**Nutrition and Health**
*Series Editors:* Adrianne Bendich

Robert C. Dumont
Youngran Chung *Editors*

# Nutrition in Pediatric Pulmonary Disease

Humana Press

# Nutrition and Health

Adrianne Bendich, PhD, FASN, FACN, Series Editor

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Robert C. Dumont • Youngran Chung
Editors

# Nutrition in Pediatric Pulmonary Disease

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*I would like to dedicate this book to Youngran Chung my wife and life partner. I also dedicate this to my mother Betty Corcoran, a person of great integrity and thoughtfulness who has always taught me through her quiet example.*

Robert (Chuck) Dumont M.D.

*I dedicate this book to my husband Chuck Dumont and to our marriage during this collaborative effort. I also dedicate this to my brother Ken Chung whose personal story of renewed health from nutrition inspired me, and to my mother Hee Ja Chung whose love and wisdom continue to guide me. And finally I dedicate this book to my late father Kyu Ho Chung who made my career in medicine possible, and for whom I chose my field in pulmonary medicine.*

Youngran Chung M.D.

# Preface

> "The doctor of the future will give no medicine, but will interest his patients in the care of the human frame, in diet and in the cause and prevention of disease."—Thomas Edison

Food as medicine is an old concept. In many traditional cultures, food goes beyond basic sustenance or pleasure as certain foods may be selected for specific medicinal effect or used for general health benefit. Both Traditional Chinese Medicine and Ayurvedic medicine utilize diets as part of a comprehensive approach to medical therapy. In contrast, Western medicine in the modern era has moved away from an emphasis on nutrition as a foundational component to treating illness and diseases. This is reflected in the fact that nutrition education is still inadequate in many medical schools and postgraduate medical training in the United States. However, in the past decade, there has been increasing attention paid to nutrition and its effect on medical conditions, both in the popular press and in clinical research. The general public is becoming more keenly aware of the importance of nutrition as well. Patients want to know what they can do to alter their diet to improve their health. An often asked question from parents is "what kind of foods should my child eat to help his asthma?" Many medical practitioners are not familiar enough with the field of nutritional medicine to give specific advice.

The idea that nutrition may be a factor in many chronic diseases is suggested when we look at our recent nutritional history. It is a fact that people living in modern industrialized countries eat a diet that has changed significantly from the diet of their ancestors. The typical western diet consists of excessive amount of sugar and easily digestible carbohydrates, a disproportionate amount of saturated fats and lopsided ratio of omega 6 to omega 3 oils, and very little nutrient-rich vegetables. We are consuming foods that are often high in calories, highly processed and packaged in the form of fast convenient foods at home as well as at restaurants. These are food products that lack the nutrients of whole fresh foods. All of this moves us toward a pro-inflammatory state. Foods are no longer grown and marketed locally and consumed soon after picking. The hybridization of foods to accommodate transport and longer shelf life has changed their composition and may be partly responsible for

the diminishing percentage of minerals from fruits and vegetables.[1] There is no conclusive data yet that our present day nutrition is the cause of specific diseases, but there is enough evidence to suggest that it is a significant contributing factor and further investigation into the impact of present day nutrition is important.

Integrative medicine is a newly emerging field that "combines conventional allopathic medicine and Complementary Alternative medicine (CAM) therapies." Its emphasis is on managing the "whole person." Modification of diet and lifestyle along with the use of selected supplements and herbs as adjunctive medical therapy has always been a mainstay of intervention in Integrative medicine. An example is the widespread use of the anti-inflammatory diet among integrative medicine practitioners along with use of specific nutritional supplements for chronic disorders with an inflammatory component. While still controversial in some circles, such an approach is beginning to take root, especially with emerging research into nutritional components such as vitamin D, probiotics, fatty acids, and simple sugars and their effects on disease. Now more than ever, attention is focusing on the potential of nutrition to improving basic health and as a medical adjunct to controlling many chronic diseases.

The intent of this book is to provide a basic understanding of nutrition, nutritional supplements, and their effects on physiologic function as it pertains to chronic pulmonary diseases. Much is already known about nutrition in several areas of pediatric pulmonary disease: optimizing nutrition in premature infants, and the importance of achieving good body mass in cystic fibrosis by increasing calories. However, we must also consider the quality of diets, and specific nutrients and nutritional supplements that might modulate disease.

The first section of this book reviews general nutritional issues: general principles, nutritional requirements and assessment, as well as an overview of feeding behavior. This is followed by a review of specific diets, focusing primarily on the vegetarian, Mediterranean, and anti-inflammatory diets. All three of these diets are recognized for their health promoting benefits. A chapter is dedicated to the potential role of supplements and herbs as this is becoming such a large part of our cultural landscape. It covers definitions and regulatory status of herbs and supplements and discussions of specific supplements such as probiotics, essential fatty acids, antioxidants, and vitamin D. It also introduces the reader to Functional Medicine, which serves as a framework with which to apply nutrition and supplements in the context of disease.

The second section addresses the effects of nutrition on specific pulmonary diseases that carry their own unique set of nutritional challenges and require tailored nutritional intervention. The first chapter in this section addresses the critical role of nutrition in the treatment of chronic lung disease of the preterm neonate, and will update the current knowledge on this issue. Obesity is now a worldwide epidemic. The second chapter discusses the complex interrelationship between obesity, obstructive sleep apnea, and pulmonary function. It expounds on the why and how

[1] From Thomas D. A study on the mineral depletion of the foods available to us as a nation over the period 1940 to 1991. Nutr Health. 2003;17:85–115.

of obesity and its morbid consequences on lung function in general, as well as its role in aggravating sleep disorders. Nutrition is not typically addressed in the asthma clinic visit. However, there is a growing body of evidence linking the effects of diet and asthma and validating the beneficial effects of nutritional supplements. With time nutritional intervention may become a regular component of asthma management. It is now evident that nutrition is also a determinant in the outcome of chronic pulmonary disease of cystic fibrosis. This chapter reviews the basic elements of cystic fibrosis nutritional management and goes beyond simply increasing calories for weight gain. It discusses the potential beneficial effects of nutritional components. The chapter on neuromuscular disease reviews relevant aspects of this condition as it pertains to nutrition. Appropriate weight gain is particularly important as it affects respiratory physiology. While there is inadequate data on specific diets or nutrients for this disease, further exploration in this area may lead to improved quality of life and medical outcome.

If eating a proper diet is important in maintaining good health in healthy people, providing a proper combination of foods in a patient with a specific disorder would be comparable to providing the optimal combination of drugs. In this book, we highlight the important role of nutrition and the need to make nutrition a core component in the therapeutic intervention of chronic pediatric pulmonary diseases.

We would like to thank Dr. Adrianne Bendich for inviting us to create this book. Her recognition and insight into the importance of nutrition and its role in various conditions of the pulmonary system in the growing child have led to the need for this book. We appreciate her foresight in creating this book, and her confidence in us to see it through. We are also indebted to all the staff at Springer, in particular Amanda Quinn, Maria Smilios, and B. Pragyan Parimita for their great support and patience during this process. As working clinicians who are caught up in the day-to-day care of our patients, the consistent gentle reminders and organizational skills of all the Springer staff were most helpful and made this book possible.

> "before considering acupuncture and herbs, the physician should first address the diet and lifestyle"—Sun Simiao, sixth to seventh century Chinese Physician

Chicago, IL, USA

Robert C. Dumont
Youngran Chung

# Series Editor Page

The great success of the Nutrition and Health Series is the result of the consistent overriding mission of providing health professionals with texts that are 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 as well as 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 has the potential to examine a chosen area with a broad perspective, both in subject matter and in the choice of chapter authors. The editors, whose training(s) is (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 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.

"Nutrition in Pediatric Pulmonary Disease," edited by Robert Dumont, MD and Youngran Chung, MD clearly exemplifies the goals of the Nutrition and Health Series. The major objective of this unique, concise volume is to provide the reader with an integration between pediatric nutrition requirements in healthy children and compare these to the increased nutritional needs of children suffering either directly from diseases of the pulmonary system or in pediatric patients whose lung function is adversely affected secondarily. The volume contains an excellent description of basic lung functions as well as detailed descriptions of the five most common causes of reduced lung function in the pediatric population. The book includes eight up-to-date informative reviews of the current standards of practice of individuals during the stages of life from infancy (including preterm birth) through adolescence.

Practicing health professionals, researchers, and academicians can rely on the chapters in this volume for objective data-driven sources about essential vitamins and minerals, proteins and fats, as well as other dietary components that have been determined to be required in the diets of healthy children as well as patients. This new comprehensive review includes an insightful discussion of the importance of the continual assessment of the nutritional quality of the sick child especially during the hospital stay. This volume is of great importance to the medical community as well as for the pulmonologist, pediatrician, neonatologist, hospitalist, clinical nutritionist, gastroenterologist, and related health professionals who have to answer patient, client, or medial/graduate student questions about the nutritional consequences of reduced pediatric pulmonary function often in addition to disease consequences to the gastrointestinal tract.

"Nutrition in Pediatric Pulmonary Disease" represents the most comprehensive compilation of recent data on the critical drivers of nutritional requirements for children with serious health problems that affect their lungs' vital capacity and, as a consequence, affect their hearts, kidneys, brain, and often the ability of the children to consume sufficient calories to maintain their body weight and strength. The expertise of the volumes' editors and their in-depth knowledge help the reader to understand the value of nutritional interventions to the health and survival of these patients. Dr. Robert C Dumont, MD, is a Board-Certified Pediatrician and is a member of the Pediatric Integrative Medicine team at the Raby Institute for Integrative Medicine at Northwestern in Chicago, IL. Dr. Dumont has been practicing Integrative Medicine for the past 20 years, and is also Board-Certified by the American Board of Integrative and Holistic Medicine (ABIHM), and has received specialized training in Medical Acupuncture, mind/body medicine, medical hypnosis, clinical homeopathy, and Functional Medicine. Previously he was medical director of Pediatric Nutrition and interim director for the Pediatric Cystic Fibrosis Center at Loyola University Medical Center. For the past 13 years he has also served as medical director of the Easter Seals DuPage Feeding Clinic developing a unique expertise in pediatric feeding problems.

Dr. Youngran Chung is a Board-Certified Pediatric Pulmonologist, a member of the Division of Pulmonary Medicine at Ann & Robert H. Lurie Children's Hospital of Chicago, and is an assistant professor of Pediatrics at Northwestern University's Feinberg School of Medicine in Chicago, IL. She has treated children with lung diseases for over 20 years and served as the Director of Pediatric Pulmonology and Cystic Fibrosis Center at Loyola University Medical Center. Dr. Chung has specialized training in Medical Acupuncture, Medical Hypnosis, Functional Medicine, and Clinical Homeopathy. She is Board-Certified in Integrative Medicine through the American Board of Integrative and Holistic Medicine (ABIHM).

The editors have included eight related chapters divided into three sections in their volume. There are three introductory chapters followed by three chapters that describe the most serious pulmonary conditions in the neonatal period and inherited diseases that affect lung function in children. The third section contains two chapters that describe the pulmonary consequences of asthma and obesity. The first section provides an overview and perspective on nutrition, foods, dietary components,

and their functions. The first chapter in this section involves a discussion of the basics of pediatric nutrition and reviews the national diet standards for healthy children including recommendations for protein, fats and carbohydrates, as well as essential micronutrients. There is an in-depth description of appropriate nutritional assessment for children as well as enumeration of the therapeutic history for children with medical conditions. Factors affecting growth are emphasized as well as excellent suggestions for data collection of the complete medical history and dietary patterns from parents and the child when possible. There are also nine tables included that help the reader to better understand the basics of clinical nutrition.

The next unique chapter examines several diets that are considered to be health promoting and might be of potential benefit for children with chronic disease. Vegetarian diets, including vegan, lacto-ovo, and other food combinations, are examined for potential benefits. Likewise, the Mediterranean and the anti-inflammatory diets are described in detail. The following chapter continues to examine the complex issue of nutritional supplements and herbs. There is a discussion of the regulatory status of supplements and more detailed discussions of specific supplements including probiotics, omega 3 oils, and antioxidants.

The second section of the volume is practice-oriented and looks at the importance of nutrients and dietary components on the growth of neonates, infants, and children who are patients with serious lung diseases. The comprehensive, extensively referenced chapter on neonatal pulmonary disease includes detailed descriptions of neonatal respiratory distress syndrome, transient tachycardia of the newborn, meconium aspiration syndrome, bronchopulmonary dysplasia, and chylothorax. There is a detailed description of the development of the fetal lung that provides the reader with a clear picture of the consequences of preterm birth with regard to lung development and potential for normal pulmonary functioning. Moreover, we learn that in utero, the fetal lung is exposed to 3–10 % oxygen whereas ambient air contains 20 % and an incubator's oxygen concentration can reach much higher. This increased oxidative stress results in a significantly increased requirement for antioxidants, such as the essential nutrients vitamins C and E, to protect against oxidative damage to the immature lungs. In addition, many of the drugs used to treat preterm infants can adversely affect the digestive tract. There is a discussion of enteral and parenteral nutrition strategies to maintain infant growth. Included is a sensitive discussion of the critical issues of treating the nutritional as well as the pulmonary conditions often seen in preterm infants.

The chapter on nutritional concerns associated with cystic fibrosis includes a detailed description of the potential consequences of this genetic defect and their effects on the lung as well as the gastrointestinal tract, hepatobiliary tract, and epidermal and reproductive systems. As this is an inherited genetic defect, the manifestations may begin in utero and the thick mucus secretions may affect the infant at birth and throughout life. The chapter describes the potential gastrointestinal complications and consequences of pancreatic enzymes insufficiency. Included as well is a discussion of the potential for the development of cystic fibrosis-related diabetes. Dietary recommendations are included in this important chapter.

The last chapter in this section describes the pulmonary as well as gastrointestinal effects of pediatric neuromuscular genetically inherited diseases including congenital muscular dystrophies, spinal muscle atrophy, and Duchenne muscular dystrophy. These neuromuscular diseases vary in the age of onset, progression of muscle weakness, and effects on nutrition and are reviewed with the aid of excellent tables that are included in this chapter. Pediatric patients can develop malnutrition due to feeding difficulties associated with upper airway muscle weakness, increased energy expenditure needed for breathing, congestive heart failure, and the secondary effects of certain medications used in treatment. The diminished physical activity and calorie expenditure associated with muscle weakness along with steroid drugs are known to increase weight gain. The insightful chapter describes the evolution of disease progression over childhood and into teen years and provides guidance to health professionals concerning the transition from overweight patients to those who no longer can maintain their weight as the disease progresses. Valuable information is provided concerning the appropriate standards for assessing growth and nutrient requirements in affected children compared to the current norms.

The third section contains two chapters that examine the nutritional and pulmonary consequences of asthma and obesity in the pediatric population. The chapter describing asthma informs us that asthma is one of the most common chronic diseases seen in children. Asthma is a disease of chronic airway inflammation that results in airway obstruction with symptoms of wheezing, coughing, chest tightness, and shortness of breath. Medical management of asthma includes drugs that relieve acute symptoms including corticosteroids and drugs that are inhaled to help control symptoms. In addition, the asthmatic child may also be taking other drugs to treat allergies and other related or unrelated conditions. The chapter reviews the various factors that have been associated with the increased risk of asthma, and examines the effect of obesity on pulmonary function in young children. There are detailed discussions of data associating low intakes of antioxidant vitamins and vitamin D, vitamin B6, and magnesium with increased risk of asthma. The potential for drugs used to treat asthma to increase nutrient requirements is discussed. Certain foods and nutrients are reviewed as potential sources of supplemental nutrition for the asthmatic child. The chapter includes important information on the critical role of maternal diet during pregnancy and risk of asthma in the offspring.

The last chapter in the volume examines the effects of obesity in childhood with the unique perspective of its effects on pulmonary structure and function. We learn that obesity has a direct effect on the ability of the diaphragm to move with each breath. Fat in the thoracic cavity and in the upper abdomen increases the pleural pressure and reduces the space available for the lungs to expand fully. Obesity is considered an inflammatory disease and this condition also puts a greater burden on the heart and the lungs to provide sufficient oxygen. The connection is via leptin that is produced by adipose tissue and, among its other functions, is responsible for stimulating the central control of respiration. In obesity, there is reduced bioavailability of leptin and this results in restrictive lung function. The chapter reviews the consequences on lung vital capacity and forced expiratory volume among other adverse effects. Obesity also adversely affects the ability to exercise as there is a

loss in respiratory functions leading to breathlessness, cough, and inability to engage in any level of strenuous exercise. This chapter, like the chapter on asthma, provides further insights into the link between obesity and asthma. The chapter also includes an informative discussion on sleep disturbances associated with disordered breathing, and apnea seen with obesity. The changes in sleep cycles also affect circadian rhythms of food consumption that can further aggravate the obese child's overall health.

The logical sequence of the Sections enhances the understanding of the latest information on the current standards of practice in the fields of pediatric pulmonology and nutrition. This unique volume serves as a critical resource for practice-oriented physicians, integrative healthcare practitioners, academicians involved in the education of graduate students and postdoctoral fellows, and medical students, interns and residents, allied health professionals, and public health nutritionists who are actively involved in the assessment of the growing prevalence of asthma, obesity, and other pediatric diseases that affect numerous organs and body systems.

"Nutrition in Pediatric Pulmonary Disease" contains over 30 detailed tables and figures that assist the reader in comprehending the complexities of nutrient interactions, quantification of intake and availability of essential nutrients, composition of diets, and the nutritional needs of preterm infants, term infants, children, teens, and pregnant women who suffer from pulmonary diseases and therefore have different nutritional requirements compared to children who do not have these lung diseases. There are in-depth discussions of the genetic aspects of the lung diseases that are inherited. The overriding objective of this volume is to provide health professionals involved in the care of the pediatric pulmonary disease patient with balanced documentation and awareness of the newest research and technical approaches to reducing the risk of adding nutrient deficiencies to their young patients who already have compromised pulmonary function. Hallmarks of the eight chapters include key words and bulleted key points at the beginning of each chapter, complete definitions of terms with the abbreviations fully defined for the reader, and consistent use of terms between chapters. There are over 570 up-to-date references; all chapters include a conclusion to highlight major findings. The volume also contains a highly annotated index.

This unique text provides practical, data-driven resources based upon the totality of the evidence to help the reader understand the basics of lung function from fetal development through to adolescence, the impact of genetic mutations that alter lung function and often negatively impact the gastrointestinal tract, and the importance of specific nutrients as well as dietary intakes and drug–nutrient interactions on the health of the pediatric pulmonary disease patient. Critical issues that are discussed include the therapeutic role of antioxidant nutrients, the anti-inflammatory functions of vitamin D, the importance of omega 3 fatty acids, and hydration and electrolyte balance especially in young children who are given multiple drugs to control their disease. The overarching goal of the editors is to provide fully referenced information to practicing health professionals and educators so they may have a balanced perspective on the value of assuring the best nutritional quality for their patients while treating their primary disease.

In conclusion, "Nutrition in Pediatric Pulmonary Disease," edited by Robert Dumont, MD, and Youngran Chung, MD, provides health professionals in many areas of research and practice with the most up-to-date, well referenced, and comprehensive volume on the current state of the science and medical practice guidelines with regard to the nutritional care of pediatric pulmonary patients. The volume will serve the reader as the most authoritative resource in the field to date and is very welcome additions to the Nutrition and Health Series.

Adrianne Bendich, Ph.D., F.A.C.N., F.A.S.N.

# About Series Editor

**Dr. Adrianne Bendich, Ph.D., F.A.S.N., F.A.C.N.** has served as the *Nutrition and Health* Series Editor for over 15 years and has provided leadership and guidance to more than 100 editors that have developed the 50+ well respected and highly recommended volumes in the series.

In addition to *Nutrition in Pediatric Pulmonary Disease*, edited by Dr. Robert Dumont and Dr. Youngran Chung, major new editions in 2012–2013 include:

1. *Diet Quality*: *An Evidence-Based Approach*, volumes one and two, edited by Dr. Victor R. Preedy, Dr. Lan-Ahn Hunter, and Dr. Vinood B. Patel, 2013.
2. *The Handbook of Clinical Nutrition and Stroke*, edited by Mandy L. Corrigan, M.P.H., R.D., Arlene A. Escuro, M.S., R.D., and Donald F. Kirby, M.D., F.A.C.P., F.A.C.N., F.A.C.G., 2013.
3. *Nutrition in Infancy*, volumes one and two, edited by Dr. Ronald Ross Watson, Dr. George Grimble, Dr. Victor Preedy, and Dr. Sherma Zibadi, 2013.

4. *Carotenoids and Human Health*, edited by Sherry A. Tanumihardjo, 2013.
5. *Bioactive Dietary Factors and Plant Extracts in Dermatology*, edited by Dr. Ronald Ross Watson and Dr. Sherma Zibadi, 2013.
6. *Omega 6/3 Fatty Acids*, edited by Dr. Fabien De Meester, Dr. Ronald Ross Watson and Dr. Sherma Zibadi, 2013.
7. *Magnesium and Health*, edited by Dr. Ronald Ross Watson and Dr. Victor R. Preedy, 2012.
8. *Alcohol*, *Nutrition and Health Consequences*, edited by Dr. Ronald Ross Watson, Dr. Victor R. Preedy, and Dr. Sherma Zibadi, 2012.
9. *Nutritional Health*, *Strategies for Disease Prevention*, *Third Edition*, edited by Norman J. Temple, Ted Wilson, and David R. Jacobs, Jr., 2012.
10. *Chocolate in Health and Nutrition*, edited by Dr. Ronald Ross Watson, Dr. Victor R. Preedy, and Dr. Sherma Zibadi, 2012.
11. *Iron Physiology and Pathophysiology in Humans*, edited by Dr. Gregory J. Anderson and Dr. Gordon D. McLaren, 2012.

Earlier books included *Vitamin D*, *Second Edition* edited by Dr. Michael Holick; *Dietary Components and Immune Function* edited by Dr. Ronald Ross Watson, Dr. Sherma Zibadi, and Dr. Victor R. Preedy; *Bioactive Compounds and Cancer* edited by Dr. John A. Milner and Dr. Donato F. Romagnolo; *Modern Dietary Fat Intakes in Disease Promotion* edited by Dr. Fabien DeMeester, Dr. Sherma Zibadi, and Dr. Ronald Ross Watson; *Iron Deficiency and Overload* edited by Dr. Shlomo Yehuda and Dr. David Mostofsky; *Nutrition Guide for Physicians* edited by Dr. Edward Wilson, Dr. George A. Bray, Dr. Norman Temple, and Dr. Mary Struble; *Nutrition and Metabolism* edited by Dr. Christos Mantzoros and *Fluid and Electrolytes in Pediatrics* edited by Leonard Feld and Dr. Frederick Kaskel. Recent volumes include: *Handbook of Drug-Nutrient Interactions* edited by Dr. Joseph Boullata and Dr. Vincent Armenti; *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 is President of Consultants in Consumer Healthcare LLC and is the editor of ten books including *Preventive Nutrition*: *The Comprehensive Guide for Health Professionals*, *Fourth Edition* co-edited with Dr. Richard Deckelbaum (www.springer.com/series/7659). Dr. Bendich serves on the Editorial Boards of the Journal of Nutrition in Gerontology and Geriatrics, and Antioxidants, and has 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 served on the Board of Directors of the American College of Nutrition.

Dr. Bendich was Director of Medical Affairs at GlaxoSmithKline (GSK) Consumer Healthcare and provided medical leadership for 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. She 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 received 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. 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. In 2012, she was recognized for her contributions to the field of clinical nutrition by the American Society for Nutrition and was elected a Fellow of ASN. Dr. Bendich is Adjunct Professor at Rutgers University. She is listed in Who's Who in American Women.

# About the Editors

**Robert C. Dumont, M.S., M.D., A.B.I.H.M., A.B.M.A.,** Pediatric Integrative Medicine, Raby Institute for Integrative Medicine at Northwestern, LLC, 500 N. Michigan Avenue, Suite 450, Chicago, IL 60611, rdumont@rabyinstitute.com, www.rabyintegrativemedicine.com.

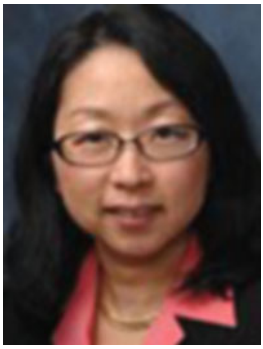
Dr. Dumont currently practices Pediatric Integrative Medicine (Complementary Alternative Medicine) at the Raby Institute for Integrative Medicine at Northwestern, LLC in Chicago, Illinois.

Dr. Dumont graduated from the Eastern Virginia Medical School in Norfolk Virginia in 1988. He joined the faculty as assistant professor of pediatrics at Columbus Children's Hospital (now Nationwide Children's Hospital) and the Ohio State University in 1994 after completing his pediatric residency and pediatric gastroenterology fellowship at those institutions. He subsequently joined the faculty at Loyola University Medical Center where he was associate professor of pediatrics. During his tenure there he was director of the Pediatric Integrative Medicine Program, medical director of Pediatric Nutrition, and interim director for the Pediatric Cystic Fibrosis Center. For the past 13 years he has also served as medical director of the Easter Seals DuPage Feeding Clinic and is an expert in pediatric feeding problems especially in special needs children.

Dr. Dumont has been practicing integrative medicine for the past 20 years, and is board-certified by the American Board of Integrative and Holistic Medicine (ABIHM), and Medical Acupuncture by the American Board of Medical Acupuncture. His training in other areas of integrative medicine include mind/body medicine through the Harvard Mind/Body Institute, medical hypnosis through the American Society of Clinical Hypnosis and the Society of Behavioral and Developmental Pediatrics, and functional medicine through the Institute for Functional Medicine. He trained in homeopathy through the American Institute of Homeopathy and holds a diploma from the Center for Education and Development of Clinical Homeopathy (CEDH) and is a senior teacher in this program for physicians. He is also a member of the Homeopathic Pharmacopeia Convention of the United States (make recommendations on homeopathic medicines to the Federal Drug Administration).

In addition to his clinical practice, Dr. Dumont has given numerous lectures in national as well as international conferences on these topics. He has also coauthored a review article on CAM in *Pediatric Pulmonology*, as well as a chapter in the use of CAM in the text book *Parasomonias*.

Dr. Dumont has dedicated himself to the integration of nutritional medicine and other Complementary/Alternative (CAM) approaches with allopathic medicine. He has explored and studied in depth many different therapeutic approaches to better understand the nature of health and illness, not just to address the symptoms of a disease but to understand the roots and origin of disease. He has always believed the concept that many chronic diseases can be derived from or influenced by improper diet and lifestyle, a concept that is core to many "alternative" medical systems, and has been expressed by Hippocrates as well as stated in ancient Chinese Medical texts. He abides by Sun Si Miao (Chinese physician, sixth century) who said "before considering acupuncture and herbs, the physician should first address the diet and lifestyle".



**Youngran Chung, M.D., A.B.I.H.M., A.B.M.A.,** Assistant Professor of Pediatrics, Northwestern University Feinberg School of Medicine, Ann & Robert H. Lurie Children's Hospital of Chicago, Division of Pulmonary Medicine, Ychung@luriechildrens.org.

Dr. Chung is currently an assistant professor of Pediatrics at Northwestern University Feinberg School of Medicine and on faculty in the Division of Pulmonary Medicine at Ann & Robert H. Lurie Children's Hospital of Chicago (formerly Children's Memorial Hospital). She earned her undergraduate degree in Bachelor of Arts from the University of Chicago, and her MD from the University of Chicago Pritzker School Of Medicine. After residency in Pediatrics, she went on to do a fellowship in Pediatric Pulmonology at Rainbow Babies and Children's Hospital/Case Western Reserve University in Cleveland, Ohio. Upon completion of her fellowship, she returned to Illinois and served as the director of Pediatric Pulmonology and Cystic Fibrosis Center at Lutheran General Hospital for 10 years, then at Loyola University Medical Center where she was associate professor of Pediatrics during her tenure there.

Dr. Chung's extensive clinical experiences drove her to explore other options in the treatment of her pulmonary patients. Since 1997, she has pursued her interest in Complementary & Alternative Medicine (CAM), starting with formal training and board certification in Acupuncture from the American Board of Medical Acupuncture, followed by training in Medical Hypnosis (American Society of Clinical Hypnosis and the Society of Behavioral and Developmental Pediatrics) and Functional Medicine (Institute of Functional Medicine) and Homeopathy. She holds a Diplomate in Clinical Homeopathy from the Center for Education and Development of Homeopathy (CEDH) where she is a senior instructor for this international teaching organization. She is board-certified through the American Board of Integrative and Holistic Medicine (ABIHM) and has been incorporating many of these CAM modalities for her patients in her clinical practice.

Inspired by the results seen in her patients, Dr. Chung is dedicated to the education of medical practitioners on safe and natural healing methods which could be incorporated into current standard medical practice. She has given presentations on CAM at medical conferences in the United States as well as abroad. Her publications in this area include a State-of-the-Art Review article on CAM use in Pediatric Pulmonary Medicine in *Pediatric Pulmonology*; an article on Homeopathy in the Illinois American Academy of Pediatrics newsletter; and a chapter on the use of CAM in Parasomnias.

Dr. Chung's interest in allopathic as well as alternative treatment approaches has always been inspired by the saying of Sir William Osler—"It is much more important to know what sort of a patient has a disease than what sort of disease a patient has".

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# Part I
# Introductory Chapters

# Chapter 1
# Basic Pediatric Nutrition; Foundation of a Healthy Diet

**Cynthia L.N. Baranoski**

**Keywords** Pediatric nutrition • Basic nutrition • Nutrition assessment • Anthropometrics and interpretation • Registered dietitian • Barriers to nutrition

**Keypoints**

- Identify past and current historical and scientific aspects of nutrition.
- Describe the basics of nutrition assessment including medical, therapeutic, psychosocial and nutrition history, anthropometrics, guidelines for and estimation of nutritional needs and intake, feeding environment, and interventions for children.
- Emphasize aspects of nutrition which are impacted by or might impact pediatric pulmonology patients.
- Highlight basic interventions to assist children with pediatric pulmonology disease.

## Introduction

Nutrition is a vital component to our lives. Although breathing is the most basic function for life, we cannot survive long without food and hydration. Proper nutrition is essential for bodily functions, normal growth, and improved overall health. Without adequate and balanced nutrition, fundamental body operations are diminished, growth is altered, and acute and chronic diseases develop. Throughout the cycle of life nutritional needs change, with popular focus on more critical times

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such as conception, birth, and end of life. When it comes to children, due to their complex, unique, and constantly changing needs, more than a basic understanding of nutrition is needed to assist professionals in identifying problems and implementing appropriate plans. Children with pulmonary disease have even greater challenges; therefore, nutrition is a primary aspect of immediate and long-term care.

## Historical Development of Nutrition and Dietetics

Nutrition as a science is relatively new, with its beginnings based in the study of palatability rather than the scientific nature of food and the effects on the human body. Ayurveda, a 5,000-year-old system of health and healing, emphasizes incorporation of six tastes in the diet for identification of best food choices, leading to intake of all nutrients necessary for humans to thrive [1]. Progress and discoveries in chemistry, anatomy, and physiology led to advanced thinking of food as sustenance for the body, rather than satisfaction of the palate. Further investigation led to understanding the destiny and consequence of what is consumed [2]. Today the dynamic field of nutrition is defined as "the science or study of the dietary requirements of humans and animals for proper health and development." Dietetics refers to "the science concerned with nutrition and food preparation" [3].

In the late nineteenth and early twentieth centuries, nourishing hospitalized patients was regulated by hospital stewards and pharmacists. In an effort to improve the nation's health, in 1917 during World War I, a group of women in Cleveland, Ohio, founded the American Dietetic Association (ADA). In January 2012 the name was officially changed to the Academy of Nutrition and Dietetics (AND), the nation's largest organization of food and nutrition professionals, comprising registered dietitians (RD), dietetic technicians registered (DTR), clinical and community professionals, food service managers, educators, researchers, and students. The vision of the Academy simply stated is—optimizing the nation's health through food and nutrition [4].

The United States government also provides guidelines and resources for the general population. One source, MyPyramid, was recently revamped, becoming ChooseMyPlate, a source for Americans looking to improve their nutrition, health, activity, and lifestyle (Fig. 1.1) [5]. MyPlate also includes information to guide parents and children over 2 years of age. Additionally, the US government provides useful information for all persons, through Healthy People 2020 and the Dietary Guidelines 2010. Though helpful, this information is not directed to those who work closely with pediatric pulmonology patients.

## Nutrition Science

Nutrition is a science that deals with components of food and fluid called nutrients, which provide for growth, maintenance, structure, regulation, reproduction, development, and health. Sources of nutrition in the American diet include foods, fluids, formulas, supplements, modular components, and blended or texture-modified

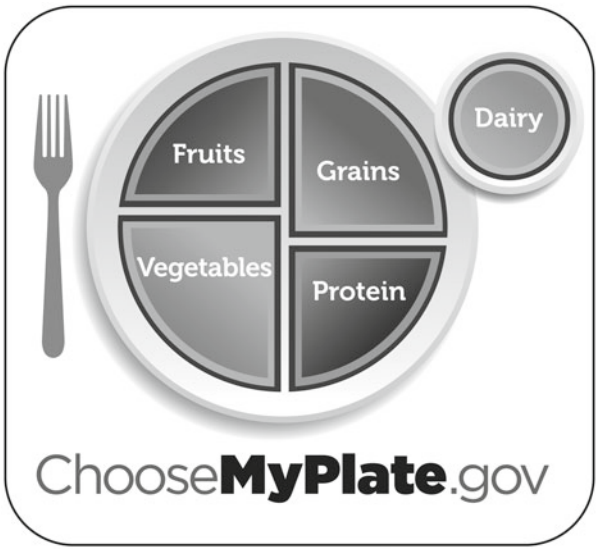


**Fig. 1.1** MyPlate

foods, provided orally, enterally via a tube, or parentally. Carbohydrates, proteins, fats, vitamins, minerals, and water are the six major categories of nutrients found in both food and the body. Dietary carbohydrates, proteins, and fats provide calories or energy the body uses to fuel daily activities. Some foods contain only fat, protein, or carbohydrate, while other foods can be a combination of any or all of these. Food and fluid can also contain widely varying amounts of vitamins, minerals, and water.

## Carbohydrates

Carbohydrates are the main source of nutrition consumed, and provide energy at about 4 calories per gram. Examples of high carbohydrate food sources include bread, rice, cereal, pasta, fruit, vegetables, and dairy (as well as cookies and candy). Three basic types of carbohydrates are simple sugars, fiber, and starch also known as complex carbohydrates.

Simple sugars are mono- and di-saccharides, which include fructose, glucose, and galactose, as well as sucrose, maltose, and lactose, respectively. Providing quick calories for the body, simple sugars are predominantly found in grains, fruit, and dairy, as well as honey, corn syrup, table sugar, and processed and sweetened foods. Starch, or complex carbohydrate, provides calories and nutrients, though is harder to assimilate than simple sugar because of its complex structure. Complex carbohydrates are the foundation for providing energy, due to the gradual breakdown and release of glucose into the blood stream. Numerous foods fall into this category, such as whole wheat bread, pasta, fruits, and vegetables.

Fiber, both soluble and insoluble, is an especially beneficial carbohydrate. Found in whole grains, fruits, vegetables, legumes, and beans, fiber provides fewer calories

than simple and complex carbohydrates due to its limited digestibility. All fiber provides a healthier consistency for stools, while supplying nutrients for bacteria in the colon. This in turn provides important nutrient growth factors that can aid the body's immune function. Additional fiber with increased fluid intake can alleviate both constipation and diarrhea. Government guidelines exist for fiber intake; however, there are no established recommendations for infants 0–12 months of age.

