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# Nutrition, Physiology and Metabolism in Spaceflight and Analog Studies

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# Nutrition, Physiology and Metabolism in Spaceflight and Analog Studies

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# Preface to the Series

The extraordinary conditions in space, especially microgravity, are utilized today not only for research in physical and materials sciences—they especially provide a unique tool for research in various areas of life sciences. The major goal of this research is to uncover the role of gravity with regard to the origin, evolution, and future of life, and to the development and orientation of organisms from single cells and protists up to humans. This research only became possible with the advent of manned spaceflight some 50 years ago. With the first experiment having been conducted onboard Apollo 16, the German Space Life Sciences Program celebrated its 40th anniversary in 2012—a fitting occasion for Springer and the DLR (German Aerospace Center) to take stock of the space life sciences achievements made so far.

The DLR is the Federal Republic of Germany's National Aeronautics and Space Research Center. Its extensive research and development activities in aeronautics, space, energy, transport, and security are integrated into national and international cooperative ventures. In addition to its own research, as Germany's space agency the DLR has been charged by the federal government with the task of planning and implementing the German space program. Within the current space program, approved by the German government in November 2010, the overall goal for the life sciences section is to gain scientific knowledge and to reveal new application potentials by means of research under space conditions, especially by utilizing the microgravity environment of the International Space Station ISS.

With regard to the program's implementation, the DLR Space Administration provides the infrastructure and flight opportunities required, contracts the German space industry for the development of innovative research facilities, and provides the necessary research funding for the scientific teams at universities and other research institutes. While so-called small flight opportunities like the drop tower in Bremen, sounding rockets, and parabolic airplane flights are made available within the national program, research on the International Space Station ISS is implemented in the framework of Germany's participation in the ESA Microgravity Program or through bilateral cooperations with other space agencies. Free flyers

such as BION or FOTON satellites are used in cooperation with Russia. The recently started utilization of Chinese spacecrafts like Shenzhou has further expanded Germany's spectrum of flight opportunities, and discussions about future cooperation on the planned Chinese Space Station are currently under way.

From the very beginning in the 1970s, Germany has been the driving force for human spaceflight as well as for related research in the life and physical sciences in Europe. It was Germany that initiated the development of Spacelab as the European contribution to the American Space Shuttle System, complemented by setting up a sound national program. And today Germany continues to be the major European contributor to the ESA programs for the ISS and its scientific utilization.

For our series, we have approached leading scientists first and foremost in Germany, but also—since science and research are international and cooperative endeavors—in other countries to provide us with their views and their summaries of the accomplishments in the various fields of space life sciences research. By presenting the current SpringerBriefs on neuromuscular physiology, we start the series with an area that is currently attracting much attention—due in no small part to health problems such as muscle atrophy and osteoporosis in our modern aging society. Overall, it is interesting to note that the psycho-physiological changes that astronauts experience during their spaceflights closely resemble those of aging people on Earth but progress at a much faster rate. Circulatory and vestibular disorders set in immediately, muscles and bones degenerate within weeks or months, and even the immune system is impaired. Thus, the aging process as well as certain diseases can be studied at an accelerated pace, yielding valuable insights for the benefit of people on Earth as well. Luckily for the astronauts: these problems slowly disappear after their return to Earth, so that their recovery processes can also be investigated, yielding additional valuable information.

Booklets on nutrition and metabolism, on the immune system, on vestibular and neuroscience, on the cardiovascular and respiratory system, and on psycho-physiological human performance will follow. This separation of human physiology and space medicine into the various research areas follows a classical division. It will certainly become evident, however, that space medicine research pursues a highly integrative approach, offering an example that should also be followed in terrestrial research. The series will eventually be rounded out by booklets on gravitational and radiation biology.

We are convinced that this series, starting with its first booklet on neuromuscular physiology in space, will find interested readers and will contribute to the goal of convincing the general public that research in space, especially in the life sciences, has been and will continue to be of concrete benefit to people on Earth.

Bonn, Germany
September 2014

Günter Ruyters
Markus Braun


DLR Space Administration in Bonn-Oberkassel (DLR)


The International Space Station ISS; photo taken by an astronaut from the space shuttle Discovery, March 7, 2011 (NASA)


Extravehicular activity (EVA) of the German ESA astronaut Hans Schlegel working on the European Columbus lab of ISS, February 13, 2008 (NASA)

# Foreword

After the publication of the first volume of this series on musculoskeletal problems in December 2014, we hereby present the next volume, entitled "Nutrition Physiology and Metabolism in Spaceflight and Analog Studies." Adequate nutrition is certainly of the utmost importance for crew health and mission success in human spaceflight. It is, however, equally important for people on Earth. In both cases, food and nutrition serve multiple roles, including providing a sufficient nutrient supply to ensure the optimal functioning of each cell and each body system, but also with regard to psychosocial interactions, especially in extreme environments.

