydrates when eaten in combination. For example, eating a high-glycemic food like white bread will spike the blood sugar, but eating it with a protein like chicken or a fat like olive oil will reduce its effect on blood sugar levels. In addition, other factors such as serving size, an individual's insulin resistance, even the time of day, can affect how the body responds to a particular carbohydrate. Even though the GI is a useful tool, it's not a complete one. Two notable examples illustrate its shortcomings. Carrots have a comparatively high GI value, despite being a nutrient-rich and healthful food. But because the amount of carbohydrate consumed from a serving of carrots is quite small, the net glycemic load is not so great. Conversely, fructose (as in the high fructose corn syrup commonly found in soda) has a lower GI value due to the way it is metabolized, despite being nutrient-poor. So, just because a food has a low GI value doesn't mean it's good for you.

25.6 How to Use It...

Common sense use of the glycemic index is as simple as replacing highly processed grains and sugars with whole grains, vegetables and fruit and avoiding high GI foods by themselves. Soft drinks and other sweetened beverages are particularly notorious in this regard.

Some examples of healthy combinations of this sort are:

- A bagel with cream cheese and smoked salmon or with peanut butter.
- Yogurt or nuts with breakfast cereal to add some protein and balance the glycemic index.
- Potatoes in a stew or with an omelet, not alone as a snack (like potato chips).
- Cinnamon and prickly pear cactus purportedly help regulate blood sugar.
- Maintain the muscle mass.

Finally, on a more celebratory note, recent research shows that a glass of wine or beer during or before meals helps to keep blood sugar levels healthy.

25.7 Why the Glycemic Index Is Important?

The body performs best when the blood sugar is kept relatively constant. If the blood sugar drops too low, you become lethargic and/or experience increased hunger. And if it goes too high, the brain signals the pancreas to secrete more insulin. Insulin brings the blood sugar back down, but primarily by converting the excess sugar to stored fat. Also, the greater the rate of increase in the blood sugar, the more chance that the body will release an excess amount of insulin, and drive the blood sugar back down too low.

Therefore, when you eat foods that cause a large and rapid glycemic response, you may feel an initial elevation in energy and mood as the blood sugar rises, but this is followed by a cycle of increased fat storage, lethargy, and more hunger. Although increased fat storage may sound bad enough, individuals with diabetes (diabetes mellitus, type-1 and type-2) have an even worse problem. Their body's inability to secrete or process insulin causes their blood sugar to raise too high, leading to a host of additional medical problems. The theory behind the Glycemic Index is simply to minimize insulin-related problems by identifying and avoiding foods that have the greatest effect on the blood sugar.

25.7.1 Drawbacks of the Glycemic Index Ratings

GI Ratings are for Individual Foods not Combinations of Foods. As pointed out by the American Diabetes Association (ADA), the differences in rates of digestion ranked by the Glycemic Index are not as great as they appear. The ADA says that differences in the GI ratings of many foods are less accurate when foods are eaten together at mealtimes. For example, jelly/jam is a food with a high GI rating. But when eaten with (say) wholemeal bread as part of a meal or snack, the combination of the jelly and bread is digested more slowly and should therefore merit a lower GI rating.

25.7.2 High-Fat Products May Score Low on the Glycemic Index

Fat slows digestion. Therefore several foods like chocolate, sausages and peanuts, end up with a low GI score. Yet there is a clear statistical correlation between the consumption of fat, fast food and rates of obesity-related disease, like heart disease and strokes. So following a diet plan based exclusively on the Glycemic Index may actually increase your risk of a heart attack and stroke.

25.7.3 The Glycemic Index Is Only Part of the Jigsaw

For diabetics who need a handy guide to which foods have what effect on blood sugar levels, or for athletes who need different “energy-giving foods” at different times, the Glycemic Index is very useful. Also, anyone suffering from insulin insensitivity will definitely benefit from a diet based on lower GI foods. But, when it comes to weight loss and nutrition, the Glycemic Index is only part of the jigsaw.

25.7.4 Glycemic Load

The glycemic load (GL) combines the GI and the total CHO (carbohydrates) content of an average serving of a food. It is defined as the weighted mean of the dietary GI multiplied by the percentage of total energy from CHO. The GL attempts to incorporate both the quality and quantity of CHO consumed. The GL corresponds rather closely to the grams of carbohydrate in a serving, not the actual GI of the food. There is not enough evidence currently to use either the GI or GL as a method

of meal planning alone for people with diabetes, but a recent randomized controlled study demonstrated that diets high in carbohydrates (high GL) with low glycemic index (GI) are best for cardiovascular risk reduction. Several Researches suggested that it is time to incorporate the concepts of GI and GL into clinical practice to help reduce cardiovascular risk. That is, to recommend that patients consume a high GL, low GI diet [43–58].

25.7.5 Should All High-GI Foods Be Avoided?

For non-diabetics, there are times when a rapid increase in blood sugar (and the corresponding increase in insulin) may be desirable. For example, after strenuous physical activity, insulin also helps move glucose into muscle cells, where it aids tissue repair. Because of this, some coaches and physical trainers recommend high-GI foods (such as sports drinks) immediately after exercise to speed recovery. Also, it's not Glycemic Index alone that leads to the increase in blood sugar. Equally important is the amount of the food that you consume. The concept of Glycemic Index combined with total intake is referred to as "Glycemic Load."

25.7.6 Benefits to Diabetes Management

A large number of studies [20, 49–72] have been conducted to illustrate the benefits of the glycemic index on the treatment and prevention of chronic diseases. In a meta-analysis of randomized controlled trials of low GI diets in the management of type 1 and type-2 diabetes, the results show that choosing a low-GI diet has a clinically significant effect on glycemic control [68–72]. A low GI diet also found to be associated with reduced serum cholesterol and high GI diet has been found to increase the risk of CVD. These findings are possibly related to the chronic hyperinsulinemia and postprandial hyperglycemia that can result from a diet consisting of high GI foods. However, long-term studies are required to confirm the effects of the GI on CVD risk. Low glycemic index foods that contain soluble fiber may also be helpful in limiting the number of hypoglycemic events. This may prove useful in the management of diabetes in individuals prone to hypoglycemia.

Using the glycemic index in practice does not suggest that other dietary guidelines or the amount of carbohydrate are to be ignored. Both source and amount of carbohydrate are important in managing blood glucose levels. Glycemic index adds additional benefit to or supplements other dietary recommendations to improve the management of diabetes.

25.7.7 Factors Affecting the Glycemic Index Value

The GI of a particular food can be influenced by several different factors. The multitude of factors often is criticized as a barrier to using the GI in practice [35–41]. The physical nature or state of the food appears to have the greatest impact on the GI rating. Practical tips for using the GI the use of the glycemic index in practice has been questioned as some consider the glycemic index too complicated for clients. Several studies [20, 48–71] have shown that the glycemic index can be utilized successfully in diabetes practice and have shown improvements in glycemic control. Some simple tips to help clients incorporate low glycemic index foods include:

- Replacing half of high GI foods with low GI foods.
- Consume one low GI food at each meal.
- Replacing all high GI breads and cereals with low GI breads and cereals.
- Increased intake of legumes as legumes have been found to lower the GI of the diet.
- Continue to recommend a variety of vegetables, especially the vegetables consisting of a low amount of carbohydrate per serving.
- Continue to recommend milk products and most fruits as part of a healthy diet as these are often classified as low and medium glycemic index foods.
- Choose less processed foods, e.g., choose steel cut oatmeal flakes vs. instant oatmeal or whole grain bread versus whole wheat bread.
- Use vinaigrette salad dressings at a meal.
- Present all high carbohydrate and low fat foods as healthy but emphasize some are “good choices” and others are “better choices.”

25.7.8 Promising Benefits for Weight Management

Maintaining a healthy weight is a goal in the prevention and management of diabetes. Approximately 80–90% of people with diabetes are overweight or obese. Low GI diets may play a role in weight management as body mass index and the glycemic index were found to be positively correlated. Consuming a low GI diet has been shown [70–83] to result in weight loss in several studies. Furthermore, it has been suggested by several studies that fat oxidation is promoted when a low GI diet is consumed; adding to the benefits for weight management using the glycemic index.

Low-GI foods may benefit weight control in two ways: (1) by promoting satiety and (2) by promoting fat oxidation at the expense of carbohydrate oxidation. These two qualities of low-GI foods stem from the slower rates at which they are digested and absorbed and the corresponding effects on postprandial glycemia and hyperinsulinemia. Even when appearance and nutrient content are matched, low-GI foods typically induce higher satiety than do their high-GI counterparts and are followed by less energy intake at subsequent meals. Weight loss associated with a low GI diet may also result in physiological changes that aid long-term weight loss. A low GI diet has been shown to affect satiety and resting energy expenditure (REE) [84, 85]. In overweight or obese adults either receiving a low-glycemic load (calculated by multiplying grams of carbohydrate in a typical serving size by the GI of that food) or low-fat energy restricted diet (1,500 kcal), the group on the low glycemic load diet reported less hunger and less of a decreasing in REE than those receiving the low fat diet. As well, insulin resistance, serum triglycerides, and C-reactive protein were significantly improved in the group on the low-glycemic load diet. Therefore, weight loss from intake of a low GI diet has shown to improve insulin sensitivity [64–83].

25.7.9 What Is the Best Weight Loss Plan? Keys to the Success

While the general principles discussed in the first section apply to all patients with diabetes, those patients with type-2 diabetes and obesity (BMI 30.0 and greater) should have the major focus placed on weight loss and increased physical activity. With so many weight loss “diets” available, confusion abounds. Most patients are looking for the quickest and easiest way to lose

weight, and most have unrealistic expectations. Obesity does not occur overnight, and its treatment requires lifetime adjustments to food (energy) intake and energy expenditure (increased activity). Energy consumed is either stored or burned. The cause of the obesity epidemic is that most people consume more energy than they burn, and the excess energy is stored as fat. The old adage remains true: “to lose weight ‘calories in’ must be less than ‘calories out.’” In other words, for weight loss to occur there simply must be a daily caloric deficit. One pound of fat is roughly equal to 3,500 kcal. Thus, a modest decrease in caloric balance (500–1,000 kcal/day) will result in a slow but progressive weight loss of 1–2 lb/week. It is a simple premise, but extremely difficult to achieve in the long term. Weight loss is a major challenge for most patients who, in our fast-paced environment, don’t eat properly and fail to establish patterns of regular physical activity. The key to success is having a patient with diabetes commit to establishing a healthy lifestyle that emphasizes and incorporates more healthy food choices and a daily exercise routine, taking into account the presence of possible complications. Initial physical activity recommendations should be moderate, gradually increasing the duration and frequency to 30–45 min of moderate aerobic activity 3–5 days per week. Developing an individualized weight loss program preferably with a registered dietitian familiar with diabetes management, along with regular follow-ups, will help promote success. It is always important that a patient check with their physician before starting an exercise program. Common keys to losing weight and keeping it off, according to data from the registry, include:

- Eat breakfast.
- Eat a calorie-aware, moderately low-fat diet that includes complex carbohydrates.
- Get plenty of exercise at moderate intensity. Walk!
- Self-monitor through frequent weigh-ins and a food and exercise diary.

25.7.10 Children and Adolescent

Type-2 diabetes is becoming increasingly prevalent among young people who are driven, as is the case in adults, by lifestyle factors leading to increased body weight [20, 45–82]. The diabetogenic process may begin as early as fetal life, with low birth weight and poor nutrition combining with sedentary lifestyle and dietary factors to produce an insulin-resistant phenotype that may accelerate the development of renal pathology and cardiovascular disease. It is important for children and adolescents to be physically active as well as following healthy eating guidelines to promote normal growth patterns, without exceeding recommended weight ranges for age and/or height.

25.8 In-Depth Approaches

25.8.1 Individualized Menus

Many patients like to have examples to follow when setting up meal plans. The menu describes in writing what foods and in what quantities should be consumed over a period of days. A dietitian creates an individualized menu based on the nutritional counseling plan chosen and incorporates the patient’s unique preferences, schedule, etc. The patient then has written examples to follow, and will learn how to create independently their own menus over time.

25.8.2 Month of Meals 1–5

These menus were created by committees of the Council on Nutritional Science and Metabolism of the American Diabetes Association, and staff of members of the American Diabetes Association National Service Center in response to frequent requests for menus from persons with diabetes and their families. The menus are designed to follow the exchange groups and provide 45–50% of calories from CHO, 20% protein and about 30% fat. The menus provide 1,200 or 1,800 cal, and instructions are provided on how to adjust caloric levels upward or downward. Each menu provides 28 days of breakfast, lunch, dinner and snacks with a different focus. For example, Month of Meals 1 has a special occasion section, while Month of Meals 2 has ethnic foods and easy to prepare food items, and dining out.

25.8.3 Exchange List Approach

The Exchange Lists for Meal Planning were developed by the American Diabetes Association and the American Dietetic Association, and have been in existence since 1950. The concept is that foods are grouped according to similar nutritional value, and can be exchanged or substituted in the portion size listed within the same group. In 1995, the exchange lists were revised from six groups to three. They include:

- Carbohydrate group – includes starches, fruit, milk and vegetables.
- Meat and Meat Substitutes group – four meat categories based on the amount of fat they contain.
- Fat group – contains three categories of fats based on the major source of fat contained: saturated, polyunsaturated or monounsaturated.

The exchange lists [86, 87] also give information on fiber and sodium content. They can be utilized for patients with type-1 or type-2 diabetes. The emphasis with type-1 patients is on consistency of timing and amount of food eaten, while with type-2 patients, the focus is on controlling the caloric and fat values of food consumed.

25.8.4 Basic Carbohydrate Counting

Basic carbohydrate CHO counting has become the most commonly used method for diabetes meal planning over the past few years.

25.8.5 Advanced Carbohydrate Counting

At the more advanced level, the focus is to finely tune food intake, medication and activity based on patterns from daily food intake and blood glucose records.

Record keeping is an important first part of advanced carbohydrate counting. The meal time, amount and type of food eaten, estimates of CHO intake for each food item containing CHO, and

total amount of CHO for each meal and snack must be recorded. Also, insulin dose, physical activity and blood glucose levels must be accurately documented for several weeks. Any unusual circumstances should be noted such as illness, stress, menstrual cycle, etc.

25.8.6 Calorie Counting and Fat Counting

These are meal planning methods [65, 87] that can be useful for people with type-2 diabetes who want to lose weight. Knowledge regarding the amount of total calories and fat grams in a given food (including pre-prepared and fast foods) and becoming adept at label reading, can help promote weight loss when incorporated into other lifestyle changes.

25.8.7 Potential Benefits of Eating Mainly Low GI Foods

- Weight loss and weight management
- Increase the body's sensitivity to insulin (thus, causing less insulin secretion)
- Improve diabetes control
- Reduce the risk for getting heart disease
- Reduce the risk for getting type-2 diabetes
- Reduce blood cholesterol levels
- Control the appetite (reduce hunger and improve satiety)
- Improve physical endurance
- Help replace carbohydrate (glycogen) stores after exercise

25.9 Limitations of the Glycemic Index and the Glycemic Load

25.9.1 Scarcity of GI Data

Although methods for determining Glycemic Index have been in existence for more than 20 years, GI values have so far only been determined for about 5% of the foods in ND's database. Seemingly similar foods can have very different GI values, so it's not always possible to estimate GI from either food type or composition. This means that each food has to be physically tested. GI testing requires human subjects, and is both relatively expensive and time-consuming. The fact that only a very limited number of researchers currently do GI testing compounds this problem. Food manufacturers continue to introduce thousands of new foods each year. Since GI testing is neither required nor common (at least in the USA), this problem is likely to get worse rather than better.

25.9.2 Wide Variation in GI Measurements

The Glycemic Index (Table 25.1) shows a single value of GI for each food. In reality, though, the measurements are not so precise. Reported values are generally averages of several tests.

There's nothing wrong with that methodology, but individual measurements can vary a significant amount. For example, baked Russet potatoes have been tested with a GI as low as 56 and as high as 111. The GI for the same fruit has even been shown to increase as the fruit ripens. This amount of variation adds a great deal of uncertainty to GI calculations.

25.9.3 GI Values Affected by Preparation Method

The Glycemic Index gets even trickier when you take into account the changes in value that occur in response to differences in food preparation. Generally, any significant food processing, such as grinding or cooking, will elevate GI values for certain foods, because it makes those food quicker and easier to digest. This type of change is even seen with subtle alterations of the preparation, such as boiling pasta for 15 min instead of 10.

25.9.4 GI Values Affected by Combination with Other Foods

While the tests for Glycemic Index are usually done on individual foods, we often consume those foods in combination with other foods. The addition of other foods that contain fiber, protein, or fat will generally reduce the Glycemic Index of the meal. The GI of this “mixed meal” can be estimated by taking a weighted average of the GI's of the individual foods in the meal. However, this averaging method may become less accurate as the total percentage of carbohydrate decreases. Therefore, foods like pizza often create a higher glycemic response than the simple weighted average of the ingredient GI's would predict.

25.9.5 Individual Differences in Glycemic Response

The rate at which different people digest carbohydrates also varies, so there are some individual differences in glycemic response from person to person. In addition it has been shown that one person's glycemic response may vary from one time of day to another. And finally, different people have different insulin responses (i.e., produce different levels of insulin), even with an identical glycemic response. This fact alone means that a diabetic cannot rely completely on the Glycemic Index without monitoring his own blood sugar response. (This, of course, is a limitation of any food index, and not a specific limitation of GI.)

25.9.6 Reliance on GI and GL Can Lead to over Consumption

It's important to remember that the Glycemic Index is only a rating of a food's carbohydrate content. If you use GI and GL values as the sole factor for determining the diet, you can easily end up overconsuming fat and total Calories. See example below...

Example – How the Glycemic Index can encourage overeating: Apples have a GI of 38 (as shown in the table above), and a medium-size apple, weighing 138 g, contains 16 g of net carbohydrates and

provides a Glycemic Load of 6. This is a low GL, and most would consider the apple to be a very appropriate snack. But now look at peanuts. A four ounce serving not only weighs less than the apple, but has a much lower GI of 14 and provides an even lower GL of 2. Based on Glycemic Load alone, you would have to believe that the peanuts were a better dietary choice than the apple. But if you take a look at the Calories contained in these two foods, you'll see that the apple contains approximately 72 cal, while the peanuts contain more than 500! Those 400+ extra Calories are NOT going to help you lose weight.