## Protein

Foods containing protein provide building blocks that repair, build, and maintain body tissues, and assist with chemical reactions in the body. Although protein provides energy at 4 calories per gram similar to carbohydrate, it is usually not the first choice of the body for energy, as carbohydrate is the body's preferred fuel source. Twenty different amino acids exist, with nine of these considered essential, meaning they need to be consumed as they are not made by the human body. Excess protein in the diet is either used for energy, like carbohydrate, or converted and stored as fat, while a deficiency in dietary protein will lead to the breakdown of bodily tissue when needed. All of the essential amino acids can be obtained by eating a variety of foods in adequate amounts, and nearly all foods except fruit contain varying degrees of specific or all amino acids. With a reasonably healthy and varied diet, most persons will consume more than enough protein in their diet. Beef, chicken, fish, turkey, eggs, pork, lamb, and dairy are examples of foods containing all the essential amino acids. Grains, such as quinoa, contain all the essential amino acids, although lower in total levels. Other foods, such as soy and legumes, contain nearly all of the essential amino acids, while whole grains and vegetables provide lesser amounts. For vegetarians, eating a variety and balance of foods and fluids will provide for all essential and nonessential amino acids in the diet.

## Fat

Fats have many roles including function of the nervous system, organ protection, body temperature regulation, and brain and vision development, especially in children. Fats provide 9 calories per gram, and are used for fuel or placed into storage for later use. Movement of fats out of our stomach and into the intestines is slower than it is for carbohydrates and proteins, therefore contributing to satiety.

Fats are made up of essential and nonessential fatty acids. As with the essential amino acids, essential fatty acids can only be obtained through foods consumed. The importance of fat in the diet is often overlooked, especially with so much focus on low fat diets to prevent obesity and high fat diets contributing to diseases. However, in the quest to lower fat intake, essential fatty acid deficiency can occur. Examples of foods containing fat include butter, oil, peanut butter, and nuts, as well as fish, meat, milk, vegetables, fast foods, and snacks which all contain a degree of fat.

Fats can be placed into three categories based on their basic structure. Monounsaturated (MUFA), polyunsaturated (PUFA), and saturated (SFA) fatty acids are found in virtually all foods, and affect blood cholesterol levels in different ways. Trans fatty acids, created by food manufacturers through a process known as hydrogenation, are associated with multiple detrimental metabolic effects.

Omega 3 and Omega 6 are considered essential fatty acids. Typical American diets are weighted heavily with Omega 6, found in many vegetable oils and processed foods. Omega 3 is required for numerous body functions, especially the inflammatory and anti-inflammatory processes. Fish oils are the best utilized source of Omega 3 in the body, while sources, such as flaxseed, canola oil, walnuts, and other vegetable oils, provide them to a lesser degree. See Chap. 3 for a more complete review.

## Vitamins and Minerals

These very large and small nutrients are found in nearly every food and fluid. Although vitamins and minerals don't supply calories, they do assist in many metabolic processes. Eating a variety of foods will provide most of the vitamins and minerals needed; however, many persons take supplements daily in pill, liquid, gel, and powdered form. Certain conditions do warrant the use of supplemental forms; however, vitamins and minerals from food sources provide added nutrients that cannot be neatly packaged into pills. Tables 1.1 and 1.2 provide examples of food sources of vitamins and minerals.

**Table 1.1** Food sources of vitamins

| | |
|---|---|
| Vitamin A | Beef liver, fortified milk, sweet potatoes, spinach, greens, carrots, cantaloupe, apricots, broccoli |
| Vitamin D | Fortified milk, fish oils, tuna fish, salmon |
| Vitamin E | Vegetable seed oils, some greens and fruits, wheat germ |
| Vitamin K | Green vegetables, soy, beans, beef liver |
| Thiamin (B1) | Legumes, sunflower seeds, pork, whole and enriched grains, dried beans, peas, brewer's yeast |
| Riboflavin (B2) | Milk, enriched grains, mushrooms, beef liver, braunschweiger sausage, ricotta cheese, nonfat milk, spinach |
| Niacin (B3) | Enriched grains, bran, mushrooms, tuna, chicken, beef liver, beef, salmon, halibut, peanuts |
| Pantothenic acid | Kidney, broccoli, liver, egg yolk. Widespread in various foods |
| Choline | Beef, egg, baked beans, navy beans, collards, broccoli, yogurt |
| Biotin | Yeast, egg yolks, peanut butter, cheese, liver, cauliflower, kidney |
| Vitamin B6 (pyridoxine) | Navy beans, animal protein, sunflower seeds, salmon, bananas, spinach, broccoli |
| Folate (folic acid) | Brewer's yeast, enriched grains, green leafy vegetables, orange juice, sprouts, sunflower seeds, organ meats, wheat germ |
| Vitamin B12 (cobalamins) | Meat, shellfish, fish, poultry, milk. Limited in plant foods |
| Vitamin C (ascorbic acid) | Papaya, citrus fruits, cantaloupe, broccoli, Brussels sprout, green peppers, kiwi, strawberries |

**Table 1.2** Food sources of minerals

| | |
|---|---|
| Sodium | Table salt, processed foods, meat, seafood, cheese, milk, bread, vegetables |
| Potassium | Avocado, spinach, dried fruits, potatoes, peaches, orange juice, bananas, squash, dairy products |
| Chloride | Table salt, seafood, meat, milk, eggs, some vegetables |
| Calcium | Dairy products, sardines, fortified soy, canned fish, tofu, fortified orange juice, leafy vegetables |
| Phosphorus | Meat, poultry, fish, dairy products, eggs, nuts, legumes, cereals, grains, chocolate, processed foods, soft drinks |
| Magnesium | Legumes, wheat bran, soybeans, green vegetables, chocolate, blackstrap molasses, nuts, carrots, seafood, brown rice, lima beans, parsley |
| Sulfur | Protein foods (meat, poultry, fish, eggs, milk, cheese, legumes, nuts) |
| Iron | Organ meats, meat, blackstrap molasses, clams, oysters, legumes, nuts, spinach, dark green leafy vegetables, dried fruits, enriched and/or whole grain breads and cereals |
| Zinc | Seafood, wheat germ, beef liver, dark meat of chicken and turkey, whole grains |
| Selenium | Meat, poultry, egg, fish, seafood, whole grains |
| Iodine | Iodized salt, white bread, saltwater fish, eggs, beef liver, dairy products |
| Copper | Liver, cocoa, nuts, whole grains, dried fruits, beans |
| Fluorine | Fluoridated water, tea, seaweed, mackerel, sardines, salt pork, shrimp |
| Chromium | Egg yolks, whole grains, pork, mushrooms, prunes, nuts |
| Manganese | Wheat bran, legumes, rice, oats, nuts, blueberries, seafood, poultry, meat |
| Molybdenum | Soybeans, lentils, pasta, grains, nuts |

## Water

Water is the largest component of the human body, comprising nearly 60–70 % by weight. The body loses about 2 quarts of water each day through processes such as perspiration, respiration, urination, and defecation, and can be replenished through fluids and foods. While absorbed in the stomach, it is predominantly reabsorbed in the small and large intestines. Benefits of good hydration are improved mental thought, body movement, metabolic function, oxygen and nutrient transport, waste removal, and temperature regulation.

## Balance Among the Nutrients

When food and fluid consumed (calories) balances with how much energy is expended (activity) on a daily basis, weight maintenance is possible. If balance doesn't exist, then too much consumed and too little energy expenditure will result in weight gain. Persons not consuming enough food with too much energy expenditure will generally be underweight. It is just as important that proper balance should exist between both macro- and micronutrients in a diet. Increased

consumption or restriction of foods in the diet for any reason should therefore be medically or nutritionally supervised. The goal is to strive for a variety of the freshest nutrient-dense foods available with minimal processing and additives for children, as well as adults [6].

## Nutrition Assessment

Dietitians can be key to the identification and management of a child's nutrition-related problem. Regardless of who is providing a nutrition screening or assessment, several pieces of information need to be gathered in order to clearly understand past, present, and future needs for the child. When time does not allow for detailed information gathering, tools such as the Subjective Global Nutrition Assessment method may be helpful through the use of clinical judgment as opposed to collected data [7]. Ideally, review of information and data prior to the face to face meeting is most valuable, and a list of relevant information needed can be found in Table 1.3. Interviewing the parent or caregiver is essential and having the child present for the evaluation aids in identifying physical signs of nutrition concerns (Table 1.4) [8]. Detailed information on medical and therapeutic history can be beneficial to determine what has been done, or what might still need to be performed for best care planning. Children with specific pulmonary diseases may have had additional testing, referrals, therapy, or procedures performed with data that also needs to be included in the assessment. Treating each child individually, and gathering as much detailed information about him/her as possible, assists with short- and long-term goals.

**Table 1.3** Data collected for nutrition assessment

| | |
|---|---|
| Child's name | Primary care physician/specialists |
| Sex | Diagnosis |
| Date of birth | Medical history |
| Contact information/parents/family | Weeks gestation |
| Current diet plan | Surgery or procedures |
| Formulas or supplements | Laboratory and test results |
| Food modifications | Enteral/parenteral feeding history |
| Feeding | Oral feeding history |
| Mode of feeding | Birth/current growth measures |
| Related problems or concerns | Bowel/bladder function |
| Feeding ability, location, and position | Medications |
| Cultural/religious food restrictions | Vitamins, minerals, or herbs |
| Other information | Food allergy or intolerances |
| Social concerns | Activity level |
| Payment and referral source | Habilitation/rehabilitation history |
| HIPAA, release and consent forms | Statement of goals and expectations |

**Table 1.4** Signs of malnutrition in children

| | Nourished | Malnourished | Potential deficiencies |
|---|---|---|---|
| Skin | Clear, no dryness or scales, smooth, firm, good color | Flaky, scaly or cracked skin, dry, rough, spotty, no subcutaneous fat | Protein energy malnutrition, essential fatty acids, vitamin A, C and B vitamins, iron |
| Eyes | Bright, clear | Pale, spotty, red, poor adjustment to light and dark | Vitamin A, B vitamins, zinc, iron |
| Nails | Pink, firm nail bed | Thin, fragile, spoon-shaped, cracker, splitting | Iron |
| Hair | Shiny, firm in the scalp | Lack of pigment, dull, thin, easily falls out | Protein energy malnutrition |
| Teeth, gums, lips | Firm gums, bright white teeth, moist lips | Discolored teeth, bleeding gums, swollen/spongy gums, cracked lips | Vitamin C, B vitamins |
| Tongue | Moist, pink/red, bumpy | Irregular shape, dry, swollen, smooth, purple | B vitamins |
| Internal organs | Heart, digestion, reflexes, mental status, regularity | Abnormal heart rate, enlarged liver, spleen, mental confusion, abnormal digestion | Protein energy malnutrition (PEM), B vitamins, folic acid |
| Bones/muscles | Good tone, posture, appropriate bone and muscle development for age | Muscle wasting, scurvy, skeletal lesions, poor tone, bumps on skull, end bones or ribs, bowed legs, developmental delay, poor growth | Protein energy malnutrition (PEM), minerals, vitamin D, vitamin C, copper |

## Medical and Therapeutic History

A complete medical and therapy history is part of a nutrition assessment. Details about medical diagnoses, birth history, complications, surgeries, procedures, laboratory work, medications, specialists seen, frequency of infections, bowel and bladder patterns, habilitation/rehabilitation history, reflux or vomiting, dental history, and family medical and growth history are necessary and should be included in either written or verbal form.

## Laboratory Testing

Basic laboratory testing for the average child can include CBC or iron profile (Fe, ferritin, TIBC), and is often routinely performed. Vitamin B12 or folate may also be tested when needed to rule out anemia. With nutritional concerns, further testing

**Table 1.5** Laboratory monitoring of nutritional status

| |
|---|
| Cystic fibrosis |
| Beta carotene |
| Vitamin A (retinol) |
| Vitamin D (25-OH-D) |
| Vitamin E (alpha-tocopherol) |
| Vitamin K (PIVKA-II) |
| Essential fatty acids (triene, tetraene) |
| Calcium, phosphorous, DEXA scan |
| Iron (Hgb, Hct) |
| Zinc |
| Serum and urine sodium |
| Protein (albumin) |
| Bronchopulmonary dysplasia |
| Alkaline phosphatase |
| Serum sodium, chloride, potassium |
| Urine specific gravity |
| Urine osmolality |
| Serum ferritin |
| Serum prealbumin, albumin |
| Serum electrolytes |
| Serum calcium, phosphorous, magnesium |
| Vitamin D (25-OH-D) |
| Complete blood count |

might include serum albumin, transferrin, prealbumin, and serum plasma retinol binding protein. These proteins can detect problems associated with inflammation, infection, liver or renal disease, protein losing enteropathy, thyroid status, and zinc or vitamin A deficiencies, and can be altered by fluid status. Serum testing for vitamins and minerals may not always be an accurate reflection of storage levels, with numerous factors potentially affecting outcomes of testing. For example, circulating vitamin D 25-OH-D concentration is the accepted measure of levels of vitamin D in the body. Numerous assays can be used to measure vitamin D, with variability existing between methods. Recommendations for supplementation, however, are standard regardless of the differences in assay outcome [8]. Children with chronic pulmonary disease can have other altered chemical indices and may need additional testing. Examples of testing are found in Table 1.5 and will be discussed in respective chapters throughout this book [9, 10].

## Anthropometrics

If growth information is not available, a dietitian can perform measurements for weight, length (lying down), stature (standing) and head circumference, as well as mid-arm-muscle circumference (MAMC) or caliper measures for body fat. With more difficult to measure children, three successive and averaged measures at one

**Table 1.6** Growth charts for boys and girls

| |
|---|
| Very low birth weight (IHDP VLBW) |
| Low birth weight (IHDP LBW) |
| CDC (Centers for Disease Control and Prevention) |
| 0–36 months |
| 2–20 years |
| WHO (World Health Organization) |
| 0–24 months |
| Down syndrome |
| Birth to 36 months |
| 2–18 years |
| Noonan syndrome |
| Achondroplasia |
| Cerebral palsy |
| Prader–Willi syndrome |
| Turner syndrome |
| Williams syndrome |
| Wolf–Hirschhorn syndrome |

visit will provide greater accuracy. MAMC and caliper measures, typically used more in research, are not routine; therefore, a trained individual with appropriate equipment is important to ensure useful information is obtained over time. Measures are usually plotted on the Centers for Disease Control and Prevention (CDC) or World Health Organization (WHO) growth charts [11], as well as charts that are available for specific conditions. Table 1.6 lists growth charts that are accepted and commonly used in the field. Very often a CDC growth chart will be plotted, in addition to a specialty chart, as not all medical practitioners have access to special charts.

Monitoring growth over time gives an understanding of short- and long-term health status, as well as estimating nutrition needs. Multiple plots of measures provide assistance in progress versus one point in time. An upward and consistent trend is the goal for all children; however, weight will fluctuate far more than length/stature, with changes in hydration, intake, and stool resulting in weight gain or loss. Accurately performed length or stature measures, therefore, are more indicative of long-term nutrition than weight measures, although a child's proportion is the best indicator of overall health.

## Interpretation of Growth

Measures are not always precise, and sharing this information with a parent can create relief or concern. Weight for Age and Length for Age represent the plotted measure for a child as compared to other children their age, with the 50th percentile considered the "average" for children studied to create the chart. Any child may fall above or below the average, and can still be considered healthy and growing.

Children with growth difficulties related to a genetic condition, poor intake, or poor tolerance often fall below average, as can children of small parents.

On the Weight for Length or Body Mass Index (BMI) chart, the 50th percentile would indicate ideal proportion, with 50th percentile weight for current length considered "ideal" weight for a child's current length or stature. A very short child, at the 5th percentile for length, who has a 50th percentile weight, might appear heavy. Disproportion can impact physical activity, therapies, and even the health of the child. Head circumference should also be considered with regard to proportion, given a larger head adds to total body weight. A child's proportion may then appear skewed on the Weight for Length or BMI chart, as a result of the extra weight contributed by a larger head.

"Weight age" and "length age" can also be estimated from growth charts. These "ages" often coincide with gross or fine motor skill levels, more than chronological age, and should be considered when planning care [12, 13].

## Special Populations

Genetics and certain conditions need to be carefully considered when interpreting growth, as children may have a diagnosis that puts them at risk of growth failure or obesity. Children with cerebral palsy, muscular dystrophy, Down syndrome, neurological impairment, Prader–Willi syndrome, Williams syndrome, and children with Fetal Alcohol Spectrum or chromosomal anomalies may all be prone to disproportionality than their typically developing counterparts [14]. Children with pulmonary disease fall into this group as well. For example, children with cystic fibrosis who have pancreatic insufficiency have been found to be smaller and lighter in weight than other children their age. A child with poorly controlled asthma may also have reduced growth rates. However, use of oral steroidal treatment can promote weight gain through appetite stimulation, glucose intolerance, and central distribution of fat. Close monitoring and dietary guidance is essential to promote proportional and steady growth for all children, especially children with chronic pulmonary disease [9].

## Physical Processing of Nutrition

Included in the medical history should be information regarding the digestive and systemic response to nutrition for children. Gastroesophageal reflux disease, constipation, diarrhea, food and environmental allergies, intolerances, dentition, oral strength, endurance, and coordination are all impacted by or impact a child's nutrition and status. Symptoms of allergies can be found in Table 1.7, and Table 1.8 lists causes of gastrointestinal problems [10]. Careful consideration of how well a child responds to nutrition is very important, as best laid plans may fail if a child cannot adequately process what is provided nutritionally.

**Table 1.7** Symptoms of food allergy and food intolerance

| |
|---|
| Symptoms of food allergy |
| • *Uticaria/angioedema*—hives, swelling |
| • *Anaphylaxis*—IgE-mediated, can be fatal |
| • *Atopic dermatitis*—60 % or more children with severe dermatitis have food hypersensitivity |
| • *Gastrointestinal disorders*—enterocolitis, malabsorption, eosinophilic gastroenteritis, allergic colitis |
| • *Respiratory reaction*—upper and lower airways |
| • *Oral allergy syndrome*—swelling of lips, tongue, palate, throat |
| Symptoms of food intolerance |
| • *Skin*—rash |
| • *Respiratory reaction*—rhinitis, wheezing |
| • *GI distress*—vomiting, diarrhea, constipation, colic, bloody stools |
| • *Fussiness, poor sleep* |

**Table 1.8** Causes of gastrointestinal problems

| Problem | Possible cause |
|---|---|
| Diarrhea | Medication, high osmolality of formula, increased rate of feeding, bacterial contamination, intolerance to cow milk protein or hydrolyzed protein, intolerance to sucrose or lactose, viral/parasitic/bacterial infection, temperature of formula |
| Gastric residuals | High osmolality of formula, medication, delayed gastric emptying |
| Nausea and vomiting | Increased rate of feeding, high osmolality, obstruction, delayed gastric emptying, increased gastric emptying, tube placement, size of tube, body position during feeding, temperature of formula |
| Constipation | Under hydration, inadequate fiber, compromised respiration, low body tone, fecal impaction or obstruction, low activity level, intolerance to cow milk or hydrolyzed protein, abnormal anatomy, fluid loss, or behavioral withholding |

## Medications and Dietary Supplements

Report of all medications, vitamins, minerals, supplements, and herbs used currently and in the past should be provided by the parent or caregiver. Interactions of any of these with each other, or with foods and fluids in a child's diet, can increase or decrease their bioavailability or effectiveness [15]. However, there are specific vitamin supplements that may be used for known deficiencies or depletion associated with the disease or due to medications. For example, in children with chronic pulmonary disease such as cystic fibrosis, fat soluble vitamins A, D, E, and K are necessary if they have associated pancreatic insufficiency. Infants with BPD may require iron, vitamin D, calcium, and phosphorous supplementation due to corticosteroid therapy. Children with asthma on nebulized beta agonist bronchodilators may have hypomagnesemia, and may need supplementation. For any additional supplements taken by the patient, it is important to make sure that they do not affect the bioavailability of medications and other nutrients [10, 16].

## Nutrition History and Intake

A thorough discussion with parents, caregivers, and the child when appropriate helps identify any nutrition-related concerns that have transpired over time. Beginning with birth, information regarding breast versus bottle feeding, breast milk versus formula, and cows milk-based formula versus hypoallergenic formula may all make a difference as to how children are responding to their current diet based on their past. Other questions to ask would include meal and snack times during the day, volumes, and progression of food introduction that took place, as this too can create a historical picture of how well children developed with their eating skills or tolerance. Questions such as what did feeding time look like in infancy, who primarily fed the infant, how were they held, and what seating or positioning systems were used over time can add to the picture being formed. A child's early experience with nutrition and feeding can have a positive or negative impact long term, and understanding the history can give insights on how to address immediate concerns [16].

## Current Intake

Having a parent document and submit a food log or journal, including a detailed listing of what, when, and how much the child consumes or receives of food and fluid, should be requested. Twenty-four-hour recalls of intake have been shown to be less accurate than food records, therefore when possible, a 3- to 5-day food record should be requested. Precise measures of food and fluid, and reporting of intake are essential, although not always easy for a parent or child to document. Not all dietitians have the ability to perform a computer analysis of a food record, which can determine levels and balance of calories, protein, fluid, vitamins, minerals, essential amino and fatty acids, carbohydrate, and total fat. Therefore, when needed, a limited review of diet and estimation of intake can then be compared to calculated needs for the child. When reviewing a diet record or recall, importance is given to variety of foods within and among the food groups, appropriate portion sizes within meals and snacks, and throughout the day, noting sources of specific nutrients such as protein, vitamins A, C, D, and calcium. Over consumption of items, such as juice, sweets, or snacks, might displace needed foods in the diet, and would be noted. Red flags should go up if a food record demonstrates a seemingly typically developing child is primarily drinking fluids and not eating, as this could indicate difficulties with oral skills related to eating and drinking [9].

## Feeding Skills and Behavior

The process of eating occurs over time from birth. Understanding a child's history of skills with eating can also assist with current plans for nutrition. An infant born full term, with no medical concerns, may accept breast or bottle feeding easily and

transition through introduction of baby foods with no difficulties. However this child, or any child, may not move through the stages of suckling, sucking, early munching, munching, rotary chewing to mature eating as easily as hoped, and therapeutic or medical interventions may be needed to assist [17]. Having the parent or caregiver explain past history of the child's feeding progress allows for a better understanding of the child's current situation. Consideration of oral-motor control, duration and frequency of feedings, food or fluid consistency, self-feeding skill development, respiratory status, use of cup, bottle, utensils, and feeding progress should be discussed.

With this information in mind, consider an infant who is chronically open mouth breathing and may not be the best at eating. Having to close his/her mouth to suck and swallow interferes with the breathing process, and the choice to breathe wins. Feeding becomes a struggle for the infant and parents, who are working hard to promote best nutrition for growth. Strategies such as bottle and nipple choice, or manipulation of fluid consistency, ensue to provide nutrition however possible. Forcing an infant to eat can also become a part of the routine, and despite all the best intentions long-term aversions may present themselves. This child may then be identified as a "picky eater" or having a "behavior" problem as a toddler, when dislike of the entire feeding time began in infancy. In fact, this child may continue to be a mouth breather as a toddler and defend himself at mealtimes, with no one identifying the root of the problem as compromised breathing with a closed mouth.

## Enteral Feedings

For those children unable to obtain adequate nutrition orally, tube feedings can assist in both short- and long-term management. Consideration of a tube feeding is often based on several factors, including the child's ability to consume at least 80 % of their expected needs orally, length of time spent on feedings in the day, poor weight gain and growth, weight loss, or low serum albumin levels. Concerns for feeding any child should be fully evaluated by an interdisciplinary team, including a physician, speech and language pathologist for oral skills, and a registered dietitian [16]. When implementing a tube feeding, schedules of times for feedings will vary from 24 h continuous, to overnight continuous with intermittent daytime bolus feedings, to daytime bolus feedings only. Choices of schedule can depend on the child's medical status, family life, and therapy received through the week. Enteral pumps are typically used, but some parents find gravity or syringe feedings less cumbersome and will choose one of these methods. Pumps will deliver formula in a more consistent manner than gravity or syringe, and this should be considered for the child with GI sensitivities.

Numerous formulas exist that can be used orally or with tube feedings. Formulas or liquid food should be treated with the same care used with food preparation, and can provide 100 % of a child's overall nutrition when given in appropriate volumes

each day. Infant, pediatric, and adult categories exist, and within each of these are a range of formulas to meet most needs. Modulars, or components of food such as carbohydrate, protein, or fat, can be added to these formulas to modify their content as needed, but should also be done with supervision. Concentration of formula or use of high calorie formulas may be needed for the pulmonary patient who has fatigue with feeding, fluid restrictions, increased caloric requirements, or inability to tolerate large volumes [18].

Increasingly popular is homemade blended formula, which can also provide for 100 % of a child's nutrition. Parents are drawn to feeding their child a diet that is varied, contains whole foods, and has been created by them versus a repetitive formula created by a manufacturer. This type of diet, however, needs supervision from a registered dietitian to ensure the parents are comfortable with the process and that the child is receiving all nutrients, as the recipes created by the parents may have too little or too much of a food or food group, or may not be well tolerated [19].

## Mealtimes, Environment, and Seating

Ensuring that a child has the ability to eat and drink in a safe, effective, and tolerated manner is a priority. Once tolerance and ability are established, further refinement of the eating experience may be necessary, and should be addressed by therapists, doctors, and parents. Schedule of eating meals and snacks should be consistent each day of the week, as often as possible. Infants will eat no less than 12 times a day when initially breast fed, and less frequently with age. Toddlers should be offered three meals and three snacks each day, approximately 2–3 hours apart, with water offered in between. Children are small, and have small stomachs; therefore, three large meals a day only may not provide optimum nutrition. Children with compromised respiratory status may require smaller, more frequent feedings to accommodate difficulty with large meals. Encouraging regular feeding times in the day instead of "grazing" all day long allows improved processing of foods and fluids by the body.

Environment defines the location of where a meal or snack will take place, but it also refers to the setting or conditions, ambiance, surroundings, and atmosphere. Suggestions for best mealtime environment include:

- Quiet, pleasant, mealtime room with minimal distractions.
- Meals with family members at the table.
- Use of feeding utensils, cups, and bowls that meet developmental ability.
- No television, electronics, or distractions.
- Quiet background music is acceptable.
- Ensure room temperature is comfortable; not too hot or cold.

Positioning during meals is important, and can impact a child's ability to concentrate on a meal, as well as the ability to eat and swallow comfortably.

- Infants need support from the person feeding them, and when being held in someone's arms, should afford least effort by the baby so they can focus on eating.
- With older children, feet should be planted firmly on something, such as the floor, the foot rest of the chair, even a stack of boxes positioned under the feet. This assists with body awareness in space and minimizes distraction.
- Children should sit with an upright posture that is well supported from behind, on the sides, in front, and above and below if necessary. Hips, knees, and feet should all be at 90° angles when possible. If this compromises breathing, however, adjustments may be required.
- Choice of appropriate chair or seating system that provides support and safety is a priority, and if positioning is in question, the family should be referred to a physical, occupational, or speech therapist for assistance.

Mealtimes, environment, and positioning should all be considered when performing a nutrition assessment, and when making recommendations to help the child and family. Any of these might be easily changed and can impact a child's ability to obtain adequate nutrition [20].

## Psychosocial Factors

Including a discussion with the parents or caregivers of factors not directly related to medical, nutrition, or feeding is also important at assessment, and should include language spoken and access to interpreters as a priority for best care and follow through of plans. Additionally one should consider housing, number of persons in the family or household, income level, financial difficulties, family and cultural food patterns, resources to food, and participation in public programs such as WIC, SNAP, school food programs, and food banks. When suggesting interventions needed for a child, any of these factors can be a barrier to best care.

## Estimation of Nutritional Needs

Determination of how much nutrition a child needs is important in the planning process. Specific nutrition needs are based on age, sex, activity, current or desired weight, stature or length, conditions with established guidelines, or recommendations made by a physician [21]. Guidelines, such as the dietary reference intakes (DRIs) and estimated energy requirements (EER) provided by the government, are meant to establish midrange intake of calories, protein, vitamins, minerals, carbohydrate, fat, fiber, and water for individuals. Calories are contributed by dietary carbohydrate, protein, and fat, and estimation of total daily calorie, protein, and fluid needs is routine. Figure 1.2 depicts the distribution of macronutrients for an average person in the United States, and emphasizes the goal of ensuring balance [22].

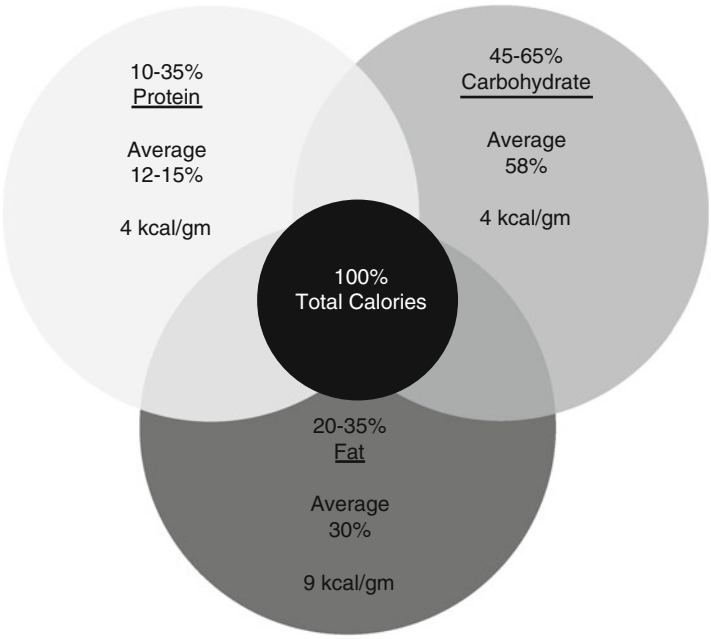


**Fig. 1.2** Caloric distribution of macronutrients

Calculations that consider age, weight, sex, activity, length, and stature are used to further define calorie needs of a specific child. For most children, use of the EER for energy or calorie needs is suggested over former RDA calculations, although some practitioners still prefer the easier to use RDAs. Estimated calories are an estimation, with the goal of assisting a child in meeting these as best as possible [23]. Calculations for low energy needs may require use of designated factors multiplied by centimeters of length instead of calculating for weight, given these children may have reduced metabolically active muscle tissue [24]. Children with pulmonary disease expend more calories from the increased work of breathing, and this needs to be taken into consideration with estimates of energy needs. Individualization is important, given children with some disorders might require as little as half the calories or as much as double that of a typically developing child. When estimating needs for more complex children, such as those failing to thrive or obese, on nutrition support or burn patients, and those being weaned from the ventilator, use of indirect calorimetry can be helpful through the measurement of oxygen consumption ($VO_2$), carbon dioxide production ($VCO_2$), and Respiratory Quotient ($VCO_2/VO_2$) [8].

Protein needs are also established using the DRIs for age, and multiplying the factor by the child's weight in kilograms. Estimation of protein intake is set by the government at an achievable level, and most children meet their protein needs through diet easily. Higher protein needs may be necessary for infants born premature or late preterm [25], as well as children with diagnoses requiring higher levels

of protein. Adequate carbohydrate intake conserves use of body protein stores; therefore, it is important that this nutrient need be met.

Fluid needs can be estimated using the Holliday-Segar method for children over 14 days of age. This calculation considers body mass in weight, with estimations of 100 cc per kg for the first 10 kg weight, plus 50 cc per kg for the second 10 kg, and 20 cc per kg for all kilograms thereafter. DRIs have been established for water based on age, sex, and condition. Consideration of diet is important when estimating intake of fluid, given foods contribute to total fluid intake daily. Experience shows that about 50 % of a child's intake can come from drinkable fluid, and the remainder from foods. Ensuring adequate hydration for the pulmonary patient can assist with insensible losses of fluid and thinning mucous secretions [26].

Vitamins, minerals, essential amino acids and essential fatty acid goals for different ages, sex, and conditions are established by the National Academy of Sciences, Institute of Medicine, and Food and Nutrition Board, and should be used unless a child's condition warrants adjustments. Guidelines for specific conditions and special needs exist, and tailoring goals for nutrition is essential to ensure they receive appropriate nutrition for their situation [22, 23].

## Prioritizing Interventions

Once an understanding of a child's overall history has been achieved, interventions need to be established and shared with the family, caregivers, and medical and therapeutic team. Table 1.9 can be shared with parents to assist them with changes.

**Table 1.9** Tips for mealtimes

- Pick one thing to change that has the best chance of success
  Try not to make too many changes at one time
- Offer meals and snacks 2–3 hours apart
- Do not encourage or promote "grazing" through the day
- Offer water to drink in between meals
- Aim for 30 minute meals, 15 minute snacks ideally
- Begin and end meals on a positive note
- Aim for a source of protein, grain, fruit/vegetable, and beverage at meals
- Snacks can be a combination of any groups, in smaller portion sizes
- Ensure positioning is adequate, comfortable, supportive
  - Feet on the floor, or touching something
  - Hips and knees at 90° angles
  - Ability to weight bear forward on arms at the table
  - Minimize distractions
- Ideally meals are for nutrition, snacks are a time for added nutrients, or used as therapy time to work on more difficult/challenging foods/fluids
- Meals should be at the table with the family as often as possible
- Changes in nutrition and skills with eating and drinking can take time

For nutrition to be successful, priority is given to medical stability, growth, tolerance, and skill. Establishing steady growth is essential, and recommendations for nutrition can only be helpful if children feel well, and if their skill level with eating supports expectations. Health and skills can affect nutrition status; therefore, referral to appropriate specialists, such as gastroenterologists, allergists, registered dietitians, and speech therapists trained in feeding is essential. Laboratory testing and results can provide information necessary for changes in intake, and added or reduced use of supplements. Additionally, establishing current status allows for replenishment of known nutrient deficits through diet modifications, foods, fluids, formulas, supplements, and, if needed, alternate routes of nutrition. Modifications will ensure that adequate overall nutrition is present to allow for steady growth and development for all children. Ensuring overall support during mealtimes is created and followed through will also allow for efficiency with nutrition and intake recommendations made.

## Conclusion

Viewing children individually and understanding their past and any impact it has had on their current state allow for best plans to be created. Knowing and understanding the basics of nutrition is essential to individualizing a plan for any child with special concerns. No one particular strategy will solve every problem related to nutrition and feeding, nor will one person be the solution for any particular child. Inclusion of a multi- and interdisciplinary team approach to nutrition is ideally the best way to help children achieve optimal progress, growth, and development. Working and communicating regularly with a child's team, and advancing through goals gradually, will serve as a cornerstone to each child's lifelong health.

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# Chapter 2
# Diets

**Robert C. Dumont**

**Keywords** Vegetarian • Vegan • Mediterranean diet • Anti-inflammatory diet • Vitamin B12 • Vitamin D • Calcium • Zinc • Iron • Iodine • Fructose • High fructose corn syrup • Phytonutrients

## Keypoints

- Three health promoting diets include the vegetarian diet, Mediterranean diet, and the anti-inflammatory diet.
- Though vegetarians can choose an unbalanced and unhealthy diet, a healthy vegetarian diet is associated with health advantages, including lower blood cholesterol levels, lower risk of heart disease, lower blood pressure levels, and lower risk of hypertension and type 2 diabetes.
- Potential nutritional risks of a vegetarian diet are deficiencies of vitamin B12, calcium, vitamin D, zinc, iodine, iron, and long-chain omega 3 fatty acids.
- The Mediterranean diet is primarily a plant-based diet with emphasis on vegetables and fruits along with whole grains, legumes, and nuts.
- The Mediterranean diet has anti-inflammatory properties and is associated with a significant reduction in overall morbidity and mortality from various chronic diseases.
- The basic elements of an anti-inflammatory diet are optimization of fatty acid ratios, maximizing vegetables and fruits, and reducing processed foods, added sugars, potential food allergens, red meat, and dairy consumption.