In fact, the pressure to keep astronauts and people in extreme environments such as Antarctica or in isolation studies healthy and fit gave a significant push to this research topic. Therefore, results from experiments in space and from so-called analog environments such as bed-rest or isolation studies can greatly contribute to the current state of knowledge and have a great impact on human life on Earth.

The list of known nutrients required by the human body is practically endless and probably incomplete. Typically, nutrients are categorized into two types: macronutrients, which are needed in relatively large amounts, and micronutrients, which are needed in very small quantities. In principle, the authors follow the same division, starting by describing the importance of energy, protein, fat, fatty acids, and carbohydrates. This is followed by a chapter on fluid and electrolyte metabolism—focusing on a number of brand-new findings from a recent isolation study on salt metabolism and its consequences for human health. Descriptions of the role of vitamins and minerals, and that of supplements, round out the book.

Each chapter follows the same structure: after a short introduction, the effects of the specific nutrient on physiological systems are described. Each chapter then closes with a summary of the relevance of the described findings for life on Earth.

Especially on the basis of these latter statements, it becomes obvious that research on nutrition physiology in spaceflight and analog studies is just as important for ensuring the well-being and performance of astronauts as it is for the rest of us here on Earth.

Bonn, Germany Günter Ruyters
March 2015

# Contents

# Chapter 1
# Nutritional Requirements in Space

Nutrients are required for the structure and function of every cell and each body system, regardless of the environment. However, changes in environment can have significant effects on nutrient metabolism and requirements. Thus, defining the nutrient requirements for spaceflight and ensuring the provision and intake of those nutrients are primary issues for crew health and mission success.

Microgravity is a unique environment that presents many challenges, from issues associated with weightlessness and unloading, to changes in air composition and pressure, to radiation and associated oxidative damage. Food and nutrition during space travel serves multiple roles, including provision of nutrient supplies to ensure optimal functioning of the many physiological systems and its role in psychological adaptation to extreme environments. Mealtimes may provide the framework for psychosocial interactions, supporting the potential role of nutrients in serving as a countermeasure to ameliorate certain negative effects of spaceflight on the human body. An adequate nutrient supply for space travelers is therefore one of the key requirements for leading a mission to success.

Effects of space travel on many physiological systems raise concerns for long-duration spaceflight (months or years), including deterioration of the musculoskeletal system, increased radiation exposure, diminished immune response, and general depletion of body nutrient stores because of inadequate food supply or intake, nutrient supply during extravehicular activities, and increased metabolism. In short-duration (days or weeks) spaceflight, other physiological systems are of concern, such as the cardiovascular and neurovestibular systems.

The deteriorating effect of spaceflight on the musculoskeletal system is nicely summarized in the first book of this series Blottner and Salanova (2015). The process of acclimatization, as Williams et al. call the adaptation process of healthy astronauts to their physiological and psychological responses to the abnormal spaceflight environment, is rather complex (Williams et al. 2009). For instance, the fluid shift at the beginning of weightlessness, which involves the shifting of body fluid from the lower extremities to the upper body, might cause nasal congestion and changes in taste and smell sensations, leading to a decreased



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appetite early in flight. At the same time, motion sickness, caused by the mismatch between orientation in the spacecraft and the concomitant visual expectation, may lead to nausea, vomiting, and decreased food intake during the first days in space (Clement 2004). This will lead to negative nutrient balance. Fortunately, this effect is transient and normally lasts only 2–3 days. However, other effects may continue which induce insufficient nutrient supply, as described later in this report.

While the International Space Station (ISS) is providing a wealth of research data, many questions remain about the mechanisms as well as potential measures to ameliorate the acclimatization processes to prepare astronauts optimally for either landing on another planet or returning to Earth's environment and gravity.

For optimized nutrient intake, the first step is to define the nutritional requirements for space travelers. Nutritional requirements include the macro- as well as the micronutrient intake. Macronutrients, protein, fat, and carbohydrates, deliver energy to maintain our bodies' mandatory processes, while micronutrients, vitamins and minerals, provide support for the many biochemical processes and elements of tissues and systems in the body.

For space travelers, the recommended intake of nutrients is not as easy to determine as one might expect. Clinical studies are mandatory to derive optimal nutrient intake as well as upper and lower levels of intake for each of the nutrients and for each gender and different age groups. Since insufficient data are available to even develop dietary reference intake levels from clinical studies in space, the recommendations for space travelers are mainly derived from the respective Earth recommendations. More and more studies are carried out to examine the effect of nutrient supply in the microgravity environment. When new data become available from these studies showing that prescribed levels of nutrient intake should be altered, a committee consisting of nutritional scientists from all space agencies responsible for astronauts on the ISS will discuss and agree on the change.