25.10 Beyond the GI

In the struggle to maintain healthy blood sugar levels, there are other tools in the health toolbox besides the glycemic index. Here are some other ways you can promote blood sugar stability:

- Cut hydrogenated or partially hydrogenated oils from the diet completely. The trans fats found in hydrogenated oils have been shown to interfere with insulin secretion and increase blood sugar levels.
- Be sure to eat enough fish or take fish oil supplements.
- Chromium and magnesium are vital for the body to properly maintain healthy blood sugar levels. Consider supplementing if dietary levels are not sufficient.
- Try to eat adequate meals throughout the day, and then minimize snacking or eating between meals. If you do snack, use the principles of the glycemic index to make good choices, such as a handful of nuts or some plain yogurt with fruit instead of potato chips or pretzels.
- Eat plenty of fiber, especially soluble fiber.

25.11 Another Way to Control Blood Sugar

As you consider the strengths and weaknesses of the Glycemic Index, it's important that you don't lose sight of the original goal. What we are really trying to do is control blood sugar levels. Is the consumption of low-GI foods the only way to do this? No, it is not. As we mentioned before, the blood sugar can also be controlled simply by limiting the total number of carbohydrates that you consume in any given meal. In the following sections, we'll explore different ways to do just that....

25.11.1 *Is Low-Carb the Answer?*

One alternative to the low-GI diet is the low-carbohydrate diet, which also centers on the concept of controlling blood sugar levels, but does so by limiting total carbohydrate consumption. Low-carb diets have become popular, partially because they are very successful at doing this. As opposed to low-GI diets, they are also very easy to plan and monitor, since carbohydrate counts are known for all foods. However, low-carb diets are not without their own difficulties, which can include, Deficiency of essential nutrients.

If the low-carb diet restricts the amount of fruits and vegetables that you eat, you may not be consuming enough Vitamin A, Vitamin C, and Dietary Fiber, which are much more abundant in plant-based foods. It's also likely that you are consuming less carotenoids (such as Alpha Carotene, Beta Carotene, Beta Cryptoxanthin, and Lycopene). Although no daily values have been established for

carotenoids, they are known to be powerful anti-oxidants, and may be necessary for optimal health. It's possible to supplement these missing nutrients, but there are also many phytochemicals present in plant-based foods that we are just beginning to learn about. Many of these phytochemicals are believed to have positive health benefits, but very few of them are yet available in supplement form.

25.11.2 Potential Risks Associated with High Fat Consumption

Low-carb diets usually contain large amounts of fat, and numerous studies suggest that higher consumption of fats (particularly saturated fats) increases the risk of heart disease and other ailments. While no definitive link has been established between low-carb diets and heart disease, this is a topic that warrants additional study.

25.11.3 Hypoglycemic Effects of Minimized Carbohydrate Consumption

The brain requires glucose to operate. In the absence of carbohydrates, the body is forced to synthesize glucose from digested or stored fats. This somewhat inefficient process results in lower than optimal blood sugar levels, which can leave you feeling lethargic, unalert and even confused. This effect is most commonly experienced as you transition from a "normal" diet to an ultra-low-carb diet, but can also reappear at times when the body is under increased stress. The decrease in mental alertness, while not harmful in of itself, is a potentially dangerous side effect. Boredom or cravings resulting from the elimination of carbohydrate-rich foods.

25.11.4 Added Expense of Special Foods

To overcome the boredom of the low-carb diet, you can turn to the new low-carb versions of foods that are now being offered in many health food and grocery stores. It's now even possible to find low-carb versions of pancakes and bagels! Unfortunately, though, the elevated cost of some of these specialty food items can add considerably to the food bill.

25.11.5 Incompatibility with Vegetarian Lifestyle

If you consider yourself a vegetarian, you'll find that it's very difficult to follow a low-carb diet, since nearly all low-carb meal plans focus on the consumption of meats and other animal-based foods.

25.11.6 What About Satiety?

A different way to limit carbohydrate consumption is simply to limit the total number of Calories that you consume for each meal. This can be a very effective method for controlling blood sugar and

losing body fat. Unfortunately, there's one BIG problem associated with this method – increased hunger! But what if you could eat less, and not be hungry? Is that possible?

A few years ago, a group of researchers from the University of Sydney in Sydney, Australia performed an interesting study in which they compared the satiating effects of different foods. These researchers include some of the same individuals that pioneered much of the work on the Glycemic Index. The result of their study, “The Satiety Index of Common Foods,” was published in the *European Journal of Clinical Nutrition*, September 1995. In this study, the researchers fed human test subjects fixed-Calorie portions of 38 different foods, and then recorded the subjects' perceived hunger following each feeding [88, 89].

The results of this study clearly indicated that certain foods are much better than others for satisfying hunger. The researchers used white bread as their reference point, and arbitrarily assigned it a “Satiety Index” of 100. Foods that did a better job of satisfying hunger were given proportionately higher values, and foods that were less satisfying were assigned lower values. Among the most satisfying foods they tested were plain boiled potatoes, raw fruits, fish, and lean meats. Subjects that consumed the prescribed portion of these foods were less likely to feel hungry immediately afterward. Foods that did the poorest job of satisfying hunger included croissants, donuts, candy bars, and peanuts.

25.11.7 An Important Outcome of This Study

Because of the limited size of the Satiety Index study, there's some uncertainty in the accuracy of the values that were recorded for each food. However, one very important general observation was made by the Satiety Index researchers. They noted that a common feature was shared by the foods with the highest Satiety Index values. All of these foods had high weight-to-Calorie ratios. In other words, these foods contained a greater amount of bulk for each Calorie. They helped make you feel full, literally by filling the stomach.

This suspected relation between bulk and satiety may seem obvious and trivial, but it opens the door to a very powerful theory – that it may be possible to predict satiety by knowing the nutrient composition of the food! And if that is true, some form of the Satiety Index could prove to be a more flexible tool for assessing diet than the Glycemic Index.

25.12 Introducing the Fullness Factor

Nutrition Data [90] mathematically modeled the Satiety Index with a multivariate analysis that used nutrient profiles of the foods tested in the previously mentioned Satiety Index study. As anticipated, there was a good correlation between the Satiety Index values and each food's Caloric density [65, 67, 74, 88–90]. There were also significant but lesser correlations between the index and each food's levels of net carbohydrates, fat, dietary fiber, and protein. From the mathematical model developed, ND was able to create an equation to convert a food's nutrient profile into a predicted satiety index, which we call the Fullness Factor. The Fullness Factor has been normalized so that all resultant values fall into a range of 0–5. The calculated Fullness Factor for white bread is 1.8, so values above 1.8 indicate foods that are likely to be more satiating than white bread, and values less than 1.8 indicate foods that are likely to be less satiating. A food's Fullness Factor is independent of its serving size.

25.12.1 Potential Advantages of the Fullness Factor (FF) and the Glycemic Index

The Fullness Factor is a calculated rather than measured value, and has a few distinct advantages over the Glycemic Index:

- Fullness Factors are instantly determinable for ALL foods.
- Knowledge of the nutrient information contained on a standard nutrition facts label is all that is required to determine the Fullness Factor. That means that the Fullness Factor is supported for all foods in ND's database, and also all new recipes. That makes it easy to use the Fullness Factor in conjunction with any diet plan.
- High-FF foods may help reduce total Caloric consumption.
- Consuming high-FF foods means satisfying the hunger with fewer total Calories, which is the most direct route to weight loss.
- The Fullness Factor may also be helpful in weight gaining diets.
- Individuals that have trouble maintaining or gaining weight can add additional Calories to their diets by altering their food selections to include more low-FF foods.

25.12.2 Potential Advantages of FF-Based Diets over Low-Carb Diets

- Diets based on the Fullness Factor have some advantages over Low-Carb diets:
- FF-based diets may better encourage the consumption of naturally healthy foods because many fruits, vegetables, and less processed foods have high Fullness Factors, it may be easier to obtain essential nutrients when on FF-based diets.
- FF-based diets offer a larger range of food selections.
- No foods are off limits in FF-based diets. FF-based diets simply encourage you to select the foods that cause you to fill up faster without as many total Calories.
- FF-based diets can easily accommodate a vegetarian lifestyle.
- While many meats are good choices for a high-FF diet, it's also relatively easy to create a high-FF diet that doesn't contain animal-based foods.

25.12.3 Putting the Fullness Factor to Work

The Better choice diets uses nutritional ratings combined with the Fullness Factor to determine which foods could potentially improve the diet and make it easier to control the weight.

25.13 Conclusions

Safe choices for weight-loss regimens include energy restricted diets calculated according to the Therapeutic Lifestyle Change Diet recommended by the National Cholesterol Education Program, the diet recommended by the Heart Association, the diet recommended by the Canadian Diabetes Association, and Canada's Food Guide to Healthy Eating. Low-carbohydrate diets and diets high in

saturated fat are not recommended. Nutrition therapy in weight management should ensure that diets are safe and that they avoid causing high levels of postprandial glucose and lipid serum concentrations induce optimal serum lipid composition to prevent coronary artery disease, do not increase the risk of hypertension or cancer, contain adequate nutrient intake and sustain weight loss. Long-term multicentre randomized intervention trials are needed to improve knowledge on these issues and to determine the contribution of diet, exercise, and metabolic and psychosocial factors to weight loss and weight-loss maintenance. A concerted effort on the part of consumers, medical professionals, research funding agencies, food industry, community leaders, government legislators and nutrition policymakers is needed to fight obesity. With all of the intrinsic problems of weight-loss interventions, preventive measures should be given a distinct priority. Significant clinical effects or epidemiologic associations have been reported relating GI or GL of diets and indicators of chronic disease risk. There is accumulating evidence that diets containing a lower level of fat and carbohydrates that elicit low glycemic responses (low GI foods or diets) cause important health benefits such as lowering total cholesterol and improving the metabolic control of diabetes. Systematic reviews from several have shown that the low GI diets improve glycemic control in type-1 and type-2 diabetes. There is also strong epidemiological evidence and some randomized control trials demonstrating the positive effect of low GI diets on a number of cardiovascular risk factors. Accumulating evidence is also showing a relationship between low GI diets and both appetite regulation and changes in body composition. Additional research also identifies that diets based upon GI may stabilize blood sugar, control appetites, improve energy, enhance memory, balance, mood and promote regularity.

Other studies have shown the effect of food volume on satiety independent of the nutrient content of foods. In addition, the water content of food increases the food volume, reduces the energy density of foods and results in higher satiety, possibly due to the effect of gastric distention produced by water. Adequate promotion of physical activity and culturally based diets with low GI and high SI might be a low cost approach for the prevention and control of obesity and diabetes in a population with a high prevalence of diabetes and high index of marginality. This approach could be cost-effective in developing countries where health care is limited for the people under the poverty level.

The clinical significance of GI remains the subject of intense debate. The European Association for the Study of Diabetes, the Canadian Diabetes Association, the American Diabetes Association¹ and the Dietitians Association of Australia all recommend high-fiber, low-GI foods for individuals with diabetes as a means of improving postprandial glycemia and weight control. More clinical research is needed to show direct causal effects between low GI diets and chronic disease.

The concept that “a calorie is a calorie” underlies most conventional weight loss strategies. According to this principle, obesity results from an imbalance between energy intake and expenditure. The proposed cure is to eat less and exercise more. However, calorie-restricted, low fat diets have poor long-term effectiveness in the outpatient setting. In a sense, these diets may constitute symptomatic treatment that does not address the physiologic drives to overeat. From a hormonal standpoint, all calories are not alike.

The optimal diet for the prevention and treatment of obesity, if one exists, remains to be determined. In particular, the effects of GI on body weight regulation must be explored in long-term clinical trials. Nevertheless, a growing body of theoretical and experimental work suggests that diets designed to lower the insulin response to ingested carbohydrate (e.g., low GI) may improve access to stored metabolic fuels, decrease hunger, and promote weight loss. Such a diet would contain abundant quantities of vegetables, fruits and legumes, moderate amounts of protein and healthful fats, and decreased intake of refined grain products, potato and concentrated sugars. Indeed, this diet bears a close resemblance to that consumed by human ancestors over the last several hundred 1000 years. Finally, reductions in dietary GI may also lower the risks for various conditions associated with hyperinsulinemia, such as diabetes mellitus and cardiovascular disease.

25.14 Summary

- Glycemic index is a useful tool in managing glycemic control.
- Cardiovascular disease risk may be reduced by consuming a low glycemic index diet.
- Studies have shown clients can successfully incorporate the glycemic index in their dietary routine with positive outcomes.
- Weight loss may be another benefit found with choosing low glycemic index foods.
- More research into the long-term use of the glycemic index is required as many of these studies, particularly for CVD and weight management, were short or medium term studies.

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Chapter 26

Importance and Benefits of Lifestyles Changes Versus Diabetes Drugs in Effective Management of Diabetes

Pankaj Modi

Key Points

- Numerous health promotion projects often their impact on the lifestyle of the intended target audience has been rather limited.
- Modest change in diet and exercise habits can be of considerable importance when extrapolated to the population
- In order to achieve maximum benefit from lifestyle interventions changes are needed in addition to individual and community-based programs
- Changes include mandating more nutrition education in schools, banning the advertising of unhealthy products and subsidizing healthy foods at the expense of less appropriate foods
- In the etiology of type 2 diabetes, the risk associated with several individual nutrients is not entirely clear
- In making recommendations regarding the prevention of type 2 diabetes, priority should be given to the following: Early identification of subjects at risk of developing type 2 diabetes,
- Promotion and evaluation of “healthy” lifestyle program: Prevention and early treatment of overweight and obesity, particularly in high risk groups; Consumption of a nutrient-dense diet, which is low in fat, particularly saturated fat, and free sugars and high in Non Starch Polysaccharides, regular physical activity, moderate alcohol intake and cessation of cigarette smoking
- Evidence-based advice to public health authorities emphasizes the role of weight reduction in the overweight and obese and an increase in physical activity
- Evidence-based advice expected to have a positive effect for prevention of other major noncommunicable diseases such as cardiovascular disease and hypertension.

Keywords Diabetes • Impaired fasting glucose • Impaired glucose tolerance • Life style changes • Metformin • MNT (Medical Nutrition Therapy) • Type 1 • Type 2

26.1 About Diabetes

Diabetes is a chronic illness that requires continuing medical care and patient self-management education to prevent acute complications and to reduce the risk of long-term complications. Diabetes

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care is complex and requires that many issues, beyond glycemic control, be addressed. A large body of evidence exists that supports a range of interventions to improve diabetes outcomes.

These standards of care are intended to provide clinicians, patients, researchers, payers, and other interested individuals with the components of diabetes care, treatment goals, and tools to evaluate the quality of care. While individual preferences, comorbidities, and other patient factors may require modification of goals, targets that are desirable for most patients with diabetes are provided. These standards are not intended to preclude a more extensive evaluation and management of the patient by other specialists as needed. For more detailed information refer to references [1–3].

The recommendations included are screening, diagnostic, and therapeutic actions that are known or believed to favorably affect health outcomes of patients with diabetes. In the next 50 years, diagnosed diabetes is predicted to increase by 165% in the USA, with the largest relative increases seen among African Americans, American Indians and people from Alaska.

26.1.1 What Is Diabetes?

Diabetes indicates that the human body is in a condition of not being able either to make insulin, or to use insulin effectively. Without insulin, sugar (glucose) is not transported into the body's cells to provide them with the energy necessary to maintain proper organ function. Diabetes is not just a single disease. Rather, it includes an entire group of autoimmune diseases that result in the same disorder: too much sugar in the blood. While the human body does need sugar (glucose) for energy, serious health damage can occur when there is too much sugar in the blood.

In 1997, ADA issued new diagnostic and classification criteria [4–13] in 2003; modifications were made regarding the diagnosis of impaired fasting glucose. The classification of diabetes includes four clinical classes:

Type 1 diabetes: Results from β -cell destruction, usually leading to absolute insulin deficiency

Type 2 diabetes: Results from a progressive insulin secretory defect on the background of insulin resistance

Other specific types of diabetes: Due to other causes, e.g. genetic defects in β -cell function, genetic defects in insulin action, diseases of the exocrine pancreas (such as cystic fibrosis), and drug- or chemical-induced (such as in the treatment of AIDS or after organ transplantation)

Gestational Diabetes Mellitus: (GDM) (diabetes diagnosed during pregnancy)

Some patients cannot be clearly classified as type 1 or type 2 diabetes. Clinical presentation and disease progression vary considerably in both types of diabetes. Occasionally, patients who otherwise have type 2 diabetes may present with ketoacidosis. Similarly, patients with type 1 may have a late onset and slow (but relentless) progression of disease despite having features of autoimmune disease. Such difficulties in diagnosis may occur in children, adolescents, and adults. The true diagnosis may become more obvious over time.

26.1.1.1 Type 1 Diabetes

Type 1 diabetes, once known as juvenile or insulin-dependent diabetes, is most often diagnosed in children, teenagers, or young adults. Incidents do occur in the older population though this is not as common. In this disorder, the beta cells of the pancreas do not produce insulin due to a malfunction of the body's immune system. About 8–10% of those with diabetes are type 1 diabetic individuals. Type 1 diabetes require three or more insulin injections daily in order to maintain health.

26.1.1.2 Type 2 Diabetes

Type 2 diabetes, once known as adult-onset or non-insulin dependent diabetes, comprises the most common form of diabetes. Approximately 90–95% of diabetic individuals have type 2 diabetes. Oral medication in the beginning stages provides assistance to type 2 diabetic individuals in maintaining proper glucose levels and avoids insulin injection use. Proper diet and exercise and major lifestyle changes with moderate exercise proven useful in maintaining healthy blood sugar levels and possibly eliminating the need for oral medication altogether and may help hamper or delay the disease progression.

26.1.1.3 Gestational Diabetes

Gestational diabetes is most likely to develop in the mother during the late stages of pregnancy and will or may disappear once a baby is born depending on the mother's fitness and well being etc. Women who suffer from gestational diabetes are more likely to develop type 2 diabetes in later life, especially in overweight individuals.