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## Introduction

While we know much about the nutritional elements in foods (carbohydrates, proteins, vitamins, minerals, etc.), it is often difficult translating these elements into a meal. It is important to effectively interpret nutrition into realistic everyday language, which is the foods we eat, our diets, our everyday meals. To achieve this, we need to regain our perspective on healthy eating. It was over 150 years ago that food industry began to emerge with the beginning of the industrial revolution. Prior to that time most people lived in a rural setting where food was locally grown and food was eaten according to the seasons. There were no chemical fertilizers. With the onset of the industrial revolution we made great leaps in areas of transportation, chemistry, and food processing. Shelf life and subsequently "improved taste" became of prime importance so food became more modified and processed. Food became an industry.

Michael Pollan speaks of our dilemma in choosing what to eat. As omnivores we have so much information and choices on what is and is not healthy (often conflicting); we become confused and even paralyzed in making healthy choices [1]. This chapter will be limited to several specific diets which are known to be health promoting: the vegetarian diet, Mediterranean diet, and the anti-inflammatory diet.

## Vegetarian/Vegan Diet

Unlike most other diets, people become vegetarians for a variety of reasons: environmental, spiritual, animal cruelty, health, etc. A vegetarian diet is defined as a diet without meat, poultry, or fish. There are two basic forms of vegetarian diets: (1) Lacto-ovo vegetarian: a vegetarian diet that includes dairy products and eggs. (2) Vegan: a diet with no consumption of nutrients from any animal source. Some people may consider themselves as "mostly" vegetarian consuming meat infrequently or eating only fish and/or poultry.

Overall, as a group vegetarians are generally healthier than those eating a (primarily) meat-based diet. Quoted from the American Dietetic Association (ADA; now The Academy of Nutrition and Dietetics) position paper on vegetarian diets: "Vegetarian diets are often associated with a number of health advantages, including lower blood cholesterol levels, lower risk of heart disease, lower blood pressure levels, and lower risk of hypertension and type 2 diabetes. Vegetarians tend to have a lower body mass index (BMI) and lower overall cancer rates. Vegetarian diets tend to be lower in saturated fat and cholesterol, and have higher levels of dietary fiber, magnesium and potassium, vitamins C and E, folate, carotenoids, flavonoids, and other phytochemicals" [2]. Despite this statement of improved health, a vegetarian diet in and of itself is not necessarily a healthy diet as vegetarians can choose an unbalanced and unhealthy diet with processed foods and added sugars. There are also specific issues for the vegetarian diet that require attention. Per the position paper of the ADA, a vegetarian diet, especially vegan diet, can potentially put a person at risk for deficiencies of vitamin B12, calcium, vitamin D, zinc, iodine, iron, and long-chain $n-3$ fatty acids.

## *Vitamin B12*

Vitamin B12 is almost exclusively found in animal products and is not found in appreciable amounts in plant foods. The lacto-ovo vegetarian who is regularly consuming eggs and dairy products can obtain adequate amounts from these foods; but vegans must obtain their B12 from other sources: fortified foods such as breakfast cereals, "milk" substitutes made from soy, rice, etc., fortified Brewer's and nutritional yeasts (yeasts do not intrinsically contain B12), B12 supplements, and multivitamins. The B12 in these fortified foods and yeast products is derived from bacteria cultures. It is therefore important to check the nutritional labels to confirm the presence and amount of B12.

## *Calcium*

Like B12, calcium is also a specific concern in vegans though not lacto-ovo vegetarians who consume sufficient amounts of dairy products as part of their diet. The few studies on bone density in vegetarians find lower calcium intake and a lower bone density in vegans. The bone density of ovo-lacto vegetarians is equivalent to or greater than their meat eating counterparts [3, 4]. Dairy is not the only source of calcium. There are many plant sources of calcium which is well absorbed in a vegan diet [5].

Calcium is found in the low oxalate dark green leafy vegetables bok choy, broccoli, collards, Chinese cabbage, kale, and mustard greens and is well absorbed from these foods [6]. Those foods high in oxalates (spinach, rhubarb, chard, and beet greens) should not be considered good sources of calcium as the oxalates bind with calcium reducing its absorption [7]. Other sources include tofu made with calcium sulfate, calcium-fortified soy milk and orange juice, and other supplemented foods (see Table 2.1 for calcium food sources). Though tofu is considered a great source of calcium, the amount is influenced from the coagulating agents used in processing. There is more calcium in tofu from calcium sulfate than tofu processed with magnesium chloride.

## *Vitamin D*

Vitamin D deficiency is not just a potential problem of vegetarians. With the reduced exposure to sunshine due to working (and playing) indoors and the increased use of protective clothing and sunscreen there is an increase in vitamin deficiency across all age groups [8]. The Institute of Medicine tripled the amount of vitamin D from an Adequate Intake (AI) of 200 IU to a Recommended Daily Allowance (RDA) of 600 IU for all children over the age of 1 year and adults up to the age of 50 and they doubled the safe upper limit (UL) from 2,000 to 4,000 IU/day [9].

**Table 2.1** Calcium food sources

| Selected food sources of calcium | | |
|---|---|---|
| Food | Milligrams (mg) per serving | Percent DV[a] |
| Yogurt, plain, low fat, 8 oz | 415 | 42 |
| Mozzarella, part skim, 1.5 oz | 333 | 33 |
| Yogurt, fruit, low fat, 8 oz | 313–384 | 31–38 |
| Cheddar cheese, 1.5 oz | 307 | 31 |
| Soymilk, calcium-fortified, 8 oz | 299 | 30 |
| Milk, whole (3.25 % milk fat), 8 oz[b] | 276 | 28 |
| Orange juice, calcium-fortified, 6 oz | 261 | 26 |
| Tofu, firm, made with calcium sulfate, ½ cup[c] | 253 | 25 |
| Tofu, soft, made with calcium sulfate, ½ cup[c] | 138 | 14 |
| Ready-to-eat cereal, calcium-fortified, 1 cup | 100–1,000 | 10–100 |
| Turnip greens, fresh, boiled, ½ cup | 99 | 10 |
| Kale, raw, chopped, 1 cup | 100 | 10 |
| Kale, fresh, cooked, 1 cup | 94 | 9 |
| Ice cream, vanilla, ½ cup | 84 | 8 |
| Chinese cabbage, bok choy, raw, shredded, 1 cup | 74 | 7 |
| Bread, white, 1 slice | 73 | 7 |
| Tortilla, corn, ready-to-bake/fry, one 6″ diameter | 46 | 5 |
| Tortilla, flour, ready-to-bake/fry, one 6″ diameter | 32 | 3 |
| Sour cream, reduced fat, cultured, 2 tablespoons | 31 | 3 |
| Bread, whole-wheat, 1 slice | 30 | 3 |
| Broccoli, raw, ½ cup | 21 | 2 |
| Cheese, cream, regular, 1 tablespoon | 14 | 1 |

Modified from Calcium—Office of Dietary Supplements—National Institutes of Health http://www.ods.od.nih.gov/factsheets/Calcium-HealthProfessional

[a]*DV* daily value. DVs were developed by the U.S. Food and Drug Administration to help consumers compare the nutrient contents among products within the context of a total daily diet. The DV for calcium is 1,000 mg for adults and children aged 4 years and older. Foods providing 20 % of more of the DV are considered to be high sources of a nutrient, but foods providing lower percentages of the DV also contribute to a healthful diet. The U.S. Department of Agriculture's Nutrient Database Web site lists the nutrient content of many foods. It also provides a comprehensive list of foods containing calcium

[b]Calcium content varies slightly by fat content; the more the fat, the less calcium the food contains

[c]Calcium content is for tofu processed with a calcium salt. Tofu processed with other salts does not provide significant amounts of calcium

Few natural food sources contain sufficient levels of vitamin D with the highest amounts found in fish liver oils (cod liver oil 1,360 IUs per tablespoon) and oily fish. Much smaller amounts are found in other animal-based foods such as beef liver, cheese, and egg yolks [10]. Therefore, most people receive vitamin D through fortified foods. Fortified food sources include cow's milk, certain brand of dairy substitutes such as soy rice, almond and hemp milk, breakfast cereals, and orange juice.

### *Zinc*

Primary zinc sources include soy products, legumes, grains, cheese, and nuts. While overt zinc deficiency is not generally evident in Western vegetarians [11], zinc deficiency is a potential problem in vegetarians. The phytic acid content of certain plant food may lower the zinc bioavailability in the vegan diets; therefore, the zinc requirements may be increased for vegetarians whose diets consist mainly of phytate-rich unrefined grains and legumes.

Food preparation techniques, such as soaking and sprouting beans, grains, and seeds as well as leavening bread, can reduce the binding of zinc by phytic acid and thus increase zinc bioavailability [12]. The presence of organic acids, such as citric acid, can also enhance zinc absorption to some extent.

### *Iodine*

Plant-based diets are typically low in iodine so vegans who do not include sources such as iodized salt or sea vegetables (kelp, seaweeds) may be at risk for deficiency [13]. Sea salt is usually not iodized so if this is taken in the place of iodized salt another source such as sea vegetables (edible kelps and seaweeds) should be considered. However, iodine taken from these sea vegetables should be monitored as the iodine content of sea vegetables varies widely with some containing substantially large amounts of iodine [14].

### *Iron*

Like zinc the nonheme iron in plant foods is subject to variable absorption depending upon the presence of various inhibitors. Inhibitors of iron include phytates in grains, seeds, and beans (inhibition is reduced with soaking and sprouting and the leavening of bread), and polyphenols in coffee, tea, and cocoa. Fermentation of soy products may also increase iron bioavailability [15]. For a more complete discussion on trace mineral absorption in the vegetarian diet see the review by Hunt [11].

### *Essential Fatty Acids*

The last area of potential concern for deficiency is omega 3 fatty acids. Though many plant foods are good sources of α-linoleic acids; the conversion rate of these to EPA and DHA is low (see Chap. 3, section on “Essential Fatty Acids”). Concurrent with this is that vegetarians and especially vegans have lower levels than non-vegetarians [16].

While fish oil supplements are generally recommended for increasing DHA/EPA levels, rudimentary source of DHA is marine algae, and supplementation can be achieved through the use of algae-based supplements [17, 18].

## Protein and the Vegetarian Diet

A healthy vegetarian diet provides more than enough protein on a daily basis. The myth of inadequate protein that arose in the early part of the twentieth century has long since been dispelled. Protein/amino acid needs are more than adequately met in a vegetarian diet that contains a varied plant food intake over the day. Certain food groups deficient in some essential amino acids can easily be made up with protein for another source. Therefore a variety of plant-based proteins over the course of a day can give an adequate amount of essential amino acids (e.g., many cereals which are low in the essential amino acid lysine are complemented with legumes which have a high lysine content) [19].

For a more comprehensive discussion of the vegetarian diet the reader is referred to the ADA position paper on vegetarian diet [2].

## Mediterranean Diet

The Mediterranean diet is based on the traditional diets of the Mediterranean region especially the island of Crete. It is the outgrowth of The Seven Countries Study by Ancel Keys of University of Minnesota and colleagues examining the relationship between diet, lifestyle, risk factors, and rates of coronary heart disease and stroke in populations contrasting in diet, especially dietary fat [20]. Comparing data from the United States, Italy, Greece, Yugoslavia, the Netherlands, Finland, and Japan, conclusions were made linking elevated cholesterol levels and saturated fatty acids with cardiovascular disease (CVD). Those populations with little CVD had saturated fatty acid intake less than 10 % and this was independent of total fat intake. Crete in particular had very low levels of coronary heart disease.

The current Mediterranean diet is an adaptation of the original 1960s diet. It is a primarily a plant-based diet with emphasis on vegetables and fruits along with whole grains, legumes, and nuts. Fish is eaten approximately twice a week and (red) meat eaten only several times a month (minimizing saturated fats). Vegetable oils rich in omega 3s and monounsaturated oils such as olive oil and canola oil are used instead of animal-based fats/oils. Spices are recommended over the heavy use of salt seen in the typical western diet.

A food pyramid based on the early 1960s Mediterranean dietary patterns of Crete, the rest of Greece, and southern Italy was devised, through a collaboration of the Oldways Preservation and Exchange Trust (www.oldwayspt.org), the Harvard School of Public Health, and the European Office of the World Health Organization

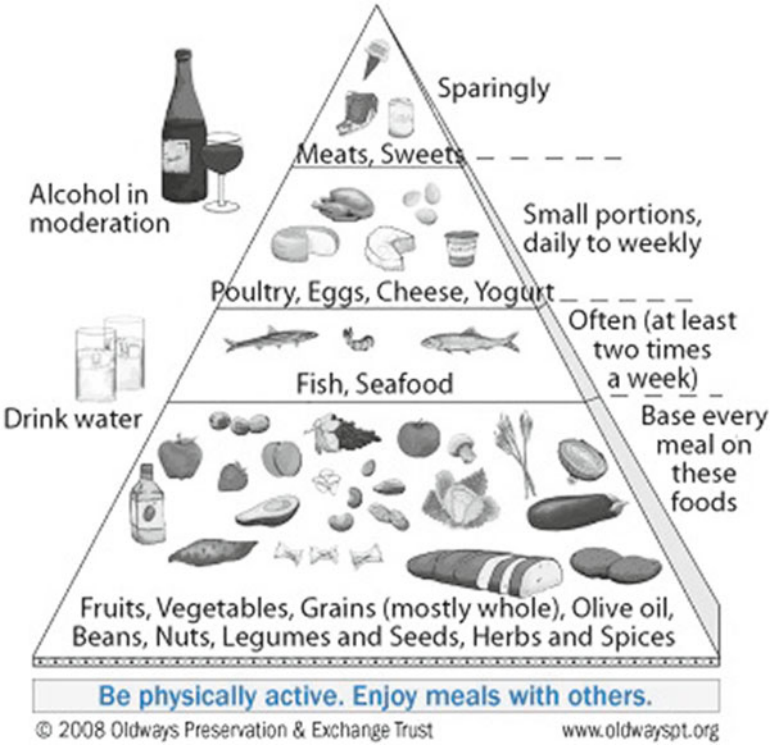


**Fig. 2.1** Mediterranean pyramid. Courtesy of the Oldways Preservation and Exchange Trust (www.oldwayspt.org)

in 1993. This is composed of a predominance of plant-based foods (fruit, vegetables, breads, other forms of cereals, potatoes, beans, nuts, and seeds), fresh fruit as the typical daily dessert, olive oil as the principal source of fat, dairy products (principally cheese and yogurt), and fish and poultry consumed in low to moderate amounts, zero to four eggs consumed weekly, red meat consumed in low amounts, and wine consumed in low to moderate amounts, normally with meals (see Fig. 2.1) [21]. The diet is especially low in saturated fat.

Since the initial Seven Countries Study in 1980, multiple studies demonstrating the health benefits of the Mediterranean diet have followed. Recent reviews have confirmed significant reduction in overall mortality, including mortality from CVDs but also have shown reduction of incidence of cancer, and incidence of neurodegenerative diseases (Parkinson's disease and Alzheimer's disease) [22–24]. Recent research has also shown evidence that the Mediterranean diet has anti-inflammatory properties reducing levels of C-reactive protein (CRP), interleukin-6 (IL-6), IL-18, and tumor necrosis factor-α (TNF-α) [25] and may serve as dietary treatment of diseases related to chronic inflammation including metabolic syndrome, visceral obesity, and type 2 diabetes [26–28]. There is one study addressing use of

Mediterranean diet in asthma, showing consistent but statistically nonsignificant improvements in spirometry and asthma-related quality of life questionnaires [29] (see Chap. 7 for further discussion). Finally, it has been recently suggested to construct a Mediterranean food lifestyle index including physical and social activity, recreation, and rest for a more holistic approach and correlate with improved morbidity and mortality [30].

## Anti-inflammatory Diet

There are many similar elements in the anti-inflammatory diet compared to the Mediterranean diet. The essence of an anti-inflammatory diet is to eliminate (or minimize) foods that promote inflammation and maximize foods that moderate inflammation.

There are several anti-inflammatory diets, but while emphasis may vary, the basic elements of an anti-inflammatory diet are optimization of fatty acid ratios, maximizing vegetables and fruits (the presence of fiber, antioxidants, and other phytonutrients) and avoiding processed foods, added sugar, and potential food allergens, and finally reducing red meat and dairy consumption.

### *Processed Foods*

Perhaps the most emphasized element is elimination or minimizing of highly processed foods. In our current times processing is unavoidable and not necessarily always negative. As defined by the United States Federal Food, Drug and Cosmetic Act [31], a processed food is "any food other than a raw agricultural commodity and includes any raw agricultural commodity that has been subject to processing, such as canning, cooking, freezing, dehydration, or milling." Humans have been cooking for thousands of years as cooking makes some foods more digestible as well as preserving (pickling, salting, and drying) foods that might become scarce in upcoming seasons. Today, processing is a necessity as few people are capable of providing their own nutrition year round so food must be transported, and preserved on grocery store shelves and in the home pantry. Additionally, our lifestyles are such that we have little time to prepare meals and many of us have lost all but the most basic skills in cooking. Processed foods offer convenience and variety to make up for our lack of time and food preparation skills. To be avoided are the extremely processed foods that upset the nutritional "balance" that unprocessed foods contain. In these foods the nutritional density and content are often diminished while the caloric density is increased with unhealthy added sugars, oils, and refined grains. Highly processed foods often contain high amounts of omega 6 fatty acids and added sugars. The omega 6 fatty acids skew the omega 6/omega 3 fatty acid ratio in favor of a pro-inflammatory state (see Chap. 3, section on "Essential Fatty Acids").

Recommended are foods that are minimally processed. This often requires some basic education from a dietician/nutritionist as the information can be overwhelming for the average person. A useful "handbook" for the average consumer is "Food Rules" by Michael Pollan [32]. The other concern raised with highly processed foods is that they can have an addictive quality. This is especially true regarding added salt, sugar, and fat according to David Kessler in his book "The End of Over Eating" [33].

## *Sugars*

Sugar is essential to life. Our bodies need (some) sugar or carbohydrates, which serves as our natural fuel as well as serving as build blocks for certain cellular components. Sugar is a component of nutritious foods such as fruits and vegetables. However, the sugar in these foods is balanced with many other important nutrients. These other components include antioxidants and other phytonutrients that help to stem inflammatory activity in our bodies. Processed foods with added sugar distort the dietary balance making food less nutrient-dense and more calorically dense. Excess sugar also acts as a pro-inflammatory agent. It has been linked to increased risks of oxidative stress, inflammation, depressed immunity, obesity, and chronic diseases such as metabolic syndrome (source) and type 2 diabetes [34, 35]. Fructose appears to be the most problematic of the sugars targeting hepatic metabolism and associated with the metabolic syndrome (increased abdominal adipose tissue, insulin resistance, dyslipidemia, and hypertension). It increases inflammation and reactive oxygen species (ROSs) and induces leptin resistance [36, 37]. Specific arguments against the use of high fructose corn syrup (HFCS) vs. sucrose have been made though the amounts of fructose are roughly equivalent, but because it is in free form and not chemically bonded as in sucrose. However, the fructose and glucose are readily cleaved from sucrose and absorbed. Also there are no differences with regard to short-term energy regulating hormones or appetite between the two sugars [38–43]. This lack of difference in effect between sucrose and HFCS leads back to the general underlying problem, which is the excess amount of added sugars and the probable specific negative effects of fructose as noted above.

Many people are oblivious to the sources of added sugar and often do not consider such "natural" sources such as fruit drinks or sweetened tea. Many are also unaware of the added sugars in pastries and processed foods such as cereal. The per capita intake of sugar in the United States has risen over the several decades increasing from 6.7 kg in 1968 peaking at to 38 kg in 2000 and at 29.2 kg in 2010 with similar increases in the rest of the world as nations become more affluent and industrialized [44]. This perpetuates its role in increasing ROSs and inducing a pro-inflammatory state.

Refined grains (often found in many highly processed foods) are also discouraged in the anti-inflammatory diet as much of the nutritious layers of the grain containing essential mineral, (mostly B) vitamins, and fiber have been removed.

Without the fiber the carbohydrates in refined grains are more quickly absorbed inducing rapid rises in blood sugar levels. The end product is a nutritionally poor, high caloric food product. Instead whole grains are encouraged.

## *Optimization of Fatty Acid Ratios*

Aside from added sugars and refined grains many highly processed foods also have added (predominantly) omega 6 oils including cottonseed, safflower, corn, and sunflower oils that add to the inflammatory effect. Some fast foods still contain the pro-inflammatory trans fats as partially hydrogenated oil or vegetable shortening. Also, eating fish or supplementing with fish oils is encouraged to provide increase in omega 3 oils and improve the omega 6/omega 3 ratio away from a pro-inflammatory state (see Chap. 3, section on "Essential Fatty Acids"). It is primarily the oily cold water fish that contain the highest amounts of the EPA/DHA essential fatty acids. There is a caution as most fish contain heavy metals. This is somewhat problematic as identification of fish that are both high in *n*−3 PUFAs and low in methylmercury (MeHg) is difficult. The amount of both omega 3 FAs and heavy metals varies from specie to specie and many of the studies on fish as a source of omega 3 oils have not collected data on the specific species of fish that were consumed. Thus interpretation of risk/benefit ratio is difficult [45]. What is generally recommended is eating smaller (oily) fish such as herring or sardines as they do not contain as high a toxic burden and are lower on the food chain so have not accumulated as much of a toxic burden than fish higher in the food chain. Suggested intake is several times a week. Selenium has also been recommended to be taken when eating fish as it chelates mercury. The alternative option is fish oil supplements.

## *Red Meat*

Similar to the Mediterranean diet, the recommendation for red meat consumption is limited to several times a month. When meat is eaten, organic (pesticide- and herbicide-free) grass-fed beef is recommended. Commercially raised cattle are fed grains such as soy and corn for accelerated growth, allowing them to be slaughtered at a younger age providing financial savings for the business. However, due to living constraints and diet in feed lots cattle gain extra fat that is mostly saturated fats and more pro-inflammatory. Organic free range grass-fed cattle are leaner with less saturated fat and higher levels of the healthier omega 3 oils and grass-based diets elevate precursors for vitamins A and E and antioxidants [46, 47].

Another factor which may link red meat to inflammation is the discovery of the dietary sialic acid, Neu5Gc, found primarily in red meat and dairy products. It may evoke an antigen–antibody reaction promoting low grade chronic inflammation possibly a contributing factor in diet-related carcinomas and other diseases in humans [48, 49].

## *Dairy, Wheat, and Other Food Allergens*

Food sensitivities other than documented IgE allergies are a controversial subject. However, many practitioners of integrative medicine consider this an important element in the causation or aggravation of disease and thus it is an important component of an anti-inflammatory diet. Some are proponents of testing for IgE and/or IgG food antibodies, while others feel that the sensitivity is not good enough and rely on elimination diets. Practitioners vary in their recommendations as to what food to include in an elimination trial ranging though most will eliminate dairy- and gluten-based food products and others possibly eliminating additional foods such as corn and soy. As an empiric trial the elimination trial may range from 4 to 12 weeks. Resolution or reduction of symptoms and a greater sense of "well-being" during the elimination period are considered signs of a food sensitivity. Foods may then be returned to the diet one by one to looking for a return of symptoms to determine which foods are responsible. Based on clinical experience most integrative practitioners (author included) would agree that dairy and gluten are frequently a significant component in chronic diseases (including pulmonary) with an inflammatory component.

## *Phytonutrients*

Encouraged in the anti-inflammatory diet is an abundance of vegetables and fruits along with legumes, nuts, and seeds (similar to Mediterranean diet). A diet rich in vegetables and fruits moderates inflammation [50–52]. Vegetables and fruits contain necessary vitamins and minerals along with phytonutrient not found elsewhere. While phytonutrients are not considered essential dietary elements such as vitamins and minerals, they are important plant constituents that can have an impact on disease and health, and in particular diminish oxidative stress and modulate the immune system. There are many thousands of identified phytonutrients. The most familiar recognized groups are the carotenoids, polyphenols, phytoestrogens, and catechins. The carotenoids (yellow and orange foods such as pumpkins and carrots) include beta carotenoid (precursor to vitamin A) and other recognized nutrients such as lycopenes (tomatoes, pink grapefruit, watermelon, guava) and lutein (leafy greens such as kale, spinach, and turnip greens). Polyphenols include the flavonoids (quercetin from apples, berries, grapes and onions, resveratrol from grapes and red wine, and components found in turmeric). Phytoestrogens comprise mostly the isoflavones from soy products and lignans with estrogen-like activity mainly from flaxseeds and sesame seeds. Catechins are found in high amounts in green tea.

In general, phytonutrients serve as antioxidants, enhance immune responses, and modulate cellular signaling processes and estrogen metabolism (Phytoestrogens). They have anticarcinogenic properties and support detoxification though cytochrome P450 (Phase I) and Phase II enzyme systems [53]. Flavonoids and other polyphenols in particular have an inhibitory effect on NF-κB signaling and downregulate the expression of pro-inflammatory markers [54, 55].

## Conclusion

There is not one ideal diet for people in general or for a patient with chronic lung disease. The diets discussed above maximizing vegetables and fruits, and minimizing added sugar and processed foods have proven health benefits and may be a consideration for chronic diseases where persistent inflammation is a component.

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# Chapter 3
# Nutritional Supplements and Herbs

**Robert C. Dumont**

**Keywords** Supplements • Herbs • Probiotics • Prebiotics • Essential fatty acids • Omega 3 fatty acids • Omega 6 fatty acids • Antioxidants • Functional medicine

**Keypoints**

- Nutritional supplements and herbs are currently not well regulated in the United States.
- The judicious use of herbs and supplements with anti-inflammatory and antioxidant properties have potential to be a valuable complement to therapeutic intervention for chronic inflammatory diseases.
- A healthy bacterial flora can modulate the immune system. There is growing evidence for the therapeutic potential of probiotics especially in chronic inflammatory diseases.

## Introduction

Herbs have long been a part of the human diet. Today herbs are used primarily for seasoning and flavor; but historically herbs had a much broader use. Herbs were the medicines of the day and were often added to the diet to enhance overall health, improve endurance, and increase resistance to infection. In Asian culture ginger was taken with seafood as it was believed to mitigate the ill effects of eating bad fish. Today sushi is still accompanied by (pickled) ginger. Aside from simple folk

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medicine, herbs and herb combinations were developed and used medicinally in the context of the cultural understanding of health and disease such as Chinese medicine, Ayurvedic medicine, and even early Western herbal traditions. Herbal medicine continues to be practiced this way by many traditional practitioners.

With the advent of modern biomedical science, medicinal herbs have been come to be described and utilized according to their chemical constituents and their influence on molecular targets to treat specific medical disorders and diseases. Over the past century minerals, vitamins and other dietary components have been identified, explored, and utilized in a similar manner. There is now a large and growing industry of dietary supplements and herbs in the United States. In an economic impact analysis submitted in 2009 to the Natural Products Foundation (NPF), the dietary supplement industry directly produced $22.5 billion in 2006. It has continued to generate over $20 billion per year since then. As US health expenditures have grown so has the dietary supplement industry maintaining itself at more than 1 % of total US health expenditures for at least the last 10 years [1].

Supplements along with other complementary alternative medicine (CAM) modalities such as herbs and homeopathy are used by many patients (including children), often without the guidance of a knowledgeable health care professional. Of healthy children seen in outpatient clinics, 20–40 % use CAM and greater than 50 % of children with chronic conditions use CAM therapies. Of teenagers using CAM, nearly 75 % use herbs and other dietary supplements. Most pediatric patients who receive CAM also receive conventional care [2]. An earlier study reported the use of CAM in cystic fibrosis (CF) to be at 60–75 % [3]. The high prevalence of CAM including supplement use underscores the importance to understanding CAM (and for the purpose of this chapter) herbs and supplements to be able to give accurate information to our patients.

## Supplements: General Background and Regulation

The increased use of nutritional supplements often without knowledgeable guidance has generated legitimate concerns, which was best expressed over 12 years ago when Jane Brody of the New York Times wrote “Consumers are, in effect, volunteering for a vast largely unregulated experiment with substances that may be helpful, harmful or simply ineffective” [4]. This statement raises questions: What are supplements? Are they safe? Are they effective? And what is the regulatory status of these substances?

The Dietary Supplement Health and Education Act (DSHEA) of the United States define nutritional supplements as a product taken by mouth that contains a “dietary ingredient” intended to supplement the diet. These products included vitamins, minerals, herbs and other botanicals, amino acids, and substances such as enzymes, organ tissues, glandulars, and metabolites [5]. The DSHEA, passed in 1994, was the first major regulatory legislation of supplements in the United States. Under DSHEA, a company is responsible for determining that the dietary supplements it manufactures or distributes are safe and that any representations or claims made about them are

substantiated by adequate evidence to show that they are not false or misleading. This means that dietary supplements do not need approval from the FDA before they are marketed. Except in the case of a new dietary ingredient, where pre-market review for safety data and other information is required by law, a firm does not have to provide FDA with the evidence it relies on to substantiate safety or effectiveness before or after it markets its products [5]. This act was amended in 2007 through the Current Good Manufacturing Practices (CGMPs) and Interim Final Rule (IFR) Facts to help to ensure manufacturers produce unadulterated and properly labeled dietary supplements and provide for a way to handle consumer complaints, and maintain records [5]. Regulation is still weak, leaving gaps regarding issues of safety and efficacy of herbs and supplements. However, many herbal substances have hundreds and even thousands of years of recorded use unlike conventional drugs. So a degree of safety data of a substance can initially be gleaned from these records.

It is important to appreciate that traditional use of herbs is often based on different pathophysiologic paradigms dependent upon the prevailing culture. In Chinese medicine asthma may potentially be one of several different "diagnoses" per Chinese Medical pathophysiology (i.e., Lung and Kidney deficiency, Spleen Qi deficiency or Liver Yin deficiency with rising Liver Yang) [6]. In Chinese medicine, the choice of an herbal formula is tailored to the individual patient. Formulas could contain from 5 to 15 different individual herbs; each herb playing its role in the overall disharmony responsible for the symptoms. Finally, the herbal formula would most likely be only part of an overall treatment including acupuncture, and more than likely dietary and lifestyle changes. Ayurvedic (Indian) medicine and even certain applications of Western herbal medicine would also use individualized combinations of herbs based on their particular paradigm/approach and as part of an overall holistic/comprehensive approach. So unlike the Western medical paradigm of "one drug fits all," any clinical studies involving herbs, especially Chinese herbs are complicated by the need to individualize treatment, which unfortunately is not the approach that has been applied in the majority of published clinical studies.

Within these traditions, herbs are considered a part of a more complete integrative approach often utilizing other modalities (such as acupuncture) and more importantly modification of diet and lifestyle to correct an underlying imbalance than merely to control symptoms. In this regard herbs (and supplements) are considered supplements and not replacements for a healthy diet and lifestyle. This same approach is applied in the modern Western biomedical model of Integrative medicine which has the same patient centered (not disease centered) approach of restoring balance through lifestyle and diet, the integration of various approaches, conventional and CAM, including the use of supplements and herbs [7].

Discussion of all herbs and nutritional supplements is well beyond the scope of this chapter; however, a few of the more frequently used groups of supplements will be discussed. For more detailed treatise on individual supplements and herbs, the reader is referred to several excellent online sources: Dietary Supplements Labels Database [8], University of Maryland Medical Center Medical Alternative Medicine Index [9], Natural Standard Research Collaboration [10].

## Probiotics

Probiotics have been a mainstay of naturopathic medicine for many years; and an important intervention of practitioners of integrative medicine. In recent years it has gained acceptance in conventional medicine with an explosion in basic and clinical research.

Our gastrointestinal system contains between 500 and 1,000 species and strains of bacterial organisms. With an estimated number of $10^{14}$, the number of intestinal bacteria outnumbers the cells or our bodies by a factor of 10:1 [11]. In general, strict anaerobes make up 95 %, facultative anaerobes: 1–10 % (*E. coli*, Klebsiella, Streptococcus, Lactobacillus, Staphylococcus, Bacillus). Very few aerobic bacteria are found. This microbiota has been viewed as a metabolic "organ," with a collective genomes estimated to contain 100 times more genes than our own human genome, living symbiotically with our physiology and performing many important metabolic functions we are unable to do on our own [12]. A healthy bacterial flora is responsible for production of nutrients (vitamins, growth factors), antioxidants (and promotion of antioxidant activity), coagulation factors, recycling of enzymes and old cells, development/enhancement of the immune system (activates MALT—mucosa-associated lymphoid tissue), decreasing production of endotoxins, and decreasing mutagenicity. Healthy bacteria also inhibit potential pathogenic bacteria through direct antimicrobial effect (Bacteriocins), reduction of pH, competition for nutrients, blockade of receptor sites, direct competition, and production of mucus (mucus shield). In brief there is a very complex and intertwined symbiotic relationship having potentially far reaching effects on other physiologic systems in the body.

## Factors Affecting Bacterial Flora

The first acquisition of bacterial flora in infants is through vaginal delivery inoculation with vaginal and fecal bacteria (the vaginal environment and its microbiota changes around the time of delivery). This initial flora is gradually changed over time according to diet. Those children who undergo Cesarean section presumably acquire their initial flora from hospital environment and health care workers. This may have significant influence on subsequent disease as Cesarean section performed in children with a maternal history of allergy significantly increases the risk of food allergies in those children [13]. There may also be associated increased risk for allergic rhinitis and asthma [14]. Prematurity and feedings can also influence colonic flora. In general, there is lower *Bifidobacterium fragilis* and higher *Clostridium difficile* in Cesarean sectioned infants. *Clostridium difficile* increases with increasing hospital stays and infants younger than 37 weeks have increased *C. difficile* [15]. Formula-fed infants have increased *C. diff*, greater heterogeneity, and larger bacterial load while breast fed infants have overall lower colonization of *C. diff*, *B. fragilis,* and Lactobacilli. When solid foods are started, the flora changes

to an adult type flora [15]. As with adults, the quality of diet in an older child will influence the health of gastrointestinal flora.

Antibiotics can have a tremendous effect on the gastrointestinal microbiota disrupting the normal balance causing a dysbiosis. Dysbiosis or disturbed gastrointestinal flora, its influence on health, and probiotic intervention has been an active area of research.

## Regulation and Safety of Probiotics

To appropriately regulate and resolve issues of safety, probiotics must be defined. Per the World Health Organization probiotics are defined as "Live microorganisms which when administered in adequate amounts confer a health benefit on the host" [16]. Suggested criteria state that "The microbe must be alive when administered, must be documented to have a health benefit and must be administered at levels shown to confer the benefit. The probiotic must be identified at the genus, species and strain level, using appropriate molecular and physiological techniques. The strain should be deposited in an internationally recognized culture collection so that scientists are able to replicate published research on the strain. Before use, the safety of the microbe must be fully considered. Properly controlled studies must be conducted which document a health benefit in the target host. The ability to keep the probiotic strains alive at required levels in the final product through the end of shelf life" [17]. In the United States probiotics are regulated under *DSHEA* as supplements so do not have to prove effectiveness nor guarantee viability.

The problems of efficacy and choosing the correct probiotic (or probiotic combination) are complicated by the many different strains as they may be applied to different disease states and even individual differences. It is not simply enough to recommend probiotics generically. All probiotic strains are different. Per Isolauri, there are "differences in immunomodulatory effects between candidate probiotic bacteria. Each probiotic strain is a unique component itself, and each strain has specific properties that cannot be extrapolated from other, even closely related, strains…" [18]. He also points out the influence of the diet on probiotic species "…. The approach of supplementation with single components, however, overlooks the role of dietary composition, with its range of nutrients and other potentially active components, and also the conceivable combined effects. Consequently, research now focuses both on characterizing specific probiotic strains and on how the food matrix and the dietary content interact with the most efficient probiotic strains" [18]. So ultimately several issues need to be further researched and clinically considered regarding the selection of probiotics: resistance to bile and acid, survival of intestinal transit, ability to adhere to intestinal cells and thrive in the intestinal environment, along with potential antipathogenic activity, Immune modulation, etc. These questions are slowly being addressed.

Today, most probiotics are combinations of Lactobacilli and Bifidobacteria species and strains. In general they enhance mucin production and decrease intestinal permeability, enhance the immune system and inhibit pathogenic bacteria.

Despite the above difficulties in research, probiotics are showing clinical and potential benefit in a number of diseases including acute diarrhea, antibiotic-associated diarrhea, Necrotizing enterocolitis, ulcerative colitis, infantile colic, allergic conditions [19], and pulmonary disease [20–24].

For many conditions, the evidence is promising but not yet sufficient to recommend for many of these conditions. Problematic in clinical studies is the use of different strains and protocols in the various studies. Despite this probiotics are generally considered as safe. The few situations that have suggested caution are the preterm infant, critically ill individuals and those with severely compromised immune system. However, adverse effects (sepsis) are rare and found only in isolated reports [25, 26].

## Prebiotics

Related to probiotics are prebiotics. Prebiotics are defined as "a selectively fermented ingredient that allows specific changes, both in the composition and/or activity in the gastrointestinal microflora that confers benefits upon host well-being and health" [27]. Prebiotics are primarily soluble short chain (oligosaccharides) that are indigestible by human enzymes and acid/bile stable thus arriving in the cecum intact. They are fermentable by healthy colonic bacteria producing short chain fatty acids (important for mucosal cell nutrition and health) and other bioactive byproducts. Prebiotics include soluble pectins, gums, beta glucans (oat gums), resistant starch, algal fibers, fructo-oligosaccharides (FOS), galacto-oligosaccharides (specifically found in breast milk), bran inulin, polydextrose, arabinogalactan, and Lactitol. Most are found in whole foods such as grains, onions, bananas, garlic, honey, leeks, artichokes, as well as fortified foods and beverages, and as a component of some dietary supplements. Most types of prebiotics stimulate the growth of Lactobacilli and Bifidobacteria over potentially pathogenic bacteria such as Clostridia [27]. They have also been shown to improve mucosal integrity, prevent mucosal inflammatory disorders in both animal models and in patients with inflammatory bowel disease [28].

## Summary

In summary intestinal flora play an important role in many areas of the body's metabolic function and especially in the modulation of the immune system. While there are large gaps in our understanding of intestinal flora and probiotics; use of probiotics (and prebiotics) may prove to play a significant role in disease modulation, especially regarding immune-related disorders.

## Omega 3 and Essential Fatty Acids

The role of fats in the diet has been a topic of discussion for many decades. Initially, the focus was on the amount or percentage of fat in the diet; but current understanding has focused on the types of fats and oils in the diet and their role in health and disease.

Fatty acids form two groups, saturated fatty acids (SFAs) and unsaturated fatty acids. The latter group is divided into monounsaturated fatty acids (MUFAs) and polyunsaturated fatty acids (PUFAs).

SFAs are so named as the fatty acid chain is completely saturated with hydrogen atoms and so contain no double bonds. Animal products are the main source for SFAs. Excess amounts of SFAs have been associated with increased inflammation, especially with coronary heart disease as first reported in 1980 [29].

MUFAs contain a single double bond (typically at the ninth position from the terminal end of the chain) and are found in high concentrations in olive, peanut, and canola oils; avocados, nuts (and nut butters), and seeds such as pumpkin and sesame seeds. They are considered a healthy fat and associated with lower levels of LDL and total cholesterol, protection against thrombogenesis, reduced LDL susceptibility to oxidation, better glycemic control [30], and a decreased risk of coronary heart disease [31].

Neither SFAs nor MUFAs are considered essential as they can be produced by the human body. PUFAs however are considered essential fatty acids (EFA). They are distinguished by their multiple double bonds. Usually, the first bond is positioned at the omega 3 or omega 6 position. The human body cannot enzymatically create double bonds at these positions; therefore, they are considered essential. Polyunsaturated fats are found in high concentrations in sunflower, corn, soybean, and flaxseed oils, and also in foods such as walnuts, flax seeds, and fish. Canola oil, though higher in monounsaturated fat, is also a good source of polyunsaturated fat.

A significant aspect of PUFAs is their unique role in the production of eicosenoids which modulate the inflammatory process. The eicosenoids include prostaglandins, prostacyclins, leukotrienes, and thromboxanes. The proportion of EFAs in the diet can influence the eicosanoid pathways; leading to a more pro-inflammatory or anti-inflammatory pathway. The predominant EFAs are linoleic acid (LA), an omega-6 fatty acid and alpha-linolenic acid (ALA), an omega-3 fatty acid. From LA, arachidonic acids (AA) are synthesized, and from ALA eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are synthesized. AAs are considered to be pro-inflammatory and EPA (and DHA) anti-inflammatory. DHA, also a structural component of cell membranes, appears to be important for visual and neurological development [32].

Though the pathway interactions of fatty acid (FA) conversion to eicosenoids is complex the primary core issue is the competition of both omega-6 and omega-3 FAs for the delta-6 desaturase (D6D) enzyme that determines whether the end product is pro- or anti-inflammatory. In general, the greater amount of LA in the diet the more AAs are created (pro-inflammatory) and the less ALA is converted to EPA

(anti-inflammatory). In the current western diet the omega 6 to omega 3 ratio has been estimated to range from 10–20–30:1. This change occurred with the advent of food processing and is a drastic change from our ancestral diet with an omega 6 to omega 3 ratio of 1:1 or 2:1 [33, 34]. This would throw most of those on a typical western diet (see section "Anti-inflammatory Diet" in Chap. 2) into a pro-inflammatory state with predisposition to diseases with an inflammatory component and perpetuate similar existing diseases.

In the current Western diet, the conversion rate of ALA to EPA and DHA is only 10 % [35, 36]. With such a low conversion rate it is thought by some that we should regard EPA and DHA as "essential" fatty acids and we should therefore promote the regular consumption of fish or regular use of fish oil supplements which is the best source for these two fatty acids.

There is one exception to the reported negative effects of omega 6 oils. Gammalinolenic acid (GLA) is an omega-6 fatty acid which modulates the immune system and inhibits the formation of pro-inflammatory leukotrienes from AAs through the production of the prostaglandin $PGE_1$ and the thromboxane $TXA_1$. Sources of GLA are black currant, borage, and evening primrose oil. While not as extensively studied as the omega 3 oils, it may impart some benefit especially when used in conjunction with omega 3 oils. Recommendations have been made for its use in Rheumatoid arthritis [37, 38]. However, it may also prove to be beneficial in pulmonary diseases such as asthma and cystic fibrosis [39, 40].

Trans fats are created fats that do not occur in nature. The trans nature of the bond reduces the kink so like SFAs they are more solid at room temperature and less susceptible to oxidation/rancidity (improved shelf life). It is well known now that this alteration is strongly associated with disease states and may be associated with activation of systemic inflammatory responses and endothelial dysfunction [41, 42].

In summary considering the effects of fatty acids on the inflammatory cascade, it is now considered optimal to have a diet low in both saturated and omega-6 fatty acids with an increased intake of omega-3 fatty acids. This would call for a decrease in processed foods and grain fed cattle and an increase in foods containing the MUFAs and omega-3 PUFAs. Supplementation with fish oil (the largest source of EPA/DHA) may also be beneficial though the evidence from clinical studies is still weak for most chronic diseases.

## Antioxidants

Oxidative stress is a significant participant in the pathology of chronic disease. The release of reactive oxygen species (ROS) can cause disruption of chemical stability of other molecular constituents of the cell through oxidation. Though the mitochondria are the greatest source of these free radical oxidants, ROS can also be generated by inflammation, infection, and physiologic stress [43]. To deal with these harmful byproducts, our cells have a built in anti-oxidation system. The three main antioxidant enzyme systems are the super oxide dismutase (SOD), glutathione peroxidase, and catalase. While these systems function well under normal circumstances; oxidative

stress can occur when the production of free radicals is beyond the protective capability of these antioxidant defenses. Relevance of oxidative stress and the role of an intact antioxidant system in inflammatory disorders and pulmonary medicine are shown in the increased risk of asthma with exposure to acetaminophen (paracetamol). The proposed mechanism behind this is the reduction of glutathione levels by acetaminophen; resulting in increased oxidant-induced inflammation and potentially enhanced T-helper type 2 responses [44]. In particular oxidative stress plays an important role in chronic pulmonary disease [45–47].

Antioxidants are found primarily in vegetables and fruits with the major recognized antioxidants being vitamin E (alpha tocopherols), vitamin C (ascorbic acid), beta-carotene, along with thousands of other phytonutrients with antioxidant properties. Other nutrients important for the functioning of the antioxidant enzyme systems are selenium, manganese, and zinc.

*Vitamin E* is fat soluble and so is especially valuable for the protection of the fatty acids in cell membranes which are vulnerable to lipid peroxidation.

*Beta-carotene*, a water-soluble substance, the most widely studied of the 600 carotenoids identified to date, does its work in the aqueous compartment of the cell. It is particularly useful scavenging free radicals in a low oxygen concentration.

*Vitamin C* (ascorbic acid) is a water-soluble vitamin, and like beta-carotene is a scavenger of free radicals within the aqueous compartment of the cell. It also regenerates the reduced form of vitamin E.

*Selenium* is required in only very small quantities but is an important and active constituent of proteins (selenoproteins) involved in thyroid hormone metabolism, optimal immune function, and as a component of the antioxidant enzyme systems especially glutathione peroxidase. Sufficient selenium levels or supplementation has been suggested to play a role in antiviral effects, male and female reproduction, and reduction of autoimmune thyroiditis [48, 49]. However, the role of selenium supplementation in chronic inflammatory disease has not yet been established.

*Zinc* plays an important role in activation of many important enzymes and for transcription factors for gene expression. Of the many physiological functions it is also an effective antioxidant and anti-inflammatory agent. Zinc induces the production of metallothionein, which is an excellent scavenger of ROS. It is a component of SOD and an inhibitor of NADPH oxidases [50–52].

*Manganese* plays its role as an antioxidant as manganese superoxide dismutase (MnSOD) an intra-mitochondrial enzyme scavenging superoxide anion radicals [53].

*Green Tea* is often overlooked as an antioxidant "supplement." It contains many polyphenols including catechins which have especially high antioxidant activity [54].

*Coenzyme Q10* or Ubiquinol is a lipid soluble compound found in inner membrane of the mitochondria where it serves to transfer electrons in energy production. As a supplement it acts as an antioxidant protecting lipids and maintaining cell membrane integrity. More recently it appears to have anti-inflammatory effects by reducing the expression of pro-inflammatory genes [55].

*Alpha lipoic acid*, like Coenzyme Q10, has a role in cellular respiration and is also a potent antioxidant; protecting cell membranes with an ability to recycle other antioxidants. It may also have anti-inflammatory properties decreasing pro-inflammatory markers [56].

Though without direct antioxidant effects *Whey* is rich in sulfated amino acids and serves as a sulfhydryl donor for the synthesis of glutathione. Pertinent to pulmonary disease are studies showing positive changes in lymphocyte glutathione levels in cystic fibrosis patients and improvement in FEV1 in children with cystic fibrosis [57–59].

*Boswellia serrata* (frankincense) is an Ayurvedic herb with anti-inflammatory effects similar to NSAIDS inhibiting pro-inflammatory mediators like leukotrienes without the adverse gastrointestinal effects of nonsteroidal anti-inflammatory drugs. A few studies suggest beneficial effects for inflammatory processes (inflammatory bowel disease, arthritis) [60–62].

Only one small study of (N = 40) asthmatic adults has been done with positive results decreasing dyspnea, number of attacks, and improvement in pulmonary function tests [63].

*Turmeric* is a familiar spice giving the characteristic yellow color to curry. Like Boswellia it is a traditional Ayurvedic medicinal herb. It has both antioxidant and anti-inflammatory activity. Curcumin is the principle active component. Curcumin's anti-inflammatory activity is through cell signaling influencing many pathways including pro-inflammatory cytokines, NF-κB, cyclooxygenase-2,5-LOX, and C-reactive protein [64].

The optimal source for antioxidants is a predominant vegetable and fruit phytonutrient rich diet as exemplified by the Mediterranean and anti-inflammatory diet (see these sections in Chap. 2).

For those who refuse these foods (especially children), it may be beneficial to use whole food based nutrition "supplements" of juice powder fruits, vegetables, and grain concentrates such as the brand Juice Plus+®. Juice Plus+® has several studies supporting its bioavailability and delivery of antioxidants and other phytonutrients, reduces oxidative stress and biomarkers of systemic inflammation [65–68].

As oxidative stress plays an important role in chronic pulmonary disease it should be a consideration in the nutritional treatment program. Ideally, a whole food dietary approach should be emphasized [69]. Consideration of individual supplementation should be chosen carefully looking for potential deficiencies in the diet, interaction with drugs and other dietary nutrients, and for toxic effects of high doses of specific supplements.

## Vitamin D

Vitamin D is traditionally associated with calcium absorption and bone metabolism but recent knowledge of its role in physiology has expanded in the past few years. It is now known to be a prohormone converted in the body to 1,25-dihydroxyvitamin

D (calcitriol). Calcitriol binds to nuclear receptors present in many different cells including many cell of the immune system [70]. Thus vitamin D modulates immune function and inflammation. Vitamin D supplementation and deficiency has been linked to many different chronic diseases including pulmonary disease as well as immune related (e.g., allergies) diseases, autoimmune diseases, diabetes, cardiovascular disease, and cancer [71, 72]. Recent findings show vitamin D deficiency across all age groups [73]. This has alerted some clinicians to performing more frequent tests for blood levels and/or increased recommendations for supplementation. Currently vitamin D deficiency is defined as 25(OH)D levels below 20 ng/mL (50 nmol/L) and vitamin D insufficiency as a 25(OH)D of 21–29 ng/mL (525–725 nmol/L) [73].

Dosing has become controversial with the US Institute of Medicine's Recommended Dietary Allowance of vitamin D is 400 IU per day for children younger than 1 year of age, 600 IU per day for children at least 1 year of age and adults up to 70 years, and 800 IU per day for older adults. This is calculated to maintain levels above 20 ng/mL. This recommendation is in contrast to the US Endocrine Society's Clinical Practice Guidelines to for maintenance of 25(OH)D above the optimal level of 30 ng/mL and recommend 400–1,000 IU/day for children less than 1 year of age, 600–1,000 IU/day for children aged 1 year or more, and 1,500–2,000 IU/day for adults aged 19 years or older [74].

## Functional Medicine

While supplements and herbs can be added to a therapeutic protocol cafeteria style, an approach or framework can be helpful to optimize the use of these supplements along with diet.

Functional medicine is presented here as a framework with which to apply dietary changes, supplements, and herbs but also as a way to approach the disease process. Proponents of this approach have argued that conventional medicine has relied too much on quelling of symptoms with pharmaceuticals. This functional approach relates the changes in our environment, lifestyle, and especially our diet as the underlying predisposing and triggering factors in chronic disease. The approach is exemplified by the statement made 2,500 years ago by Hippocrates: "Illnesses do not come upon us out of the blue. They are developed from small daily sins against nature. When enough sins have accumulated, illnesses will suddenly appear."

The concept of functional medicine was created by Jeffrey Bland, PhD in 1990 to address the growing problems associated with chronic disease [75]. It has since come to define the clinical approach of a growing number of physicians and other health care practitioners. Functional medicine "is a science based personalized healthcare approach that assesses and treats underlying causes of illness through individually-tailored therapies to restore health and improve function" [76]. Rather than focusing on a disease entity and its symptomatic presentation, emphasis is placed on the environmental and dietary triggers of disease and the underlying genetic influences and metabolic imbalances that predispose and mediate disease through the functional

medicine framework. Recognized is the dynamic homeostatic balance constantly challenged by the complex interaction of environmental influences such as diet, nutrients, exercise, sleep, trauma, emotional and psychological stress, and genetic predispositions. These interactions can overwhelm this homeostatic balance and result in an imbalance of one or more fundamental physiological processes expressed as chronic or recurrent disease. The primary focus is to reestablish a healthier lifestyle and diet. Safe non-pharmacological approaches are emphasized including herbal and supplement support to augment this approach and to assist in "rebalancing" the body. Conventional drug therapy would still be utilized where needed.

Also recognized are the web-like interconnections of physiological systems. This concept states that when one system is thrown into imbalance it can effect (and overtax) other systems of the body. For example, the chronic infection and inflammation in cystic fibrosis (CF) overwhelms the detoxification and antioxidant systems which would then exacerbate the existing problems of CF. Modulation of inflammation and support of the detoxification and antioxidant systems would be utilized to mitigate expression of the disease. Another well-known example is the growing evidence of the relationship between the bowel flora and its effect on the immune system and extra intestinal disease which can be influenced with probiotics [77].

From a functional medicine viewpoint, a state of imbalance of key physiologic systems is brought about by inappropriate diet, lifestyle, stress, and exposure to toxins as these factors interact with our own particular genetic predispositions. Once the body's systems are stressed sufficiently, disease is expressed uniquely in each individual.

Therapeutically, the primary goal of functional medicine is correction of lifestyle and diet. Secondly, is to reestablish a state of healthy balance between the various systems of the body (digestive, immune, inflammatory, oxidation-reduction, hormonal, etc.) through the improved lifestyle and dietary corrections along with the use of various supplements and herbs to supplement and support the various systems. Pharmaceutical interventions are also used where appropriate.

Rather than a focus on anatomical systems (i.e., heart and vascular system, renal or neurologic) the approach is through the functional systems. The goals are Digestive (and microbiological) balance, the Immune system (and Inflammation) regulation, Detoxification, Oxidation/Reduction, Hormone and Neurotransmitter Regulation, Structural and Membrane Integrity, and Psychological and Spiritual Equilibrium. All of these systems are considered in the evaluation and if needed, corrected and supported through the judicious use of supplements but most importantly through correction and improvement of diet and lifestyle. A more extensive review is available elsewhere [78, 79].

## Summary

Herbs and supplements provide a vast potential for the augmentation of health and management of disease. There are already a growing number of clinical studies and trials to determine their effects on physiological systems in general and diseases in

particular. However, much remains to be done to better define their role in disease intervention and prevention. It is the author's opinion that application of supplements is best done in conjunction with attention to lifestyle and diet and through a framework as provided by the functional medicine approach.

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# Part II
# Pulmonary Distresses in Neonates and Inherited Diseases

# Chapter 4
# Nutrition in Neonatal Pulmonary Disease

**Janice Cox**

**Keywords** Prematurity • Later preterm infant • Low birth weight • Respiratory distress syndrome • Transient tachypnea of the newborn • Meconium aspiration syndrome • Bronchopulmonary dysplasia • Chylothorax

**Keypoints**

- The preterm infant, already at high nutritional risk due to insufficient nutrient stores along with increased nutritional demands, is further compromised by chronic respiratory disease.
- Infants with severe BPD have respiratory difficulties which interfere with oral feeding, so standard feeding regimens may not provide adequate protein or energy intake.
- Nutritional strategies used to prevent BPD include optimizing nutrient delivery including vitamin A and antioxidants to support healthy growth and development of lung tissue.
- Nutritional management in the newborn infant with chronic pulmonary diseases should accommodate the different needs of infants born at varying weeks of gestation.
- Also requiring correction is the nutritional abnormalities which often accompany drugs such as diuretics, corticosteroids, bronchodilators, and antibiotics which are frequently used in these infants.

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## Introduction

This chapter provides an overview of the most common pulmonary conditions encountered in the newborn infant population for which there are nutritional implications, the goals of nutrition management, and evidence-based interventions to achieve these goals. The pulmonary diseases and conditions covered in this chapter include neonatal respiratory distress syndrome (RDS), transient tachypnea of the newborn (TTNB), meconium aspiration syndrome (MAS), bronchopulmonary dysplasia (BPD), and chylothorax.

Because the occurrence of RDS and BPD is related to degree of premature birth, references to prematurity and birth weight are found throughout this chapter. The definitions of these terms include:

- Term: 40 weeks of gestation (range 37–42 weeks)
- Early term: 37–38 weeks of gestation
- Late preterm: 34–36 6/7 weeks of gestation
- Preterm: 28–34 weeks of gestation
- Extremely preterm: 22–28 weeks of gestation
- Low birth weight: less than 2.5 kg at birth
- Very low birth weight: less than 1.5 kg at birth
- Extremely low birth weight: less than 1 kg at birth

Brief descriptions of fetal lung development, pathophysiology and complications of lung diseases in this population as they relate to nutrition in this population are included in the overview to provide initial perspective. Specific nutrition recommendations are given for prevention of complications or progression of respiratory distress to chronic lung disease (CLD), support of normal growth and development, and additional considerations of medical treatments for respiratory disease that may potentially compromise nutritional status.

## Overview

Respiratory compromise is one of the most common causes of morbidity and mortality in neonates [1–3]. Because respiratory compromise is most often associated with premature birth, a brief description of fetal lung development provides initial perspective. During the first 3–7 weeks of gestation, the main structures of the trachea, bronchi, and pulmonary arteries develop. Structural anomalies such as pulmonary agenesis, arteriovenous malformations, congenital cysts, and tracheo-esophageal atresia or fistulas may occur during this phase of development. From 7 to 16 weeks' gestational age, the conducting airways and bronchioles are formed and membranes between pleural and peritoneal cavities are closed. Structural anomalies such as pulmonary hypoplasia, lymphangiectasia (which causes chylothorax when postnatal feedings commence), and diaphragmatic hernia may occur during this phase of fetal development [4, 5].

The next 10 weeks, from 16 to 26 weeks' gestational age, involves maturation of both structure and function. If fetal lung development is interrupted by premature

birth during this phase, severe respiratory compromise is likely to occur due to underdeveloped structures of peripheral airways, capillary beds, and alveoli as well as lower levels of surfactant and protective antioxidants. At birth, capillary beds and alveoli must provide an adequate gas exchange surface area to accept oxygen into circulation. Alveoli surface area is a function not only of anatomical size, but also the ability to expand, a function enhanced by the presence of surfactant which is not produced in sufficient quantities until later in gestation. After birth, lung tissue is exposed to higher levels of oxygen, causing oxidative stress and triggering inflammation which can further disrupt alveolar development [4, 5].

Between 26 and 36 weeks' gestational age, peripheral airways, capillary beds, and alveoli continue to mature, increasing gas exchange surface area, surfactant, and antioxidant levels. Surface area is estimated to be 1–2 $m^2$ at 30–32 weeks compared to 3–4 $m^2$ at term. Lung volume at 30 weeks' gestational age is only 34 % of lung volume at term, but alveoli growth and development continues into the second year of life [4].

Reports indicate that preterm infants may have reduced pulmonary function well into childhood even if they did not exhibit respiratory symptoms during the first few months of life [4]. The cause for this finding is not known, but during fetal development, lung tissue is exposed to an oxygen concentration of only 3–10 %. After birth, inhaled oxygen concentrations are significantly different, even in room air, which may cause oxidative and inflammatory tissue changes, later affecting pulmonary growth and function even in infants who do not develop respiratory compromise.

## *Respiratory Distress Syndrome*

The definition of RDS most commonly used is that of the Vermont Oxford Neonatal Network: "classic ground-glass appearance of lung tissue on X-ray and arterial blood oxygen level less than 50 mmHg in room air, central cyanosis in room air, or need for supplemental oxygen to maintain arterial blood oxygen level of 50 mmHg." [6] This impairment of ability to oxygenate is caused by the immature structure and function of the alveoli as well as their decreased number in preterm infants, with the net result being a decreased gas exchanging surface area and increased risk for atelectasis [5].

Morbidity reports vary by site, but for infants who survive to at least 12 h of age, 61–100 % of those born at 22–26 weeks' gestational age are reported to develop RDS [3]. At 26–28 weeks' gestational age, the incidence of RDS is 55–100 % and gradually decreases to 2–9 % by 34–36 weeks' gestational age [3, 7, 8]. Term infants are much less likely to develop RDS (0.6–4 %), but when they do, it is more likely to be due to transient tachypnea or MAS, than to immature lung development [7–10].

Most efforts to prevent or treat RDS are focused on improving the maturity and function of lung tissue: preventing or delaying premature birth, providing corticosteroids prenatally, and providing surfactant [6]. The effects of fetal nutrition on lung growth and development have been studied in animals. These studies show that lung tissue size and surface area are decreased when nutrition is inadequate during fetal development, though when compared to the overall effect on body weight, some sparing of lung tissue accretion seems to occur. Evidence is conflicting

regarding the extent to which fetal undernutrition impairs tissue maturation and what effect this may have on respiratory function later in life [11, 12]. These studies also indicate that catch-up growth of lung tissue occurs when adequate fetal nutrition is restored [11], although morphologic changes, such as reduced alveolar number, may occur and may be exacerbated if postnatal nutrition is then inadequate [13]. Human studies of postnatal nutrition during this phase of development primarily focus on the relationship of early nutrient intake with overall growth and neurodevelopmental outcome, but early nutrition has also been shown to affect the severity of respiratory illness [14, 15].

## *Transient Tachypnea of the Newborn*

Transient tachypnea, by definition, is of short duration, usually 12–48 h. Fluid that is normally present in the alveoli during fetal development must be removed at birth so that air can fill the alveoli to provide oxygen delivery. This fluid gradually decreases in volume as the fetus progresses to term, and is removed as the chest is compressed in the vaginal canal during birth and by resorption into the lymphatic vessels and blood capillaries with the first few breaths after birth. When this fluid is not cleared adequately, TTNB may occur. Factors that increase the risk for development of TTNB include birth by Caesarian-section, maternal diabetes, maternal hypertension, and late preterm birth [7, 8, 16]. Fluid management is an important nutrition related factor in treating TTNB.

## *Meconium Aspiration Syndrome*

Meconium is the fetal gastrointestinal contents, comprises various gastrointestinal secretions and substances swallowed during fetal development. Meconium may be passed into the amniotic fluid in response to stress such as hypoxia, placental insufficiency, maternal hypertension, or exposure to nicotine or cocaine. When meconium is present in amniotic fluid, there is greater risk of aspiration. Aspirated meconium may initially cause airway obstruction, but may also cause inflammation and inactivate surfactant resulting in severe hypoxia.

Because meconium is not often found in amniotic fluid until 34 weeks' gestational age, MAS occurs primarily in late preterm and term infants. Infants at higher risk for MAS include those with thicker meconium, or those who aspirate meconium deeper into the respiratory tract, require intubation, or are less vigorous at birth [10]. Meconium may be present in the amniotic fluid of as many as 20 % of all newborns, but only 2–9 % of those infants develop MAS, and only 30 % of those who develop MAS experience severe hypoxia and require mechanical ventilation.

Nutrition becomes an important factor in the management of MAS only when hypoxia is severe and extracorporeal membrane oxygenation (ECMO) is required.

Meeting nutritional needs early, particularly protein needs, using parenteral nutrition if necessary, is important in the care of these infants [10, 17].

## *Bronchopulmonary Dysplasia*

BPD, now referred to as CLD is a complication of RDS. Although both BPD and CLD are terms used for this condition, BPD is the preferred nomenclature to distinguish this from adult chronic lung conditions. BPD was first described by Northway et al. in 1967 [18]. This description was based on changes in lung function and the radiologic appearance of the lungs, with positive pressure mechanical ventilation and exposure to high amounts supplemental oxygen sited as causative factors. The stages of severity were based on radiographic changes in the lung, pulmonary function tests, and the continued need for mechanical ventilation or supplemental oxygen [18]. Due primarily to changes in medical management of RDS, and the resulting changes in the progression of lung disease, the definition of BPD has changed over time. The pulmonary fibrosis and cystic changes, radiologic appearance, and emphysema typical of BPD in the past have become rare with the advent of antenatal steroid use, which enhances lung development and neonatal pulmonary surfactant administration, which supports alveolar stability. Changes in mechanical ventilation using lower airway pressures, gas volumes, and oxygen concentrations have reduced lung tissue damage. Pulmonary changes most commonly seen with current treatment modalities include dilated alveolar ducts, with reduced alveolar surface area and capillary development [19–21].

Because diagnostic criteria and stratification of severity of disease have evolved over time, reported incidence varies depending upon the definition used:

- Traditional definition: Supplemental oxygen required at 36 weeks' gestational age [22]
- National Institute of Child Health and Human Development (NICHD) definition: At 36 weeks' gestational age or discharge home, whichever comes first and based on a history of required oxygen supplementation of >21 % for at least 21 days
  - Mild BPD: no further supplemental oxygen requirements
  - Moderate BPD: need for supplemental oxygen of <30 %
  - Severe BPD: need for supplemental oxygen of ≥30 % and/or positive pressure [22]
- Physiologic definition: Need for mechanical ventilation, continuous positive airway pressure, or supplemental oxygen to maintain oxygen saturation ≥88 % for 1 h

Due to these variations in the definition of BPD, incidence reports are often difficult to compare. The NICHD reported incidence of respiratory morbidity for infants born at 28 weeks' gestational age or less between January 1, 2003 and December 31, 2007 using the traditional definition was 42 %; using the NICHD definition, the incidence was 68 %; and using the physiologic definition, the incidence

was 40 %. In other reports which use the traditional definition of BPD and stratify infants by birth weight, incidence is reported as 42–52 % of infants 501–750 g, 25–34 % of infants 751–1,000 g, 11–15 % of infants 1,001–1,250 g, and 5–7 % of infants 1,251–1,500 g [23, 24]. Two recent studies using the NICHD definition report the incidence of BPD as 26–28 % of infants 501–1,500 g birth weight (Horbar) and 28 % of infants 28 weeks' gestational age and less [25].

Nutritional strategies used to prevent BPD include optimizing nutrient delivery to support normal growth and development of lung tissue and optimizing vitamin A status. BPD and the medical therapies used to treat BPD may affect protein, energy, electrolyte, and mineral needs.

### *Chylothorax*

Chylothorax is a condition rather than a specific diagnosis. Chylothorax occurs when there is a disruption in the function of the thoracic duct. Long-chain triglycerides from enteral feedings are picked up from the lacteals of the small intestine, and are carried as chyle—an emulsion of chylomicrons in lymph—through the lymphatic system to the thoracic duct, where they are delivered into the general circulation. If the thoracic duct is obstructed or damaged, chyle leaks into the pleural space and may lead to respiratory failure. Congenital causes of chylothorax are rare with an estimated prevalence of 1 in 10,000–15,000 births [26]. Diagnoses include lymphatic dysplasia or intrauterine conditions that cause obstruction and ultimately fistulas or rupture of the thoracic duct. The occurrence of chylothorax at birth may occur more frequently in infants with Noonan, Turner, or Down syndromes [27]. Acquired causes of chylothorax are usually complications from thoracic surgery to repair congenital cardiac defects especially those that involve the aortic arch, or surgical repair of tracheo-esophageal fistulas or diaphragmatic hernias [28].

Symptoms may appear within the first 24 h of birth or may not present until 7–10 days of life when feedings are well established and fat intake is significant [27]. Although spontaneous recovery occurs in more than 50 % of neonatal cases of chylothorax, many neonates with chylothorax require at least conservative medical treatment, which may include thoracentesis and mechanical ventilation to prevent respiratory failure. If chyle output exceeds 50 mL/kg/day for more than 3 days despite maximum medical therapy, surgical intervention is usually considered [29, 30]. Nutritional strategies are designed to provide optimal nutrition either parenterally or enterally, the latter without increasing the production of chylous leakage into the pleural cavity.

## Nutrition Management

At birth, the placental supply of nutrients is lost. For the healthy term infant, who has been gradually "outgrowing" his intrauterine environment, this is not problematic. He has been swallowing amniotic fluid throughout his gestation to prepare his

gastrointestinal tract for its role in the digestion and absorption of nutrients after birth. He has also accrued a rich store of vitamins, minerals, and even energy during his third trimester of intrauterine life. These stores will help meet his nutrient needs until his mother's milk supply is fully established. As he begins to nurse at his mother's breast, she will produce colostrum, which is rich in protein, vitamin A, carotenoids, vitamin E, minerals, and electrolytes as well as many immunologically derived components from her circulation [31]. During the next 10–14 days, his mother's milk supply will increase in volume and mature in nutrient content to provide all the nutrients he needs to support his rapid growth and development.

The normal continuity of this transitional process is interrupted when respiratory compromise precludes oral feeding. Enteral feeding tolerance may be slow to progress, and nutrients may need to be delivered parenterally. The mother needs encouragement and support to establish lactation so that her milk can be used in her baby's nutritional management [32]. When respiratory disease is accompanied by prematurity, there are additional confounding factors. Nutrient stores are not sufficient. Gastrointestinal enzymes are present in significant amounts early in gestation, but premature birth places demands on the gastrointestinal tract which often stretch beyond its capabilities, particularly when hindered by other conditions or treatments that accompany premature birth.

The goals of nutritional management in the newborn infant with respect to pulmonary conditions and diseases are to:

- Support normal overall growth and development, including pulmonary tissues, accommodating the different needs of infants born at varying weeks of gestation.
- Adjust for differences in nutritional demands related to pulmonary compromise.
- Protect pulmonary tissues from oxidative damage inherent in respiratory support and correct nutritional abnormalities or potential abnormalities which accompany treatment of pulmonary conditions or diseases.

Recommended intakes for parenterally delivered nutrients are given in Table 4.1. Recommendations for enterally or orally delivered nutrients are given in Table 4.2. Depending upon the route of nutrient delivery, specific lab work is assessed at regular intervals to insure nutritional adequacy and safety [47, 48]. Adequacy of intake is also assessed by measuring weight, length and head circumference, and comparing growth progress to established norms. The Fetal-Infant Growth Chart for Preterm Infants is used to assess the growth of infants born at less than 37 weeks' gestational age, from 22 weeks' gestational age through term, up to 10 weeks past term [49]. The growth of term infants is compared to growth charts for infant boys and infant girls, 0–24 months of age, published by the World Health Organization [50].

## *Respiratory Distress Syndrome*

The goal of specific nutritional strategies for infants with RDS is primarily to promote normal growth and development of lung tissue and prevent progression to BPD. See Table 4.3.