26.1.2 What Causes Diabetes?

The underlying causes of type 1 diabetes and gestational diabetes remain uncertain, though research is ongoing. Links have been made with type 2 diabetes to excess weight accompanied by a lack of exercise and or sedentary lifestyles [6–15]. By the early twenty-first century, definite understanding with evidences were established indicating that the extensive use or consumption of ingredients such as high fat diets, fried foods, fructose corn syrup, sweet soda pop and baked goods, were found to be the culprits in developing metabolic disorders that lead to obesity. Obesity leads to an increased risk of developing diabetes, even among children and teenagers.

Risk factors for developing type 2 diabetes include a high body weight, physical inactivity, and smoking, whereas moderate consumption of alcohol or coffee appears to be protective [16–23]. The most serious of these factors is overweight. With every 1-unit increase in BMI, the risk of developing type 2 diabetes increases by ~10–30%. There is substantial evidence that lifestyle interventions focused on diet and physical exercise can reduce the diabetes incidence in individuals at high risk of developing diabetes [6–21]. Although the direct effect of lifestyle interventions on diabetes incidence in other target populations is relatively unknown, it is suggested that a relatively small shift of the entire general population toward more healthy behavior could lead to a reduction in the incidence of diabetes. Many people with type 2 diabetes can control their blood glucose by following a healthy meal plan and exercise program, losing excess weight, and taking oral medication. Some people with type 2 diabetes may also need insulin to control their blood glucose.

26.1.3 Diabetes Risk Factors and Complications

Diabetes comes with a high cost to individuals who do not properly maintain control of the blood glucose levels and for those who are failing to oral agent therapies. The complications include:

- Heart disease – individuals with diabetes have a higher risk of congestive heart failure and atherosclerotic heart disease than the rest of the population
- Blindness and eye diseases (Retinopathy)
- Kidney problems and failure (Renal failure)
- Nerve damage (Neuropathy)
- Poor circulation in legs and feet that can lead to neuropathy – because oxygen does not circulate properly with high blood sugar levels, healing of wounds will be delayed since the body needs oxygen to heal. In addition, with numbed sensation (as in neuropathy) a diabetic individual might not notice injury to a limb, and consequently be at greater risk for infections and amputations.

Other types of diabetes result from specific genetic conditions (such as maturity-onset diabetes of youth), surgery, medications, infections, pancreatic disease, and other illnesses. Such types of diabetes account for 1–5% of all diagnosed cases.

26.1.4 Diagnosis of Diabetes

Three ways to diagnose diabetes are recommended and each must be confirmed on a subsequent day unless unequivocal symptoms of hyperglycemia are present. Although the 75 g oral glucose tolerance test (OGTT) is more sensitive and modestly more specific than the fasting plasma glucose (FPG) to diagnose diabetes, it is poorly reproducible and difficult to perform in practice. Because of ease of use, acceptability to patients, and lower cost, the FPG has been the preferred diagnostic test. Though FPG is less sensitive than the OGTT, the vast majority of people who do not meet diagnostic criteria for diabetes by FPG but would by OGTT will have an A1c value well under 7.0% [1–13]. Though the OGTT is not recommended for routine clinical use, it may be useful for further evaluation of patients in whom diabetes is still strongly suspected but who have normal FPG or IFG (impaired fasting glucose).

The use of the A1c for the diagnosis of diabetes has previously not been recommended due to lack of global standardization and uncertainty about diagnostic thresholds. However, with a worldwide move toward a standardized assay and with increasing observational evidence about the prognostic significance of A1c, an Expert Committee on the Diagnosis of Diabetes was convened in 2008. This joint committee of ADA, the European Association for the Study of Diabetes, and the International Diabetes Federation will likely recommend that the A1c become the preferred diagnostic test for diabetes.

26.1.4.1 Diagnosis of Prediabetes

Hyperglycemia not sufficient to meet the diagnostic criteria for diabetes is categorized as either impaired fasting glucose (IFG) or impaired glucose tolerance (IGT), depending on whether it is identified through the FPG or the OGTT:

IFG = FPG 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L)

IGT = 2 h plasma glucose 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L)

IFG and IGT have been officially termed “prediabetes.” Both categories of prediabetes are risk factors for future diabetes and for cardiovascular disease (CVD).

26.1.4.2 Testing for Diabetes and Prediabetes in Asymptotic Patients

To test for prediabetes or diabetes, an FPG test or 2 h OGTT (75 g glucose load) or both are appropriate. An OGTT may be considered in patients with IFG to better define the risk of diabetes. For many illnesses, there is a major distinction between screening and diagnostic testing. However, for diabetes, the same tests would be used for “screening” as for diagnosis. Type 2 diabetes has a long asymptomatic phase and significant clinical risk markers.

26.1.4.3 Testing for Prediabetes and Type 2 Diabetes in Adults

Type 2 diabetes is frequently not diagnosed until complications appear, and approximately one-third of all people with diabetes may be undiagnosed. Although the effectiveness of early identification of prediabetes and diabetes through mass testing of asymptomatic individuals has not been definitively proven (and rigorous trials to provide such proof are unlikely to occur), prediabetes and diabetes meet established criteria for conditions in which early detection is appropriate. Both conditions are common, increasing in prevalence, and impose significant public health burdens.

Prediabetes: Impaired glucose tolerance and impaired fasting glucose.

Prediabetes is a condition in which individuals have blood glucose levels higher than normal but not high enough to be classified as diabetes. People with prediabetes have an increased risk of developing type 2 diabetes, heart disease, and stroke.

- People with prediabetes have impaired fasting glucose (IFG) or impaired glucose tolerance (IGT). Some people have both IFG and IGT.
- IFG is a condition in which the fasting blood sugar level is 100–125 milligrams per deciliter (mg/dL) after an overnight fast. This level is higher than normal but not high enough to be classified as diabetes.
- IGT is a condition in which the blood sugar level is 140–199 mg/dL after a 2 h oral glucose tolerance test. This level is higher than normal but not high enough to be classified as diabetes

Ignoring these symptoms and not looking after your health can lead to diabetes and its complications. People with IFG and IGT are advised to implement changes in their lifestyles and watch their diets. Bringing changes to life styles can be of great help in delaying the diabetes and thereby avoiding lots of health related expenses.

26.1.4.4 Screening for Type 1 Diabetes

Generally, people with type 1 diabetes present with acute symptoms of diabetes and markedly elevated blood glucose levels, and most cases are diagnosed soon after the onset of hyperglycemia. However, evidence from type 1 prevention studies suggests that the measurement of islet autoantibodies identifies individuals who are at risk for developing type 1 diabetes.

26.1.5 Total Prevalence of Diabetes and Prediabetes

Under 20 years of age: 0.25% or approximately 250,000 of all people in this age group have diabetes. About one in every 400–600 children and adolescents has type 1 diabetes. Two (2) million

adolescents (or 1 in 6 overweight adolescents) aged 12–19 have prediabetes. Although type 2 diabetes can occur in youth, the nationally representative data that would be needed to monitor diabetes trends in youth by type is not available. Clinically based reports and regional studies suggest that type 2 diabetes [22, 23], although still rare, is being diagnosed more frequently in children and adolescents, particularly in American Indians, African Americans, and Hispanic/Latino Americans.

Age 20 years or older: 23.5 million or 10.7% of all people in this age group have diabetes.

Age 60 years or older: 12.2 million or 23.1% of all people in this age group have diabetes.

Men: 12.0 million or 11.2% of all men aged 20 years or older have diabetes although nearly one-third of them do not know it.

Women: 11.5 million or 10.2% of all women aged 20 years or older have diabetes although nearly one quarter of them does not know it. The prevalence of diabetes is at least two to four times higher among non-Hispanic Black, Hispanic/Latino American, American Indian, and Asian/Pacific Islander women than among non-Hispanic white women.

Non-Hispanic whites: 14.9 million or 9.8% of all non-Hispanic whites aged 20 years or older have diabetes.

Non-Hispanic blacks: 3.7 million or 14.7% of all non-Hispanic blacks aged 20 years or older have diabetes.

26.1.5.1 Race and Ethnic Differences in Prevalence of Diagnosed Diabetes

Sufficient data are not available to derive prevalence estimates of both diagnosed and undiagnosed diabetes for all minority populations [22, 23]. For example, national survey data cannot provide reliable estimates for the Native Hawaiian and other Pacific Islander population. However, national estimates of diagnosed diabetes minority groups are available from national survey data and from the Indian Health Service (IHS) user population database, which includes data for approximately 1.4 million American Indians and Alaska Natives in the USA who receive healthcare from the IHS. Because most minority populations are younger and tend to develop diabetes at earlier ages than the non-Hispanic white population, it is important to control for population age differences when making race and ethnic comparisons. After adjusting for population age differences, 16.5% of the total adult population served by IHS had diagnosed diabetes, with rates varying by region from 6.0% among Alaska Native adults to 29.3% among American Indian adults in southern Arizona. After adjusting for population age differences, national survey data for people diagnosed with diabetes, aged 20 years or older include the following prevalence by race/ethnicity:

6.6% of non-Hispanic whites

7.5% of Asian Americans

10.4% of Hispanics

11.8% of non-Hispanic blacks

Among Hispanics rates were:

8.2% for Cubans

11.9% for Mexican Americans

12.6% for Puerto Ricans.

Prevalence of impaired fasting glucose (IGF) in people younger than 20 years of age (USA)

- In 2007, 8.0% of US adolescents aged 12–19 years had IFG.

Prevalence of impaired fasting glucose in people aged 20 years or older, USA, 2007

- In 2008, 27.9% of US adults aged 20 years or older had IFG (36.4% of adults aged 60 years or older). Applying this percentage to the entire US population in 2007 yields an estimated 57

million American adults aged 20 years or older with IFG, suggesting that at least 57 million American adults had prediabetes in 2007.

- After adjusting for population age and sex differences, IFG prevalence among US adults aged 20 years or older in 2007 was 23.1% for non-Hispanic blacks, 27.3% for non-Hispanic whites, and 26.9% for Mexican Americans.

Prevalence of diagnosed and undiagnosed diabetes in the USA, all ages, 2007

Total: 23.6 million people or 7.8% of the population have diabetes.

Diagnosed: 17.9 million people

Undiagnosed: 5.7 million people

Prevalence of diagnosed and undiagnosed diabetes among people aged 20 years or older, USA, 2007

Age 20 years or older: 23.5 million or 10.7% of all people in this age group have diabetes.

Age 60 years or older: 12.2 million or 23.1% of all people in this age group have diabetes.

Men: 12.0 million or 11.2% of all men aged 20 years or older have diabetes.

Women: 11.5 million or 10.2% of all women aged 20 years or older have diabetes.

Direct and Indirect Costs of Diabetes in the United States

The total annual economic cost of diabetes in 2007 was estimated to be \$174 billion. Medical expenditures totaled \$116 billion and were comprised of

\$27 billion for diabetes care,

\$58 billion for chronic diabetes-related complications,

\$31 billion for excess general medical costs.

Indirect costs resulting from increased absenteeism, reduced productivity, disease-related unemployment disability, and loss of productive capacity due to early mortality totaled \$58 billion. This is an increase of \$42 billion since 2002. This 32% increase means the dollar amount has risen over \$8 billion more each year [24–29]. The 2007 per capita annual costs of health care for people with diabetes is \$11,744 a year, of which \$6,649 (57%) is attributed to diabetes. One out of every five health care dollars is spent caring for someone with diagnosed diabetes, while one in ten health care dollars is attributed to diabetes.

26.1.6 Medical Expenditures Attributed to Diabetes

People with diagnosed diabetes, on average, have medical expenditures that are approximately two to three times higher than those without diabetes [24–29]. Diagnosed diabetes patients account for 6–8% of the total US population. \$58.3 billion was spent on inpatient hospital care and \$9.9 billion on physician's office visits directly attributed to diabetes. Diabetes-related hospitalizations totaled 24.3 million days in 2007, an increase of 7.4 million from the 16.9 million days in 2002. The average cost for a hospital inpatient day due to diabetes is \$1,853 and \$2,281 due to diabetes-related chronic complications, including neurological, peripheral vascular, cardiovascular, renal, metabolic, and ophthalmic complications.

26.1.6.1 Indirect Costs of Diabetes

Estimated Indirect Costs of Diabetes in 2007 was around \$58 billion. In 2007, diabetes accounted for 15 million work days absent, 120 million work days with reduced performance, 6 million reduced

productivity days for those not in the workforce, and an additional 107 million work days lost due to unemployment disability attributed to diabetes. Diabetes caused 445,000 cases of unemployment disability in 2007. The value of lost productivity due to premature death related to diabetes is \$26.9 billion.

The Increase in the Cost of Diabetes Reflects Three Causes

- The growth in diabetes prevalence
- Medical costs rising faster than general inflation
- Improvements made in the methods and data sources influencing cost estimates

The actual national burden of diabetes likely exceeds the \$174 billion estimate because it omits the social cost of intangibles such as pain and suffering, care provided by non-paid caregivers, excess medical costs associated with undiagnosed diabetes, and diabetes-attributed costs for health care expenditures categories not studied.

According to CDC, in 2007 23.6 million Americans had diabetes, with nearly a third undiagnosed. Another 57 million have prediabetes, and are likely to have the disease if they do not alter their living habits [24–29]. The 23.6 million represents a 13.5% increase from the 20.8 million in 2005. Many factors contribute to this rise, including higher prevalence of overweight and obesity, changes in diagnostic criteria, improved or enhanced detection, decreasing mortality, a growing elderly population, and growth in minority populations in whom the prevalence and incidence of diabetes are increasing.

Dietary trends across the world are of increasing concern. The rates of obesity and overweight are rising to epidemic proportions, with alarming increases in developing countries. Poor diet is a key risk factor contributing to a large portion of the world's disease burden. There has been a significant change in dietary habits and physical activity levels worldwide because of industrialization, urbanization, economic development and food market globalization (WHO). Diseases and conditions linked to poor diet include cardiovascular disease (29.2% of global deaths), diabetes (171 million people worldwide), and cancers (12.5% of global deaths; WHO). Obesity has reached alarming proportions and is still increasing with 1 billion adults overweight worldwide and at least 300 million of them clinically obese (WHO). Nutrition and physical activity in combination determine the bodies' energy balance and thus rates of obesity.

26.2 Prevention and Delay of Type 2 Diabetes

Diabetes requires a lifelong management plan, and persons with diabetes have a central role in this plan. Lifestyle modifications are an opportunity for diabetics to take charge of their health. Therefore, it is important to learn as much as possible about diabetes and to take an active role in making decisions about health care and treatment. Lifestyle modifications (changes in day-to-day habits) are an essential component of any diabetes management plan [1–21, 30–51]. Lifestyle modifications can be a very effective way to keep diabetes in control. Improved blood glucose control can slow the progression of long-term complications. Multiple small changes can lead to improvements in diabetes control, including a decreased need for medication. Nutrition is undoubtedly a major modifiable determinant of disease. The WHO has estimated that up to 2.7 million lives could be saved each year if fruit and vegetable consumption were sufficiently increased (WHO). Lifestyle changes related to diet have the potential to modify disease outcomes and costs of management.

Compelling scientific evidence exists that lifestyle change prevents or delays the occurrence of type 2 diabetes [30–51]. This body of evidence, obtained from three independent randomized, controlled trials from three countries, has definitively established that maintenance of modest weight loss (3–5 kg [7–10 lb]) through sustained lifestyle interventions including diet and physical activity reduces the incidence of type 2 diabetes in high-risk persons by 40–60% over 3–4 years. Patients with IGT or IFG should be referred to an effective ongoing support program for weight loss of 5–10% of body weight and for increasing physical activity to at least 150 min/week of moderate activity such as walking.

26.2.1 Identification of the Candidates for a Primary Prevention

The number of persons in the USA who meet the criteria of the American Diabetes Association for pre-diabetes is unknown [1–21]. The last nationally representative survey of the US population assessed by oral glucose tolerance testing was the Third National Health and Nutrition Examination Survey, which was conducted and tested on adults 40–74 years of age. Based on the data from that study, it was estimated that 17.9 million overweight adults 45–74 years of age in the USA would meet the American Diabetes Association criteria in 2007. Because the cut-point for impaired fasting glucose was recently decreased from 6.1 to 5.6 mmol/L (110–100 mg/dL), this estimate is low. If data on glucose tolerance were available on the remaining adults 25–39 years and those older than 74 years, the total number of persons with pre-diabetes would probably approach the 18.2 million who are currently estimated to have diabetes. Saydah and colleagues estimated that 14 million Americans meet the criteria of the Diabetes Prevention Program for intervention. By any definition, the number of persons at high risk is substantial.

It is unclear how best to identify persons at high risk for diabetes. Use of the oral glucose tolerance test is inconvenient and time-consuming. No diabetes prevention trial has been conducted in persons with impaired fasting glucose, but about 24% of persons with prediabetes have impaired fasting glucose, and their demographic and cardiovascular risk factors [52] are generally similar to those of persons with impaired glucose tolerance. Data are even more limited on the relationship between positive and negative results on non-fasting tests and subsequent classification by glucose tolerance testing.

Candidates for primary prevention might be identified in the clinical care system at an “opportunistic” encounter: i.e. during a visit by patients to their health care provider for a condition unrelated to diabetes prevention. This option is attractive because in 2000, 72.2% of US adults reported they had visited a physician for a routine checkup in the previous year. Opportunistic screening has important limitations, however: persons with limited or no access to clinical care will be missed and those with health insurance, those with access to higher-quality health care, and those who are more likely to use the health care system will be preferentially identified.

The US Preventive Services Task Force concluded that the evidence was insufficient to recommend for or against routine screening of asymptomatic adults for type 2 diabetes, impaired fasting glucose, or impaired glucose tolerance but noted that intensive lifestyle intervention should be considered for patients with the latter two conditions [30–51]. The recommendation of the Task Force was consistent with that of American Diabetes Association: Opportunistic screening should be considered in persons 45 years of age or older, particularly those with a body mass index of 25 kg/m² or greater, and in younger overweight adults with another risk factor for type 2 diabetes.