**Table 4.1** Recommended daily parenteral nutrient intakes[a,b]

| Nutrient | Initial dose (days 1–3) | Transition dose (week 1–2) | Growing preterm infant | Growing term infant | Maximum dose |
|---|---|---|---|---|---|
| Fluid[c] (mL/kg) | | | | | |
| <1 kg BW | 50–120 | 90–140 | 120–150 | | |
| 1–1.5 kg BW | 70–90 | 90–140 | 120–150 | | |
| >1.5 kg BW | 60–120 | 120–150 | 120–150 | 120–150 | |
| Term infants[d] | 40–60 | ↑ 20 mL/kg/day | | 150–180 | |
| Energy (kcal/kg) | 40–60 | 60–85 | 90–115 | 90–108 | |
| Dextrose (mg/kg/min) | 5 | 5–10 | 5–15 | 5–15 | 18 |
| Carbohydrate (g/kg) | 7 | 8–15 | 10–20 | 8–20 | 25 |
| Protein (g/kg) | 2.5–3.5 | 3.5–4 | 3.2–3.8 | 2.5–3 | 4 |
| Fat (g/kg) | 0.5–3 | 1–3 | 0.5–3 | 0.5–3 | 4 |
| Sodium (mEq/kg) | 0–1 | 2–5 | 2–4 | 2–4 | 20 |
| Potassium (mEq/kg) | 0 | 0–2 | 2–3 | 2–3 | 9 |
| Chloride (mEq/kg) | 0–1 | 2–7 | 2–7 | 2–7 | |
| Acetate (mEq/kg) | As needed | As needed | As needed | As needed | 6 |
| Calcium (mEq/kg) | 1–3 | 2–3 | 3 | 2 | 4 |
| Phosphorus (mMol/kg) | 0–0.6 | 1.3–2 | 1.3–2 | 1–1.5 | 2 |
| Magnesium (mEq/kg) | 0 | 0.2–0.3 | 0.2–0.3 | 0.25–0.5 | 1 |
| Iron (mg/kg)[e] | – | – | (0.1–0.2) | (0.1) | 1 |
| Zinc (μg/kg) | 150 | 150 | 400 | 250 | |
| Copper (μg/kg) | 20 | 20 | 20 | 20 | |
| Manganese (μg/kg) | 0–1 | 0–1 | 1 | 1 | |
| Chromium (μg/kg) | 0–0.1 | 0–0.1 | 0.05–0.3 | 0.1–0.2 | |
| Selenium (μg/kg) | 0–1.3 | 0–1.3 | 1.5–4.5 | 2 | |
| Pediatric multivitamin[f] | | | | | |
| <1 kg | 30 % dose | 30 % dose | 30 % dose | | 1 dose |
| 1–2.5 kg | 65 % dose | 65 % dose | 65 % dose | 65 % dose | |
| <2.5 kg | 1 dose | 1 dose | 1 dose | 1 dose | |
| Vitamin A[g] (IU) | | | | | |
| <1 kg BW | 5,000 × 12 | – | – | – | |

[a]Reference [33]
[b]Reference [34]
[c]Reference [35]
[d]Reference [36]. Fluid restriction may be used in the management of transient tachypnea in late preterm or term infants
[e]Iron is not usually given parenterally due to incompatibility with other nutrients in the admixture; iron is not indicated during sepsis or in patients with multiple blood transfusions
[f]Vitamin A content of pediatric multivitamin products is 2,300 IU/dose; recommended intake is 700–1,500 IU/kg for preterm infants and 2,300 IU/d for term infants. Vitamin E content is 10 IU/dose; recommended intake 2.8–3.5 IU/kg/day for preterm infants and 7 IU/d for term infants
[g]Recommendations for additional vitamin A for extremely low birth weight are intramuscular doses of 5,000 IU, given 3 times weekly for 4 weeks (12 doses total) [37]. Due to drug shortages, vitamin A is not currently available in this dosage form

**Table 4.2** Recommended daily enteral nutrient intake for selected nutrients

| | Preterm infants[a,b,c,d,e,f] | | Term infants[c,g,h,i,j] | | |
|---|---|---|---|---|---|
| Nutrient | Per kg | Per 100 kcal | Per kg[g] or per day[h] | Formula per 100 kcal[i] | Breast milk per 100 kcal[c] |
| Fluid (mL) | See Table 4.1 | | 150–180/kg, See Table 4.1 | 125–150 | 143 |
| Energy (kcal) (A) | 110–135 | 100 | 115/kg | 100 | 100 |
| Protein[d] (g) | | | | | |
| <1 kg weight | 3.8–4.2 | 3.6–4.1 | | | |
| 1–1.8 kg weight | 3.4–4 | 2.8–3.3 | | | |
| 1.8–2.5 kg weight | 2.8–3.4 | 2.4–2.8 | | | |
| >2.5 kg weight[g] | | | 1.8–2.2 | 1.7–3.4 | 1.28 |
| Lipid[e] (g) (A) | 5.3–8.4 | 4.4–6.2 | 31/day | 4.4–6.4 | 6 |
| LA (mg) | 385–1,540 | 350–1,400 | | 350–2,240 | 432 |
| LNA (%kcal) | 0.7–2.1 % | 0.7–2.1 % | | 77–256 mg | 60 mg |
| DHA (mg) | 12–30 | 11–27 | | – | Varies |
| AA (mg) | 18–42 | 16–39 | | – | Varies |
| Carbohydrate[a,b] (g) | 11.6–13.2 | 9.6–12.5 | 12/day | 9–13 | 10.4 |
| Sodium[a] (mg) | 69–115 | 63–105 | 120/day | 25–50 | 26 |
| Potassium[a,b] (mg) | 66–132 | 60–160 | 400/day | 60–160 | 83 |
| Calcium[a,b] (mg) | 120–230 | 123–185 | 210/day | 50–140 | 40 |
| Phosphorus[a,b] (mg) | 60–90 | 55–109 | 100/day | 20–70 | 21 |
| Magnesium[a,b] (mg) | 7.9–15 | 6.8–17 | 30/day | 4–17 | 4.2 |
| Iron[a] (mg) | 2–3 | 1.8–2.7 | 0.27/day | 0.2–1.65 | 0.057 |
| Zinc[a] (mg) | 1.1–2 | 1–1.8 | 2/day | 0.4–1 | 0.17 |
| Selenium[a,b,f] (μg) | 1.3–10 | 1.8–9 | 7/day | 1.5–5 | 2.9 |
| Vitamin A[a,b] (IU) | 1,332–3,330 | 700–2,460 | 1,332/day | 100–500 | 319 |
| Vitamin D[a,b] (IU) | 800–1,000/d | 75–270 | 400/day[j] | 40–100 | 2.8 |
| Vitamin E[a] (IU) | 6–12[j] | 2–10 | 6/day[j] | 0.5–5 | 0.45 |
| Choline[a] (mg) | 8–55 | 7–50 | 125/day | 7–30 | 14 |
| Inositol[a] (mg) | 4.4–53 | 4–48 | – | 4–40 | 22 |

[a]Reference [38]
[b]Reference [39]
[c]Reference [40]
[d]References [41, 42]
[e]*LA* linoleic acid, *LNA* α-linolenic acid, *DHA* docosahexaenoic acid, *AA* arachadonic acid. Breast milk content of DHA and ARA varies with maternal diet
[f]Reference [43]
[g]Reference [44]
[h]Reference [45]
[i]Reference [46]
[j]Reference [34]

**Table 4.3** Grades of recommendations for nutritional management of neonatal pulmonary disease

| Nutritional management strategy | Grade[a] |
|---|---|
| Respiratory distress syndrome | |
| Fluids: start intravenous fluids at 70 to 80 mL/kg/d and individualize to allow 2.5–4 % weight loss (total of 15 % weight loss) within the first 5 days. Increase fluids to prevent dehydration and allow adequate nutrient delivery [6, 35] | D |
| Electrolytes: restrict sodium intake during the first few days. Begin sodium after the onset of initial diuresis, monitoring fluid balance and serum electrolyte levels to guide administration [6, 51] | B |
| Protein: provide 2.5 to 3.5 g protein/kg/d within the first 24 to 48 h of life [41, 42, 52] | B |
| Subsequent protein needs are 3.5–4 g/kg/day [52, 53] | B |
| Energy: initial energy intake should be 40–60 kcal/kg/day, and increased by day 6 to levels that support tissue accretion [14] | A |
| Energy needs of ventilated extremely low birth weight infants may be 25 % higher than non-ventilated infants, although intake greater than 110–135 kcal/kg/day may not be beneficial [52–54] | D |
| Parenteral lipid and multivitamin preparations (MVP): if administered as a total nutrient admixture, protecting infusion from light exposure is associated with a decrease in BPD [55–57] | C |
| Co-administration of lipids with MVP separately from dextrose/amino acid solution may protect lung tissue from oxidative damage [58] | C |
| Vitamin A: extremely low birth weight infants may benefit from 5,000 IU given intramuscularly 3 times weekly for 4 weeks (12 doses total) [37] | A |
| Transient tachypnea of the newborn | |
| Term infants: limit fluids to 40 mL/kg/day on day of life 1 and adjust fluids as necessary to prevent dehydration, hypoglycemia, or more than 10 % weight loss from birth weight; increase fluids by 20 mL/kg/day until 150 mL/kg/day or ad libitum feedings are achieved [36] | B |
| Late preterm infants: limit fluids to 60 mL/kg/day on day of life 1; adjust and increase fluids as for term infants [36] | B |
| Meconium aspiration (for infants who require extracorporeal membrane oxygenation) | |
| Parenteral nutrition: initiate 24 to 48 h of birth [17] | C |
| Protein: provide 3 g/kg/day [59] | C |
| Energy: provide at least 80 kcal/kg/day but not more than 100 kcal/kg/day [59] | C |
| Fat: if required, provide through separate venous access [60] | C |
| Enteral feedings: begin enteral feedings when infant is medically stable and gradually increase feedings while tapering parenteral nutrition [17] | C |
| Bronchopulmonary dysplasia | |
| Fluids: although higher early fluid intake and less weight loss during the first 10 days of life may be associated with increased risk of BPD, restriction of fluid does not prevent BPD and may prevent provision of adequate nutrition [35, 61] | B |

| | |
|---|---|
| Maintenance fluids are 120–150 mL/kg/day [51] | C |
| Protein: providing an average intake of at least 3.3 g protein during the first 20 days of life to prevent early protein deficits and support fetal growth rates [62] | C |
| Intakes of 3.5–4 g/kg/day may be needed to support normal growth [52, 53] | D |
| Energy: energy needs of preterm infants with chronic lung disease may be 15–25 % higher than healthy preterm infants, although intake greater than 125–135 kcal/kg/day may not be beneficial [51–54, 63, 64] | C |
| Feeding problems: reducing noxious stimuli to face and mouth; encourage kangaroo care and nonnutritive suckling at breast, and use hunger and satiety cues for feedings [65] | C |
| When fluid restriction is needed in management of pulmonary edema, consider use of nutrient dense feedings, with up to 30 kcal/oz to provide adequate nutrient intake [51, 66, 67] | C |
| Drug nutrient interactions | |
| Corticosteroids: insure optimal protein intake during dexamethasone therapy [68] | C |
| Diuretics: monitor serum levels of sodium, potassium, chloride, and phosphorus and supplement these nutrients if needed to prevent electrolyte imbalances and osteopenia [69, 70] | D |
| Aminoglycosides/vancomycin: as for diuretics [71] | D |
| Chylothorax | |
| Parenteral nutrition: if chylothorax worsens after initiating feedings, parenteral nutrition prevents further chylous fluid accumulation [72] | D |
| Fat: when feedings are started, defatted breast milk supplemented with medium chain triglycerides (MCT) or formulas containing MCT may prevent recurring chylothorax [28, 72] | D |
| Protein: insure optimal protein intake for gestational age [26] | D |

[a]Support for grade of recommendation [6]

*A* at least one high quality meta-analysis of randomized controlled trials or one large sufficiently powered randomized trial, *B* high quality systematic review of case controlled studies or lower grade randomized controlled trial with high probability of causal relationship, *C* a well-conducted case controlled study with low risk of bias, *D* evidence from cohort studies, case reports, expert opinion, or standard of practice

## Fluid and Electrolytes

Extracellular water contraction is normal during the first few days of life. Although there is no strong evidence to recommend fluid restriction during this time to prevent chronic lung changes, overhydration may be associated with increased risk of BPD, patent ductus arteriosus (PDA), and necrotizing enterocolitis (NEC) [35, 61, 73, 74]. Daily weight loss of 2.4–4 % up to a total initial weight loss of 8–15 % during the first 3–5 days of life is considered physiological [6]. Greater weight losses may signify dehydration or depletion of energy stores and loss of lean tissue.

Fluid administration must be individualized to prevent over- or underhydration based on gestational age, weight, and clinical condition. Infants of lower gestational age have greater extracellular fluid volumes and disproportionately greater potential fluid losses due to greater body surface area to weight ratios, immature skin tissue, and immature renal function [74, 75]. Infants with lower birth weights have less subcutaneous fat stores are more susceptible to heat losses and the resulting evaporative fluid losses with interruptions in their thermoneutral environment. Infants placed in radiant warmers will lose more fluid due to evaporative losses than infants cared for in double-walled incubators. Fluid status is managed by keeping daily weight changes within the prescribed range, maintaining normal urine output of 1–2 mL/kg/h, and maintaining serum sodium levels within the normal range. Initial, transitional and growth fluid requirements for preterm and term infants are given in Table 4.1.

Sodium needs are minimal during the first few days in preterm infants, in part because initial water losses—from interstitial spaces and insensible losses—exceed sodium losses, and many medications used during the first few days of life are inadvertent sources of sodium [51, 74, 76]. Initial, transitional, and growth sodium requirements for preterm and term infants are also given in Table 4.1. Beyond the first week of life, sodium intake for preterm infants may need to be adjusted frequently. Preterm infants may experience late-onset hyponatremia due to immature renal function and require 5–7 mEq sodium/kg/day to maintain normal serum values.

## Energy and Protein

Optimizing energy and protein intake for preterm infants during the first 24–48 h of life and throughout the first week of life improves growth and neurological outcome and has been shown to decrease the odds ratio of adverse outcomes such as NEC, late-onset sepsis, and BPD [14, 15, 77–79]. Inadequate nutrient intake, particularly during the first few days and weeks of life, may compromise the preterm infant's ability to resist oxidative damage, barotrauma, and infection due to reduced surfactant synthesis, and decreased growth, development, and repair of lung tissue [80, 81]. Respiratory effort may be compromised by increased ribcage compliance and decreased intercostal muscle strength associated with inadequate protein and energy intake, and with osteopenia associated with vitamin D insufficiency, calcium and phosphorus depletion [82]. Optimizing early nutrient intake reduces postnatal cumulative nutrient deficits, improves growth outcomes, and reduces subsequent morbidity [41, 83]. Nutrient intake, specifically the intake of energy and protein is adjusted to promote normal

growth. Energy intake of 140–150 kcal/kg/day along with protein intake of 4–4.5 g/kg/day may be needed if deficits accrue early in the course of care [38].

Human milk is the optimal enteral feeding choice for both term and preterm infants, but the nutrient content of human milk does not match the placental supply of nutrients for infants who are born prematurely. Human milk fortifiers can be added to mother's own milk or donor breast milk to meet the nutrient needs of the rapidly growing preterm infant. Not all human milk fortifiers provide the total recommended amount of protein or the recommended protein: energy ratio depending upon the protein content of an individual mother's milk. Human milk fortifier manufacturers' nutrient content tables use 1.4–1.6 g protein/dL (2–2.3 g/100 kcal) as the protein content of human milk. Early milk contains this level of protein, but protein content decreases rapidly during the first week postpartum. Mature milk is generally present by 2–4 weeks postpartum and is likely to contain 1.05 ± 0.2 g protein/dL (1.5 ± 0.3 g/100 kcal) [40]. (Lawrence) A liquid protein fortifier (Liquid Protein Fortifier®, Abbott Nutrition, which contains 1 g extensively hydrolyzed protein/6 mL) may be used to individualize protein supplementation when mother's milk contains less than 1.4–1.6 g protein/dL. Product labels for powdered protein supplements indicate intended use for children over 3 years of age. When human milk is not available, preterm infant formulas may be used to meet the specific needs of prematurely born infants, and standard term infant formulas may be used for term infants.

## Antioxidants

At birth, lung tissue is exposed to oxygen, which may cause oxidative stress, trigger inflammation, and disrupt alveolar development. Medical management efforts to reduce the effects of oxygen toxicity include lower targeted oxygen saturation levels, gentler ventilation techniques, and nasal continuous positive airway pressure ventilation [20]. Peroxides generated by the exposure of intravenous lipid emulsions and multivitamin preparations to light have also been implicated in the progression of lung disease due to oxidative stress. Protecting total nutrient admixtures from exposure to light by covering the infusion bag and tubing with foil or using tinted tubing is associated with a decrease in the production of peroxides and a decrease in the progression of RDS to CLD [55, 57]. Lipid and vitamin peroxidation as well as the inflammatory response to high levels of oxygen exposure may be significantly reduced when multivitamins are co-administered with parenteral lipids, but infused separately from dextrose and amino acids, whether or not they are shielded from light exposure [58]. In addition, several nutrients may function as antioxidants and have been studied with respect to their potential ability to further protect lung tissue from oxidative damage: vitamin A, vitamin E, and selenium.

Vitamin A plays a role in airway epithelial cell differentiation and repair. Preterm infants have lower plasma concentrations at or shortly after birth. These levels are often in the range indicating marginal or deficient status. The risk for RDS progressing to CLD may be increased in preterm infants with low vitamin A status [84]. Vitamin A administered parenterally in total nutrient admixtures or dextrose/amino acid solutions is often inefficient, with as little as 20 % of the vitamin A content actually

administered due to adsorption onto plastic containers and tubing. Administering vitamin A in the lipid emulsion increases actual delivery to 90 % [85]. Enterally administered vitamin A, either from human milk or formula may not adequately improve vitamin A status, as enterally administered supplemental doses of as much as 5,000 IU/kg/day from postnatal day 1 through 28 did not increase plasma levels by day 7 or day 28, nor were there significant differences in survival, oxygen requirement at 28 days or 36 weeks' gestational age, or survival without BPD [86]. The current recommendation is to provide a 5,000 IU intramuscular dose three times per week for 4 weeks (12 doses total) for infants ≤1,500 g birth weight or <32 weeks' gestational age [37, 87]. A confounding factor exists at this time in that vitamin A is not currently available due to drug industry shortages.

Although vitamin E deficiency may be associated with oxygen toxicity, there currently is no evidence that supplementing vitamin E beyond sustaining normal serum levels has benefit. Vitamin E deficiency is characterized by mild hemolytic anemia (>10 % erythrocyte hemolysis in hydrogen peroxide) and a serum vitamin E level of <0.6 mg/dL [88]. Risk of sepsis and NEC may be increased if serum levels exceed 3.5 mg/dL [89]. Earlier reports of vitamin E deficiency in preterm infants occurred when formulas had high concentrations of polyunsaturated fatty acids and low levels of vitamin E. Current vitamin E content of infant formulas and human milk fortifiers as well as parenteral multivitamin preparations provide adequate intake without additional supplementation [88, 89].

Selenium plays a role in the enzyme system glutathione peroxidase and superoxide dismutase. Both function as intracellular antioxidants in the lung and other organs, thus selenium may theoretically play a role in protecting lung tissue from oxidative damage. Selenium deficiency has not been described in preterm infants, although low serum concentrations of selenium and glutathione peroxidase have been reported in infants on selenium-free parenteral nutrition. Although animal studies show increased risk of oxidative lung injury with low selenium level, reported symptoms of selenium deficiency in humans include cardiac and skeletal myopathy, but not respiratory compromise [43, 51]. One study reported that preterm infants who developed chronic lung changes had lower serum levels of selenium (38.5 ± 14.1 μg/L) at 30 days of age than infants who did not (45.5 ± 18.7 μg/L), although diet was not reported [90]. Normal serum selenium levels are 45–90 μg/L in infants 0–2 months of age [91]. Supplementation of selenium above the amounts available in breast milk and infant formula has not been shown to reduce the risk of BPD [92].

## Inositol

Inositol is a component of membrane phospholipids and plays a role in lung epithelial cell differentiation and the synthesis of lung surfactant during fetal development [51]. Earlier studies showed reduction in death or progression of lung disease in infants with RDS who were supplemented with parenterally administered inositol in doses of 80 mg/kg/day for 5 days or 120 mg/kg/day for 10 days, or enterally administered inositol doses of 160 mg/kg/day for 10 days [93–95]. Subsequent studies have not been reported, perhaps because the production of endogenous surfactant is

not as critical since the advent of surfactant replacement therapy. Inositol content of current parenteral nutrient admixtures is 1.6–2 mg/dL; colostrum of mothers of preterm infants is 35–45 mg/dL; colostrum of mothers of term infants is 18–48 mg/dL; and mature milk is 12–31 mg/dL [96, 97]. Current recommendations for intake and formula content are given in Table 4.2. Although plasma levels of inositol decline during the first month of life, particularly in infants who receive most of their nutrition parenterally, clinical outcomes do not correlate with plasma levels and inositol is not currently added to parenteral nutrition admixtures [98].

## *Transient Tachypnea of the Newborn*

Because TTNB is caused by inadequately cleared alveolar fluid, it is reasonable that fluid management might impact respiratory outcome. During the first 3 days after birth, a healthy breast fed term infant receives between 2 and 20 mL per feeding, or about 100 mL of breast milk per day [31]. This intake provides approximately 25–40 mL/kg/day of fluid. Although TTNB usually resolves within the first 72–96 h, nipple feedings may be delayed if respiratory support is required, and intake may include parenteral as well as enteral fluids. In one study report, the standard of care for combined parenteral and enteral fluid administration for term infants was 60 mL/kg/day and for late preterm infants 80 mL/kg/day. When fluids were restricted to 40 mL/kg/day and 60 mL/g/day, respectively, mimicking low fluid intakes normally taken at breast, the duration of respiratory support required for infants with severe TTNB was significantly decreased, and was safe for all patients studied. Urine output did not fall below 1 mL/kg/h, weight loss did not exceed 10 % of birth weight, and there was no difference between the standard and restricted fluid groups for incidence of hypoglycemia or need for phototherapy [36].

## *Meconium Aspiration Syndrome*

Nutrition becomes an important factor in the management of MAS only when the severity of respiratory compromise requires treatment with ECMO [10, 17]. The use of high frequency ventilation (HFV) and nitric oxide (iNO) in combination has proved very successful in treating severe hypoxemia associated with MAS, and has reduced the need for ECMO. In geographical areas where HFV and iNO are not available, or when hypoxemia is severe and does not respond to other therapies, ECMO may still be required.

Infants receiving ECMO have markedly elevated levels of C-reactive protein and demonstrate significant, though quite variable negative nitrogen balance. Reported average protein losses of $2.3 \pm 0.6$ g/kg/day translate to a significant reduction in total body protein over a typical 8 day ECMO course of therapy due to increased protein turnover, increased protein degradation, and increased amino acid oxidation [59]. Although both protein and energy intake affect nitrogen balance, excess energy intake may increase carbon dioxide production and further complicate respiratory

support. Current nutrition recommendations for infants receiving ECMO are to start nutrition support as soon as possible, provide 2.5–3 g protein/kg/day, and also provide at least 80 kcal/kg/day to minimize amino acid oxidation, but not more than 100 kcal/kg/day to prevent increased carbon dioxide production [17, 59]. Increased protein needs due to increased protein degradation may continue for 3 or more weeks after weaning from ECMO therapy [99].

Parenteral nutrition is the primary initial source of nutrition for infants receiving ECMO, to provide an immediate source of adequate nutrition and provide a period of time to assess gastrointestinal tract perfusion and motility. Provision of parenteral lipids using the ECMO circuit may increase the frequency of clot development and disruption of normal ECMO blood flow. The current recommendation is to administer parenteral lipids through a separate intravenous access to avoid increased risk of clot formation [60]. When the infant is clinically stable, enteral feedings can generally be started and are well tolerated without complication. Infants who cannot advance to full oral feedings within 1 month are more likely to require longer hospitalization and tube feedings at discharge [17, 100].

## *Bronchopulmonary Dysplasia*

The nutritional strategies for preventing BPD are discussed in the RDS section of this chapter. Infants with RDS who develop BPD have additional nutritional challenges. These infants may be less likely to achieve reference growth during the first year after discharge or beyond [101, 102]. Nutrient needs during convalescence may be greater than their healthy counterparts, yet they are also are more likely to experience feeding difficulties [67, 85, 102, 103]. Drugs frequently used in this population may also affect nutritional status, including diuretics, corticosteroids, bronchodilators, and antibiotics.

### Nutrient Intake and Growth

Numerous reports are available documenting impaired growth and growth recovery, with deficits in total body fat and fat free mass in infants with BPD [51, 101, 102, 104]. The growth of infants with BPD has improved during the past 10 years, particularly with improved nutrition during the 1–3 weeks of life, but also with improved nutrient intake throughout hospitalization and after discharge [62, 66, 67, 85, 105]. Very low birth weight infants whose documented weight gain is at least 21 g/kg/day during initial weeks of hospitalization demonstrate better growth and developmental outcomes at 18–22 months' corrected age [83]. Although rapid weight gain during infancy may be a risk factor for increased adiposity later in life, infants who demonstrate postnatal growth delay between 4 and 36 months' corrected age are more likely to have smaller physical size, lower cognitive scores, and lower academic achievement at age 8 [53, 106].

Infants who receive at least 3.3 g protein/kg/day protein during the first 20 days of life and receive energy intakes of 120 kcal/kg/day earlier are more likely to achieve intrauterine growth rates than those who receive less protein and take longer to reach feeding goals [62]. Energy needs of preterm infants with CLD may be 15–25 % higher than healthy preterm infants due to increased work of breathing or recurrent infections. Providing 3.5–4 g protein/kg/day and 110–135 kcal/kg/day appear to be necessary to support normal growth in this population, although intakes greater than 135 kcal/kg/day may not provide additional benefit [51, 52, 54, 63, 64]. When energy needs are greater due to increased work of breathing or recurrent infections, or if fluid volume tolerance is less than 150 mL/kg/day, standard feeding regimens may not provide adequate protein or energy intake. Deficits begin to accrue, causing growth lag. Although the effect on weight is most readily observed, the head circumference is more likely to fall below the 10th percentile when growth does not keep pace with intrauterine rates and is associated with poor long-term developmental outcome [62, 83].

Most ready-to-use human milk fortifiers and preterm infant formulas provide 20, 22, or 24 cal per ounce. All are enriched in protein, mineral, and vitamin content to approximate established guidelines [39]. Ready-to-use preterm formulas that contain 30 cal per ounce and 3 g protein/100 kcal may be used during hospitalization alone or in combination with other standard caloric strength feedings to provide recommended intake of nutrients when fluid tolerance is less than 150 mL/kg/day and energy needs are 120 kcal/kg/day or greater.

Studies reporting nutritional strategies for the discharged infant with BPD are less definitive. Providing human milk fortification or formulas enriched with protein, vitamins, and minerals is associated with improved growth, bone mineralization, and increased lean body mass in preterm infants [98, 107, 108]. This may not be as evident in infants with BPD [67]. Infants with BPD are more likely to experience nutrient deficits and growth delay early in their neonatal course, which may confound results from studies that focus primarily on intake after discharge.

Nutrition strategies for discharge that include the use of modular products such as glucose polymers, vegetable oil, or medium chain triglyceride oil to increase energy intake when fluid tolerance is limited often do not provide adequate protein, mineral, or vitamin intake. Adding powdered formula to human milk in place of commercially available fortifiers does not provide the recommended intake of protein, minerals, and vitamins. Some infants may benefit from continued use of human milk fortification or preterm formula after discharge, depending upon weight at discharge. Product literature guidelines discourage intakes exceeding 20 packets of human milk fortifier per day or 355–540 mL per day of preterm infant formulas to prevent excessive intake of individual nutrients. Manufacturers' guidelines also include information regarding use, storage, and preparation. Preterm infant discharge formulas are available for use through 9–12 months of age, and may be concentrated to 22, 24, or higher caloric density using product literature guidelines. Standard pediatric formulas have been used with some success, although these may require vitamin supplementation, as these products are intended for older children [109].

### Feeding Problems

Feeding difficulties for infants with BPD may be related to several factors. Successful feeding requires the ability to efficiently coordinate a pattern of suck—swallow—breathe for a long enough period of time to allow consumption of an adequate volume of feeding to support normal growth and development. Infants with severe BPD may have poor feeding coordination and endurance. These infants may need to breathe more frequently, stop breathing for a longer period of time to swallow, suck less frequently with weaker pressures, and swallow less often than infants without BPD or with mild to moderate BPD [110]. Mild to moderate oxygen desaturation may continue to be a problem for infants with moderate to severe BPD up to 2–6 months corrected age, a factor that may also be linked to growth lag [111]. Oral aversion may develop in infants with BPD who require prolonged need for ventilator equipment, orogastric feeding tube placement, or tape placed near the mouth. Feeding therapists can design strategies to reduce noxious oral–facial stimulation and develop individual feeding plans to help pace feedings and increase oral feeding success. When infants continue to require tube feedings after hospital discharge, dietitians can provide a feeding plan that accommodates hunger and satiety cues, and provide guidelines for increments in feeding volumes to support growth but prevent overfeeding [112]. Spoon feedings may be started at 4 months' corrected age. These foods are of thicker consistency than milk or formula, so they may be swallowed more easily and can provide pleasant oral stimulation for the infant with residual respiratory problems [51].

### Drugs That Affect Nutrition

Several drugs frequently used in the treatment of BPD may affect nutritional status. Glucocorticoids have been used for their anti-inflammatory effect since lung tissue inflammation plays a key role in the pathogenesis of BPD. Dexamethasone is the most widely studied glucocorticoid, with numerous reports documenting efficacy in down-regulating lung inflammation, reducing pulmonary edema, facilitating extubation, and reducing the risk of CLD. However, dexamethasone given in doses of approximately 0.5 mg/kg/day at or before 7 days of age has also been associated with short-term adverse outcomes such as gastrointestinal bleeding, intestinal perforation, hyperglycemia, and growth failure [113]. All parameters of physical growth are negatively affected by high dose dexamethasone administration, but growth resumes off treatment, and protein intake correlates positively with weight gain [68]. Doses of 0.35 mg/kg/day are associated with decreased weight gain and increased proteolysis, though not decreased protein synthesis. These differences are no longer apparent when the dexamethasone dose is weaned to 0.1 mg/kg/day [114]. However, early high dose dexamethasone is no longer recommended due to long-term adverse outcomes of neurodevelopmental compromise and cerebral palsy [113]. Hydrocortisone, another corticosteroid currently used in the treatment of infants with BPD, is not associated with adverse neurodevelopmental or growth outcomes, although gastrointestinal perforation remains a significant risk [113]. Betamethasone is a corticosteroid given to mothers who are at risk for delivering before 34 weeks' gestational age to reduce infant mortality and decrease severity of RDS [20]. Multiple

courses of antenatal corticosteroids are associated with decreased fetal growth in weight, length, and head circumference. The long-term implication of these findings and whether or not postnatal protein needs are affected remains unknown [115].

Diuretics are useful in the management of pulmonary edema, which is characteristic of both early and later stages of BPD. The diuretics most commonly used in neonates are furosemide, chlorothiazide, and spironolactone. Furosemide is associated with hyponatremia, hypokalemia, hypochloridemia, and hypercalciuria. Chronic use may cause nephrocalcinosis and bone demineralization, which may be attenuated by concurrent use of chlorothiazide. Hypokalemia is more common with chlorothiazide, often requiring potassium supplementation unless used concurrently with spironolactone, which is potassium sparing. Electrolyte abnormalities occurring with any diuretic may be associated with growth failure. Monitor electrolyte levels regularly and supplement as needed. When diuretics are being used, optimize calcium and phosphorus intake for preterm infants by using preterm infant formula or preterm follow-up formula, and use human milk fortifier for preterm infants receiving their mothers' milk or donor milk. All diuretics may increase renal calcium and phosphorus losses in preterm infants and may lead to osteopenia [69, 70]. If use of other formulas is indicated for reasons of intolerance or allergy, mineral supplements may be needed to prevent osteopenia. Standard infant formulas may not provide adequate amounts of vitamin D for infants who have not reached term.

Aminoglycosides and vancomycin are antibiotics that may be used frequently for the treatment of infections in ELBW infants, who are also at highest risk for developing BPD. These antibiotics, particularly when used in tandem, may alter renal function, causing increased tubular losses of potassium and phosphorus during drug therapy and for 1–2 weeks after cessation of treatment. Calciuria may also be present, although increased calcium excretion may be due to phosphorus depletion and decreased bone deposition. Potassium and phosphorus supplements may be needed to normalize serum levels [71].

### Chylothorax

When chylothorax does not resolve spontaneously, nutritional strategies are designed to provide optimal nutrition either parenterally or enterally, the latter without increasing the production of chylous leakage into the pleural cavity. Parenteral nutrition may be required to reduce the flow of lymph and insure adequate nutrient intake, particularly of protein, fat (thus energy), fat soluble vitamins, and electrolytes. If chyle accumulation increases when feedings are started, using medium chain triglycerides in place of long chain triglycerides may reduce the flow of lymph from the thoracic duct and prevent reaccumulation of chyle [26, 28].

Repeated thoracentesis may cause protein, energy, and electrolyte depletion. Protein intake recommendations are based on standards for gestational age and nonedematous body weight. When long chain triglycerides must be restricted, mother's milk can be defatted, the fat replaced with medium chain triglycerides, and protein increased with fortification. Several commercially available formulas contain at least a portion of the fat content as medium chain triglycerides. See Table 4.4 for strategies using breast milk or formula to treat chylothorax.

**Table 4.4** Nutrient content of various feeding regimens to limit long chain fatty acid intake for treatment of chylothorax

| Nutrient | Standard infant 20 kcal/oz | Preterm infant formula[a] 24 kcal/oz | Pregestimil®[b] 20 kcal/oz | Enfaport®[b] 30 kcal/oz | Defatted human milk[c] | Defatted human milk[c]/Enfaport®[d] | Defatted human milk[c]/SHMF[e] | Defatted human milk[c]/soy/MCT[f] |
|---|---|---|---|---|---|---|---|---|
| Volume (mL) | 148 | 124 | 148 | 100 | 100 | 147 | 143 | 148 |
| Energy (kcal) | 100 | 100 | 100 | 100 | 33–36 | 100 | 100 | 100 |
| Protein (g) | 2.1–2.5 | 3.3 | 2.8 | 3.5 | 0.9 | 3.2 | 2.9 | 2.9 |
| Fat (g) | 5.3–5.5 | 5.4 | 5.6 | 5.4 | 0–0.35 | 4–4.2 | 4.8–5.1 | 5.1–5.5 |
| MCT oil (%) | 0 | 50 | 55 | 84 | – | 79–84 | 80–87 | 76–88 |
| Linoleic acid (mg) | 860–1,000 | 700 | 940 | 350 | 0–50 | 257–294 | 356–389 | 330–395 |
| Carbohydrate (g) | 10–11 | 10 | 10.2 | 10.2 | 7.3 | 12.8 | 10.6 | 9.5 |
| Calcium (mg) | 78 | 180 | 94 | 94 | 28 | 90 | 112 | 37 |
| Vitamin A (IU) | 300 | 1,250 | 350 | 350 | – | 257 | 401 | – |
| Vitamin D (IU) | 60 | 150 | 50 | 50 | – | 37 | 78 | – |
| Vitamin E (IU) | 2 | 4 | 4 | 4 | – | 2.9 | 2.1 | – |
| Vitamin K (IU) | 9 | 12 | 12 | 12 | – | 8.8 | 5.4 | – |
| Zinc (mg) | 0.75–1 | 1.5 | 1 | 1 | 0.24–0.38 | 0.9 | 1 | 0.3 |

[a]Similac® Special Care® 24 high protein (Abbott Nutrition). Other preterm formulas contain less MCT and more long chain triglycerides

[b]Pregestimil® and Enfaport® (Mead Johnson & Company)

[c]Description of the process to remove fat from human milk is described elsewhere. Residual fat after processing was reported by the authors to be zero [28]. After a similar defatting process at Bronson Mothers' Milk Bank, fat content of milk was 0.35 g/100 mL (Duff C. Bronson Mothers' Milk Bank, Bronson Children's Hospital, Kalamazoo, MI. 20 Nov 2012, Personal communication). Other nutrient values are representative [28, 116, 117]

[d]Defatted human milk/Enfaport® is a 1:1 mixture of defatted human milk and Enfaport®

[e]Defatted human milk/SHMF is 100 mL of defatted human milk + 2 packets of Similac® human milk fortifier (Abbott Nutrition) + 0.4 mL soy oil + 3.5 mL MCT oil + 5 mL Liquid Protein Fortifier® (Abbott Nutrition). Fat content of Similac® human milk fortifier is MCT. Other human milk fortifiers contain long chain triglycerides. Liquid Protein Fortifier® contains 1 g extensively hydrolyzed casein, 4 kcal, and 5 g water per 6 mL

[f]Defatted human milk/soy/MCT is 100 mL of defatted human milk + 0.5 mL soy oil + 4 mL MCT oil + 8 mL Liquid Protein Fortifier®. This feeding requires fat soluble vitamin supplementation. See text

## Summary

Nutrition plays an important role in the health and well-being of the newborn infant, particularly when respiratory disease occurs and interrupts the normal initiation and progression of breast or bottle feedings. This chapter provides guidelines for the nutritional management of infants who develop respiratory compromise during the their first weeks of life, to minimize the nutritional impact of preterm birth, and adjust for the different nutritional demands related to pulmonary compromise and the medical therapies used to treat pulmonary diseases in this population.