Other settings offer opportunities for screening and identification. For example, public health agencies and community-based organizations may wish to conduct screening and identification

efforts outside the clinical setting, such as mass screening programs in the general population. Such efforts would identify persons who may benefit from primary prevention. However, such programs have a responsibility to ensure medical follow-up of all participants with a positive result on a screening test. This additional responsibility of ensuring clinical follow-up poses a substantial challenge. The same challenge also applies to persons in whom diabetes is diagnosed because of screening, because these persons also require appropriate treatment. Analysis of data from the Third National Health and Nutrition Examination Survey indicates that screening for prediabetes could also identify some of the 6.5 million persons 45–74 years of age with previously undiagnosed diabetes [52]. The total number of overweight adults in the United States who are 45–74 years of age and have prediabetes or undiagnosed diabetes is estimated to be 18.6 million. This challenge to an already stretched health system is formidable.

The difficult challenges facing opportunistic and population-wide screening for prediabetes [30–39] raise the question of whether the blood glucose criterion should be eliminated. The idea of broadening eligibility for lifestyle intervention is appealing. First, the lifestyle intervention of the Diabetes Prevention Program [40–51] is consistent with current recommendations for the general public on diet, nutrition, and physical activity. Second, the epidemic of overweight and obesity that is thought to be largely responsible for the diabetes epidemic has affected all segments of the US population. Finally, lifestyle changes could have substantial collateral benefits, including decreased blood pressure, improved blood lipid levels, and better health-related quality of life. Reflecting the steady increase in overweight and obesity that has occurred over the past 20 years, 61% of US adults 20–74 years of age were overweight or obese, indeed, 29.9% of all US adults are obese. Another approach might target the 47 million Americans who meet the criteria for the metabolic syndrome. Given budgetary realities, provision of lifestyle intervention on this scale would probably substantially reduce the intensity and effectiveness of the intervention. In addition, many people in this large pool will have normal glucose tolerance and may never develop diabetes if the eligibility for primary prevention of type 2 diabetes is broadened.

26.2.2 *How Should Lifestyle Interventions Be Delivered?*

Although lifestyle interventions have great appeal, prescription medications are the intervention of choice in current practice [30–51]. Sixty percent of visits to a physician's office result in a prescription being written [53]. However, adherence to drug therapy for chronic health conditions is poor, adverse effects of medication errors are too common, and prescription drugs contribute strongly to the escalating cost of health care. Pharmaceutical interventions for chronic health conditions are appealing and straightforward [53]. In contrast, even the most highly motivated physicians typically have minimal education or training in lifestyle intervention, and they usually have inadequate access in their practice to the resources needed to support lifestyle intervention. Well-intentioned attempts by physicians to practice "lifestyle medicine" with scarce resources can lead to embittered rejection of health promotion.

Primary prevention of type 2 diabetes raises several issues related to integration of lifestyle intervention in clinical practice [30–51]. Although the specific interventions vary, all involve dietary change and increased physical activity to achieve weight loss. A fundamental issue is the appropriate role of physicians. No efficacy study had physicians directly involved in delivering interventions, but physicians did provide clinical oversight during the intervention process, working with intervention staff and providing encouragement to patients.

Integration of lifestyle intervention into current health care systems will require that physicians have ready access to effective programs and providers of lifestyle intervention, perhaps within the physician's own institution or at commercial firms that provide lifestyle programs by referral. Wherever interventions are provided, they must be linked to the community, its culture, and its values. Currently, it is unknown whether other practicing professionals could deliver interventions in the community with the efficacy similar to that of the interventionists of the Diabetes Prevention Program, who were trained in counseling on nutrition, exercise, and behavior modification. A new category of health interventionist may be needed, in substantial numbers, to deliver and sustain lifestyle intervention in the large number of persons who would be eligible for these services. Who will be responsible for administration of lifestyle intervention, how will quality be assessed and ensured, and how will society pay for these services and this new class of provider? Dietitians, diabetes educators, health educators, nurses, and community health workers are leading candidates. Efforts are under way to define clinical roles and responsibilities for facilitating adherence to lifestyle change. A detailed description of the proven lifestyle intervention developed by the Diabetes Prevention Program has been published.

Despite strong supporting evidence, the premise that lifestyle intervention should be integrated into clinical medicine has been questioned [40–51]. In one scenario, a meaningful decrease in diabetes will be achieved only by changing the underlying environmental factors that contribute to obesity and sedentary behaviors in the general population. Furthermore, because lifestyle interventions delivered within the health care system are assumed to be expensive and the groups at greatest risk for diabetes are least able to negotiate their “obesogenic” environments, lifestyle intervention will inevitably fail. In comparison, the cost of effective environmental solutions for diabetes prevention is said to be “trivial.” Although environmental approaches, such as pedestrian-friendly community design and improved access to healthy food choices could support change in the general population, little evidence is available on cost effectiveness. Changes at multiple levels will probably be needed to sustain lifestyle intervention.

26.2.3 Outcome Goals and Behavior Targets

Although the clinical goals might be prevention of diabetic complications and normalization of glucose tolerance, it is critical to present patients with specific outcome goals they can assess and short-term behavior targets they can achieve. An initial weight loss goal of 7–10% of baseline weight and a physical activity goal of 150 min/week to be achieved within 6 months are suggested [30, 31]. In addition, a single waist measurement (measured at the maximum horizontal girth) should be used to help track high-risk visceral fat, which correlates with fasting plasma glucose, levels, hemoglobin A1c levels, and insulin sensitivity, independent of BMI < 28. A waist measurement is considered at high risk when it is more than 40 in. in men and more than 35 in. in women [52].

26.2.4 Individualized Plans

Individual tailoring of diet and physical activity treatment plans is recommended by major guidelines focused on diabetes, obesity, and exercise. The Diabetes Prevention Program individually tailors short-term behavior targets (e.g., adjusting targets to match progress) and specific methods used to achieve them (e.g., trying ethnic foods) [54, 55].

26.2.4.1 Step by Step

Shaping: Patients often are overwhelmed by large goals that seem unachievable. Target behaviors should be phased in using small steps. The physical activity target can be gradually increased from 60 min/week of any enjoyable physical activity to more intense activity for longer periods. By starting gradually, the patient can build confidence in small steps, with each step having a higher likelihood of lasting success. Small steps also yield many opportunities for physician praise. The approach is designed to gradually improve adherence by praising small steps made toward the goals [54, 55].

Stepped Care: The technique is to start simple, adding more complex or expensive interventions only when needed. If self-monitoring and simple self-selected dietary changes result in weight loss, the focus can shift to maintenance. If patients are following the plan but no weight loss results, the physician can coach them to expand dietary changes and see what happens. If patients are not following the plan, the physician can explore the obstacles, brainstorm solutions with the patients, and adjust the plans. Patients with continuing problems may need to be referred to a diabetes educator or a registered dietitian or a qualified nurse case manager, or a behavior counselor.

26.2.4.2 Long Term Assistance

Achieving permanent changes in diet and physical activity patterns is a multiyear project. The longer the period of intervention, the more likely that improvement in weight loss and physical activity will be maintained. In the studies of patients who improved impaired glucose tolerance, the intensity of the interventions decreased after an initial 6–12 month period. Thus, frequent visits with a member of the health care team for at least 6 months, gradually tapering to no less often than every 3 months, is advised. This decrease in the intensity of medical care can coincide with referral to non-medical community supports for maintenance (e.g., diet groups, organized physical activities). Adherence and office visit compliance can be enhanced by regular mail or telephone contact by trained staff between office visits [54–57].

26.2.5 Cost Benefits of Lifestyle Intervention Opposed to Diabetes Drugs Therapy

26.2.5.1 What Are the Economic Implications?

Lifestyle intervention is often assumed too expensive for the health care system. However, few careful economic evaluations of diabetes prevention have been published [58–71].

Economic studies must answer two key questions about an intervention: how much does it cost, and is it a good value? To be useful for policymakers, both questions should be answered from the perspectives of payers and society. From the payer perspective (for example, a health insurer), only the direct medical costs of the intervention are relevant, because these are the costs for which the payer must reimburse the health care system. Direct medical costs include the costs of delivering the intervention, the costs of treating adverse effects of the intervention, and any cost savings that may occur from improved health status of those receiving the intervention (for example, reduction in hospital days and in use of prescription medications). From the societal perspective, additional costs are important. These include patient-specific direct medical costs (such as deductibles and copayments), direct non-medical costs (such as out-of-pocket costs to purchase exercise equipment and

cost of participant time to exercise), and indirect costs (such as cost of time lost from work because of injury while exercising).

Economic evaluation of the Diabetes Prevention Program allows the cost, and the cost-effectiveness, of lifestyle intervention and Metformin therapy to be directly compared from both the payer and societal perspectives. The Diabetes Prevention Program is unique in including a prospective economic evaluation in its study design. Data have been systematically collected on direct medical costs, direct non-medical costs, and indirect costs [72–79].

In the DPP, both the Metformin and lifestyle interventions were more expensive than the placebo intervention. In the Metformin intervention, most of the additional cost relative to the placebo intervention was accounted for by the cost of Metformin. In the lifestyle intervention, most of the additional cost relative to the placebo intervention was accounted for by staff time used for counseling and adherence monitoring. Although the lifestyle intervention cost 37% more than the Metformin intervention in year 1, the lifestyle intervention cost 12% and 7% less than the Metformin intervention in years 2 and 3. Because the cost of the lifestyle intervention was greater than the cost of the Metformin intervention in year 1 but less in subsequent years, the cost of the lifestyle intervention relative to the Metformin intervention decreased with follow-up beyond 3 years. To the extent that the cost of the Metformin intervention was reduced by using less expensive generic Metformin and to the extent that the lifestyle intervention was delivered with less staff time, thus, the cost of the interventions was substantially reduced [72–79].

26.3 Lifestyle Changes Versus Metformin

Recent large Diabetes Prevention Program (DPP) clinical trials from Asia, Europe, and North America have demonstrated that behavioral and medication interventions could delay or prevent the development of type 2 diabetes in persons with impaired glucose tolerance, which is defined by a plasma glucose level between 7.77 mmol/L (140 mg/dL) and 11.04 mmol/L (199 mg/dL) 2 h after a 75 g oral glucose load [1–20].

It was estimated through a number of clinical studies that the cost of identifying the IGT and the cost of the interventions represents less than one-half of the total direct medical costs for Diabetes Prevention Program (DPP) over 3 years ($\$2,919/\$7,375 = 40\%$ in the lifestyle, and $\$2,681/\$7,420 = 36\%$ in the Metformin group). It was shown that participation in the experimental interventions was associated with decreased direct medical costs of the care outside the DPP [72–88]. Compared with the placebo intervention group, participants randomized to the Metformin intervention group spent fewer days in the hospital, made fewer emergency room and urgent care visits, and took fewer prescription medications. When compared with the placebo intervention group, participants in the lifestyle intervention spent fewer days in the hospital, made less urgent care visits, outpatient visits, and calls to providers. In addition, they reported taking fewer prescription medications. Taken together over 3 years, this reduced health care utilization and decreased the direct medical costs of care outside the DPP by \$272 in the Metformin intervention group and \$423 in the lifestyle intervention group relative to the placebo intervention group. These cost savings offset a portion of the direct medical cost of the experimental interventions [80–88].

The direct non-medical costs affect the individual and society. To fully assess the impact of direct non-medical costs and to describe the resources used to estimate their costs, it was found that the participants in the lifestyle intervention group spent more time traveling to appointments, attending appointments, exercising, and they purchased more services and products related to physical activity and diet. While the lifestyle group spent substantially more time engaged in leisure time physical

activity than either Metformin or placebo participants, they reported greater enjoyment of these activities. Thus, the resulting direct non-medical cost was negligible. Both Metformin and lifestyle participants reported spending less time shopping and cooking than placebo participants. Lifestyle participants also reported lower food costs than Metformin and placebo participants – largely because of decreased cost of food consumed at restaurants. Because of more frequent DPP visits, participation in the lifestyle intervention was associated with substantially greater transportation costs. Compared to the placebo intervention group, the incremental direct non-medical cost was \$1,445 over 3 years. Over 60% of this incremental cost was related to greater participant time. In contrast, direct non-medical costs were \$9 less in the Metformin intervention group than in the placebo intervention group [88–90].

When leisure-time physical activity was valued independently of the participants' exercise preference at \$0, \$8, or \$16 per hour, the incremental direct non-medical cost of the lifestyle intervention compared with the placebo intervention increased substantially and ranged from \$1,469 to \$4,056 over 3 years. In contrast, direct non-medical costs decreased in the Metformin intervention group compared with the placebo intervention group (–\$12–\$352). Thus, the cost of the lifestyle intervention relative to the placebo intervention is sensitive to the value assigned to time spent exercising. Despite the greater frequency of lifestyle visits, the difference in indirect costs among intervention groups was small. The latter may reflect flexible scheduling arrangements that permit people to reduce time lost from work or usual activities. Compared with the placebo group, the indirect costs related to morbidity and mortality was lower in the lifestyle group but higher in the Metformin group. Thus, when compared with the placebo group, indirect costs were \$174 less in the lifestyle group and \$230 greater in the Metformin group over 3 years.

Over a lifetime, the placebo intervention was associated with the lowest direct medical costs and the lifestyle intervention was associated with the most QALYs (Quality Adjusted Life Years). Compared with the placebo intervention, the lifestyle intervention costs \$635 more over a lifetime and produced a gain of 0.57 QALY. The cost per QALY was approximately \$1,100. Compared with the placebo intervention, the Metformin intervention costs \$3,922 more over a lifetime and resulted in a gain of 0.13 QALY. When compared with the placebo intervention, the Metformin intervention costs approximately \$31,300 per QALY. Compared with the Metformin intervention, the lifestyle intervention costs \$3,287 less over a lifetime and resulted in a gain of 0.45 QALY. Thus, the lifestyle intervention dominated the Metformin intervention. The Metformin intervention was relatively cost-effective in the younger age groups but cost more than \$100,000 per QALY in participants 65 years of age or older. The reduced benefit (□ QALYs) of the Metformin intervention in the older age groups may explain the dramatic increased in the incremental cost-effectiveness ratios with age.

In general, health outcomes were best for the lifestyle intervention, intermediate for the Metformin intervention, and worst for the placebo intervention. It was estimated that the lifestyle intervention increased life expectancy by 6 months and reduced the cumulative incidence of blindness by 39%, end-stage renal disease by 38%, amputation by 35%, stroke by 9%, and coronary heart disease by 8%. The Metformin intervention increased life expectancy by 0.2 year and reduced the cumulative incidence of blindness by 16%, end-stage renal disease by 17%, amputation by 16%, stroke by 3% and coronary heart disease by 2% [88–90].

Cost-saving interventions present no difficulty with respect to policy implications. They should be rapidly and widely implemented since they are more effective and less expensive than existing therapies. However, most new treatments in diabetes are more effective and costly, requiring incremental resources per QALY. There is no universally accepted rule to evaluate such treatments. Researchers have proposed a system to rate interventions based on the likely magnitude of the net benefit associated with their application (cost per QALY). They argue that interventions that cost less than \$20,000 per QALY are an appropriate way to use resources, while those that

cost \$20,000–\$100,000 per QALY are probably appropriate, but those that cost greater than \$100,000 per QALY may not be a good use of resources.

26.3.1 What Are the Ethical Implications?

Different perspectives exist on the putative benefits of health promotion programs directed to disease prevention, such as weight loss to prevent type 2 diabetes. Some assert that the health promotion activities should be widely applied because the results are obviously beneficial with no substantial adverse effect whereas others describe the health promotion as inherently “tyrannical.” The thinking of most health professionals probably falls between these two extremes. What are the ethical implications of translating diabetes prevention by lifestyle intervention into clinical practice? [47, 91–103].

Possible harm associated with health recommendations has recently received considerable attention, especially medical errors. An opposing view holds that an even greater proof will be necessary in population-wide health promotion than in clinical care because of constraints on personal liberty and autonomy [98–103]. Evidence that health promotion aimed at the general public will improve health needs to be even stronger than evidence for treating sick patients.

Although efficacy studies, such as the Diabetes Prevention Program, are an essential step in improving health, they may not affect medical practice because of the “translation gap.” This effect may reflect ethical tension between the high internal validity, and often low “generalisability,” of clinical trials. All of the major efficacy studies of lifestyle for primary prevention of diabetes were restricted to persons with glucose intolerance who are at very high risk for type 2 diabetes. Strong internal validity is desirable in an efficacy study to establish causation. Lifestyle intervention can indeed prevent the development of type 2 diabetes in persons at high risk. However, the effectiveness of lifestyle intervention for persons at lower risk for diabetes is unknown. Is it ethical to await the results of a new, extensive series of randomized controlled trials to evaluate intervention efficacy in groups at lower risk for diabetes? Alternatively, is it acceptable to infer intervention efficacy in groups other than those defined by the eligibility criteria of the Diabetes Prevention Program? [95–103]

Despite high interest on the part of the public and media in lifestyle approaches and support from respected authorities, the public is becoming overburdened with health recommendations. Many of which are unclear, inconsistent, and impractical. Disease prevention programs that do not work in the real world, even if grounded in science, and may erode public confidence in lifestyle change as a worthy goal.

A third source of potential harm from broad-based disease prevention programs relates to the concepts of “limits” and “opportunity cost,” i.e. the opportunity forgone by spending fixed resources on one program instead of another. In medicine, as in all endeavors, available resources, including time, personnel, knowledge, and money, are limited. Strong scientific and economic evidence supports the benefits of secondary and tertiary prevention of complications of diabetes. Although gaps exist in clinical practice, the situation is improving. Implementation of lifestyle programs for primary prevention of diabetes without full consideration of the effect on resources needed for other proven, effective diabetes treatment programs could set back efforts to reduce the overall burden of diabetes [98–103].

In addition to lifestyle counseling, Metformin may be considered in those who are at very high risk for developing diabetes (combined IFG and IGT plus other risk factors such as A1C >6%, hypertension, low HDL cholesterol, elevated triglycerides, or family history of diabetes in a first-degree relative), who are obese and under 60 years of age. (E) Monitoring for the development of diabetes in those with pre-diabetes should be performed every year. (E)

Based on the results of clinical trials and the known risks of progression of pre-diabetes to diabetes, an ADA Consensus Development Panel concluded that persons with pre-diabetes (IGT and/or IFG)

should be counseled on lifestyle changes with goals similar to those of the Diabetes Prevention Program (DPP) (5–10% weight loss and moderate physical activity of 30 min per day) [7–12]. Regarding the more difficult issue of drug therapy for diabetes prevention, the consensus panel felt that Metformin should be the only drug considered for use in diabetes prevention. For other drugs, the issues of cost, side effects, and lack of persistence of effect in some studies led the panel to not recommend their use for diabetes prevention. Metformin use was recommended only for very-high-risk individuals (those with combined IGT and IFG who are obese and under 60 years of age with at least one other risk factor for diabetes). In addition, the panel highlighted the evidence that in the DPP, Metformin was most effective compared to lifestyle in those with BMI of at least 35 kg/m² and those under age 60 years.

26.4 Diabetes Prevention and MNT (Medical Nutrition Therapy)

Medical nutrition therapy (MNT) is an integral component of diabetes management and diabetes self-management education (DSME) [104–109]. (Medical nutrition therapy is the preferred term and should replace other terms, such as diet, diet therapy, and dietary management). MNT for diabetes includes the process and the system by which nutrition care is provided for diabetic individuals and the specific lifestyle recommendations for that care [110–122].

Medical *nutrition* therapy (MNT) is the development and provision of a nutritional treatment or therapy based on a detailed assessment of a person's medical history, psychosocial history, physical examination, and dietary history. It is used to treat an illness or condition, or as a means to prevent or delay disease or complications from diseases such as *diabetes*. The purpose of the assessment is to:

1. Determine the persons' need for therapy
2. Set parameters to plan a therapy
3. Develop a therapy plan
4. Determine the best method to initiate the therapy
5. Evaluate the effectiveness of the therapy

Goals of MNT that apply to individuals at risk for diabetes or with pre-diabetes

26.4.1 Achieve and Maintain

- Blood glucose levels in the normal range or as close to normal as is safely possible
- A lipid and lipoprotein profile that reduces the risk for vascular disease Blood pressure levels in the normal range or as close to normal as is safely possible
- To prevent, or at least slow, the rate of development of the chronic complications of diabetes by modifying nutrient intake and lifestyle
- To address individual nutrition needs, taking into account personal and cultural preferences and willingness to change
- To maintain the pleasure of eating by only limiting food choices when indicated by scientific evidence

Whether for management or prevention of diabetes and its complications, basic to the nutrition recommendations is the underlying concern for optimal nutrition through healthy food choices and

an active lifestyle. The ADA supports and incorporates the nutrition recommendations from major organizations, such as the US Department of Agriculture (Dietary Guidelines for Americans), American Heart Association, National Cholesterol Education Program, American Institute for Cancer Research, and Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.

ADA's goal in issuing the evidence-based position statement is to bring awareness of beneficial nutritional interventions to people with diabetes and their health care providers. But the recommendations also emphasizes the diabetes-preventative aspects of nutrition, such as the association between drinking sugared beverages and the obesity epidemic, the connection between obesity and the risk of diabetes, and the importance for all Americans of consuming recommended levels of fiber.

The 2006 medical nutrition therapy recommendations “accentuate the impact of food intake in the diabetic population; the need to monitor blood glucose after meals and monitor blood pressure and cholesterol; and how diet affects these values. They are very similar to the 2005 US Department of Agriculture (USDA) dietary guidelines and in general, as well as American Heart Association recommendations.”

The 2007 ADA update recommends:

Lifestyle changes, including nutritional education and behavior modification, reduced calorie and fat intake, and regular physical activity for overweight and obese individuals;

Daily fiber intake of 14 g/1,000 kcals (as recommended by the USDA);

- Saturated fat intake of <7% of total calories, minimal trans fat intake, and cholesterol intake of <200 mg/day for individuals with diabetes, plus carbohydrate monitoring to regulate blood glucose;
- Normal dietary protein intake (15–20% of energy) and avoidance of high-protein weight-loss diets and micronutrient supplementation except for specific deficiencies;
- Limited daily alcohol intake: one drink for women and two drinks for men; and
- Specific nutritional interventions for individuals with diabetes who are experiencing micro vascular complications, cardiovascular disease, hypertension, hypoglycemia, and acute illness.
- Because patients look to clinicians for guidance on how to integrate nutrition into their overall diabetes management, clinicians or dietitians should address nutritional issues at each patient visit, helping patients find nutrition information, and following ADA recommendations to refer diabetic patients to registered dietitians.

Although many studies have focused on the role of single nutrients, food, or food groups in disease prevention or promotion, emerging research suggests there are health benefits from food patterns that include mixtures of food containing multiple nutrients and non-nutrients [114–117]. Although this approach makes it difficult to elucidate mechanisms through which the diet composition affects a particular health outcome, it does represent a practical approach to making realistic nutrition recommendations for improving health.

26.5 Effectiveness of MNT

Evidence-based nutrition recommendations attempt to translate research data and clinically applicable evidence into nutrition care. However, the best available evidence must still be moderated by individual circumstances and preferences. The goal of evidence-based recommendations is to improve the quality of clinical judgments and facilitate cost-effective care. This is accomplished by increasing the awareness of clinicians and patients with diabetes to the evidence supporting nutrition services and the strength of that evidence, in both quality and quantity.

The nutrition prescription is determined by considering the treatment goals and lifestyle changes the diabetic patient is willing and able to make, rather than predetermined energy levels and percentages of carbohydrate, protein, and fat. The goal of nutrition intervention is to assist and facilitate individual lifestyle and behavior changes that will lead to improved metabolic control.

Lifestyle changes that are characterized by decreased physical activity and increased energy consumption have together promoted obesity, which is a remarkably strong risk factor for diabetes that both genes and behavior influence itself.

The current nutrition principles and recommendations for diabetes focus on lifestyle goals and strategies for the treatment of diabetes. Now, for the first time, the recommendations specifically addresses the lifestyle approaches to diabetes prevention; they distinguish MNT for treating and managing diabetes from MNT for preventing or delaying the onset of diabetes, as the two may not necessarily be the same [47, 91, 92, 94–97, 103, 122].

Individuals who have prediabetes or diabetes should receive individualized MNT; a registered dietitian familiar with the components of diabetes MNT best provides such therapy. Nutrition counseling should be sensitive to the personal needs, willingness to change, and ability to make changes of the individual with prediabetes or diabetes.

Clinical trials/outcome studies of MNT have reported decreases in HbA1c (A1C) of 1% in type 1 diabetes and 1–2% in type 2 diabetes, depending on the duration of diabetes. Meta-analysis of studies in nondiabetic, free-living subjects and expert committees report that MNT reduces LDL cholesterol by 15–25mg/dL. After initiation of MNT, improvements were apparent in 3–6 months. Meta-analysis and expert committees also support a role for lifestyle modification in treating hypertension.

26.5.1 Nutrition Recommendations for the Management of Diabetes

26.5.1.1 Carbohydrates

A dietary pattern that includes carbohydrate from fruits, vegetables, whole grains, legumes, and low-fat milk is encouraged for good health. Monitoring carbohydrate, whether by carbohydrate counting, exchanges, or experienced-based estimation remains a key strategy in achieving glycemic control. The use of glycemic index and load may provide a modest additional benefit over that observed when total carbohydrate is considered alone. Sucrose-containing foods can be substituted for other carbohydrates in the meal plan or, if added to the meal plan, covered with insulin or other glucose-lowering medications. Care should be taken to avoid excess energy intake. As for the general population, people with diabetes are encouraged to consume a variety of fiber-containing foods. However, evidence is lacking to recommend a higher fiber intake for people with diabetes than for the population as a whole. Sugar alcohols and nonnutritive sweeteners are safe when consumed within the daily intake levels established by the Food and Drug Administration (FDA). Control of blood glucose in an effort to achieve normal or near-normal levels is a primary goal of diabetes management. Food and nutrition interventions that reduce postprandial blood glucose excursions are important in this regard, since dietary carbohydrate is the major determinant of postprandial glucose levels. Low-carbohydrate diets might seem to be a logical approach to lowering postprandial glucose. However, foods that contain carbohydrate are important sources of energy, fiber, vitamins, and minerals and are important in dietary palatability. Therefore, these foods are important components of the diet for individuals with diabetes. Issues related to carbohydrate and glycemia have previously been extensively reviewed in American Diabetes Association reports and nutrition recommendations for the general public [114–121]. Both the quantity and the type or source of carbohydrates found in foods influence postprandial glucose levels.

26.5.1.2 Dietary Fat

There are potential benefits from low fat diets [123–127]. Low-fat diets are usually associated with modest loss of weight, which can be maintained as long as the diet is continued and if combined with aerobic exercise. In type 2 diabetic subjects, restrained eating behaviors combined with dietary fat restriction have been shown to have beneficial effects on glycemia, plasma lipids, and/or weight. A higher intake of total dietary fat is associated with higher levels of plasma LDL cholesterol, and the adverse effect of a higher carbohydrate intake on triglycerides has been found in individuals who have undiagnosed diabetes or have gained weight during the previous year. In type 2 diabetic subjects, restrained eating behaviors combined with dietary fat restriction have been shown to have beneficial effects on glycemia, plasma lipids, and/or weight. A higher intake of total dietary fat is associated with higher levels of plasma LDL cholesterol, and the adverse effect of a higher carbohydrate intake on triglycerides has been found in individuals who have undiagnosed diabetes or have gained weight during the previous year.

26.5.1.3 Whole Grains and Fiber

Recent studies have provided preliminary evidence for reduced risk of diabetes with increased intake of whole grains and dietary fiber [125–129]. A higher glycemic load was related to increased incidence of diabetes. The glycemic load is defined as the product of the glycemic index value of a food and its carbohydrate content in an average serving. It incorporates both the quality and quantity of carbohydrate consumed. However, glycemic load or glycemic index was not related to diabetes incidence in the Iowa Women's Health Study.

26.5.1.4 Micronutrients and Diabetes

Adequate intake of micronutrients within the range of Dietary Reference Intake (DRI) prevents deficiency diseases and is important in maintaining the health and well-being of patients with diabetes. Nutrient recommendations for adults, adolescents, children with type 1 or type 2 diabetes and for women with diabetes during pregnancy and lactation are similar for people with or without diabetes. However, uncontrolled diabetes is often associated with micronutrient deficiencies.

Individuals with diabetes should be educated about the importance of acquiring daily vitamin and mineral requirements from natural food sources, and about the potential toxicity of mega doses of vitamin and mineral supplements. In select groups, such as elderly individuals, pregnant or lactating women, strict vegetarians, or individuals on calorie-restricted diets, supplementation with a multivitamin preparation is advisable. However, vitamin and mineral supplementation in pharmacological dosages should be viewed as a therapeutic intervention and, as with medications, be subjected to placebo-controlled trials to demonstrate its safety and efficacy. Evaluation of the micronutrient status of patients with diabetes begins with a careful clinical history. This should include a food/nutrition history to document use of “health food,” over-the-counter vitamin, mineral, and herbal supplements, food supplements; and methods of preparing food [130–132].

26.5.1.5 Alcohol

When compared to abstinence and heavy drinking, moderate alcohol intake has been related to improved insulin sensitivity and reduced risk for diabetes. However, insufficient data exist to support a specific recommendation for moderate alcohol intake for prevention of type 2 diabetes, and potential adverse effects of heavy drinking must be carefully considered [133–135].

26.5.1.6 Cows Milk

Type 1 diabetes accounts for ~10% of all diabetes and, like type 2 diabetes, has both genetic and environmental determinants. Early introduction of cow's milk in infants may be an environmental factor contributing to the development of childhood diabetes, but the research evidence has been equivocal. Currently there are no clear dietary determinants of type 1 diabetes [136–139].

26.5.1.7 Complimentary Dietary Supplements

Some people with diabetes use complementary therapies for their health condition. For example, they may try acupuncture or biofeedback to help with painful symptoms. Some use dietary supplements in efforts to improve their blood glucose control, manage symptoms, and lessen the risk of developing serious complications such as heart problems.

This section addresses what is known about a few of the many supplements used for diabetes, with a focus on some that have been studied in clinical trials, such as alpha-lipoic acid, chromium, omega-3 fatty acids, and polyphenols [140–152].

Alpha-lipoic acid (ALA, also known as lipoic acid or thioctic acid) is an antioxidant – a substance that protects against cell damage. ALA is found in certain foods, such as liver, spinach, broccoli, and potatoes. Some people with type 2 diabetes take ALA supplements in the hope of lowering blood glucose levels by improving the body's ability to use insulin; others use ALA to prevent or treat diabetic neuropathy (a nerve disorder). Supplements are marketed as tablets or capsules.

ALA has been researched for its effect on insulin sensitivity, glucose metabolism, and diabetic neuropathy. Some studies have found benefits, but more research is needed. (There are some studies, reported from outside the USA, of ALA delivered intravenously; however, this research is outside the scope of this fact sheet.)

Because ALA might lower blood sugar too much, people with diabetes who take it must monitor their blood sugar levels very carefully.

Chromium is an essential trace mineral – that is, the body requires small amounts of it to function properly. Some people with diabetes take chromium in an effort to improve their blood glucose control. Chromium is found in many foods, but usually only in small amounts; relatively good sources include meat, whole grain products, and in some fruits, vegetables, and spices. In supplement form (capsules and tablets), it is sold as chromium picolinate, chromium chloride, and chromium nicotinate.

Chromium supplementation has been researched for its effect on glucose control in people with diabetes. Study results have been mixed. Some researchers have found benefits, but many of the studies have not been well designed. Additional high-quality research is needed. At low doses, short-term use of chromium appears to be safe for most adults. However, people with diabetes should be aware that chromium might cause blood sugar levels to go too low. High doses can cause serious side effects, including kidney problems – an issue of special concern to people with diabetes.

Omega-3 fatty acids are polyunsaturated fatty acids that come from foods such as fish, fish oil, vegetable oil (primarily canola and soybean), walnuts, and wheat germ. Omega-3 supplements are available as capsules or oils (such as fish oil). Omega-3s are important in a number of bodily functions, including the movement of calcium and other substances in and out of cells, the relaxation and

contraction of muscles, blood clotting, digestion, fertility, cell division, and growth. In addition, omega-3s are thought to protect against heart disease, reduce inflammation, and lower triglyceride levels.

Omega-3 fatty acids have been researched for their effect on controlling glucose and reducing heart disease risk in people with type 2 diabetes. Studies show that omega-3 fatty acids lower triglycerides, but do not affect blood glucose control, total cholesterol, or HDL (good) cholesterol in people with diabetes. In some studies, omega-3 fatty acids also raised LDL (bad) cholesterol. Additional research, particularly long-term studies that look specifically at heart disease in people with diabetes, is needed.

Omega-3s appear to be safe for most adults at low-to-moderate doses. Safety questions have been raised about fish oil supplements, because some species of fish can be contaminated by substances such as mercury, pesticides, or PCBs. In high doses, fish oil can interact with certain medications, including blood thinners and drugs used for high blood pressure.

Polyphenols – antioxidants found in tea and dark chocolate, among other dietary sources – are being studied for possible effects on vascular health (including blood pressure) and on the body's ability to use insulin. Laboratory studies suggest that EGCG, a polyphenol found in green tea, may protect against cardiovascular disease and have a beneficial effect on insulin activity and glucose control. However, a few small clinical trials studying EGCG and green tea in people with diabetes have not shown such effects.

No adverse effects of EGCG or green tea were discussed in these studies. Green tea is safe for most adults when used in moderate amounts. However, green tea contains caffeine, which can cause, in some people, insomnia, anxiety, or irritability, among other effects. Green tea also has small amounts of vitamin K, which can make anticoagulant drugs, such as warfarin, less effective.

Other supplements are also being studied for diabetes-related effects. For example:

Preliminary research has explored the use of garlic for lowering blood glucose levels, but findings have not been consistent. Studies of the effects of magnesium supplementation on blood glucose control have had mixed results, although researchers have found that eating a diet high in magnesium may lower the risk of diabetes.

There is not enough evidence to evaluate the effectiveness of coenzyme Q10 supplementation as a CAM therapy for diabetes; studies of its ability to affect glucose control have had conflicting findings. Researchers are studying whether the herb ginseng and the trace mineral vanadium might help control glucose levels. Some people with diabetes may also try botanicals such as prickly pear cactus, gurma, Coccinia indica, aloe vera, fenugreek, and bitter melon to control their glucose levels. However, there is limited research on the effectiveness of these botanicals for diabetes.

26.5.2 Barriers to Progress

Clinically, the major barrier to the combination of lifestyle modification and pharmacological treatment relates to the different specialty groups that focus on each approach. Although physicians feel competent to prescribe medication, they have little or no experience with lifestyle intervention. The lack of time the physician has available for each patient in primary care settings poses another barrier to use of lifestyle intervention. Conversely, the behaviorists who are most expert at lifestyle intervention are not qualified to prescribe drugs. From a research perspective, a major barrier is the complexity of the study design required for investigation of multiple behavior changes. Such studies require large sample sizes and relatively long duration.

26.5.3 Research on Multiple Lifestyle Changes

Research is needed to determine which lifestyle interventions act synergistically with each other and which combinations are less effective. Although it is often assumed that modification of multiple lifestyle factors will enhance prevention and treatment efforts for diabetes, research in other areas (e.g., smoking plus weight loss) suggests that targeting multiple behaviors may, in some cases, have a negative impact on treatment. Therefore, it is important to compare the effects of targeting a single lifestyle factor, sequencing of several lifestyle factors, or targeting multiple factors simultaneously. Whether physical activity has a special role as a catalyst for other lifestyle behavior changes deserves specific attention.

26.5.4 Research Combining Lifestyle and Pharmacological Treatment

Research is needed to develop strategies to maximize the effectiveness of the combination of lifestyle and pharmacological treatments. Such research should be multidisciplinary and examine lifestyle plus medication approaches for treatment of obesity, diabetes, and other CHD factors. Questions related to the timing of the two approaches, the impact of patient preference or choice (versus clinicians' choice) regarding these two modalities, and ways to train physicians and other clinicians in the use of lifestyle approaches within clinical settings deserve attention.