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# Chapter 5
# Nutrition in Cystic Fibrosis

**Anne C. Coates and John D. Mark**

**Keywords** Cystic fibrosis • Nutrition • Dietary supplements • Antioxidants • Omega-3 fatty acids

## Keypoints

- There exists a strong link between nutritional status, lung function, and survival in cystic fibrosis (CF). Based on this link, aggressive nutritional support is a fundamental component of the recommended treatment regimen for the management of this disease.
- Dietary strategies emphasize a high energy and high protein diet, together with pancreatic enzyme replacement therapy.
- Patients with CF are prone to specific nutrient deficiencies especially the fat soluble vitamins such as A, D, E, and K and deficiencies in antioxidants (vitamin C, selenium, and zinc).
- Chronic inflammation plays a role in the pathology of CF. Modification of the overall composition of fats, optimizing the ratio of Omega 6 to Omega 3 oils may be beneficial.
- Studies in the use of dietary supplements in cystic fibrosis are few and difficult to interpret.

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# Overview of Cystic Fibrosis

## *Introduction*

Cystic fibrosis (CF) is a chronic multisystem disease and the most common recessive life-threatening illness in North America. In the United States, there is an estimated incidence of 1 in 2,906 Caucasian and 1 in 10,338 non-Caucasian live births [1]. Affected individuals demonstrate dysfunction of a multifunctional ion-channel protein, the cystic fibrosis transmembrane conductance regulator (CFTR) [1]. This protein acts as an important ion channel which regulates the hydration of airway surface liquid. In addition, mutations in CFTR give rise to a range of clinical manifestations extending from classic CF with airway obstruction and pancreatic insufficiency to single organ pathology. Mucosal obstruction of exocrine glands such as goblet cells in the respiratory and gastrointestinal tracts is the chief contributor to morbidity and mortality in patients with cystic fibrosis.

This chapter will primarily focus on gastrointestinal dysfunction in cystic fibrosis and traditional and integrative nutritional therapies to address the underlying pathophysiology of this complex disease. A strong link has been established between nutritional status, lung function, and survival in children and adults with CF [2]. Understanding this link and how to diagnose and manage nutritional needs of individuals with CF will contribute to improving their quality of life and life expectancy.

## *The Genetics of Cystic Fibrosis*

CF has a simple Mendelian autosomal recessive inheritance. Individuals with CF have two copies of the mutant CFTR gene, one inherited from each parent. Carriers have one normal and one mutant CFTR gene and their health is not typically affected because the normal CFTR gene may ensure production of enough protein to allow normal cellular function. Carriers have a 50 % chance of passing their mutant CFTR gene onto their children. When both parents are carriers there is a 25 % chance in every pregnancy that the child will have CF, a 25 % chance that the child will have two normal CFTR genes and a 50 % chance that the child will be a carrier [3].

In 1985, the gene encoding CFTR was localized to 7q21–34 on the long arm of chromosome 7 [4]. Advances in understanding the molecular biology and function of CFTR have primarily occurred since 1989 when the gene sequence was first identified [5–7]. More than 1,600 known deleterious mutations of CFTR have been reported to the Cystic Fibrosis Genetic Analysis Consortium [8, 9]. This number is expanding with further investigation in previously under represented ethnic groups and less severely affected individuals.

The most common mutant allele results from a deletion of a nucleotide triplet encoding for phenylalanine at amino-acid position 508 in the normal position. This

**Table 5.1** Relationship between the amount of functional CFTR produced and phenotypic (clinical) expression

| Percentage of normal CFTR function | Manifestations of CFTR |
|---|---|
| <1 | Classic disease with pancreatic insufficiency and recurrent respiratory infection |
| <4.5 | Progressive pulmonary disease |
| <5 | Clinically demonstrable sweat abnormality |
| <10 | Cogenital bilateral absence of the vas deferens (male infertility) |
| 10–49 | No known abnormality |
| 50–100 | No known abnormality (asymptomatic heterozygotes—"carriers") |

Courtesy of the www.cysticfibrosismedicine.com

**Table 5.2** The six different classes of CFTR dysfunction

| Mutation | What's gone wrong |
|---|---|
| Class I | Stop signal in CF gene occurs too soon; no CFTR is made |
| Class II | CFTR is misfolded keeping it from reaching the right place; affects 80 % of CF patients |
| Class III | CFTR is made and in right place, but does not function normally |
| Class IV | Opening in CFTR is faulty |
| Class V | CFTR is made in smaller than normal quantities |
| Class VI | CFTR degrades too fast; not enough protein is present |

Courtesy of the cystic fibrosis foundation (CFF)

ΔF508 is present in approximately 70 % of defective CFTR alleles and in 90 % of patients with cystic fibrosis in the United States. The frequency of this mutation varies with ethnicity and is most commonly found in Caucasians. Different gene mutations result in different levels of disease severity, as the amount of functioning CFTR protein produced appears to be related to clinical status (Table 5.1).

The CFTR dysfunction can be divided into one of six classes. There are various mechanisms by which mutations in the CF gene produce quantitative or qualitative changes in CFTR function as described in Table 5.2. For example, ΔF508 is categorized as a class II defect. The CFTR protein is rapidly recognized as misfolded and is degraded shortly after synthesis, before it can reach its crucial site of action at the cell surface. Note that there is absence of gastrointestinal symptoms until the percentage of normal CFTR function is <1 %.

Although primarily a chloride channel, CFTR has been implicated in the regulation of other membrane channels, such as the epithelial sodium channel (ENaC) in addition to calcium-activated chloride and potassium channels. Defective CFTR disrupts movement of ions and water in the respiratory, gastrointestinal, hepatobiliary, epidermal, and reproductive systems [1]. In the respiratory tract, this causes dehydration of the airway which leads to the accumulation of thick, tenacious secretions, and ultimately chronic pulmonary infection and airway obstruction.

The diagnosis of cystic fibrosis occurs most commonly after clinical suspicion is confirmed by laboratory testing although prenatal and newborn screening offer

unique situations where the diagnosis of CF is made solely on the basis of laboratory confirmation. A history of chronic cough, chronic production of sputum, recurrent asthma not responsive to care are among the most common clinical complaints and findings leading to the diagnosis [1]. Failure to thrive, malnutrition, steatorrhea, malabsorption are frequent complaints that may also lead to the diagnosis. Demonstration of elevated $Cl^-$ and $Na^+$ in sweat collected by the quantitative pilocarpine iontophoresis test (QPIT) has been the gold standard for the diagnosis of CF as greater than 97 % of individuals with cystic fibrosis have had a positive sweat test. There are other sweat testing devices; however they have not been accepted as diagnostic tests.

CFTR gene mutation analysis in most laboratories will only search routinely for the commonest mutations within their region. The majority of the more than 1,600 mutations are rare and the functional consequences of these rare mutations are not always known [10]. Even though the presence of two mutations is suggestive of the diagnosis of CF, two mutations in the CFTR gene does not necessarily result in classic CF disease. So although an abnormal CF mutation is likely to give a positive sweat test, the road from genotype to clinical manifestation can be unpredictable. For example, pancreatic sufficiency has been associated with certain mutations although insufficiency may emerge with time. Understanding this complex interplay between the genetic background and clinical manifestation of this disease may help identify early signs of specific organ pathology such as pancreatic insufficiency and tailor appropriate medical intervention.

## *Gastrointestinal and Nutritional Underpinnings of Cystic Fibrosis*

Although the primary cause of morbidity and mortality in CF is related to the respiratory system, the disease can also manifest in multiple other organ systems which includes the gastrointestinal (GI) system as mentioned above. Gastrointestinal disease can begin in utero in the pancreas where dysfunctional CFTR produces a deficiency in exocrine pancreatic secretions which include proteolytic enzymes, secondary to the progressive plugging of the pancreatic ducts by viscous secretions [10]. The combination of the in utero deficiency of proteolytic enzymes with dysfunctional goblet cells of the small intestine leads to obstruction of the distal ileum by tenacious meconium. Approximately 15 % of infants with CF are born with intestinal obstruction known as meconium ileus [10].

The loss of pancreatic enzyme activity leads to intestinal malabsorption of fats, protein, and carbohydrates after birth. Infants manifest poor or absent weight gain, chronic abdominal distention, absence of subcutaneous fat and muscle tissue, steatorrhea, and rectal prolapse [10]. An untreated child may have a robust appetite but fail to meet the increased daily caloric intake requirements in the setting of respiratory distress and malabsorption. If the pancreatic enzyme replacement therapy (PERT) (will be discussed in greater detail in section "Traditional Nutritional

Therapies in Cystic Fibrosis" of this chapter) is suboptimal in older children, distal intestinal obstruction syndrome (DIOS), which is a blockage of the intestines with inspissated stool, may result [10].

Aggressive nutritional support has been a fundamental component of the recommended treatment regimen for the management of CF as this is based on the hypothesis that improved nutritional status improves pulmonary function. Patients with CF require a high-calorie, high-fat diet which is usually 120–150 % of the daily recommended intake for age [11]. Independent of lung function, poor nutritional status has also been found to be a predictor of mortality, short stature, and the development of CF-related diabetes mellitus (CFRD) [12, 13]. Striving to improve outcomes by early identification of patients at nutritional risk, enhancing education regarding supportive therapies and then initiating such therapies prior to a precipitous decline in nutritional status is now the standard of care.

CFRD is the most common comorbidity in persons with CF [11]. As the life expectancy of patients with CF continues to increase, the need to proactively diagnose and aggressively treat CFRD and its potential complications has become more apparent. CFRD negatively impacts lung function, growth and mortality, making its diagnosis and management crucial in a population already at high risk for early mortality. CFRD is a unique entity, requiring a thorough understanding of its unique pathophysiology to facilitate the creation and utilization of an effective medical treatment plan. However, the hallmark of CFRD is insulin deficiency, necessitating the use of exogenous insulin as the mainstay of therapy [11] which we will discuss further in section "Nutrition and Lung Health in Cystic Fibrosis" of this chapter.

Dietary education and therapy is a cornerstone of glycemic control in patients with diabetes [11]. Glycemic control remains crucial to decrease the risk of microvascular complications; however, because patients with CFRD do not experience the macrovascular and microvascular complications that drive the nutritional recommendations for other diabetes populations, the additional diagnosis of CFRD does not alter CF dietary recommendations [14]. In the next section, the complex interplay between nutrition, CFRD, and lung health in individuals with CF is discussed.

## Nutrition and Lung Health in Cystic Fibrosis

### *Introduction*

Lung disease is a significant reason for morbidity and pulmonary function is the primary predictor of death among individuals with CF [15]. The rate of forced expiratory volume in 1 s ($FEV_1$) decline is a useful index of disease severity. Deteriorating $FEV_1$ is a key marker for disease progression [16]. The lung disease seen in patients who have CF primarily involves the airways and produces obstructive changes. Severe obstructive lung disease increases energy expenditure from the high demands of the work of breathing [17], and this is prominent in CF patients who have more advanced stages of lung disease [12, 18].

The nutritional status of a CF patient can be seen as the result of a dynamic process influenced by energy intake and the presence of all of the factors known to influence the energy balance against the metabolic demands imposed by the lung disease. Optimization of the nutritional status is essential for effective treatment of individuals with CF especially to prevent the development of end stage lung disease. The body weight at any point in time reflects the status of this balance between the energy requirements and metabolic demands. Malnutrition results from a discrepancy between energy and micronutrient requirements and food intake modified by malabsorption [19, 20].

From a clinical perspective, regardless of disease entity, the link between malnutrition and lung dysfunction is well established. Pancreatic insufficiency and the resultant chronic malabsorption is a major determinant of malnutrition in patients who have CF. This state is compounded by the added effects of chronic infection and inflammation with poor appetite and the development of comorbidities like CFRD. Pulmonary infections and inflammation, which increase the resting metabolic rate, are major causes of the downward spiral of weight loss, lung dysfunction, and malnutrition [21]. Although likely a multifactorial process with complex interactions, malnutrition can be better understood if viewed as a vicious spiral that is incrementally affected by the development of nutritional deficiencies from early in life. As malnutrition develops, the effects and rate of progression of the process is magnified with each cycle.

## *Cycle of Inflammation*

Pulmonary inflammation is another major cause of the decline in respiratory function in patients with cystic fibrosis and may precede the onset of chronic infection. An intense inflammatory state appears early in the CF airways. Bronchoalveolar lavage studies in infants suggest that inflammation may even precede colonization with bacteria [10].

Immune-mediated inflammation also contributes significantly to the lung damage present in patients with CF [10]. Elevated levels of interleukin-8, interleukin-6, tumor necrosis factor α, and leukotriene $B_4$, along with reduced levels of anti-inflammatory cytokines and proteases, have been found in the airways of patients with cystic fibrosis.

Toll-like receptors, which recognize a variety of inflammatory mediators (including neutrophil elastase, bacterial lipopolysaccharide, and other microbial products), mediate inflammatory effects in part by activating the transcription factor nuclear factor-κB, which governs a molecular pathway that induces the production of inflammatory proteins and cytokines [22, 23]. These and other inflammatory mediators such as $alpha_1$-antitrypsin influence the progression of lung disease [24, 25]. If inflammation is both a primary defect related to dysfunctional CFTR and a result of infection, then anti-inflammatory therapy in the form of medications and diet may be helpful to mitigate its effects.

### *Insulin Therapy and Lung Function*

Similar to chronic inflammation, CFRD negatively impacts lung function. The physiology of CFRD is complex however insulin deficiency is the hallmark of CFRD necessitating the use of exogenous insulin as the mainstay of therapy [11]. Once CFRD develops, modest peripheral insulin resistance also arises [26, 27]. Insulin resistance is the inability of insulin to produce its usual biological actions at circulating concentrations that are effective in normal subjects. A significant challenge to glycemic control in regards to insulin resistance occurs in CF patients during times of declining clinical status. Decreased lung function, active infection, inflammation, or the addition of corticosteroids are associated with an increase in both cytokine production and counter-regulatory hormones, causing increased insulin resistance in patients with CF making glycemic control difficult [28, 29].

CFRD is associated with a significant decline of numerous clinical parameters, making the timely diagnosis and treatment important [30]. Patients with CFRD have more severe pulmonary disease as manifested by a lower $FEV_1$, more pulmonary exacerbations, a higher prevalence of the CF sputum pathogens *Pseudomonas aeruginosa* and *Burkholderia cepacia* complex, lower nutritional measurements and a higher prevalence of liver disease than those without CFRD [31, 32]. Mortality rates are higher among patients with CF with diabetes than in those without CFRD.

Based on multiple studies, subcutaneous insulin therapy remains the treatment of choice in CFRD. There is evidence that CF patients on insulin therapy who achieve glycemic control demonstrate improvement in weight, protein anabolism, pulmonary function, and survival. Reported outcomes included improved lung function, nutritional status and blood glucose/A1C, decreased pulmonary exacerbation rates, and decreased mortality [11]. There is little evidence regarding the superiority of specific insulin regimens in CFRD, and clinical judgment should be used to choose the best regimen for each patient.

Treatment goals aim to prevent the cascade of wasting precipitated by reduced lung function, chronic inflammation, increased energy expenditure, decreased intake due to poor appetite and increased losses due to malabsorption. Traditional nutritional therapies utilized to achieve these goals will be discussed in the next section.

## Traditional Nutritional Therapies in Cystic Fibrosis

### *Introduction*

Optimization of growth and nutritional status is essential for effective treatment of patients with CF. Therefore, nutritional and growth status monitoring and management are vital to CF health care. Achieving and maintaining normal patterns of growth for children with CF in large part requires management of gastrointestinal and pulmonary symptoms as well as nutrient and energy intakes. Dietary strategies concentrate upon providing a high energy and high protein diet, together with PERT.

Of note, only patients who have documented pancreatic insufficiency should receive PERT. Currently the clinical guidelines for nutrition management offer evidence-based recommendations for the increased energy intake required to support growth and development for children with CF and pancreatic insufficiency [33]. In cases where insufficient evidence was cited for an evidence-based recommendation, the previously published CF Foundation Pediatric Consensus Statements continue to provide recommendations for nutrition care and the consensus statement on the use of pancreatic enzymes continues to provide recommendations for dosing [33].

## *Nutritional Approach*

The CF Foundation recommends maintenance of normal ranges of weight- and stature-for-age using the body mass index (BMI) percentile method (at or above the 50 % percentile), because normal growth status was associated with improved $FEV_1$ and survival [33]. A consensus document on the nutritional assessment and management in CF by Ramsey and colleagues introduced the concept of anticipatory guidance by specialist CF dieticians [34]. Five response categories for the provision of nutritional support were identified:

1. Routine management of all patients: high energy, high fat, high salt, nutritional education and dietary counseling, PERT and vitamin-mineral supplementation for those with pancreatic insufficiency.
2. Anticipatory guidance of patients at risk of developing energy imbalance, but are maintaining adequate nutritional status: energy dense dietary education, close monitoring of dietary intake, and behavioral management counseling.
3. Supportive intervention for patients with decreased weight velocity and/or slightly compromised nutritional status: anticipatory guidance plus oral supplements, such as fortified milk drinks, desserts, and glucose polymers.
4. Rehabilitative care for patients whose nutritional status is compromised: overnight supplementation via an enteral tube.
5. Resuscitative and palliative care for patients whose nutritional status is significantly compromised: 24-h continuous enteral tube feeds and/or total parental nutrition, particularly in those awaiting organ transplantation.

These five categories underscore the principal aim of nutritional management in CF which is to prevent malnutrition secondary to energy imbalance. Comprehensive assessments of body composition, dietary intake, and biochemical markers should be routinely conducted in order to detect deterioration early [35].

## *Pancreatic Enzyme Replacement Therapy*

Pancreatic enzymes play a critical role in macronutrient digestion. Their secretion is predominantly stimulated by exposure of the duodenal mucosa to nutrients. Pancreatic

exocrine insufficiency (PEI) occurs when the amounts of enzymes secreted into the duodenum in response to a meal are insufficient to maintain normal digestive processes which is the case in individuals with CF. ~85–90 % of patients with CF are PEI. An accurate assessment of pancreatic function is essential in the management of CF as the main clinical consequence of PEI is fat maldigestion and malabsorption, which may result in malnutrition, abdominal pain, malodorous, greasy stools, and rectal prolapse [36]. Protein and other nutrients are lost as well [37].

PERT is the mainstay of treatment for PEI. The primary treatment goal is to deliver sufficient enzymatic activity into the duodenal lumen simultaneously with the meal or snack in order to restore nutrient digestion and aid in absorption [37]. There is a wide variety of commercial pancreatic enzymes available. Enteric-coated pH-resistant microsphere preparations are most commonly used. These preparations were developed to protect the enzymes from degradations by acid and pepsin in the stomach [16]. Both generic and name-brand or proprietary preparations are available but there is insufficient evidence to support efficacy of generic preparations thus the CF Foundation recommends the use of name-brand preparations for PERT [33]. Ideally, the dose of enzyme should be determined by nutrient intake of fat, protein, and carbohydrate. However, an approach based on the patients age and weight is typically used [16].

Timing related to meals can influence the effectiveness of pancreatic enzymes. If taken before the meal, enzymes may be emptied from the stomach before the meal is emptied. If enzymes are taken after the meal, some of the meal may be emptied before the enzymes. In both cases, digestion may be incomplete. Enzymes should be taken with the meal to ensure adequate mixing with the chyme, a thick semifluid mass of partially digested food and digestive secretions that is formed in the stomach and intestine during digestion [36]. Other factors that affect efficacy are enzyme bead size, diet content, acidity of gastric juices, and GI transit time [21].

Initially, PERT was thought to be free of major side effects, but there is an increasing recognition of fibrosing colonopathy and its association with very high doses of oral pancreatic enzymes in patients with cystic fibrosis [36]. Fibrosing colonopathy is colonic narrowing with circular intramural fibrosis that may be limited to the ascending color or may extend to involve the entire colon [16]. Patients at higher risk for this complication include children under 12 years of age who have been taking enzymes with lipase intake exceeding 6,000 U/kg/meal for more than 6 months. For this reason, maximum dose recommendations have been made [36].

## *Enteral Therapies*

Generally, nutritional interventions start with addition of high-calorie foods to the patient's regular diet and use of nutritional energy supplements [37]. Despite a high-calorie diet with oral supplementation and PERT, patients with CF may still have

inadequate weight gain. At that point, assuming other comorbidities such as CFRD are being adequately treated, evaluation for gastrostomy tube placement to receive nocturnal enteral feedings should be strongly considered. The purpose and goals of enteral feedings should be explained to the patient and family, and their acceptance and commitment to this intervention should be realistically assessed. Enteral feedings should be presented as a supportive therapy to improve quality of life and outcome. A possible way of assuring that families and patients understand this concept is to introduce the idea of enteral feeds at diagnosis or early in the course of CF, before nutritional failure is present.

Calorically dense formulas (1.5–2.0 kcal/cm$^3$) usually are necessary for provision of adequate calories. Non-elemental formulas are tolerated and absorbed as well as elemental formulas when enzymes are provided [38]. The amount of calories delivered should then be titrated based on the rate of weight gain, fat stores, and growth. The goal of dosing pancreatic enzymes during enteral feeding is to expose all formula to the enteric-coated beads in the duodenum.

## Non-conventional Nutritional Therapies in Cystic Fibrosis

### *Introduction*

It is estimated that 33–66 % of the CF population use or have used nontraditional therapies [39, 40]. Use of herbal or dietary supplements therapies alone is lower but is the most popular non-conventional therapy which is similar to the general population [41]. One questionnaire study in CF adults inquiring about dietary supplements use found 19 % of patients were currently using dietary supplements and 10 % had reported past use [42]. An area of concern for health care providers is that the intake of such supplements (in addition to other non-conventional therapies) is not always relayed to their health care providers which could result in possible drug/supplement interactions. In addition to complementary and alternative medicine (CAM) use, there is also the use of special diets in addition to other CAM therapies.

### *Special Diets for Cystic Fibrosis*

As previously discussed, the use of high caloric diets has been promoted in the care of children and adults with cystic fibrosis since good nutrition has been associated with improved lung health. The appropriate nutritional management can help with growth and survival. High energy diets are commonly recommended along with traditional nutritional supplements (both oral and enteral). However, the exact content of such high energy/caloric diets has not been part of the various guidelines in terms of what types of fats, proteins, and carbohydrates would be best for both growth and overall nutritional value. Traditionally, cystic fibrosis care providers

(including dietitians) have suggested increasing any type of fat or protein to help increase caloric intake. This has raised some concern that an increase in "unhealthy" fats such as saturated fats and partially hydrogenated fats (e.g., trans fats) may lead to an increase risk of cardiovascular disease [43]. It has been thought that CF patients are at relatively low risk for cardiovascular problems. One study found lower total cholesterol, lower LDL, and higher triglyceride levels than controls [44, 45]. Microvascular complications appear to be less common but increasing the exposure of CF patients to cardiovascular risk factors in the diet is unclear. Thus, as CF patients now proceed into adulthood with a longer life expectancy, they may have a higher incidence of cardiovascular disorders.

In overall diet composition, one study looking at food diaries in 27 children with CF showed the mean calorie contribution from fat was 38 % and the mean poly unsaturated fat intake was 92 % [46]. Another concern in addition to cardiovascular problems is that the increased intake of these unhealthy fats coupled with excessive omega-6 fatty acids found in many vegetable oils, may increase the oxidative stress on the CF patient. This is significant since oxidative stress plays a significant role in the pathophysiology of CF. By increasing the intake of omega-6 fatty acids, this may lead to a more pro-inflammatory pathway which could result in the release of such mediators as leukotriene B4 [47]. Due to the dysfunctional fatty acid metabolism in cystic fibrosis, it may be beneficial to have a diet with an increased intake of plant sources of omega-3 fatty acids such as seeds, vegetable oils (canola, flaxseed, and soybean), green leafy vegetables, nuts, and beans, along with monounsaturated fats such as olive oil which is high in oleic acid. Omega-6 fatty acids are important as well as omega-3 fatty acids in cellular and immune function; however a more optimal ratio of omega-3 to omega 6 fatty acids would be 1:4 whereas in the current North American European diet is felt to be closer to 1:16 [48]. Sources of omega-6 fatty acids include oils (sunflower, corn, soybean) and such foods as avocado. By increasing the diet in omega-3 fatty acids and decreasing omega-6 fatty acid content may improve overall lung health in patients with CF. There are recommendations from the CF foundation for increasing the intake of both omega-3 and monounsaturated fats as it could be beneficial to CF patients [37]. Another potential health benefit of olive oil is that it may displace omega-6 fatty acids while not impacting omega-3 fatty acids, providing a better balance between these two important fatty acids.

One example of a diet with increased omega-3 fatty acid content that has been popularized for many chronic inflammatory disorders including cystic fibrosis is the "Mediterranean Diet." The diet emphasizes plant-based meals with small amounts of meat or chicken and utilizes more fish and other seafood. It also has more servings of grains, fresh fruits, vegetables and contains higher amounts of fiber. The diet is higher in monounsaturated plant-based fats such as olive oil. The variety of fish which increases omega-3 fatty acids in the form of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) is found in salmon, mackerel, herring, and tuna. It has been shown that following the Mediterranean diet may lead to lower blood glucose, lower cholesterol and triglycerides, and other health problems [49]. This diet has been studied in adult CF patients and one study showed a higher energy intake and a lower intake of omega-6 essential fatty acids in the CF patients, resulting in a

higher omega-3 to omega-6 fatty acid ratio in the CF patients' diet. A Mediterranean diet may not be enough as CF patients also need additional supplementation in order to normalize their fatty acid pattern but it has been suggested as an alternative approach to improving nutrition in CF patients and decreasing the amount of oxidative stress from the diet high in more unhealthy fats [50].

## *Vitamin and Non-vitamin Supplementation in Cystic Fibrosis*

In addition to changing overall diet composition to improve omega-3 fatty acid intake, CF patients may take omega-3 fatty acid supplements, usually in the form of fish oil capsules with a recommended dose of 1,000 mg per day. There have been several randomized controlled studies omega-3 fatty acid supplementation in both children and adults with CF [51]. Although some subjects complained of steatorrhea, diarrhea, and abdominal pain, most tolerated the supplements well with some patients needing to adjust their dose of pancreatic enzymes. The study results varied from increased weight gain in the omega-3 fatty acid group [52], improvement in lung function [53] and improved fatty acid status within cellular membranes [52, 54] along with a decrease in inflammatory markers [52]. A Cochrane review of omega-3 fatty acid supplementation in CF concluded that omega-3 supplementation may provide some benefits with relatively few side effects but evidence was insufficient to recommend their routine use and further studies were recommended to determine significant therapeutic effect along with assessing the influence of disease severity, dosage and duration of treatment [55].

CF patients are routinely advised to increase their vitamin intake especially the fat soluble vitamins such as A, D, E, and K due to chronic fat malabsorption [56]. It has also been described (perhaps in part due to the increase in oxidative stress in CF patients) that deficiencies in antioxidants are greater in CF patients then healthy controls [57]. These deficiencies include the vitamins mentioned above in addition to vitamin C, selenium, and zinc. Antioxidant enzymes such as glutathione peroxidase have also been found to be low in CF patients along with iron and other essential elements [57]. There have been several studies attempting to increase the levels of glutathione by oral supplementation. This has been done by using glutathione in doses up to 3 g per day [58], increasing glutathione levels by increasing cysteine stores using lipoic acid [59] or whey protein [60]. Due to the rapid metabolism of glutathione, oral supplementation has not been shown to increase levels. However, supplements using whey protein has shown some promise but long-term pulmonary improvement has not yet been shown. Inhaled glutathione has also been studied and pulmonary function improvements following these treatments were found. Utilizing this type of therapy may be useful; however, more clinical trials to investigate half-life issues, optimal dose, and overall safety are needed [61].

Other antioxidants and essential minerals important in airway metabolism which have been studied in CF include oral *N*-acetylcysteine [62], vitamin E (α-tocopherol) [63], Vitamin A (carotenoids) [64, 65], Co-Enzyme Q10 (CoQ) [66], zinc [67], selenium [68] and iron [69]. The results are mixed most likely due to the wide variability in CF patients in respect to absorption of the various supplements and disease severity. Recommendations for doses to be considered for many antioxidants have been published [37] and are age specific. These doses may not meet the specific needs of an individual due the wide variability in clinical presentation, *clinical* status, and differing rates of pulmonary decline. Each patient should be counseled as to whether supplementation is necessary, which antioxidants should be considered and, if possible, levels of supplements (including minerals and vitamins) monitored. Studies in the use of antioxidants (supplements or antioxidant-rich fruits and vegetables) in treating other chronic inflammatory disorders have not supported their general use. This may be, in part due to study design of such trials, incorrect formulations, or suboptimal delivery of antioxidants [57]. Supplementation of vitamin D is important for lung function in addition to bone health. It has been shown that vitamin D deficiency is common in CF and there is consensus for vitamin D recommendations which include yearly screening (preferably at the end of winter). The appropriate serum level to monitor is the serum 25-hydroxyvitamin D measurement with a minimal acceptable level of 30 ng/mL [70]. There are age-specific doses for intake including a stepwise approach to increase vitamin D when optimal levels are not obtained.

Due to these the multiple areas of nutritional deficiencies, there are many dietary supplements (single and in various combinations) that have been promoted for CF patients. Overall, studies in the use of other dietary supplements in cystic fibrosis are few and difficult to interpret due to small numbers and the difficulty in studying such a variable and progressive disease. An Internet search will result in hundreds of supplements to consider. Many, such as increasing taurine intake to help with fat absorption have been studied [71], but for the most, have not gone beyond small pilot type studies. Dietary supplements such as micronutrients, essential fatty acids, grapefruit seed extract, ginkgo, green tea, cat's claw, milk thistle, choline, and bromelain have been suggested but the data to support routine use along with the specific dose information are not available nor is their safety profile. One recent double blind, randomized controlled study investigating supplementing oral magnesium in children with CF did show improved respiratory muscle strength in the magnesium group [72]. Although considered to be an optional dietary supplement, some dieticians and CF health care providers believe that probiotics should be a routine addition to the CF regimen. There has been increasing awareness that the role of intestinal bacteria is important in both the development and modulation of the immune system. Dendritic cells in the gut may be key to directing the beneficial immune response to probiotic bacteria and subsequently reducing inflammation. There may be an important link between the microbiota of the gut and maintaining and promoting lung health [73]. Since CF includes significant gastrointestinal involvement including chronic inflammation, probiotics have been promoted as adjuvant therapy similar to other chronic

inflammatory bowel disorders. Two studies of patients with CF who were treated with probiotics demonstrated a reduced rate of pulmonary exacerbations in comparison to pretreatment period [74, 75].

## Conclusion

The aim for every child with CF should be to achieve normal growth and development. This requires regular and accurate surveillance, adequate calories and nutrients, and a plan for prompt intervention when growth is suboptimal [37]. Since cystic fibrosis is a multi-organ disease with multiple manifestations due to different genetic mutations and other host factors, there is no single nutritional regimen that can be recommended. However, individual determination of nutritional status, a unique and aggressive nutritional approach with tailored supplementation should be made for every patient with cystic fibrosis since the relationship between nutrition and overall survival is crucial.

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# Chapter 6
# Nutrition and Neuromuscular Disease

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**Keywords** Nutrition • Neuromuscular disease • Macronutrients • Micro nutrients • Nutritional supplements • Nutraceuticals

## Keypoints

- Children with neuromuscular disorders require special attention to their nutritional status and are at risk for overfeeding and underfeeding which can lead to serious medical consequences.
- Contributing factors to nutritional problems include feeding difficulties, swallowing impairment, gastrointestinal complications, medications, as well as other comorbidities such as cardiac, respiratory and orthopedic complications and physical inactivity.
- Careful assessment and routine monitoring is required for this disease, keeping in mind the progressive nature of the disease and its changing nutrient requirements throughout the life-span of these patients.

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## Abbreviations

| | |
|---|---|
| DMD | Duchenne muscular dystrophy |
| FSHMD | Facioscapulohumeral muscular dystrophy |
| LGMD | Limb girdle muscular dystrophy |
| NMD | Neuromuscular dystrophy |

## Introduction

Nutrition is a critical aspect of the long-term management of a patient with neuromuscular disease. Nutrition assessment with routine monitoring from diagnosis is essential. With a thorough nutrition follow-up, nutrition risk and gastrointestinal issues can be appropriately identified and dealt with as soon as possible. Complications of undernourishment or overnourishment are minimized this way, thus improving the overall picture. Attention to nutrition assessment, nutrition requirement, gastrointestinal tolerance, and pharmacological side effects is all part of optimum nutritional care and can lead to clinical improvement and improved quality of life. With appropriate nutrition intervention including macronutrient and micronutrient supplements the natural progression of the disease can be slowed and quality of life improved.

Pediatric neuromuscular disease (NMD) is a group of genetic disorders with a variable inheritance, age of onset, progression of muscle weakness, and effect on nutrition (Table 6.1). Some of the most common neuromuscular disorders seen in the pediatric population are Duchenne muscular dystrophy (DMD), 1 in 3,500 male births, congenital muscular dystrophies from 0.68 to 2.5 per 100,000, and spinal muscle atrophy (SMA), 1 in 15,000–20,000 (5–7 per 100,000) live births. NMD patients can develop malnutrition due to feeding difficulties associated with upper airway muscle weakness/bulbar muscle involvement, increased work of breathing, congestive heart failure, and medications, while diminished physical activity and calories expenditure associated with muscle weakness and steroid therapy are some of the factors leading to overweight in patients with NMD (Table 6.2). For example, 44 % of the patients with DMD can develop either malnutrition or obesity [1]. This chapter has used DMD as a representative disease to describe the nutritional issues in NMD, but the pathophysiologic and therapeutic principles can be adapted to the care of patients with other types of NMD.