26.5.5 Bariatric Surgery

Bariatric surgery should be considered for adults with BMI ≥ 35 kg/m² and type 2 diabetes, especially if the diabetes is difficult to control with lifestyle and pharmacologic therapy. Patients with type 2 diabetes who have undergone bariatric surgery need life-long lifestyle support and medical monitoring. Although small trials have shown glycemic benefit of bariatric surgery in patients with type 2 diabetes and BMI of 30–35 kg/m², there is currently insufficient evidence to generally recommend surgery in patients with BMI <35 kg/m² outside of a research protocol. The long-term benefits, cost-effectiveness, and risks of bariatric surgery in individuals with type 2 diabetes should be studied in well-designed randomized controlled trials with optimal medical and lifestyle therapy as the comparator [152–155].

26.5.6 Diabetes Self-management Education

People with diabetes should receive DSME according to national standards when their diabetes is diagnosed and as needed thereafter. Self-management behavior change is the key outcome of DSME and should be measured and monitored as part of care. DSME should address psychosocial issues, since emotional well-being is strongly associated with positive diabetes outcomes.

26.5.7 Weight Loss

Excess body fat is perhaps the most notable modifiable risk factor for the development of type 2 diabetes. It is estimated that the risk of type 2 diabetes attributable to obesity is as much as 75%. Because of the effects of obesity on insulin resistance, weight loss is an important therapeutic objective for persons with type 2 diabetes. Short-term studies have demonstrated that weight loss in subjects with type 2 diabetes is associated with decreased insulin resistance, improved measures of glycemia and dyslipidemia and reduced blood pressure. However, long-term data assessing the extent to which these improvements can be maintained are not available. The reason long-term weight loss is difficult for most people to accomplish is probably because energy intake, energy expenditure and thereby body weight are regulated by the central nervous system. This regulation appears to be influenced by genetic factors. Furthermore, environmental factors often make losing weight difficult for those genetically predisposed to obesity.

Evidence demonstrates that structured, intensive lifestyle programs involving participant education, individualized counseling, reduced dietary fat and energy intake, regular physical activity and frequent participant contact are necessary to produce long-term weight loss of as much as 5–7% of starting weight. When dieting to lose weight, fat is probably the most important nutrient to restrict. Spontaneous food consumption and total energy intake are increased when the diet is high in fat and decreased when the diet is low in fat. Exercise by itself has only a modest effect on weight loss. However, exercise is to be encouraged because it improves insulin sensitivity, acutely lowers blood glucose, and is important in long-term maintenance of weight loss. Weight loss with behavioral therapy alone also has been modest and behavioral approaches may be most useful as an adjunct to other weight loss strategies. However, optimal strategies for preventing and treating obesity long-term have yet to be defined.

Standard weight loss diets provide 500–1,000 fewer calories than are estimated to be necessary for weight maintenance. Although many people can lose some weight (as much as 10% of initial weight) with such diets, the medical literature documents that without the other components of an intensive lifestyle program, long-term outcomes are poor. The majority of people regain the weight they have lost.

Meal replacements provide a defined amount of energy often as a formula product. Use of meal replacements once or twice daily to replace a usual meal can result in significant weight loss, but meal replacement therapy must be continued if weight loss is to be maintained. Very low calorie diets (VLCDs) provide 800 or fewer calories daily and produce substantial weight loss and rapid improvements in glycemia and lipemia in persons with type 2 diabetes. When VLCDs are stopped and self-selected meals are reintroduced, weight gain is common. Thus, VLCDs appear to have limited utility in the treatment of type 2 diabetes and should only be considered in conjunction with a structured weight maintenance program.

Despite these difficulties, several recent studies have demonstrated the potential for moderate, sustained weight loss to substantially reducing the risk for type 2 diabetes. Clinical trial data also support the potential for weight loss to reduce risk for diabetes. In the Da Qing Study, diet, exercise, and diet plus exercise all reduced the incidence of diabetes compared to the control condition [45]. In the Swedish Obese Subjects Study, obese individuals with sustained weight loss 2 years after bariatric surgery demonstrated substantially lower risk of type 2 diabetes and hyperinsulinemia compared to control subjects. Results from a 2-year clinical trial showed reduced risk for progression from impaired glucose tolerance to diabetes among individuals randomized to orlistat compared to those randomized to behavioral therapy [47, 91, 92, 106, 122, 156–160].

26.5.8 Exercise

Although, obesity is generally regarded as the salient modifiable risk factor for type 2 diabetes, decreased physical activity also has been identified as a diabetes risk factor, independent of its impact on energy balance. A relationship between physical activity and type 2 diabetes was suggested by studies in societies that had abandoned traditional lifestyles typically involving large amounts of habitual physical activity and subsequently experienced major increases in rates of type 2 diabetes. More recently, the fact that an active lifestyle may prevent or delay the development of type 2 diabetes has been demonstrated in a number of prospective studies [47, 91, 92, 111–113, 122, 156–160]. Protection from diabetes appears to occur from moderate intensity activities, such as brisk walking, as well as from participation in vigorous physical activity. Moreover, physical activity may provide some protection against mortality at all levels of glucose tolerance, as has been demonstrated in middle-aged men. Of interest in this regard was a large prospective observational study demonstrating that cardio respiratory fitness levels in men influenced the effects of obesity on health. No elevated mortality risk in obese men was observed if they were physically fit, and lean men had increased longevity only if they were physically fit. Thus, moderate-to-high cardio respiratory fitness may reduce mortality risk across all categories of body composition.

26.5.8.1 Frequency and Type of Exercise

The US Surgeon General's report recommended that most adults accumulate at least 30 min of moderate-intensity activity on most, ideally, all days of the week. The DPP lifestyle intervention, which included 150 min/week of moderate intensity exercise, had a beneficial effect on glycemia in those with prediabetes. Therefore, it seems reasonable to recommend 150 min of exercise per week for people with diabetes. Resistance exercise improves insulin sensitivity to about the same extent as aerobic exercise. Clinical trials have provided strong evidence for the A1C-lowering value of resistance training in older adults with type 2 diabetes and for an additive benefit of combined aerobic and resistance exercise in adults with type 2 diabetes.

26.5.8.2 Physical Activity

People with diabetes should be advised to perform at least 150 min/week of moderate-intensity aerobic physical activity (50–70% of maximum heart rate). In the absence of contraindications, people with type 2 diabetes should be encouraged to perform resistance training three times per week. ADA technical reviews on exercise in patients with diabetes have summarized the value of exercise in the diabetes management plan. Regular exercise has been shown to improve blood glucose control, reduce cardiovascular risk factors, contribute to weight loss, and improve well being. Furthermore, regular exercise may prevent type 2 diabetes in high-risk individuals. Structured exercise interventions of at least 8 weeks' duration have been shown to lower A1C by an average of 0.66% in people with type 2 diabetes, even with no significant change in BMI. Higher levels of exercise intensity are associated with greater improvements in A1C and in fitness.

26.6 Conclusions

In summary, compared with the placebo intervention, the DPP lifestyle and Metformin interventions provide substantial health benefits at an attractive cost. The lifestyle intervention, compared with the Metformin intervention, provided greater health benefits at lower costs and from the perspective of

a fiscally prudent policymaker, represents the intervention of choice. Investment in DPP lifestyle and Metformin interventions in high-risk individuals with impaired glucose tolerance may help stem the current epidemic of diabetes.

The DPP demonstrated that both medication and lifestyle interventions could delay or prevent progression from IGT to type 2 diabetes (1). This analysis demonstrates that such preventive strategies are associated with modest incremental costs. From the perspective of a large health system, both the Metformin and lifestyle interventions cost \$750 per participant per year, or \$2,250 per participant over 3 years. From a societal perspective, the incremental costs of both the Metformin and lifestyle intervention are greater and the relative increase is greater in the lifestyle than the Metformin intervention. This is not surprising in light of the greater direct nonmedical costs associated with the lifestyle intervention. Nevertheless, the incremental increases remain small. The costs of such prevention strategies must be balanced against the savings related to avert disease. It is likely that the cost of the Metformin intervention will decrease substantially with the availability of less expensive generic formulations of Metformin. It is also likely that the cost of the lifestyle intervention could be reduced by improving the efficiency of utilization of staff time by using group visits. Ultimate determination of the value of these interventions to health systems and society will require a formal assessment of costs relative to the health benefits achieved in the DPP.

A complete medical evaluation should be performed to classify the diabetes, detect the presence of diabetes complications, review previous treatment and glycemic control in patients with established diabetes, assist in formulating a management plan, and provide a basis for continuing care. Laboratory tests appropriate to the evaluation of each patient's medical condition should be performed. People with diabetes should receive medical care from a physician-coordinated team. Such teams may include, but are not limited to, physicians, nurse practitioners, physician's assistants, nurses, dietitians, pharmacists, and mental health professionals with expertise and a special interest in diabetes. It is essential in a collaborative and integrated team approach that individuals with diabetes assume an active role in their care.

The management plan should be formulated as an individualized therapeutic alliance among the patient and family, the physician, and other members of the health care team. A variety of strategies and techniques should be used to provide adequate education and development of problem-solving skills in the various aspects of diabetes management. Implementation of the management plan requires that each aspect is understood and agreed on by the patient as well as the care providers and that the goals and treatment plan are reasonable. Any plan should recognize diabetes self-management education (DSME) as an integral component of care. In developing the plan, consideration should be given to the patient's age, school or work schedule and conditions, physical activity, eating patterns, social situation and personality, cultural factors, and presence of complications of diabetes or other medical conditions.

Based on evidence from these trials and from the analyses of multiple risk factors, early identification of risk factors and intervention may contribute to the prevention of diabetes. A high BMI is one of the most potent risk factors for the development of diabetes. Therefore, persons should be targeted for intensive lifestyle prevention if they have BMI ≥ 25 plus two or more of the following risk factors: family history of diabetes, ethnicity of American Indian, African American, Hispanic or Asian/Pacific Islander, and/or insulin resistance. For these persons, an individualized strategy that focuses on losing weight, improving dietary composition, increasing physical activity, and avoiding smoking should be pursued. Lifestyle change should focus on increasing physical activity to improve the insulin sensitivity independent of the effect on BMI.

Weight loss alone may reverse the course of insulin resistance and normalize blood glucose concentrations. Sustaining weight loss is a difficult task, but even modest weight loss may confer substantial benefits for diabetes prevention. Dietary change should include a reduction in saturated and

trans fats, an increase in fruits, vegetables, and whole-grain foods, as well as maintenance of a low glycemic load. Lifestyle change should also focus on increasing physical activity to improve the insulin sensitivity independent of the effect on BMI.

The primary goals of MNT for diabetes are to improve metabolic control (glucose and lipids), provide appropriate calories, and improve overall health through optimal nutrition. Medical Nutrition Therapy (MNT) proved to be more cost effective by providing alternatives to more costly therapies. Medical nutrition therapy (MNT) can improve patients' health and quality of life, effectively treat and manage disease, reduce complications and decrease the need for prescription drugs. It can help patients manage conditions such as cardiovascular disease, hypertension, diabetes, kidney disease, obesity and related complications, cancer, and HIV/AIDS. Findings from the Diabetes Prevention Program showed that diet and exercise could effectively delay diabetes in a diverse American population of overweight persons with impaired glucose intolerance by 58%. A 50–70% reduction in recurrent cardiovascular disease events (cardiac death, nonfatal heart attacks, angina, and stroke) may be achieved in people on diet treatment alone.

Central to the nutrition recommendations is the need to individualize MNT, integrate nutrition into the overall diabetes management plan, and use an interdisciplinary team approach. Nutrition recommendations for people with diabetes should be based on the nutrition assessment, the desired treatment outcomes, and modification of usual food intake. Measurement and documentation of desired outcome should provide the information needed to evaluate how well MNT has been integrated into the overall diabetes management plan.

Prevention programs should target communities as well as individuals. Approaches that focus on individuals at risk work well for those who are motivated, but community-based prevention programs can benefit more people by facilitating the spread of culturally relevant messages and providing access to social support systems [90]. Additional economic evaluations are needed to examine the longer-term effect of diabetes prevention, including an analysis that uses mathematical models to estimate potential future reductions in micro vascular and macro vascular complications of diabetes and associated costs of maintaining lifestyle change [47]. A within-trial economic evaluation of diabetes prevention also needs to be supplemented with cost studies performed in real-world clinical and public health settings.

Experts all agree that if people at high risk of developing the disease follow a proper diet and lifestyle change, the development of the disease into full-blown diabetes can actually be delayed for more than 10 years or reduce the risk of having the disease by as much as 58%. However, with people who are already diagnosed with the disease, a strict diet and lifestyle change needs to be carefully planned and executed. First, everything is dependent on the responsibility of the person himself to adhere and be ready for a change from what he has been accustomed to in his life. To decrease the risk of diabetes and cardiovascular disease (CVD), healthy food choices and physical activities leading to moderate weight loss is highly recommended.

The campaign of the National Diabetes Education Program, codirected by the Centers for Disease Control and Prevention and the National Institutes of Health, [Small Steps, Big Rewards] can serve to promote awareness of the benefit of modest adaptations in lifestyle to prevent or delay the onset of diabetes [92].

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Chapter 27

Cost of Pycnogenol Supplementation and Traditional Diabetes Treatments per Unit of Improved Health Outcome

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Key Points

- Pycnogenol® may be cost effective in reducing the risk for diabetes-related complications.
- Diabetic retinopathy may be a good target area for Pycnogenol supplementation because of Pycnogenol's proven efficacy in improving diabetic retinopathy, diabetes-related cardiovascular disease, and other diabetes-related health complications.
- The cost of diabetes treatment may be reduced after Pycnogenol supplementation but a long term study should explore this possibility.
- The lack of side effects associated with Pycnogenol and demonstrated health benefits for diabetics may make it a suitable treatment for those wishing to reduce their risk for diabetes-related complications.

Keywords Cost–benefit • Diabetes • Glycemic control • Nutritional supplementation • Pycnogenol

27.1 Overview

This chapter analyzes the potential health and cost benefits of Pycnogenol supplementation for type II diabetics. Since there is an increasing prevalence of diabetes and a corresponding increase in the cost of diabetes, a cost-benefit analysis should provide a clear assessment of areas in which Pycnogenol supplementation could help mediate the increasing cost of diabetes. Additionally, Pycnogenol may provide significant health benefits for diabetics beyond the effects achieved by conventional medicine and could potentially increase quality of life. The following review will describe the prevalence and impact of diabetes while exploring some of the pathologies that may be improved with Pycnogenol supplementation. Following this review, a cost-benefit analysis will compare the improvements achieved by Pycnogenol with those achieved with standard, pharmaceutical regimens.

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27.1.1 Prevalence of Diabetes

In 2007, 23.6 million Americans were afflicted with diagnosed diabetes, an additional 5.7 million Americans were undiagnosed for diabetes, and 57 million had prediabetes that will develop into diabetes if lifestyle interventions do not occur [1]. Additionally, one in six overweight adolescents between 12 and 19 years had prediabetes in 2007 [2]. All ethnicities are affected by diabetes and prediabetes, however the prevalence of diagnosed diabetes is two to four times higher in Hispanics, Native Americans, and African Americans than in the majority population [3]. Globally, more than 171 million people have diabetes with an expectation that the number will double by the year 2030 [4]. The worldwide prevalence of diabetes highlights the importance of identifying cost-effective treatments and measures that may prevent the development of diabetes in predisposed individuals.

27.1.2 Complications Associated with Diabetes

Diabetes is associated with a myriad of complications including hypertension, retinopathy, nephropathy, neuropathy, cardiovascular disease, cerebrovascular disease and microvascular disease [5]. For example, 31.4% of diabetics over the age of 35 have been diagnosed with cardiovascular disease [6]. Along with cardiovascular disease, retinopathy represents one of the most common co-morbidities associated with diabetes and 40.3% of diabetics have been diagnosed with some stage of diabetic retinopathy [1]. Additionally, diabetics have twice the prevalence of physical disability as those without diabetes [7]. Most importantly, the age-adjusted mortality among adults in the United States with diabetes is two times the mortality of those without diabetes [8].

27.1.3 Pycnogenol as a Biological Mediator of Diabetes

Pycnogenol® is a registered trade mark of Horphag Research. Despite the prevalence of diabetes and the abundance of negative health effects, maintenance of health as well as a retarded progression of the disease for diabetics is possible with strict glucose and glycated hemoglobin A1c (HbA1c) control. This paper will explore the costs and benefits of Pycnogenol Pycnogenol, a maritime pine bark extract of *Pinus pinaster*, as a supplement to support glycemic control in diabetics. Pycnogenol is classified in the United States Pharmacopeia 28 as a supplement and consists of phenolic acids, catechin, taxifolin, and procyanidins [9]. Pycnogenol acts as a strong antioxidant and inhibits α -glucosidase [9, 10]. Pycnogenol has been found to work as an antidiabetic compound for the treatment diabetes-associated cardiovascular disease, microangiopathy, ulcers, microcirculatory impairments, and retinopathy [11–17]. Its role in mediating diabetes will be explored throughout this paper and recommendations for the alterations of current diabetic treatment regimens will reflect an analysis of the costs and benefits of Pycnogenol supplementation.

27.2 Reduction of Blood Glucose and HbA1c by Pycnogenol Supplementation

27.2.1 Impact of Glycemic Control on the Pathology of Diabetes

There are several indicators that relate to the relative severity of diabetes. HbA1c levels are hugely important in determining the risk of diabetes-related complications. For each increased unit of

HbA1c, the relative risk of developing heart failure increases 10–15% in diabetics [4]. Additionally, a 1 unit reduction in HbA1c is associated with a 37% decrease in risk for cardiovascular complications [18]. Along with HbA1c, the levels of glucose significantly impact the health of a diabetic. Hyperglycemia and hyperglycemia-induced free radical production results in an increased risk of microvascular complications, sensory neuropathy, myocardial infarction, stroke, and death [17–21]. Hyperglycemia also results in the formation of advanced glycated end-products through the reaction of sugars and amino groups in proteins, lipids, and nucleic acids. These advanced glycated end-products initiate proinflammatory processes that may increase the risk for microvascular disease. Strict glucose and HbA1c control is imperative in managing diabetes to prevent these and other adverse health effects, but additional costs are also related to poor glycemic control [22]. A retrospective analysis of a health plan database found that good glycemic control (HbA1c $\leq 7\%$) resulted in a decrease of 20% in direct medical costs compared to those with poor glycemic control (HbA1c $> 9\%$) [22]. Thus, poor glycemic control not only results in serious health consequences, but significantly increases the cost of treating diabetes.

The ability of Pycnogenol to block alpha-glucosidase is essential to reduce the risks and costs associated with hyperglycemia. Pycnogenol has been found to inhibit up to 93.63% of alpha-glucosidase activity *ex vivo*, and treatment with Pycnogenol has been associated with an 8.1% decrease of HbA1c levels in humans [17, 23]. When alpha-glucosidase is inhibited, glucose resorption and postprandial hyperglycemia are reduced [10]. The reduction of HbA1c levels, hyperglycemia and the inhibition of alpha-glucosidase has been identified in other studies after Pycnogenol supplementation, and has been shown to reduce diabetes-related complications [10–12, 21]. Specifically, microvascular diseases such as diabetic retinopathy, ulceration have been reduced after treatment with Pycnogenol [12, 13, 17, 24]. Overall, through the blockage of alpha-glucosidase and potentially other undetermined pathways, Pycnogenol has demonstrated its capacity to lower blood glucose levels and HbA1c levels that produce the adverse health effects listed above. Such biological changes should reduce health care costs of diabetes, which will be evaluated below.

27.3 Effects of Pycnogenol Supplementation on Cardiovascular Risk Factors

27.3.1 Impact of Cardiovascular Disease on Diabetics

Diabetes was determined to be an independent risk factor for cardiovascular disease [25]. Because of this correlation, 31.4% of diabetics over the age of 35 in the USA were diagnosed with cardiovascular disease in 2000 [6, 25]. Factors associated with diabetes such as hyperglycemia, elevated levels of peroxidized LDL, enhanced platelet aggregation, and increased oxidizability of LDL result in cardiovascular complications and various manifestations of microangiopathy, as reviewed by Gulati [14]. As a result of these risk factors, the mortality rate of diabetics from stroke is three times higher than non-diabetics; and, the medical costs for survivors of an acute stroke analyzed by Brandle et al. averaged \$26,600, compared with the per capita annual healthcare costs for diabetics of \$11,744 [1, 26, 27]. Diabetics also have an excessive incidence of myocardial infarction, compared to nondiabetics, which results in an increase in medical costs of more than 190% [19, 27]. A higher incidence of myocardial infarction in diabetics has been related to elevated atherosclerosis-promoting LDL and VLDL levels, which highlights the importance of maintaining a healthy balance of cholesterol in diabetics [19, 25].

Although cardiovascular disease is very prevalent and highly monitored among diabetics, it remains one of the major causes of death in diabetics [19]. Pycnogenol produces vasodilation, a

reduction in blood pressure, an increase in HDL levels, and a reduction in the peroxidation of LDL [12]. After Pycnogenol supplementation, diabetics have been able to control blood pressure under a lower dose of ACE inhibitors; the antihypertensive effect of Pycnogenol is mediated through several different pathways including a reduction in TXA2 levels and Endothelin 1 levels [12]. Because Pycnogenol reduces cardiovascular risk factors, diabetics may experience a reduction in risk for cardiovascular disease after Pycnogenol supplementation.

27.4 Microvascular Disease

27.4.1 Impact of Microvascular Damage on Diabetics

According to the NIH, 40–45% of diabetics have been diagnosed with some form of retinopathy, which can lead to cataracts, glaucoma, vision loss and blindness [1]. The inflammatory processes increased by a state of hyperglycemia have been shown to increase capillary permeability, which in the eye may result in macular edema [1]. Additionally, a decrease in glutathione peroxidase activity and a decrease in the levels of ascorbic acid has been found in the eyes of diabetics which may permit an increase in oxidative damage to the retina [27, 28]. Along with diabetic retinopathy, diabetic microangiopathy, specifically ulceration, represents a significant problem for diabetics. Because of microangiopathy, diabetics account for 50% nontraumatic amputations in the USA [29]. Since microangiopathy and retinopathy are both forms of microvascular damage, they both develop after increased capillary permeability and distal and macular edema, respectively [27–29].

27.4.2 Pycnogenol as a Mediator of Microvascular Disease

Many of the effects of Pycnogenol work to inhibit microvascular disease including retinopathy and microangiopathy in diabetics. Its ability to reduce blood glucose levels helps prevent hyperglycemia-induced inflammatory processes, and its vasodilatory capacity helps to limit the degeneration of capillaries by increasing collagen stability. Supplementation with Pycnogenol has increased visual acuity, retinal blood flow, and a decrease in retinal edema [15, 17]. Through these mechanisms, retinopathy was slowed and the condition was improved [15, 17]. For microangiopathy, similar results were found after Pycnogenol treatment. Because of the increased capillary permeability that leads to stasis and distal edema, healing of distal tissues is impaired and microabrasions that occur on a daily basis may lead to increased ulcer formation [13]. After only 4 weeks of treatment with Pycnogenol, capillary permeability has been significantly decreased and a decrease in visible edema has occurred in diabetic patients [24]. Another study showed similar results by demonstrating an improvement in microcirculation after 6 weeks of Pycnogenol treatment. Additionally, this study found that oral treatment resulted in the healing of 86% of ulcers compared to 61% of ulcers healed in the control group. This study also examined Pycnogenol as a topical agent and found that the most effective healing of ulcers occurred after oral and topical treatment of Pycnogenol [13]. These studies have shown that Pycnogenol may act as an effective treatment for both diabetic retinopathy and microangiopathy and improve the quality of life for diabetics suffering from microvascular disease.

27.5 Costs of Type II Diabetes

While type II diabetes is associated with serious health effects, the cost of treatment and loss of productivity contribute to the overall medical cost of type II diabetes. The total economic cost of diabetes in 2007 for the USA was estimated to be 147 billion dollars, excluding the losses in quality of life. The per capita annual cost of health care for people with diabetes was \$11,744 [1]. Globally, direct health care costs of diabetes range from 2.5% to 15% of annual health care budgets, which depend on local prevalence and type of treatments available [5]. The significant costs of poorly controlled diabetes clearly place a strain on individuals and communities. Any effort that may reduce the skyrocketing cost of diabetes-related complications and treatments may have positive impact and reduce the global financial burden of diabetes.

27.5.1 Cost of Pycnogenol Supplementation and Potential Benefits

According to retail prices, a dose of 125 mg/day, Pycnogenol would cost about \$226.30 per year in the USA. Metformin, a popular prescription drug for diabetes would cost \$581.67 per year for an average dose of 2,000 mg/day. Repaglinide (Prandin), a common nonsulfonylurea used for promoting insulin secretion, costs \$928.68 per year for an average dose of 2 mg/day and the sulfonylurea Glipizide costs around \$335.76 per year for an average dose of 20 mg/day. The cash prices listed for Metformin, Repaglinide, and Glipizide were obtained from a chain pharmacy in the USA and are current as of November, 2009. As with any supplement, the costs of taking Pycnogenol will be added on top of the costs of the traditional treatment regimen. However, the benefits of taking Pycnogenol may outweigh the additional cost. To answer this question, costs of Pycnogenol treatment will be compared with the standard pharmaceutical approach. The following sections will analyze the cost of Pycnogenol and compare its efficacy to that of traditional pharmacological treatments. It should be noted that the effects of dietary changes, exercise, and lifestyle changes have been reviewed using a cost-benefit analysis for diabetes in the Chapter 26 by P. Modi.

27.5.1.1 Comparative Cost of Pycnogenol Supplementation and Metformin, Sulfonylurea, Trolitazone, and Repaglinide Treatment to Promote Glycemic Control

Glycemic control is a vital component of managing diabetes and will be analyzed according to the ability of the following treatments to lower HbA1c levels and fasting glucose. Pycnogenol has been shown to produce a decrease in HbA1c of 0.8 percentage points and has lowered fasting blood glucose 23.7 mg/dL after 12 weeks of treatment [12]. Metformin is mainly used to control hyperglycemia and promote weight loss [30]. In diabetics, Metformin has been shown to consistently decrease fasting glucose levels by 52 mg/dL and HbA1c by 1.4 percentage points with a dose of 2,000 mg/day [31]. Along with Pycnogenol and Metformin, Glipizide, an inexpensive sulfonylurea, has been shown to decrease HbA1c levels 1.82 percentage points and fasting glucose levels between 57 and 74 mg/dL with a daily dose of 20 mg [32]. Finally, Repaglinide lowers fasting glucose levels 36.1 mg/dL and HbA1c levels by 1.1 percentage points with a dose of 2 mg each day [30, 33]. Overall, these treatments have fairly similar effects and each acts to promote glycemic control. The relative efficacy described here will be looked at in terms of cost and dose in order to determine the cost-effectiveness of each therapy.

Table 27.1 Cost-effectiveness of pycnogenol and traditional treatments for type II diabetes

	Pycnogenol (125 mg/day)	Metformin (2,000 mg/day)	Glipizide (20 mg/day)	Repaglinide (2 mg/day)
<i>Improvement in</i>				
HbA1c (%)	0.80 [12]	1.4 [31]	1.82 [32]	1.1 [33]
Fasting glucose (mg/dL)	23.7 [12]	52 [31]	74 [32]	36.1 [33]
LDL level (%)	11.94% [12]	15% [30]	no effect [30]	9.51% [34]
<i>Cost for each increment of improvement</i>				
HbA1c (cost for a reduction of 1 percentage point)	\$181.04	\$415.48	\$184.48	\$844.25
Fasting glucose (cost per mg/dL reduction)	\$9.55	\$11.19	\$4.54	\$25.73
LDL level (cost for each percent reduction)	\$18.95	\$38.78	N/A	\$97.65
Total yearly cost	\$226.30	\$581.67	\$335.76	\$928.68

Table 27.1 outlines the effects described in the above paragraph and provides a visual comparison of the costs for each health outcome. The costs of each treatment according to health outcome were determined by applying the cost of each treatment to the relative health benefits so a specific cost per effect level is measured. Even though Pycnogenol will be an additional cost to the treatment of diabetes, good glycemic control, measured by HbA1c levels below 7%, are associated with a 20% reduction in medical costs, which may actually pay for the additional expense [22]. Glipizide and Pycnogenol have a similar cost for each reduction of HbA1c, as seen in Table 27.1. However, since Glipizide is a sulfonylurea, it may not achieve the desired glycemic control in 75% of patients, which may reduce its overall cost-efficacy [30]. Repaglinide may not be as cost-effective in lowering HbA1c levels because this result is best achieved if Repaglinide is used along with Metformin treatment [35]. Pycnogenol shows promise with HbA1c levels, but has a much lower capacity to lower glucose levels.

Table 27.1 shows the cost comparison of the chosen therapies. Although the glucose-lowering effect of Pycnogenol treatment is not as pronounced as the other treatments, it is relatively cost-effective, with only the Glipizide more cost-effective. Once again, this table highlights the potential of Pycnogenol as an effective supplement to promote glycemic control. Although glycemic control is vital to reduce risk factors for comorbidities in diabetics, diabetes is an independent risk factor for cardiovascular disease [25]. The connection between diabetes and cardiovascular disease makes control of risk factors for cardiovascular disease an important focus when treating diabetes.

27.5.1.2 Comparative Cost of Pycnogenol Supplementation and Metformin Treatment to Reduce Risk Factors for Cardiovascular Disease

Pycnogenol has been shown to mediate some of the negative cardiovascular effects associated with type II diabetes including a decrease in blood pressure, reduced microbleedings, increase HDL levels while reducing LDL levels [12, 14]. The ability of Pycnogenol and pharmaceutical treatments to reduce LDL levels will be looked at in an attempt to examine the cost-effectiveness of each treatment with respect to reducing risks for cardiovascular disease. Although diabetes treatments have other effects that reduce the risk for cardiovascular disease, LDL levels are easily quantified, and there is data measuring LDL levels for both traditional treatments and Pycnogenol supplementation. In a further cost-benefit analyses, it may be very beneficial to explore some additional cardiovascular risk factors under a lens of a comparative cost-benefit analysis. For more information on risk factors for cardiovascular disease and the effect of Pycnogenol, see Chap. 28.

Table 27.2 Side effects for diabetes treatments

	Pycnogenol	Metformin	Glipizide	Repaglinide
Side effect prevalence	Minimal	Common	Minimal	Minimal
Side effect description	Dizziness, nausea [11]	Abdominal pain, diarrhea [36]	Hypoglycemia [37]	Hypoglycemia [30]

The effects on LDL levels for the traditional treatments can be seen in Table 27.1. A reduction in LDL levels in diabetics is incredibly important to reduce risk for more serious cardiovascular disease. Pycnogenol, as a supplement to other diabetes treatment regimens, may actually be more cost-effective than the other listed treatments in its ability to reduce LDL levels; however, it is an additional cost. The cost of Pycnogenol must be considered on an individual basis to determine whether the cost is beneficial or potentially superfluous in order to achieve an effective cost-benefit.

27.5.1.3 Other Considerations

The monetary cost associated with a given benefit can highlight a specific treatment's promise to increase health in a cost-effective way. However, along with the monetary cost of any pharmaceutical therapy come side effects that may reduce the overall satisfaction with the drug and desire to continue treatment. There are multiple, potentially significant side effects associated with Metformin treatment, including gastrointestinal discomfort, diarrhea, a reduction in vitamin B12 absorption, hypoglycemia, and lactic acidosis, that are not experienced with Pycnogenol or the other treatments [30]. These side effects may reduce the overall cost-effectiveness and desirability of Metformin treatment. All of the most common side effects associated with the treatments chosen for comparison are shown in Table 27.2. Pycnogenol is very rarely associated with negative side effects but transitory dizziness and gastrointestinal problems such as diarrhea or constipation have been noted. However, dizziness was only reported in one study looking at treatments for diabetes so the potential for benefit should still be balanced with the small potential for a temporary side effect.

27.6 Conclusion

Pycnogenol shows promise as a supplement to traditional diabetes treatments and is competitively cost-effective as compared to the pharmaceutical regimen. Since Pycnogenol effectively lowers HbA1c levels, blood glucose, LDL levels, and has an antihypertensive effect, it appears to have potential to significantly reduce the risk for developing diabetes-related co-morbidities in diabetics receiving supplements. Because of the ability of Pycnogenol to reduce factors directly associated with the costs of diabetes, supplementation with Pycnogenol may be able to reduce the overall medical costs of living with type II diabetes. Diabetes is a global financial burden and reductions in the cost of treatment could have a positive impact the medical costs of diabetes. While this chapter reviews the potential cost and benefits of Pycnogenol supplementation in diabetics, a long term clinical study would be needed to quantify how much Pycnogenol reduces the medical costs of diabetes. Because of the multitude of benefits offered by Pycnogenol to diabetics, it seems likely that Pycnogenol supplementation could drastically reduce the overall cost of type II diabetes, even if is added as a supplement and additional cost to a traditional regimen. Along with a study exploring the potential reduction in the costs of diabetes after Pycnogenol supplementation, it would be interesting

to see if Pycnogenol could maintain its efficacy after reducing the dose of traditional medicines. If a reduction is possible and safe, the cost of treating type II diabetes may be decreased substantially and the burden of negative side effects associated with pharmaceuticals may be alleviated. Additionally, since diabetes is associated with an increased rate of mortality, it would be interesting to see if Pycnogenol could increase survival, which may be another cost-benefit.

Because Pycnogenol appeared to be relatively cost-effective, Pycnogenol should positive effects for patients who are maxed out on traditional treatments and still have uncontrolled diabetes. Because of the promise of increased glycemic control and decrease in cardiovascular disease, micro, and macrovascular health effects Pycnogenol may help those individuals whose diabetes is uncontrolled. The cost-effectiveness of Pycnogenol may also make this supplementation accessible to a wide population in need of improved glycemic control. The cost and prevalence of diabetes continues to increase, which makes a cost-effective supplement like Pycnogenol very promising as a mediator of this cost and should be considered as a supplement for type II diabetics after considering the potential benefits.

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Chapter 28

Pycnogenol Supplementation and Cardiovascular Health: Treatment and Cost-Benefit Analysis

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Key Points

- Major risk factors for cardiovascular disease include hypertension, diabetes, dyslipidemia, endothelial function, and clotting abnormalities.
- Pycnogenol®, an extract of bark from the French maritime pine *Pinus pinaster*, is a clinically researched dietary supplement that counteracts several cardiovascular risk factors.
- Pycnogenol may be cost effective in reducing the risk for cardiovascular disease.
- The minimal side effects and health benefits associated with Pycnogenol may make it a suitable treatment for those wishing to reduce their risk for cardiovascular disease.

Keywords Cardiovascular disease • Cholesterol • Cost–benefit • Diabetes • Endothelial function • Hypertension • Pycnogenol

28.1 Overview

This review will detail the relationship between cardiovascular disease (CVD) as the leading cause of death and disability in the USA, and the correlating costs for treatment and maintenance of cardiovascular health. The different risk factors and consequences related to cardiovascular disease will be reviewed, as will the actual costs of treating CVD and maintaining costs involving CVD throughout a lifetime. The specific focus is on Pycnogenol, a clinically researched dietary supplement that counteracts several cardiovascular risk factors. We will explore Pycnogenol as an alternative for conventional cardiovascular care, and will evaluate its cost-effectiveness as an approach to reducing the risk factors associated with CVD.

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28.2 Biological Profile of Pycnogenol

The bark extract of the French maritime pine (*Pinus pinaster*), better known by its trade name Pycnogenol, has been demonstrated in numerous studies as an effective mediator of improving cardiovascular health. Pycnogenol® is a registered trade mark of Horphag Research. It is composed of water-soluble phenolic substances chemically classified as flavonoids [1]. As an antioxidant; Pycnogenol exhibits various antioxidant and anti-inflammatory effects, including free radical scavenging activity, sparing activity of α -tocopherol and recycling of ascorbate radical, inhibition of lipid peroxidation, protection of nerve cells against β -amyloid (glutamate induced toxicity), protection of erythrocytes in G6PD deficient humans, increased antioxidant capacity and activity in humans, anti-inflammatory effects, inhibition of proinflammatory cytokine actions, inhibition of histamine release from mast cells, wound healing effects as reviewed by Gulati [2]. Antioxidants enhance endothelial nitric oxide (NO) synthase expression and subsequent NO release from endothelial cells [3].