In patients with NMD with progressive muscular weakness such as DMD, the transition from overweight to underweight may occur during the teenage years [2]. Many individuals under 14 years of age with DMD plot above the 90th percentile for age on standard growth charts. By the time patients reach 17 years of age, a majority would have fallen below the 10th percentile for age [2] due to multiple factors (Table 6.2). Natural progression of muscular dystrophy leads to a decrease in mobility and activity that will lead to a decline in energy expenditure and thus energy imbalances. Deterioration of pulmonary function and muscle strength can also lead to impairment in gas exchange and altered energy requirements. Overfeeding and underfeeding are separate but serious concerns in this population. Underfeeding, or

**Table 6.1** Common pediatric neuromuscular disorders

| Diagnosis | Inheritance | Usual age of onset | Course | Nutritional consequences |
|---|---|---|---|---|
| Duchenne MD | X-linked recessive | Second year of life (delayed walking) | Progressive Muscle weakness | Mostly malnutrition May be obesity |
| Becker MD | X-linked recessive | Teenage years | Slower compared to DMD | Milder if any |
| LGMD | AD or AR | Variable from infancy to adulthood | Variable | Milder |
| FSHMD | AD | Adolescence and young adulthood | Slowly progressive | Mild if any |
| Myotonic dystrophy | AD | Variable (infancy-adulthood) | Progressive | Heavier than other forms of NMD |
| Congenital muscular dystrophy | – | Early infancy | Progressive | Feeding problems and malnutrition |
| Spinal muscular atrophy | | | | |
| Type 1 | AR | 0–6 month | Progressive | Malnutrition |
| Type 2 | | 7–18 month | Progressive | Malnutrition if bulbar involvement |
| Type 3 | | >18 month | Slow progression | Less common than type 2 |
| Type 4 | | Two to three decade | Mild motor impairment | None |
| Congenital myopathies | Variable | Birth-early infancy | Variable | Swallowing difficulties may be associated with malnutrition |
| Congenital fiber type disproportion | – | Birth-first year | 90 % Static or improve | May develop malnutrition |

Abbreviations: *MD* muscular dystrophy, *LGMD* limb girdle muscular dystrophy, *FSHMD* facioscapulohumeral muscular dystrophy

negative energy balance, will expose the patient to an accelerated loss of lean body mass which does not have the potential to regenerate. Overfeeding, or positive energy balance, in a patient with limited mobility or activity will lead to an increase in fat mass, which can negatively impact mobility and respiratory function.

Patients with neuromuscular disease and progressive muscular weakness can develop cardiac, respiratory, and orthopedic complications [3]. However, with appropriate interventions, including focused nutrition, the natural progression of the disease can be slowed and quality of life improved [4]. Maintaining appropriate nutritional status, defined as weight for age from 10th to 85th percentiles, is essential. Prevention of under- and overfeeding should be the goal from diagnosis throughout life as both under- and overweight can have a negative effect on almost every organ system [4].

**Table 6.2** Factors contributing to malnutrition in patients with NMD

| |
|---|
| • Dysphagia |
| Difficulties in pre-oral phase of swallowing (DMD, LGMD, FSHMD) |
| Limitation in opening mouth (MG) |
| Macroglossia (DMD) |
| Dryness of the mouth in dermatomyositis and polymyositis (DMPM) |
| Abnormal posterior swallowing time (SMA, MD, DMPM, FSHMD, MG) |
| • Increased work of breathing |
| • Medications (bronchodilators) |
| • Congestive heart failure |
| • Systemic inflammation |
| Factors contributing to obesity in patients with NMD |
| • Diminished physical activity and calorie expenditure associated muscular weakness |
| • Altered body composition (increased intramuscular fat mass (DMD)) |
| • Poor diet choice (possibly associated with limited income) |
| • Steroid therapy |

Chronic glucocorticoid (Deflazacort) use, shown to preserve gross motor and pulmonary function [5], is an established therapy for DMD. Utilization of glucocorticoid therapy is associated with a significant increase in strength, muscle function, and pulmonary function [6]. Unfortunately, glucocorticoids are associated with many nutrition-related complications, including hyperglycemia, short stature, decreased linear growth, long bone, and vertebral bone fracture [7]. Finally, glucocorticoid use can lead to unintentional weight gain.

Appropriate assessment and nutritional management is an important part of care of a patient with NMD. The focus of nutritional assessment is determination of body composition, calculation of nutrient requirements, and management of GI and bone complications.

## Body Composition Assessment

Body composition assessment in individuals with muscular dystrophy comes with various obstacles. The natural and relentless path of muscular dystrophy is characterized by muscle wasting or a decrease in lean body tissue and an increase in intramuscular fat and adiposity. In addition, utilization of glucocorticoid therapy can lead to weight gain. Due to the natural progression of the disease, using

conventional nutritional assessment methods may lead to a false or misleading understanding of the individual's status; standard anthropometrics are not reliable in these individuals.

### *Length/Height*

Length or height measurements may be difficult to obtain across the life-span as many individuals are wheelchair bound, unable to stand, have scoliosis, or contractures. At advanced stages of the disease, upper arm length, tibial length, or knee height can be measured and used in place of linear height [2]. It is recommended for length or length equivalents to be checked every 6 months or during each follow-up visit and monitored closely [2]. For purposes of monitoring trends, length or height can be plotted on standard growth charts. There should be close consideration and understanding that these individuals should only be assessed using trends and not against the standard curves as their growth expectancy is not the same as those individuals who do not suffer from muscular dystrophy. There are no established separate charts for DMD children.

### *Weight*

Ideally, weight should be checked every 6 months and trends monitored. Weight history may be plotted on a standard growth chart to monitor trends. Of particular concern is the transition from overweight to underweight that may occur during the teenage years [2]. Many individuals with DMD under 14 years of age plot above the 90th percentile for age on standard growth charts. By the time patients reach 17 years of age, a majority will have fallen below the 10th percentile for age [2]. These alarming results reveal justification for early nutrition intervention to both prevent excessive weight gain during childhood and weight loss during adolescence. It is not recommended to compare individuals with DMD against the standard curves; normal growth curves and percentiles do not allow room for the progressive loss of muscle seen in muscular dystrophy. However, patients who are below the 10th percentile may be considered markedly underweight and those above the 85th percentile may be considered overweight. When adequate nutrition cannot be safely accomplished with oral feedings, gastrostomy tube (G-tube) placement under the guidance of dietitian is strongly recommended [8].

### *BMI*

Body mass index (BMI), often used in clinical practice in both pediatric and adult populations, is a surrogate measurement of body fat based on an individual's

**Table 6.3** Methods to assess body composition in patients with muscular dystrophy

| | Reliable | Caution | Not recommend |
|---|---|---|---|
| Body composition assessment in muscular dystrophy | DEXA<br>MRI/CT<br>Total body water | Weight<br>Length/height | BMI |

weight and height. However, one of the major limitations of BMI is its failure to distinguish between fat mass, edema, and muscle mass. This is particularly true with DMD, due to the compartmental disruptions between muscle and fat mass in muscular dystrophy, BMI does not accurately reflect underweight or obesity in muscular dystrophy. BMI may lead to a false representation of body composition; patients may have a normal BMI yet there may be an excess of body fat and an undesirable amount of lean body mass. Utilization of BMI in patients with DMD is not recommended.

## *Body Composition*

Utilizing height and weight without accurate body composition measurement can be problematic. Both dual energy X-ray absorptiometry (DEXA) and magnetic resonance imaging (MRI) were found to be accurate and noninvasive measures that are appropriate for monitoring nutritional status in pediatrics populations [2, 9]. If possible and feasible, these methods, along with computed tomography (CT) and total body water, may improve nutritional and overall management and treatment in these individuals [10]. One possible area for routine body composition assessment is utilization of diagnostic MRI and CT scans. Patients may undergo frequent routine scans to monitor disease progression. Although these patients are routinely evaluated by high-resolution diagnostic imaging, the information content of these images is barely exploited. These high-quality images can provide accurate and practical studies of body composition. More research is needed to develop protocols to integrate data from diagnostic MRI and CT assessment into routine clinical care.

Assessment of body composition is imperative to monitor growth and determine nutrient requirements. As seen in Table 6.3, DEXA, MRI/CT, and total body water are the most reliable methods of assessment and should be utilized when available. In the absence of direct measurement of muscle and fat mass, length/height and weight can be utilized with caution. Unfortunately, as the disease progresses, both length/height and weight become less reliable. The most important component of length/height and weight is assessment of trends over time. Throughout the lifespan both length/height and weight should be measured every 6 months and be plotted on standard growth charts. Growth is plotted on standard growth charts to obtain trends across time and should not be compared to the standard population. Utilization of BMI is not recommended for patients with DMD.

## Nutrient Requirements

Despite the well-documented body composition changes, nutrient requirements are often difficult to determine in patients with DMD (Table 6.4). Nutrient requirements change throughout the life-span with the decrease in metabolically active lean body mass and the increase in metabolically inactive fat mass. The loss of lean body mass also leads to loss of muscle strength and deterioration of pulmonary function, resulting in impaired gas exchange and altered energy requirements.

Due to the risk of being underweight or overweight, recommending appropriate nutrient intake is crucial to appropriate care. A negative energy balance associated with underfeeding may lead to an accelerated loss of lean body mass and a positive energy balance due to overfeeding in a patient with limited mobility or activity will lead to an increase in fat mass which can negatively impact mobility and respiratory function. Diets should be routinely assessed for energy, protein, fluid, calcium, and vitamin D. Calcium and vitamin D may play a vital role in the individual's care and bone health. In patients with NMD, calcium homeostasis may be affected by prolonged immobilization (immobilization hypercalciuria) and chronic use of corticosteroids (osteoporosis).

### *Energy Requirements*

As in other hospitalized and healthy individuals, indirect calorimetry serves as the gold standard in muscular dystrophy. Routine utilization of indirect calorimetry provides a direct determination of daily calorie requirements throughout the life-span. A direct assessment of energy requirements will hopefully avoid both under- and overweight conditions. While the most reliable method, indirect calorimetry, is not widely available in clinical settings. Predictive equations can be utilized to estimate daily energy requirements. Limited research is available to provide direction in this area, and studies that have addressed the topic have a small sample size that may limit the general use of findings [9–15]. Energy requirements have been reported to be higher and lower than age-matched controls [11–15]. In terms of predictive equations, the Harris–Benedict equation was found to overestimate needs in this population [10, 11], while the 1985 Schofield weight equation may provide the best estimation of energy requirements [11]. Until better methods become available, the

**Table 6.4** Methods to assess nutrient requirements in muscular dystrophy

| | Reliable | Caution | Not recommend |
|---|---|---|---|
| Assessment of nutrient requirements in muscular dystrophy | Indirect calorimetry<br>Diet recall<br>Serum vitamin and calcium determination | Predictive equations | Nutraceuticals |

best method for estimating nutrient requirements may be a multi-faceted approach that considers usual intake, body composition assessment, and predictive equations. For patients who are at a normal weight with appropriate weight gain, a 24-h recall or 3-day food diary will likely provide an accurate estimation of energy requirements. For patients who are below the 10th percentile for weight, daily calorie intake determined by 24-h recall or 3-day food diary represents an energy level that is too low. Utilizing predictive equations in this situation may help to provide a calorie goal to improve weight status. Similarly, both 24-h recall or 3-day food diary and predictive equations can be utilized to determine appropriate calorie recommendations for overweight patients. In this situation, the patient is obviously in positive energy balance. Weight loss by energy restriction alone is not recommended to avoid loss of lean body mass. In this situation, maintenance of the current weight, while introducing a healthy diet and physical activity, may help to normalize weight.

## *Macronutrient Requirements*

Limited information is available to direct macronutrient requirements. Patients should eat a balanced diet with adequate carbohydrate, protein, fat, and fluid. The proportion of macronutrient intake should be similar to children without NMD. Protein and fluid intake should meet the dietary reference intake (DRI) recommendations. Patients should undergo routine assessment of nutrient intake to determine appropriateness of intake.

## *Micronutrient Requirements*

Patients with NMD should receive a daily multivitamin supplement to ensure adequate intake [4]. With the initiation of glucocorticoid therapy, calcium and vitamin D status become paramount to maintain bone health. Glucocorticoid therapy can lead to a suppression of bone formation and an acceleration of bone resorption, leaving the bones at risk for fractures and osteoporosis. Current guidelines suggest calcium and vitamin D be consumed through diet. A 24-h recall or 3-day food record can be completed to assess intake. As routinely recommended, vitamins and minerals should be consumed through food. This can be achieved not only through foods rich in calcium (dairy products) and vitamin D (fish and fortified milk and cereals) but also through sunlight exposure for production of vitamin D. If intake remains low, supplementation may be needed. The amount of supplementation may depend on the patient's diet and/or serum levels of calcium and vitamin D. A 500–1,000-mg calcium supplement is recommended. If vitamin D intake is low or if serum vitamin D levels are found be to <20 ng/dL, 1,000 IU of vitamin D supplement is recommended. Unfortunately the assessment of energy, macronutrient, and micronutrient requirements is often empirical. Indirect calorimetry should be utilized for daily energy determination, but unfortunately limited resources lead to

under use of this tool. Clinicians are then left to rely on predictive equations. Due to changes in body composition, traditional predictive equations may not appropriately estimate energy requirements. The recommended method for determining calorie requirements is routine monitoring of both body weight and calorie intake. Early recognition of increased weight status can lead to an appropriate intervention to prevent overweight status. Balanced macro- and micronutrient intake is important. In addition, attention should also be given to both calcium and vitamin status to ensure adequate bone mineral density.

## Nutraceuticals

A topic of interest in muscular dystrophy is the usefulness of nutraceuticals. Currently, the supplement with the most interest in muscular dystrophy is creatine [2]. Creatine, when consumed in an oral diet, is delivered to skeletal muscle and used for energy production by serving as a precursor to the formation of ATP [16]. In animal studies, creatine has been shown to reduce skeletal muscle degeneration and enhance mitochondrial function in X chromosome-linked muscular dystrophy mice [17]. Results from the few published studies looking at creatine are inconclusive, thus a final recommendation cannot safely be made [3, 16] and additional research is needed before creatine use is recommended for patients with NMD.

A review article on creatine monohydrate as a therapeutic aid in muscular dystrophy reported that few studies have looked at the human response to creatine as a therapeutic agent to alleviate the symptoms of MD and those that have are contradictory [16]. A randomized control trial on the use of creatine and glutamine versus placebo reported no significant difference in the primary outcome measures between the two groups [18]. On the other hand, a review by the Cochrane Collaboration [19] reported "The data analysis reveals there is high quality evidence that short- to intermediate-term supplementation with creatine monohydrate in people with muscular dystrophy resulted in a modest, but significant, increase in maximal isometric force" but "Long-term studies (greater than 1 year) are not currently available to assess the safety of creatine monohydrate supplementation in people with muscle disorders" [19]. Tarnpolosky et al. [20] reported that creatine supplementation led to an increase in fat-free mass and handgrip strength in the dominant hand and a reduction in a marker of bone breakdown and was well tolerated in children with NMD. Bushby et al. [3], in a review of diagnosis and management of DMD, reported "No recommendations for the use of creatine are established."

Additional supplements of interest include enzyme CoQ10, carnitine, glutamine, arginine, fish oils, vitamin E, and green tea extract. With the absence of evidence-based research and expert opinion, there are no recommendations for the use of these supplements [3].

When approaching nutrition care in a population that is at such high risk for obesity and malnutrition of macronutrients and micronutrients, recommendations need to be made carefully. It is best to use reliable resources to direct the use of any supplements based on best available research evidence.

## Gastrointestinal Complications

The progression of muscular dystrophy is well documented. First, individuals will have impairment with ambulation and may eventually loose ambulation all together [21]. A loss in ambulation leads to wheelchair dependence (11–28 years of age). This may eventually lead to the individual requiring assistance with eating and drinking (12–23 years of age) and being unable to maintain respiratory function, leading to mechanical ventilation (14–31 years of age) [22]. Requiring assistance with eating is merely the tip of the nutrition-iceberg. Further impairment in gastrointestinal function may include involvement in smooth muscle. This can lead to gastroparesis, gastric distention, constipation, gastroesophageal reflux, dysphagia, which will lead to nutritional disturbances [23]. Each of these issues impacts nutrition status significantly.

### *Feeding Difficulty*

Feeding difficulties are associated with loss of muscle mass. The loss of strength and coordination can lead to a decrease in neck range of motion, decrease in head control, and difficulty opening the mouth and ultimately inadequate oral food/beverage intake. Feeding issues are a common problem and progressively increase with age [22]. Decreasing energy intake leads to a negative energy balance and accelerated muscle wasting. If muscle control and movement impairment have been observed during meal times, it may be beneficial for the individual to be helped during feeding times. This can range from food items being chopped into small pieces to having the individual fed by a caregiver or family member. Decreasing meal time frustration for the individual should be a goal. With negative meal time experiences, individuals may refuse food or consume inadequate amounts only leading to further issues.

### *Swallow Impairment*

If head/neck control becomes problematic, swallow ability should be observed at all meal times. It is common to eventually have muscle control and swallow function also affected. Aspiration and aspiration pneumonia is a serious complicated in neuromuscular disorder with marked muscle weakness and should be avoided at all costs. Several facial features should be observed when attempting to assess swallowing/chewing function [22]. If facial weakness, macroglossia, anterior open bite, malocclusion, poor oral hygiene, or glossopharyngeal breathing are observed, a speech and language pathologist (SLP) should be consulted. SLP is a valuable resource when assessing swallowing ability of the individuals with NMD.

As previously mentioned, aspiration and aspiration pneumonia is a serious complication of muscular dystrophy. The prevention of this should be sought after in each individual. When swallowing and chewing is of concern, an SLP should be consulted to conduct a clinical swallow evaluation or a videofluoroscopic swallow study if indicated. This will allow for the appropriate consistency of diet to be provided to the patient, thus minimizing the risk of swallowing complication.

## *Gastroesophageal Reflux Disease (GERD)*

When activity and mobility are further impaired, leaving the individual immobile, the risk of additional gastrointestinal issues rises. This population is more likely to develop gastroesophageal reflux and esophagitis due to the involvement of pharyngeal muscles [24]. In the setting of GERD, patients can be advised to alter dietary intake to improve symptoms. Eating smaller, more frequent meals, remaining upright after eating, and avoiding spicy or acid foods may improve GERD symptoms. Use of commonly used mechanical devices for airway clearance such as mechanical in-exsufflator (Cough Assist®) and devices for mechanical ventilation may also contribute to GERD and aspiration. Practitioners may consider using proton pump inhibitors to treat reflux that may lead to esophagitis.

## *Constipation*

Constipation is often present due to the combination of lost muscle tone and decreased physical activity. It is imperative to maintain good hydration, a balanced diet including dietary fiber, and possibly stool softeners and promotility agents to prevent or treat chronic constipation [25]. Constipation, if left untreated, may lead to abdominal distention, fecal impaction, loss of appetite, inadequate intake, anorexia, and early satiety. These are all complication that could only lead to inadequate macronutrient and micronutrient intake, which as explained above, is common in this population. Laxatives, stool softeners, and stimulants may be required frequently to avoid constipation and impaction. When pharmacological treatments like these are added to the daily regimen of these patients, optimal hydration becomes even more important. Especially with the use to fiber supplementation, inadequate hydration may only lead to exacerbation of constipation.

## *Enteral Nutrition Support*

Gastrostomy feeding tubes can be an option when dealing with problematic nutrient delivery. Due to muscle control and feeding difficulties associated with muscular

dystrophy, placing feeding tubes for enteral nutrition support may decrease the risk for aspiration, malnutrition/undernutrition, and accelerated muscle wasting. Gastrostomy feeding may lead to an improvement in nutritional status [24]. This may provide a stress-free route for providing macronutrients and micronutrients, thus optimizing nutritional status. Depending on goals and plans of care the patient or the family wishes to pursue, this may be a treatment option worth pursuing. As stated previously, those with neuromuscular dystrophy are at risk for aspiration and respiratory issues. This can be exacerbated by gastroesophageal reflux. The reflux of gastric content may cause erosion or irritation of the esophageal lining and may even lead to aspiration. Due to the possibility of these complications, fundoplication with gastrostomy tube placement [24] should be considered.

Patients with neuromuscular dystrophy can exhibit gastrointestinal abnormalities throughout their lifecycle. In DMD, the worsening gastrointestinal functions parallel the degeneration of neuromuscular function of the disease [23]. Patients may initially demonstrate feeding difficulties, followed by impaired swallowing. Without early and appropriate interventions, nutritional status can quickly deteriorate. Assessment by an SLP is imperative to recommend modified diet consistency to decrease aspiration risk while maximizing nutrient intake. Both GERD and constipation can by managed with a combination of dietary and pharmaceutical interventions. Ultimately, transition to enteral nutrition via G-tube placement may be required to maintain calorie intake.

## Bone Health

Patients with DMD are at risk for poor bone health due to a combination of factors, including decreased mobility, muscle weakness, and glucocorticoid therapy. These factors can be the cause of long bone and vertebral fractures, osteopenia, osteoporosis, kyphoscoliosis, bone pain, and reduced quality of life [4]. Vitamins and minerals should be ideally consumed through food. This can be achieved through foods rich in vitamin D and calcium (dairy items) but also through sunlight exposed for vitamin D. If normal levels cannot be maintained or adequate amounts cannot be consumed, supplementation should be considered. Routine assessment of serum calcium, phosphorus, alkaline phosphatase, 25-hydroxy-vitamin D, magnesium, and parathyroid hormone along with urinary calcium, sodium, and creatinine are recommended to monitor bone health. Measuring these parameters can help assess bone health and need for supplementation. In addition to these tests, bone density should be measured via DEXA scan. A measurement at baseline should be obtained followed by every 3 years or at that start of glucocorticoid therapy. For those patients with a history of fractures, those on glucocorticoid therapy, or those with a DEXA *Z* score less than 2, it should be repeated on an annual basis. If kyphoscoliosis or back pain is present at examination, it may be beneficial to complete a spine radiograph to assess for vertebral compression fractures. If height is below the 5th percentile, or if linear growth is failing, it is recommended to asses bone age (left wrist) radiography.

## Conclusion

A patient with neuromuscular disorders requires a multidisciplinary team approach. Nutrition assessment with routine monitoring from diagnosis is essential. With a thorough nutrition follow-up, nutrition risk and gastrointestinal issues can be appropriately identified and dealt with as soon as possible. Complications of undernourishment or overnourishment are minimized this way, thus improving the overall picture.

Attention to nutrition assessment, nutrition requirement, gastrointestinal tolerance, and pharmacological side effects are all part of optimum nutritional care and can lead to clinical improvement and improved quality of life. With inadequate or suboptimal nutrition, the natural course of the disease can only worsen. Poor nutrition can lead to negative impacts on almost every organ system [4]. With appropriate nutrition intervention, the natural progression of the disease can be slowed and quality of life improved [4].

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# Part III
# Asthma and Obesity

# Chapter 7
# Asthma and Nutrition

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**Keywords** Asthma • Nutrition • Nutrients • Obesity • Vitamins • Diets

**Keypoints**

- Asthma is one of the most common chronic diseases of children and its incidence has been escalating over the past few decades.
- The parallel increase in prevalence of obesity and asthma in recent decades raises concern about the relationship between obesity and asthma.
- There is mounting evidence associating obesity, chronic low-grade systemic inflammation, and asthma.
- Micronutrient deficiencies and poor antioxidant status may be an important contributing factor in asthma.
- Studies show that a Mediterranean diet may positively improve asthma control.

## Introduction

As we become more aware of the role of nutrition in chronic diseases, there are increasing questions on how nutrition affects asthma, one of the most common chronic diseases of childhood. Many parents of asthmatic children who are concerned about side effects of chronic medications are motivated to modify their children's basic food choices, and/or use nutritional supplements if it is safe and has the potential to reduce medications. Food is something parents provide daily to their

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children and can give without prescription. It can give them a sense of involvement and is part of fostering self-care. Modern medicine has given us effective drugs to control asthma symptoms and while these are essential to the care of patients with asthma, we also need to explore the potential power of foods and its nutritional components. It is especially important to see if there are specific common nutrient deficiencies that can affect asthma, either inherent to the disease or acquired through chronic use of drugs.

In this chapter, nutrition and its relationship with asthma will be explored along with a review of some dietary supplements that may be relevant to asthma.

## Overview

Asthma is one of the most common chronic diseases of children. It is a disease of chronic airway inflammation that results in airway obstruction with symptoms of wheeze, cough, chest tightness, and shortness of breath. Management of asthma includes drugs that relieve acute symptoms (e.g., short-acting beta-agonists and systemic corticosteroids); drugs that aim to control symptoms or prevent exacerbations (e.g., inhaled corticosteroids, leukotriene inhibitors). Depending on the severity, a child with asthma may be on several asthma medications plus drugs for allergies.

Prevalence of asthma in both adults and children has been rising, and in children it has doubled in the past 30 years [1]. The 2008–2010 average annual asthma prevalence was higher in children (9.5 %) than in adults (7.7 %) [2]. According to the CDC, it is most prevalent in heavily populated urban areas of the Northeast, Chicago, Denver, Los Angeles, and Oakland. In Philadelphia, the prevalence of asthma among children is as high as one in four. Prevalence of asthma is only slightly higher in Hispanic and African-American children than in Caucasian children, but the severity of illness is greater in African-Americans (higher ED visits, hospital admissions, and deaths). Asthma prevalence is also increasing in many other industrialized countries, including the United Kingdom (one in seven) and Australia (one in four).

Environmental factors and genetic predisposition are among the known factors involved in asthma. Environmental factors such as the hygiene hypothesis which proposed that lack of exposure to infections at critical point in the development of the immune system may lead to an increased risk of asthma and other atopic diseases has not yet been born out by evidence [3]. Recently, increasing attention has been focused on nutrition as a contributing factor in asthma. One of the hypotheses is that changes in diet and nutrient contents of foods are playing a role in asthma. Certain dietary factors associated with modern life in industrialized society may be contributing to the chronic inflammation associated with asthma. Some dietary factors that may impact asthma include: (a) excess nutrition (obesity), (b) quality of nutrition (e.g., micronutrient deficiencies; inflammation-promoting foods), and (c) food allergies. While food allergy is an important cause of asthma and asthma severity, this area will not be included in this chapter.

## Obesity and Asthma: Is There a Link?

In the USA, nearly one in five youths aged 6–11 years is overweight. Figure 7.1 shows the prevalence of obesity in all children 2–19 years of age, which has grown from 5.5 % in 1980, to 13.9 % in 2000, and to 16.9 % in 2008. The parallel increase in asthma and obesity in recent decades does raise the question of a potential link between these two conditions. There is increasing evidence showing that excess weight in children is associated with higher rates of asthma. Longitudinal cohort studies have been conducted in children show that obesity leads to asthma [4–10]. Furthermore, a systematic review showed strong evidence that obesity precedes and is associated with the persistence and intensity of symptoms of asthma [11]. Obesity in children seems to be associated with higher rates of asthma, and this relationship appears to be stronger among nonatopic than atopic individuals [12].

### *Possible Mechanisms*

#### Does Obesity Cause Inflammation?

There are several theories that have been proposed regarding the association between obesity and asthma [13, 14]. Obese individuals and asthmatics seem to have polymorphisms for receptors that are significant in both inflammation and asthma [15]. One theory is that there is a state of low-grade systemic inflammation in obese people, with obesity-related changes in adipose-derived hormones, leptin and adiponectin. Leptin has been shown to increase airway reactivity in mice studies [16]. Animal experiments evaluating the effects of leptin and obesity on airway inflammation in response to both allergic and nonallergic exposures suggest that airway inflammatory response is enhanced by both endogenous and exogenous leptin [15].

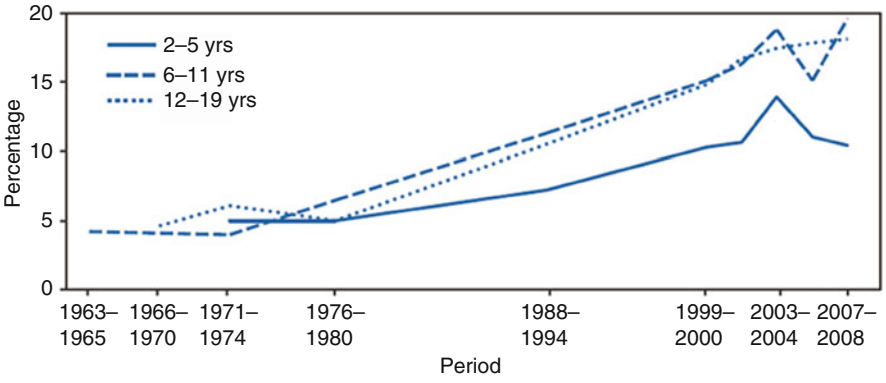


**Fig. 7.1** Prevalence of obesity during childhood age group, United States 1963–2008. Taken from Morbidity and Mortality Weekly Report (MMWR) January 21, 2011 vol. 60, No. 2. http://www.cdc.gov/obesity/data/index.html

Serum levels of adiponectin released by adipocytes on the other hand are markedly decreased in individuals with visceral obesity [17]. Adiponectin has an anti-inflammatory function and is therefore protective for asthma.

A study involving a weight-loss program for obese Brazilian adolescents showed improved lung function, asthma severity, and inflammatory biomarkers profile, including increase in serum adiponectin and decrease in leptin [18]. While further studies are needed, studies of weight-loss intervention such as this do suggest that a relationship between obesity, adipose-derived hormones, and asthma exist even if the exact mechanism is unclear.

### Obese People Eat More Inflammatory Foods (Fat)?

There is evidence that inflammatory changes in the airways can be induced by what we eat. A high-fat meal has been shown to induce airway inflammation in healthy volunteers [19]. Obese children exhibit higher consumption of foods that are high in saturated fats and low in antioxidants [20]. It was shown that diets high in saturated fatty acids and low in antioxidants are associated with increased asthma risk as well as severity.

### Mechanical Restriction in the Obese?

Another proposed mechanism is airway narrowing due to decreased lung volumes [21]. But based on current available data, obesity does not appear to reduce vital capacity or total lung capacity significantly. Obesity-related symptoms in children may be related to greater airflow obstruction as shown by their mild obstructive impairment in pulmonary function test [22]. A discussion of potential mechanisms linking obesity with asthma risk is reviewed in an excellent article by Lang [23].

## *Does Decreasing Obesity Result in Improved Asthma?*

If obesity is a risk factor for asthma, then studies that show decrease in prevalence or symptoms of asthma with weight loss would demonstrate this link. The interventional study from Brazil mentioned above subjected obese asthmatic adolescents to a 1-year weight-loss interdisciplinary intervention, which consisted of medical, nutritional, exercise, and psychological therapy. This resulted in beneficial changes in lung function as well as inflammatory biomarkers profile. The change in adiponectin level seen was an independent predictor of improvement in lung function [18]. In a systematic review on weight loss and asthma, all 15 studies noted an improvement in at least one asthma outcome after weight loss. This improvement was noted across studies that differed in sample age, gender, or country of origin and regardless of the interventions used [24].

In summary, there does seem to be a link between obesity and asthma while the mechanism behind it remains unclear.

## Role of Antioxidants in Asthma

Antioxidants are found primarily in vegetables and fruits with the major recognized antioxidants being vitamin E (alpha tocopherols), vitamin C (ascorbic acid), and beta-carotene. Other nutrients important for the functioning antioxidant system are selenium, manganese, and zinc (see Chap. 3 for further discussion on antioxidants). In the lungs, antioxidants provide a line of defense necessary for battling damaging oxidative stress. Vitamin C for example, one of the key antioxidant vitamins, is abundant in the extracellular fluid lining the lung. Its potential role in asthma is suggested by the following: vitamin C inhibits phosphodiesterase in vitro (similar to theophylline); deficiency increases airway hyperreactivity to histamine in guinea pigs; promotes relaxation of isolated tracheal smooth muscle; and is required for production of epinephrine in response to stressors [25].

Evidence is mounting that there is a relationship between antioxidant intake and asthma. This link between lower intake of antioxidants and increased prevalence of asthma was noted earlier by Seaton et al. [26]. There has been a decline in the consumption of antioxidants in modern industrialized society due to more consumption of processed foods and less of fruits and vegetables. There has also been a decrease in the mineral content of store-bought fruits and vegetables [27, 28]. One of several factors for this may be the different modes of production as well as longer storage required for distribution. For example, it has been shown that vitamin C decreases by 65 % in pineapple 2 weeks after harvest [29]. Since antioxidants such as vitamin C, E, and carotenoids can only be obtained from dietary consumption, it is reasonable to ask whether our modern western diet (low in fruits and vegetables) results in deficiencies of antioxidants, and that this has an impact on those already at risk of developing asthma, or influence the severity of asthma. Antioxidant supplements such as vitamin C, E, the carotenoids, and others may modulate the oxidative airway injury resulting from inflammation. This could be useful since it has been shown that asthmatics have impaired antioxidant system due to the aberrations in oxidant-antioxidant balance [30]. Supporting this idea is a case-controlled study of the dietary intakes of healthy subjects and asthmatics, which showed that asthmatic patients have a lower intake of vitamins A, C, and E than do non-asthmatic subjects [31]. Furthermore, in an investigation by Gilliland, low antioxidant levels were associated with a higher incidence of asthma, and children with low intake of vitamin A, C, and E had lower lung function [32]. In a large population sample study of children, lower serum levels of vitamin C and carotenoids were found in asthmatic children when factors such as body weight, socioeconomic status, passive smoke exposure, urban environment, and ethnicity were taken into account [33].

While there seems to be a link between lower levels of antioxidants and asthma, supplementation with individual antioxidants have not consistently shown a beneficial effect on asthma. A meta-analysis determined that dietary intake of antioxidants, vitamins C and E, and β-carotene does not significantly influence the risk of asthma [34]. Furthermore, a Cochrane review based on evaluation of nine trials, although generally small and greatly variable in their designs, concluded that it is

not possible to recommend either the use or avoidance of vitamin C supplements in asthma [35].

However, it has also been shown that certain antioxidant deficiencies, including vitamin C and selenium, appeared to be associated more with asthmatics exposed to environmental pollutants such as cigarette smoke and ozone [36]. It is possible that the protective role of supplementation with antioxidants may be more important in these environments [37, 38]. Despite the link between oxidative stress, low antioxidant status, and asthma, it may not be a straightforward issue of deficiency resolved by supplementation.

Earlier studies on other antioxidants such as selenium and vitamin E supplementation have not consistently shown a link with asthma [39], and randomized controlled trials on selenium and vitamin E supplements in adults with moderate to severe asthma reported no beneficial effect on the measured parameters [40]. In asthmatic children also, a meta-analysis by Nurmatove [41] as well as a large case-controlled study [42] confirmed that studies done on selenium (as well as vitamin C) do not have sufficient evidence for an association between intake of these nutrients and the prevalence of asthma. But most of the studies in children measured serum levels of selenium, which is not ideal for representing the body level. A recent study looked at hair zinc and selenium levels. They found that hair selenium and zinc levels were negatively correlated with number of wheezing attacks as well as number of acute respiratory tract infections [43].

In summary several observational studies have linked antioxidants with asthma. But interventional studies with supplementation of individual antioxidants have not consistently been positive. Systematic reviews also conclude that there is insufficient evidence on the use of antioxidant supplements and further research studies are needed especially in children [44]. Factors that could influence the outcome of some negative studies on supplementation include inadequate dosage, using an antioxidant in isolation rather than in a complex antioxidant mixture, and not choosing the right study population. It may be that the role for antioxidant supplementation, especially vitamin C in some asthma patients, may make more of an impact in those with poor dietary habits with chronic smoke or ozone exposure. It has also been suggested that antioxidants used in combinations work synergistically and are more likely to be effective [37, 38]. Utilizing antioxidants as part of a whole food diet rich in antioxidants is more likely to be effective than an isolated supplement.

## Other Micronutrient Deficiencies

### *Vitamin D*

Low vitamin D levels in children have been found to be associated with increased frequency of asthma exacerbations and increased markers of allergy and asthma severity [45, 46]. A study by Searing demonstrated significant associations between

inhaled corticosteroid use, oral corticosteroid use, and total steroid dose with lower vitamin D levels [47]. They also showed that in vitro, the presence of vitamin D in culture restored the immunosuppressive function of dexamethasone, suggesting that vitamin D supplementation might potentiate the anti-inflammatory function of corticosteroids in asthmatic patients.

Relationships between $25(OH)D_3$, the asthma control test (a standardized tool to assess asthma control), spirometry, corticosteroid use, and exacerbations were examined in a recent investigation [48]. Twenty-two of 36 children with severe therapy-resistant asthma underwent fiberoptic bronchoscopy, bronchoalveolar lavage, and endobronchial biopsy with assessment of airway inflammation and remodeling. Higher serum vitamin D levels were associated with better asthma control. Lower $25(OH)D_3$ levels seen in children with severe therapy-resistant asthma were associated with increased airway smooth muscle mass and worse asthma control and lung function. The authors conclude that detecting vitamin D deficiency in severe, therapy-resistant asthmatics may have important implications in treatment.

Vitamin D-deficient asthmatic children treated with inhaled corticosteroids may have poorer lung function. A recent study aimed to look at whether vitamin D levels modulate the effects of inhaled corticosteroids on a clinical level. In this investigation that involved data from the Childhood Asthma Management Program (CAMP), they found that those who were deficient in vitamin D (levels $\leq$20 ng/mL), showed less improvement in pre-bronchodilator forced expiratory volume in 1 s (FEV1) after 1 year of treatment with inhaled corticosteroids than children with sufficient levels of vitamin D. The investigators suggested that if vitamin D levels are low in asthmatic children on inhaled corticosteroids, supplementation with vitamin D should be considered [49].

Despite these emerging data, vitamin D supplementation for asthma still remains a matter of debate. It has been suggested that these data do not necessarily demonstrate that vitamin D enhances response to inhaled corticosteroid therapy and that the question of whether or not therapeutic use of vitamin D will be beneficial in asthma either as primary therapy or as adjunctive therapy to inhaled corticosteroids can only be answered with a prospective, blinded, randomized, placebo-controlled trial [50].

## *Vitamin B6*

Vitamin B6 may have an anti-allergy effect by its effect on inhibiting histamine as shown in vivo and in vitro. There is laboratory evidence that low vitamin B6 levels are common in patients with asthma with mean circulating vitamin B6 concentration 42–65 % lower in asthmatics versus healthy control. Low vitamin B6 has also been associated with theophylline use [51]. Supplementation with vitamin B6 resulted in improvement in children and adults with asthma but was not beneficial for steroid-dependent asthmatics [52]. Vitamin B6 supplementation may increase magnesium requirements, so magnesium may need to be given along with vitamin B6 [25].

**Table 7.1** Some micronutrient deficiencies which may be seen in asthma

| Micronutrient deficiency | Etiology | Benefits |
|---|---|---|
| Vitamin B12 | Antacids/acid blockers<br>Sulfite-sensitive asthmatics have decreased sulfite oxidase activity | Promotes nonenzymatic oxidation of sulfites |
| Vitamin B6 | Theophylline[a] | Anti-allergy effect (inhibits mast cell degranulation in vitro) |
| Vitamin D | Dietary, lifestyle<br>Corticosteroid use? | Inhibits smooth muscle proliferation; increases glucocorticoid bioavailability in bronchial smooth muscle cells |
| Magnesium (in erythrocytes) | Low intake; beta-adrenergic agonists; theophylline; glucocorticoids; epinephrine | Relaxes bronchial smooth muscles; anti-inflammatory; decreased responsiveness to histamine |
| Selenium | Low intake[b] | Affects immune system (promote differentiation into Th1)[c] |
| Zinc | Low intake[b] | Affects immune system (promote differentiation into Th1)[d] |
| Magnesium | Low intake[b] | Relaxes bronchial smooth muscle; anti-inflammatory; decreased responsiveness to histamine |

[a]Shimizu T, Maeda S, Arakawa H, Mochizuki H, Tokuyama K, Morikawa A. Relation between theophylline and circulating vitamin levels in children with asthma. Pharmacology. 1996;53(6):384–9

[b]Norton RL, Hoffmann PR. Selenium and asthma. Mg, selenium, zinc are depleted in refined flour. Mol Aspects Med. 2012;33:98–106

[c]Guo CH, Liu PJ, Hsia S, Chuang CJ, Chen PC. Role of certain trace minerals in oxidative stress, inflammation, CD4/CD8 lymphocyte ratios, and lung function in asthmatic patients. Ann Clin Biochem. 2011;48:344–51

[d]Sprietsma JE. Zinc-controlled Th1/Th2 switch significantly determines development of diseases. Med Hypotheses. 1997;49:1–14

## *Magnesium*

There is evidence that children with higher serum magnesium concentrations are less likely to have asthma [53]. Adults who received oral Mg supplements showed improvement in objective measures of bronchial reactivity to methacholine and peak expiratory flow rate and in subjective measures of asthma control and quality of life [54]. Table 7.1 shows micronutrient deficiencies that may be associated with asthma.

## Diets and Asthma

### *Antioxidant Foods*

Intake of antioxidants may be lower due to dietary changes that have occurred in the modernized world (see previous section), and people may be more susceptible to oxidant attack and airway inflammation [26]. Adults whose dietary intake were low in vitamin C and manganese were associated with more than a fivefold increase in bronchial reactivity as measured by methacholine challenge. Low intake of magnesium was also associated with increase bronchial reactivity, and those with low zinc intake had more atopy and asthma symptoms [55]. Flavonoids, contained in many fruits and vegetables, may reduce asthma inflammation through their antioxidant, anti-allergic, and anti-inflammatory properties (e.g., flavonoids are scavengers of nitric oxide) and can inhibit the release of histamine and modulate arachidonic acid metabolism and production of cytokines [40, 56]. It was demonstrated that in subjects aged 16–50 years, asthma is less common and less severe in those who consume more dietary flavonoids contained in apples and red wine.

The limitations in studying antioxidant foods and its effect on asthma include difficulties in quantifying the intake of nutrients in the diet; in measuring the concentrations of nutrients in the blood; and reverse causation (patients with asthma and allergic diseases can vary their diet) as well as other confounders.

### *Fruits and Vegetables*

Vegetables and fruits contain antioxidants and phytochemicals as well as fiber. There is convincing evidence for reduced risk of developing chronic diseases such as hypertension, heart disease, stroke, and diabetes mellitus by increasing its consumption. There is evidence that lower consumption of fruits, vegetables, and minerals appear to be associated with higher risk of asthma as well [40]. Recent reviews have shown that increasing consumption of vegetables and fruits may contribute to the prevention of asthma although data is variable and there are not enough longitudinal studies [4, 57].

The majority of studies on fruits and vegetables have been indicative of a protective effect on asthma with highest consumption of fruits in children showing protective effect in the prevention of asthma symptoms [41]. A recent investigation of diet quality in children 11–14 years old and asthma showed that vegetable intake is inversely associated with allergic asthma and moderate/severe airway hyperresponsiveness [58].

### *Fats (Ratio of Polyunsaturated to Saturated)*

Another food component that is hypothesized to contribute to asthma is an increased consumption of omega-6 polyunsaturated fats (PUFA) in proportion to omega-3 PUFAs. Omega-6 fats are found largely as linoleic acid in foods such as margarine

and vegetable oils and are thought to promote a proinflammatory state. Omega-3 fats are anti-inflammatory, so the Western diet which has a higher ratio of omega-6 to omega-3 favors an inflammatory airway environment.

A prospective birth cohort study of 2,602 children in Australia investigated whether childhood asthma was associated with the ratio of omega-6 to omega-3 fats in the diet. They found evidence to promote a diet with increased omega-3 and reduced omega-6 fats to protect children against symptoms of asthma [59]. Diets containing the fatty acids gamma-linolenic acid (GLA) and eicosapentaenoic acid (EPA) decrease leukotriene synthesis. A study evaluated their impact on asthma management and quality of life by looking at adult subjects consuming a medical food emulsion containing GLA and EPA. This study showed improvement in quality of life and decreased reliance on rescue medication [60]. But not all interventional studies using dietary supplements of antioxidants and *n*−3 PUFA consistently show clinical benefit for asthma. There is increasing evidence that the benefit of these nutrients is present when consumed as part of a whole diet. A Mediterranean diet is an example of consuming such nutrients in the form of whole foods (see below).

## *Fish Oil*

Fish oils are an excellent source of omega-3 PUFAs. Epidemiological studies suggest that a diet high in marine fatty acids (fish oil) may have beneficial effects on inflammatory conditions such as cardiovascular disease, rheumatoid arthritis, and possibly asthma. Although there are studies that suggest that fish oil supplements could benefit asthma [61], a Cochrane review in 2012 [62] concluded that there was no improvement in asthma with fish oil supplement.

## *Effects of a Proinflammatory Diet*

The hypothesis that systemic inflammation results in airway hyperresponsiveness would lead us to the question of whether an anti-inflammatory diet (see Chap. 2) along with reduction of excess body fat would significantly impact risk of asthma. There is evidence that inflammatory changes in the airways can be induced by what we eat. A high-fat meal has been shown to augment neutrophilic airway inflammation and also suppress bronchodilator recovery in asthma [19, 63]. Therefore, a high-fat diet may contribute to chronic airway inflammation. This is in line with the recent study showing increased risk of severe asthma with high consumption of fast foods which is high in trans-fats [64]. Fast foods lack much of the nutrients present in vegetables and fruits and is high in omega-6 PUFAs and added sugars. Since this type of food has become increasingly prevalent in our present society, we should be concerned with the possible effects of high consumption of these by individuals with asthma. In this recent large scale study (The Phase Three of the International

Study of Asthma and Allergies in Childhood), there was an increased risk of severe asthma (as well as severe eczema and rhinoconjunctivitis) in adolescents and children who consumed fast food ≥3 times per week, and conversely, there was a potential protective effect associated with consumption of fruit ≥3 times per week.

### *Mediterranean Diet*

Many studies have shown the health benefits of Mediterranean diet (see Chap. 2) for other chronic inflammatory conditions such as cardiovascular disease and rheumatoid arthritis. Recent studies have emerged showing that adults who adhered to the Mediterranean diet had improved asthma control [65]. A number of recent studies also showed that adherence to a Mediterranean diet was associated with decreased risk of asthma symptoms in children as well [66]. For example, a cross sectional study involving 700 Greek children showed that greater adherence to a Mediterranean diet was inversely associated with ever had wheeze ($p=0.001$), exercise wheeze ($p=0.004$), ever had diagnosed asthma ($p=0.002$), and with any asthma symptoms ($p<0.001$) [67]. Adherence to the Mediterranean diet was shown to be associated with lower risk of asthma in both urban and rural areas. Since urban environment seems to increase the likelihood of asthma, adherence to the Mediterranean diet seems to mitigate this and offer protection [68].

In summary, a Mediterranean diet is a diet with no known risk and should be encouraged in individuals with asthma.

### *Maternal Diet—Does Dietary Intervention During Pregnancy Reduce the Likelihood of Childhood Asthma?*

It is known that environmental factors affect gene expression and manifestation of disease. Early fetal exposures to nutrition and other environmental factors may program organ development and future development of disease. Maternal diet may be a significant factor in the development of the fetal airway and immune system. There is a prospective cohort study from a Mediterranean island involving pregnant women presenting for antenatal care over a 12-month period. A reduced risk of wheeze and atopy among children at age 6.5 years was observed in those whose mothers had a high adherence to a Mediterranean diet during pregnancy [69]. High consumption of fruits, vegetables, and antioxidants during pregnancy was shown to decrease the risk of wheeze and eczema in the offspring aged 16–24 months [70].

The effects of individual nutrient deficiencies have been looked at also. Deficiency of vitamin D during pregnancy is associated with higher risk of asthma [71]. Mothers consuming high levels of vitamin D in foods while pregnant reduced the risk of their offspring developing asthma and allergic rhinitis at age 5 years [72]. Cord-blood levels of 25(OH)D were inversely associated with wheeze throughout

early childhood but had no association with incident asthma [73]. Previous studies have shown that high-dose vitamin D supplementation can increase risk of asthma, so further studies are needed to clarify ideal supplementation dosage.

There is evidence for beneficial association between the intake of vitamin E during pregnancy as well, and a reduction of the risk of wheezing at age of 2 years [74]. Low levels of zinc in the diet of women during pregnancy were associated with an increased likelihood that their children would develop wheezing and asthma in childhood [75]. Deficient intake of selenium as well as zinc have also been shown to be associated with higher childhood asthma prevalence, as has increased dietary ratio of omega-6:omega-3 PUFA during pregnancy. So there is definitely a need to explore further the potential of dietary intervention during pregnancy to reduce the likelihood of childhood asthma [44].

## Summary

There is no "magic bullet": combination of foods or supplements that works for all asthmatics. Determining if and what foods/micronutrients are beneficial or harmful in asthma is a complex issue. There are other factors in asthmatic patients, including food allergies, gastroesophageal reflux, and potential food–drug interactions, that contribute to the severity of their symptoms. The method of foods prepared is also an important issue, and this is generally not addressed in these investigations (for example, antioxidants of vegetables lose much of their antioxidant properties if boiled). While it can be beneficial to look for micronutrient deficiencies and intervene with an individual supplement, it may be more effective when the supplement is taken in concert with other supplements and along with a healthier whole food diet.

For many reasons involving the complexity of these studies, studies of nutrition in asthma are not always consistent in their findings, but most would agree that nutrition is likely to be an important contributing factor in asthma. Further investigation in this field needs to continue as it has potential to be a significant non-pharmaceutical intervention that could add to current asthma therapy.

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# Chapter 8
# Obesity, Sleep, and Pulmonary Disease in Children

**David Gozal and Leila Kheirandish-Gozal**

**Keywords** Obesity • Lung function • Spirometry • Sleep apnea • Asthma • Wheezing • Inflammation • Lung volumes • Airway function

**Keypoints**

- There is an association between obesity and respiratory conditions such as asthma as well as sleep-disordered breathing.
- Obesity is associated with impaired lung function even among healthy children, and the obese child is always at increased risk for development of respiratory complications during any challenging situation.
- Sleep disorders can either promote the onset or aggravate existing obesity.
- Although adenotonsillectomy is curative in some obese children with obstructive sleep apnea syndrome (OSAS), there is a high likelihood that residual OSAS will occur, so postoperative reevaluations should be considered.

## Introduction

The prevalence and severity of overweight in children and adolescent is dramatically increasing worldwide. For example, the overall 2007 prevalence of overweight and obesity in children in the United States ranged from 20 to 35 % among the various states (Fig. 8.1; [1]). The increase in both the prevalence of obesity and its severity

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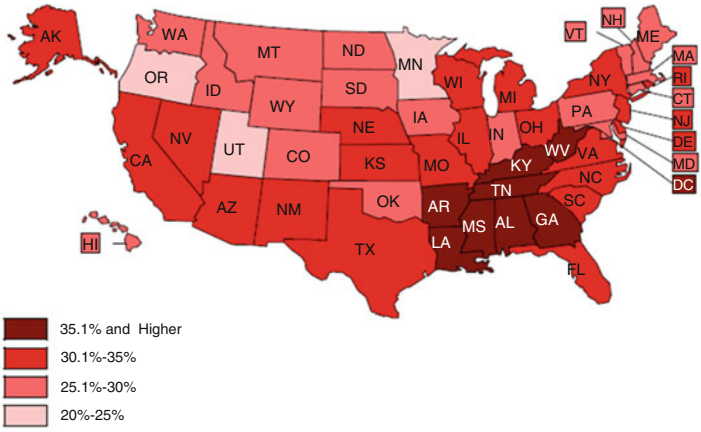


| Age (years) | 1963-65<br>1966-70 | 1971-74 | 1976-80 | 1988-94 | 1999-2000 | 2001-02 | 2003-04 |
|---|---|---|---|---|---|---|---|
| 2-5 | - | 5% | 5% | 7.2% | 10.3% | 10.6% | 13.9% |
| 6-11 | 4.2% | 4% | 6.5% | 11.3% | 15.1% | 16.3% | 18.8% |
| 12-19 | 4.6% | 6.1% | 5% | 10.5% | 14.8% | 16.7% | 17.4% |

**Fig. 8.1** Childhood overweight and obesity trends in the United States in 2007. Obesity is defined as body mass index (BMI) at or above the 95th percentile of the 2,000 Centers for Disease Control and Prevention BMI-for-age growth charts. Children with BMI between the 85th and 95th percentile are classified as overweight. BMI is calculated as weight in kilograms divided by the square of height in meters. Only children age 10–17 years are included in the map data. *Sources*: http://www.ncsl.org/issues-research/health/childhood-obesity-trends-state-rates.aspx and http://www.ncsl.org/issues-research/health/obesity-statistics-in-the-united-states.aspx

in children has also spurred a parallel increase in the prevalence of obesity-associated morbidities, such as type 2 diabetes mellitus and insulin resistance, dyslipidemia, systemic hypertension, atherosclerosis, nonalcoholic fatty liver/steatohepatitis, depression, and decreased quality of life, all of which used to be rare pediatric conditions even as recently as a decade ago. These short- and long-term morbid consequences of obesity, and more particularly the clustering of respiratory, metabolic, and cardiovascular risk factors in the context of obesity, further stress the importance of increasing the public awareness to this problem, and prioritization of the overweight child and adolescent as a major public health concern and as an emergency.

Among the multiple morbidities associated with obesity, the respiratory system is not immune to its adverse and deleterious effects. In this chapter, we will review the following topics:

1. The effects of obesity on lung function in children
2. To explore potential contributions of obesity to an asthmatic phenotype
3. The complex interrelationships between sleep and obesity
4. The impact of obesity on sleep-disordered breathing and hypoventilation in children

## Obesity and Lung Function in Children

Obesity can be associated with impaired lung function even among healthy children (see Fig. 8.2). Although the mechanisms have not been extensively investigated in children, there is little doubt that the effect of obesity on respiratory function is likely to be determined by the distribution of adipose tissue mass. Visceral and subcutaneous abdominal and thoracic fat are likely to have direct effects on the downwards movement of the diaphragm and on chest wall properties. In addition, visceral fat is a metabolically active tissue depot that can therefore contribute and promote the formation and propagation of low-grade systemic inflammation in obesity, thereby further potentially compromising bronchial and alveolar functions (Fig. 8.2). Adipose tissue will also accumulate as pericardial fat, which, when combined with obesity-associated increase in the size of the heart and major blood vessels, can further reduce the overall capacity of the thoracic cavity.

Intra-abdominal pressures and pleural pressures are increased in obese subjects compared to non-obese and may even exceed atmospheric pressures at functional

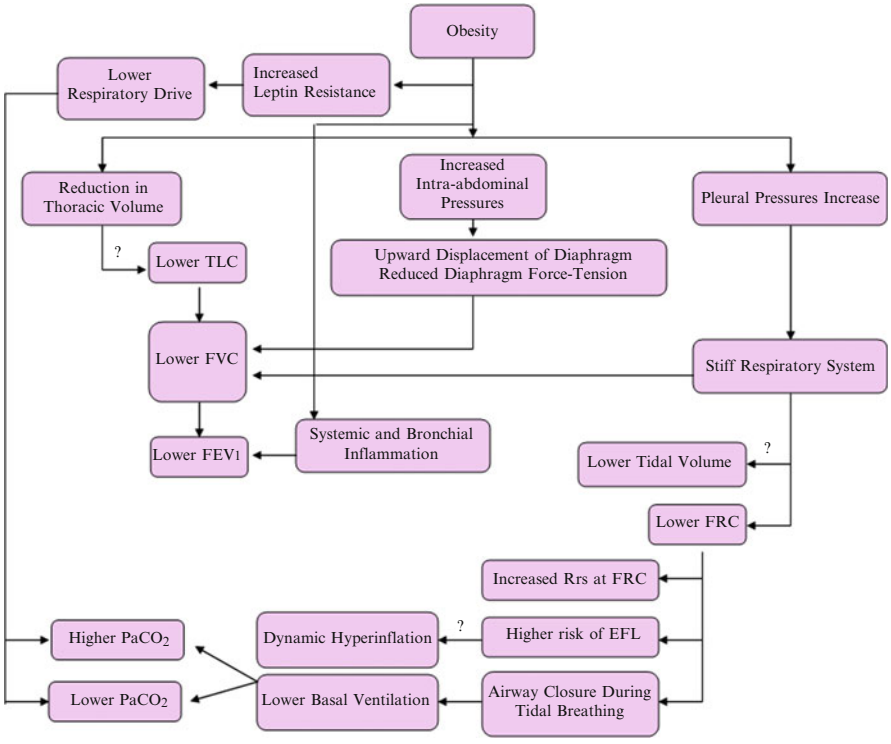


**Fig. 8.2** Effects of obesity on lung function and potential mechanisms. *EFL* expiratory flow limitation, *FRC* functional residual capacity, *Rrs* respiratory system resistance, *TLC* total lung capacity

residual capacity (FRC) in some patients [2, 3], even if some compensatory increases in passive tension in the diaphragm in response to increased intra-abdominal pressures may occur. Changes in the properties of the chest wall with increased wall stiffness have also been proposed and can contribute to some of the alterations in respiratory system mechanics associated with obesity. Obesity has been consistently associated with reductions in the compliance of the total respiratory system, likely due to reductions in the compliance of the chest wall and lungs. Although some studies have reported that lung compliance may be is normal in obese subjects, it is usually decreased, with lung compliance being exponentially associated with BMI [4–6]. The decreased lung compliance in obesity may originate from varying contributions by increased pulmonary blood volume, closure of dependent airways resulting in small areas of atelectasis, and increased alveolar surface tension due to a reduction in FRC. The above-described changes in respiratory mechanics will lead to changes in breathing patterns and resting lung volumes placing any obese child at a disadvantage from the respiratory standpoint (Fig. 8.2). More rapid and shallower patterns of tidal breathing in response to the elastic mechanical loading will manifest more readily during physical activity rather than at rest, and obese subjects will preferentially increase their respiratory frequency. When bronchoconstriction occurs (see below), there is an even more pronounced decrease in tidal volumes in overweight or obese children. However, we should emphasize that most of these changes are seen in severe obesity and are unlikely to be apparent in most healthy obese children except when the respiratory system is challenged, such as during exercise or bronchoconstriction [7–12]. Increased respiratory system stiffness will adversely affect resting lung volumes such that FRC is very commonly reduced in obesity [13]. With increasing severity of obesity, the reduction in FRC may become so extreme that the FRC values may approach those of residual volume (RV), thereby creating a situation in which a negligible expiratory reserve volume (ERV) is present [14, 15]. Because the effects of increasing BMI on total lung capacity (TLC) and RV are more modest, small decreases in TLC and RV emerge, and therefore, the RV/TLC ratios usually remain within the normal range. Low operating lung volumes (i.e., low FRC) that are due to reduced respiratory system compliance will increase airway resistance and manifest as expiratory flow limitation, alterations in the distribution of ventilation, and abnormal gas exchange [16–19]. In turn, the presence of expiratory flow limitation during tidal volume breathing promotes the generation of intrinsic positive end-expiratory pressure (PEEPi) and dynamic hyperinflation, particularly when obstructive airway disease such as asthma is present. Mild hypoxemia and increased alveolar–arterial oxygen difference are occasionally reported even in eucapnic obese individuals. Reduction in oxygenation is unlikely elicited by abnormalities of gas transfer since most studies suggest that the diffusion capacity for carbon monoxide (DLCO) is normal, even in morbid obesity [20, 21]. However, obesity is associated with peripheral and central leptin resistance, which in turn leads to reduced bioavailability of leptin, and the latter, by virtue of its stimulant effects on central respiratory control networks, has been implicated in diminished hypercapnic responses and in

mechanisms promoting alveolar hypoventilation in obesity [22–26]. Indeed, leptin is a potent respiratory stimulant, which in addition to its central chemoreceptor modulatory properties, appears to affect overall respiratory drive and also modulate peripheral chemoreceptor activity [27–29]. Thus, compensatory mechanisms that would need to be more effectively recruited in the context of mild initial gas exchange abnormalities in obese children may prove ineffectual and further exacerbate the progression of respiratory disturbance.

The effect of obesity on lung function is often described in terms of a restrictive rather than obstructive pattern, characterized by reduction in TLC and vital capacity. The mechanisms for the reduction in TLC in the obese are not well understood but may in fact be due to reduced intrathoracic volume since respiratory muscle strength and maximum inspiratory and expiratory pressures appear to be preserved in obesity. A reduction in TLC, in the absence of any changes in residual volume, necessarily points to a reduction in vital capacity (VC). Consistent with a mild restrictive pattern of lung function in the obese, there is a progressive linear decrease in VC with increasing BMI that parallels the decrease in TLC. Similarly, increasing BMI is also associated with a decrease in both FEV 1 and FVC, but such effects tend to be relatively minor. It should be pointed out, however, that the adverse effects of obesity on spirometric values increase with increasing duration of obesity and may reflect the cumulative effects of systemic inflammatory processes within the respiratory system, including remodeling [30]. As would be anticipated, improvements in lung function will occur after implementation of weight reduction [31]. In contrast to the relative rarity of dyspnea at rest, breathlessness during exercise is a very common complaint among obese children when compared to normal weight controls. However, increased symptoms that emerge during physical activity in the obese are most likely related to the increased metabolic costs of motion in the context of heavier limbs and abnormal respiratory mechanics, rather than be the result of deconditioning [32–35].

## Potential Contributions of Obesity to an Asthmatic Phenotype

Among pre-pubertal children, obesity has been associated with greater chest symptoms such as breathlessness and cough [36–39], as well as with more pronounced objectively defined exercise-induced bronchospasm [40, 41]. Despite variable reported relationships between obesity and spirometric lung volumes in children, whereby elevated BMI has been associated with either increased, decreased, or unchanged spirometric lung volumes (see above), there is evidence of a strong link between obesity and airflow obstruction. In healthy older post-pubertal children, however, the evidence appears to be more consistent with obesity-related reductions in spirometric lung volumes and increases in airflow obstruction [42, 43], suggesting that the sustained duration of obesity leads to progressive undermining of lung function and increased hyper-reactivity of the airways, potentially culminating in the emergence of asthma [30].

Although explanations for obesity-associated patterns of lung dysfunction in children are lacking, the impact of obesity on growth itself, and the modifying influences of gender, race, socioeconomics, genetics, and other obesity-related comorbidities remain to be defined. Notwithstanding, there is little doubt that the presence of an obese phenotype adversely affects the prevalence and severity of asthma in children, and that the treatment of asthma in obese children is more complex, requires more intensive therapy, and is fraught with increased likelihood for adverse outcomes [44–52].

## Complex Interrelationships Between Sleep and Obesity

In recent years, overall quite compelling evidence on the potentially important role of sleep and sleep disorders in either promoting the onset or aggravating existing obesity and its complications has emerged. Conversely, the role of obesity in the pathophysiology of sleep disorders, particularly sleep-disordered breathing, is becoming increasingly apparent (Fig. 8.3). Thus, the existence of bilateral and mutual interactions linking sleep and obesity in children is worthy of exploration, particularly since additional and complex links between obesity, sleep, sleep apnea, and asthma are being uncovered (Fig. 8.3; [53–59]).

The progressive reductions in sleep duration and increased sleep irregularity over the last century have been accompanied by a marked surge in the prevalence of childhood obesity, as described in the beginning of this chapter. An increasingly growing body of evidence suggests the existence of a strong association between sleep duration and obesity. However, associations between BMI and time of bedtime or with bedtime irregularity or even with technology in the bedroom have also been proposed as important contributors to the increases in obesity rates.

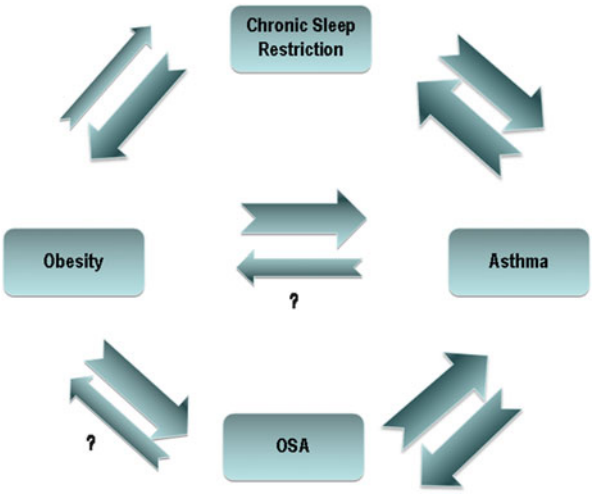


**Fig. 8.3** Interactions between sleep, obesity, asthma, and obstructive sleep apnea

Inadequate amounts of sleep as well as circadian alterations in food consumption and rhythmicity lead to alterations in some of the neuropeptides that regulate appetite and ultimately promote obesogenic behaviors. Specifically, increased levels of ghrelin, altered levels of leptin, reduced central biological activity of orexin, and other complex alterations in hypothalamic pathways of metabolic homeostasis have all been implicated by experimentally induced or existing sleep perturbations or by abbreviated sleep duration and lead to increased food intake.

Most studies to date support the presence of a strong association between sleep duration and obesity, and the magnitude of such association is particularly prominent in children and adolescents and declines over time [60, 61]. Although some degree of predisposition for the presence of such association appears to be necessary, particularly considering that sleep-associated changes in BMI appear to be primarily affecting those children whose BMI is already elevated [62] or children with specific genetic background [63], the cumulative findings from a multitude of studies support that obesity and shorter/irregular sleep patterns are interdependently associated and confer incremental risk for cardiovascular, inflammatory, and metabolic risk factors [64–68].

## Impact of Obesity on Sleep-Disordered Breathing and Hypoventilation in Children

The obstructive sleep apnea syndrome (OSAS) in children is characterized by recurrent events of partial or complete upper airway obstruction during sleep, resulting in disruption of normal gas exchange (intermittent hypoxia and hypercapnia) and sleep fragmentation [69–71]. The clinical spectrum of obstructive sleep-disordered breathing includes frank OSAS (traditionally defined as an obstructive apnea–hypopnea index (AHI) > 1–2 events/h total sleep time), the upper airway resistance syndrome (UARS; traditionally associated with low AHI and globally normal gas exchange patterns, but evidence for increased respiratory-related arousals, i.e., sleep fragmentation), and the low end of the spectrum, primary or habitual snoring (i.e., habitual snoring in the absence of apneas, gas exchange abnormalities, and/or disruption of sleep architecture). The usual nighttime symptoms and signs of OSAS in children include snoring, noisy breathing, snorting episodes, paradoxical chest and abdominal motion, retractions, witnessed apnea, difficulty breathing, cyanosis, sweating, and restless sleep. Daytime symptoms can include mouth breathing, difficulty to wake up, moodiness, nasal obstruction, daytime sleepiness, hyperactivity, and cognitive problems. Since its initial characterization in 1976 by Guilleminault and colleagues [72], this complex, yet relatively frequent disorder is now recognized as a major public health problem in the pediatric age range. Indeed, the prevalence of OSAS in children is currently estimated at up to 2–4 % of children [70], with habitual snoring during sleep, the hallmark indicator of increased upper airway resistance, being much more frequent in children and potentially affecting up to 27 % of children [69–71].

The pathophysiological mechanisms underlying the occurrence of obstructive sleep apnea in children involve a dynamic imbalance in upper airway function that is particularly manifest during sleep. In this setting, a combination of alterations in structural and anatomical characteristics (e.g., enlarged tonsils and adenoids), protective reflexes, and neuromotor abnormalities of the upper airway are all implicated to a greater or lesser degree in any given particular child, such that isolated contributions of any particular factor are rarely if ever sufficient to elicit the occurrence of OSAS [73, 74]. Indeed, there are children with "kissing tonsils" who do not have OSAS, and those with minimal if any upper airway lymphadenoid tissue hypertrophy who suffer from severe OSAS.

It has become apparent that the contribution of obesity to increased risk of OSAS is rather unequivocal in children even if prospective large-scale cohort studies examining the risk accrual to OSAS in obese children are still lacking [75–80]. Indeed, at any level of OSAS severity, the size of adenoids and tonsils required to achieve that level of breathing disturbance during sleep is smaller in obese children than in age-, gender-, and ethnicity-matched non-obese children [81–84]. Furthermore, for every increment in BMI by 1 kg/m$^2$ beyond the mean BMI for age and gender, the risk of OSAS appears to be increased by 12 % in adolescents [85]. The possibility that obesity promotes enhanced proliferation of lymphadenoid tissues in the upper airway has been invoked and could further interact with additional effects of adipose tissue deposition in the upper airway tissues to promote increased upper airway collapsibility [86, 87]. Hence, childhood obesity is undoubtedly associated with a higher risk for development of OSAS, with the relatively large differences in reported prevalence rates across the various cross-sectional series being most likely the result of differences in cohort selection (mostly clinical referral samples), ethnic predisposition, and heterogeneity in the diagnostic criteria used for both OSAS and obesity.

Although the clinical presentation of a child with OSAS is usually vague and requires increased awareness of the primary care physician, the implications of OSAS in children, especially obese children, are broad and sometimes complex. If undiagnosed or alternatively if treated late, pediatric OSAS can lead to a wide array of morbid consequences that affect multiple end-organ systems, some of which may be irreversible [88–90]. Taken together, it is clear that there is an additive or even synergistic interaction between OSAS and obesity regarding both the pathophysiology and mechanisms leading to disease causation and consequences. It is highly likely that a critical component of such pathways revolves around inflammation [91–98].

Based on aforementioned considerations, one would expect that surgical removal of tonsils and adenoids in obese children would yield lesser improvements in OSAS compared to non-obese children. Mitchell and colleagues showed that adenotonsillectomy in obese children resulted in significant reductions of their respiratory disturbance indices with complete resolution of OSAS in 46 % of patients [99]. However, in a series of studies since then, it has become quite apparent that obesity is a major determinant for adverse surgical outcome with marked decreases in the proportion of cases in which there is normalization of the postoperative sleep study, leading to the recommendation of a post-surgical sleep study in

obese children [100–104]. Taken together, although adenotonsillectomy may be curative in some obese children with OSAS and should remain the first line of treatment, there is a high likelihood that residual OSAS will occur, and therefore, postoperative reevaluations seems appropriate [70, 71]. Furthermore, obese children with OSAS show an increased incidence of postoperative cardiac and respiratory complications [105–108].

## Obesity Hypoventilation Syndrome

This syndrome, also known as Pickwickian syndrome, is defined as a combination of obesity and awake arterial hypercapnia ($PaCO2 > 45$ mmHg) in the absence of other known causes of hypoventilation. There are only a few reports of children with obesity hypoventilation syndrome [109–112]. Children with obesity hypoventilation syndrome will present with vague symptoms usually excessive daytime sleepiness, fatigue, and/or morning headaches. However, the presence of daytime hypercapnia and hypoxemia may lead to polycythemia, pulmonary hypertension, and to right ventricular failure. Decreased ventilatory responses to hypercapnia and hypoxia are usually found both during sleep and wakefulness. As discussed above, the pathogenesis of the disorder is not fully understood, and may represent a combination of mechanical loading of the respiratory system secondary to extreme obesity in the presence of susceptible individuals who may be predisposed due to genetically determined low sensitivity to chemoreceptor stimulation (see Fig. 8.2). For most of these patients, tonsillectomy and adenoidectomy will not be sufficient to completely resolve the problem, and both weight loss and bilevel positive airway pressure (BiPAP) by nasal mask will be necessary and should be implemented following recently published guidelines [113].

## Summary

The effects and interactions of obesity with the respiratory system are complex and onerous to the preservation of the healthy homeostatic regulation of function. Therefore, the obese child is always at increased risk for development of respiratory complications during any challenging situation, even if respiratory function appears to be preserved under normal conditions. The associations between obesity and asthma as well as with sleep-disordered breathing and the adverse impact of obesity on the morbidity of the latter conditions further reinforce the concept that the obese child should be viewed as a high-risk individual that merits every effort aiming at weight reduction and alleviation of increased adiposity.

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