Pycnogenol has also been shown to recycle ascorbic radicals in the bloodstream and protect vitamin E against oxidation [4]. In clinical studies, Pycnogenol was found to counteract increased platelet aggregation in smokers [5], improve microcirculation [6], and increase capillary integrity in vascular disorders [7]. It was also shown to act as an anti-inflammatory agent by inhibiting UV-induced erythema [8] among many other health benefits. Ongoing research revolving around the numerous health benefits of Pycnogenol gives us continuous insight into neutralizing risk factors that may lead to cardiovascular disease.

28.3 Role of Pycnogenol in Reducing Risk Factors for Cardiovascular Disease

28.3.1 Hypertension

Hypertension, or a blood pressure (BP) higher than 140/90 mmHg, is the most common risk factor for cardiovascular and cerebrovascular morbidity and mortality including stroke, coronary heart disease, heart failure, and kidney failure [9]. In the USA, high blood pressure is responsible for 40,000 deaths annually in the USA, while being the most modifiable risk factor for stroke. Hypertension affects about one in four adults, or almost 50 million people, making it the most common chronic condition in the country [10, 11]. Prehypertensive individuals have a high probability of developing hypertension and carry an excess risk of cardiovascular disease as compared with those with a normal BP (systolic BP <120 mmHg and diastolic BP <80 mmHg) [12]. Recent data indicate that the prevalence of hypertension is increasing [13] and that control rates among those with hypertension remain low [14]. While higher blood pressure increases the likelihood of a cardiovascular event, hypertension is not often well controlled, and too few patients are adequately treated [15].

In a study done by Zibadi et al. [16], it was determined that the antihypertensive effect of Pycnogenol is controlled in part by suppression of serum endothelin-1, a vasoconstrictor peptide produced by endothelial cells, which is generally higher in patients with Type II diabetes and hypertension [17]. This effect most likely works in conjunction with multiple mechanisms, including the inhibitory effect of Pycnogenol on angiotensin converting enzyme (ACE) [18]. These effects should lead to a decrease in serum angiotensin-II levels which in turn improves flow-mediated vasodilation. Other vasodilatory mechanisms that Pycnogenol affects include production of nitric oxide [19], which opposes the actions of endothelium-derived constricting factors including angiotensin-II,

endothelin-I, and reactive oxygen species [20]. Vasodilation decreases hypertension by increasing arterial volume and thereby decreasing pressure, therefore the cost benefits of Pycnogenol will be compared to an ACE inhibitor.

28.3.2 Diabetes

Cardiovascular disease is one of the major causes of death in diabetics, despite its prevalence and treatment [21]. Factors associated with diabetes such as hyperglycemia, elevated levels of lipid peroxidation products, enhanced platelet aggregation, and increased oxidizability of LDL, result in cardiovascular complications and various symptoms of microangiopathy [5]. As a result of these risk factors, the mortality rate of diabetics from stroke is three times higher than nondiabetics.

Because diabetes is a major risk factor for heart disease, improving diabetes should result in a decrease in occurrences of heart failure and likelihood of elevated heart disease. Diabetics have an excessive incidence of myocardial infarction when compared with nondiabetics, which has been related to elevated atherosclerosis-promoting LDL and VLDL levels.

Pycnogenol has been shown to reduce fasting and postprandial serum glucose levels [22] and to lower glycosylated hemoglobin (HbA1c) [16] in patients with Type II diabetes mellitus, as well as produce vasodilation, reduce blood pressure, increase HDL levels, and reduce the peroxidation of LDL [16, 23, 24] as in nondiabetic hypertensive patients. Through these mechanisms, circulation improves in diabetics, blood pressure is lowered, and retinal microbleedings are reduced [23]. After Pycnogenol supplementation, diabetics are better able to control blood pressure under a lower dose of ACE (angiotensin converting enzyme) inhibitors.

For more information on the cost-benefits of Pycnogenol in reducing diabetes, see the chapter written by G. Bentley (Chap. 27).

28.3.3 Dyslipidemia

Dyslipidemia may lead to reduced endothelial function, due to the stiffening of arteries induced by lipid accumulation. In a study involving Pycnogenol supplementation and measures of oxidative stress and plasma lipoproteins, an increase in plasma polyphenol levels was found to correspond with a significant increase in oxygen radical absorbance capacity (ORAC) in blood, as well as normalization of plasma lipoproteins [25]. Significantly reduced LDL-cholesterol levels and increased HDL-cholesterol levels were observed. In another study performed by Durackova et al., total cholesterol levels in patients suffering from erectile dysfunction were decreased from 5.41 to 4.98 mmol/L and LDL-cholesterol levels from 3.44 to 2.78 mmol/L after 3 months of Pycnogenol supplementation [24]. Pycnogenol has been found to protect LDL from oxidation by way of its radical scavenging activity [26]. Peroxidation of lipids may result in cell damage, aside from increasing the risk of cardiovascular disease.

28.3.4 Endothelial Function

Endothelial dysfunction is the initial step in the pathogenesis of atherosclerosis, resulting in cardiovascular outcomes [21]. The overactivity of platelets poses as a risk factor for atherosclerosis as well [5]. Platelet aggregation is often triggered by cigarette smoking.

Pycnogenol stimulates the activity of endothelial NOS (e-NOS) [19], which catalyses the synthesis of NO in isolated aortic rings, generating a relaxing signal through cyclic GMP to smooth muscle cells. By another function, antioxidants such as bioflavonoids (like those in Pycnogenol) enhance endothelial NO synthase expression and subsequent NO release from endothelial cells [19]. Endothelial dysfunction resulting from oxidative stress could also be reduced after supplementation with Pycnogenol [17].

28.3.5 Platelet Aggregation

Cigarette smoking increases platelet aggregation inside blood vessels within 2 h of smoking a cigarette. Platelet aggregation poses a risk for cardiovascular disease in that it increases the risk of thrombosis and decreases blood flow, as do high serum lipid levels and atherosclerosis. In a dose-dependent manner, Pycnogenol inhibits epinephrine-induced platelet aggregation in vitro; this is highly beneficial, as smoking doubles plasma epinephrine concentration [27, 28].

28.4 Cost Benefit Analysis of Supplementation with Pycnogenol

As the leading cause of morbidity and mortality in the USA, the cost to control risk factors and subsequently health consequences of cardiovascular disease is rising every year. The total direct and indirect cost of cardiovascular diseases and stroke in the USA for 2009 is estimated at \$475.3 billion, with \$73.4 billion of that being just the cost of hypertensive disease [11] and \$174 billion the cost of Type 2 diabetes [29]. This includes health expenditures (direct costs) and lost productivity resulting from morbidity and mortality (indirect costs). While Pycnogenol is a supplement and not a replacement for any treatment, the added cost may negate the cost of standard treatment in the long run. The following sections will analyze the cost of Pycnogenol and compare its efficacy to the efficacy of four pharmaceutical drugs commonly used to control cardiovascular risk factors: the ACE-inhibitor ramipril, the enzyme-blocker pravastatin, the calcium-channel blocker nifedipine, and aspirin as an inhibitor of platelet aggregation.

28.4.1 Comparative Cost of Pycnogenol Supplementation and ACE-Inhibitor Treatment to Reduce Hypertension

ACE inhibitors are used by tens of millions of Americans to treat high blood pressure, heart failure, to prevent repeat heart attacks, and to prevent the decline of kidney function in people with high blood pressure and/or diabetes [30]. However, they should not be used as the initial treatment for most people with high blood pressure who do not have heart disease, diabetes, or kidney disease, because generic diuretic can usually control hypertension by itself [30].

According to the results from the study performed by Zibadi et al., Pycnogenol aids in controlling blood pressure with a lower dose of ACE inhibitors in individuals with Type 2 diabetes [16]. In the study 58.3% of the subjects treated with Pycnogenol achieved normal blood pressure levels at the

end of 12 weeks, while reducing their pretrial dose of ACE inhibitors by 50% as well. A 17.8% decrease also occurred in the serum endothelin-1 levels, which plays a key part in modulating endothelial function.

ACE inhibitors come in many different doses and brands, depending on the symptoms the patient is experiencing. If we look at the yearly cost of an ACE-inhibitor such as ramipril, which is recommended for those with hypertension due to diabetes or kidney disease [30], we find that a 10 mg generic brand capsule of ramipril is around \$1.67 per capsule, or \$698.21 yearly. A 50% dose reduction of ramipril actually does not change the price as much, since the price of a 5 mg capsule is \$1.30, or \$474.38 yearly. That means, with Pycnogenol supplementation at a dose of 200 mg daily, the yearly cost would be \$616.73, which is actually cheaper than exclusively treating hypertension with ramipril alone. ACE inhibitors are generally safe, but they can cause side effects, including a persistent dry cough, fatigue, weakness, dizziness, and potassium imbalance. They can also cause a rare but life-threatening swelling of the windpipe [30]. In multiple studies involving Pycnogenol supplementation, the side effects of Pycnogenol have been statistically insignificant or not present at all [17, 31, 32].

28.4.2 Comparative Cost of Pycnogenol Supplementation and Pravastatin to Reduce Cholesterol Levels

Buildup of cholesterol and other fats along the walls of the blood vessels causes atherosclerosis and decreases blood flow and subsequent oxygen supply to the heart, brain, and other parts of the body. Lowering blood levels of cholesterol and other fats may help to decrease your chances of getting heart disease, angina (chest pain), strokes, and heart attacks [33]. Pravastatin is in a class of medications called HMG-CoA reductase inhibitors (statins). It works by slowing the production of cholesterol in the body [33]. It is used together with lifestyle changes (diet, weight-loss, exercise) to reduce the amount of cholesterol and other fatty substances in the blood.

In a study performed by Nakamura et al., it was found that after treatment with 10–20 mg pravastatin daily, mean total cholesterol was reduced by 11.5% (from 6.27 to 5.55 mmol/L) and mean LDL cholesterol by 18.0% (from 4.05 to 3.31 mmol/L) [34]. In a study performed by Durackova et al. evaluating the effects of Pycnogenol on lipid metabolism, it was found that Pycnogenol lowered mean total cholesterol by 7.9% (from 5.41 to 4.98 mmol/L) and LDL cholesterol by 19.2% (from 3.44 to 2.78 mmol/L) [24]. While the reductions are not identical, they are comparable; therefore we can suggest that the substitution of Pycnogenol for pravastatin would have comparable long-term effects on lipid metabolism, and therefore would lower the lifelong cost of living without cholesterol treatment.

The daily cost of treatment with pravastatin comes to about \$1.67, or \$608.21 yearly. This is more than twice as much as the cost of yearly supplementation with Pycnogenol, which is about \$222.65 for a 100 mg dose. In a study comparing cost-effectiveness of pravastatin in a placebo-controlled trial in younger (31–64 years) and older patients (65–74 years) with previous acute coronary syndromes, the life expectancy to age 82 years of additional survivors was 9.1 years in the older and 17.3 years in the younger [35]. Incremental costs per life-year saved were \$7,581 in the older and \$14,944 in the younger, if discounted at 5% per annum. Pravastatin therapy was more cost-effective among older than younger patients, because of their higher baseline risk and greater cost offsets, despite their shorter life expectancy.

28.4.3 Comparative Cost of Pycnogenol Supplementation and Nifedipine Treatment to Improve Endothelial Function

According to Zibadi et al., Pycnogenol aids in controlling blood pressure with a lower dose of ACE inhibitors in individuals with Type 2 diabetes [16]. In hypertension, recent clinical guidelines generally favor diuretics and ACE inhibitors, although calcium channel antagonists are still favored as primary treatment for older black patients [36]. Pycnogenol supplementation may also be paired with a lower dose of nifedipine (calcium antagonist), as this resulted in a 20% decrease in serum endothelin-1 [16]. In another study by Liu et al. [17], the daily dose of 20 mg nifedipine was reduced to 10 mg nifedipine with supplementation of 100 mg Pycnogenol daily in patients with systolic blood pressure not exceeding 140 mmHg. When comparing pharmaceutical prices, a 20 mg nifedipine pill costs \$2.50, while a 10 mg pill costs \$1.50. This comes to about \$912.50 and \$547.50 per year, respectively. Adding in the cost of one 100 mg Pycnogenol pill each day, which costs between \$0.61 and \$0.78, the yearly cost of supplementation is between \$223 and \$285. This, added on to the \$547.50, gives a total of between \$770.50 and \$832.50. This saves about \$80 a year, and also reduces the side effects of taking a double dose of nifedipine, which include constipation, dizziness, flushing, giddiness, headache, heat sensation, heartburn, lightheadedness, nausea, weakness [37].

28.4.4 Comparative Cost of Pycnogenol Supplementation and Treatment with Aspirin to Reduce Platelet Aggregation

Aspirin has been shown to inhibit platelet aggregation induced by cigarette smoking [5]. In a study that assessed the effect of Pycnogenol on platelet function in humans [5], it was found that smoking-induced platelet aggregation was inhibited by 500 mg aspirin and 100–125 mg Pycnogenol. Additionally, a single dose of 200 mg Pycnogenol reduced the platelet reactivity index to normality for over 10 days after supplementation. The platelet reactivity after smoking was reduced by 0.75% with aspirin, and 12.7% with Pycnogenol. Therefore, Pycnogenol's antiaggregatory effect is greater than aspirin's effect in smokers.

Yearly supplementation with aspirin, depending on the dosage, could cost between \$4.85 (325 mg) and \$60.71 (81 mg), while yearly supplementation with Pycnogenol costs between \$142.35 and \$222.65. While aspirin is available over the counter and can be purchased at a much lower cost than Pycnogenol, it can also cause main serious side effects. Aside from nausea, vomiting, stomach pain and heartburn, aspirin may also cause hives, rash, bloody vomit, loss of hearing, fast heartbeat and breathing, etc. [38]. The dosage of Pycnogenol required to achieve comparable effects on platelet aggregation is more than half the dose of aspirin. Aspirin also significantly increases bleeding time after smoking while Pycnogenol does not [5].

Table 28.1 summarizes the percent reductions in various cardiovascular risk-factors as an effect of taking Pycnogenol versus commonly used cardiovascular risk-reducing drugs. In studies studying cholesterol levels and platelet reactivity, Pycnogenol was tested on its own as opposed to supplementation with the more common treatment. However, Pycnogenol has been shown to have the same effect on lowering systolic blood pressure and serum endothelin-1 as a supplementation to 50% of the pharmaceutical drug treatment as the effect that is produced at 100% pharmaceutical drug treatment. Table 28.2 reviews the cost differences in daily and yearly supplementation with Pycnogenol versus pharmaceutical drug treatments. Pycnogenol would be an additive cost to the halved dose of Ramipril and Nifedipine, but could potentially replace the cost of Pravastatin and aspirin if chosen as a substitute treatment.

Table 28.1 Comparison of risk-factor reduction with cardiovascular risk-reducing drugs versus Pycnogenol

Improvement in:	Pycnogenol	Ramipril (10–5 mg daily)	Pravastatin (10–20 mg daily)	Nifedipine (10 mg daily)	Aspirin (500 mg daily)
Systolic BP	5% Decrease 200 mg daily [5]	50% Dose reduction [20]	–	–	–
Mean total cholesterol	7.9% 120 mg daily [35]	–	11.5% [37]	–	–
LDL-cholesterol	19.2% 120 mg daily [35]	–	18.0% [37]	–	–
Serum endothelin-1	20% 100 mg daily [14]	–	–	50% dose reduction [14]	–
Platelet Reactivity	12.7% 125 mg daily [16]	–	–	–	0.75% [16]

Table 28.2 Cost comparison of cardiovascular risk-reducing drugs with Pycnogenol

Drug	Dose (mg)	Cost per Pill	Yearly cost
Pycnogenol	100	\$0.61	\$222.65
	200	\$0.39	\$142.35
Ramipril	10	\$1.67	\$608.21
	5	\$1.30	\$474.38
Pravastatin	40	\$1.67	\$608.21
	20	\$1.67	\$608.21
Nifedipine	20	\$2.50	\$912.50
	10	\$1.50	\$547.50
Aspirin	325	\$0.01	\$4.85
	81	\$0.17	\$60.71

28.5 Conclusion

Pycnogenol supplementation has been shown to decrease multiple cardiovascular risk factors with efficacy comparable to common pharmaceutical drug treatments. There have been studies depicting Pycnogenol's role in decreasing systolic blood pressure, decreasing glycosylated hemoglobin, reducing hyperlipidemia, decreasing platelet aggregation, and improving endothelial function, among numerous other effects.

While Pycnogenol is a dietary supplement and not a replacement for standard treatment, its cost may negate aspects of CVD risk in an effective and cost-efficient manner, especially when applied in early heart disease prior to pharmaceutical drug therapy. If the dose and cost of traditional treatment can be decreased by additive or substitutive use of Pycnogenol, Pycnogenol may be a preferred choice of treatment.

Based on the cost-benefit analysis done in this chapter, Pycnogenol has comparable effects to traditional drug therapies that treat cardiovascular risk factors. Based on this, we can suggest that the lifelong cost of living with cardiovascular disease would be reduced by Pycnogenol supplementation to about the same degree as it would with traditional treatments. However, in order to actually calculate the cost-benefits of Pycnogenol supplementation, a randomized control trial would have to be conducted with a large number of subjects who would be followed over their lifetime to chart the cost effectiveness of Pycnogenol versus traditional treatment.

Due to the relative cost-effectiveness of Pycnogenol, supplementation should be beneficial for patients at risk for CVD who are maxed out on the traditional treatment but still exhibit uncontrolled risk factors. An added reduction in hypertension, LDL-cholesterol, endothelin-1 and platelet aggregation gives the potential for further health improvement in patients with that situation. The cost-effectiveness of Pycnogenol may also serve as an open treatment for those who cannot afford the traditional treatments to control cardiovascular risk factors. While CVD remains the leading cause of death in the USA, innovative and effective therapies are necessary, and Pycnogenol offers a potential cost-effective treatment that may help reduce the prevalence of CVD.

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