# Chapter 2
# Nutrition in Space

## 2.1 Introduction

The popular perception is that space food is liquid and consists of a formula of easily digested macronutrients such as amino acids, fatty acids, and di- or oligosaccharides, which also contains the micronutrients required to keep a person healthy. A formula diet is different from food for astronauts in space, which sometimes in layman's terms is called "astronaut's diet." A formula diet is developed for people who, mostly because of disease, are not able to chew more solid food adequately or to digest the more complex nutrients from the food so that they can easily be absorbed in the gastrointestinal tract. Formula diets are also intended for patients who might need a huge amount of energy, which cannot easily be provided by regular food components.

Food for astronauts for their stay in space is actually very different (Fig. 2.1). It very much reflects recipes for food on Earth with the exception that it has very strict microbiological constraints. Therefore, aside from its nutritional value, its most important characteristic is the preservation process, so that space food should never provide a risk of food poisoning. To keep astronauts' food safe, the hazard analysis critical control point (HACCP) system was developed by NASA, and it has now been adopted by the food industry globally. This system paves the way for a very secure and high-quality food system that keeps the microbiological content of food very low. Preservation of food for spaceflight is mainly done by thermostabilization or freeze drying. Therefore, food is mainly packed in cans or pouches as illustrated in Fig. 2.1.

Regardless of the kind or source of food, our daily diet provides us with all the macro- and micronutrients that we need for the functioning of our bodies. While not considered nutrients in the purest sense, fluid and dietary fiber are also important nutritional components.

Inadequate nutrient supply can imply either too low or too high levels of intake of nutrients, and either can affect our body and may in the long run even induce



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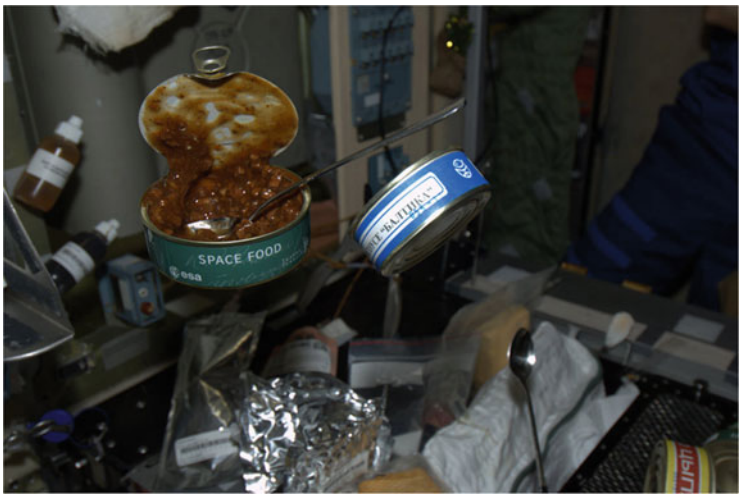


**Fig. 2.1** Space food preserved in cans. The small bottles on the *left* are salt and pepper solutions. ©ESA

diseases. As often seen in the Western world, excess intake of energy leads to positive energy balance, which increases fat mass and can lead to metabolic diseases such as glucose intolerance. Although astronauts rarely have positive energy balances and therefore usually do not gain fat mass (Smith et al. 2009), results from Apollo, Skylab, and Space Shuttle missions show that they nevertheless develop glucose intolerance (Leach and Alexander 1975; Leach and Rambaut 1977) and insulin resistance (Stein et al. 1994).

Usually a difficulty one faces with space missions is the small number of crewmembers available to participate in research. One way to overcome that is to examine further aspects of physiological adaptation of astronauts to microgravity in analog models, situations on Earth that reflect aspects of space travel. Kakurin et al. (1976) demonstrated that in bed rest an angle of −6-degree head-down tilt best mimics the hypokinesia and microgravity-induced blood redistribution characteristic of spaceflight.

However, even in these analog studies, it is very difficult to achieve an adequate sample size for sound scientific experimentation. Unfortunately, there are many situations where a small sample size is hard to avoid, and yet the research is still important to perform. These situations include clinical trials of unique study populations such as astronauts, as mentioned, but also individually tailored therapies, isolated environments, emergencies, public health urgency, restricted or limited resources coupled with an important need, or rare diseases. Although various trial designs and certain statistical analysis techniques improve the quality of trials with small sample sizes, these studies are still prone to variability and are at risk of failing to demonstrate the effectiveness of an intervention. Generation of data from larger sample sizes achieved by combining single, smaller data sets can

therefore improve the interpretation of data, but only if the experiments are adequately standardized (Institute of Medicine 2001).

We describe in the following report how metabolic research is carried out in microgravity and in analog models. We also present a summary of the nutrient supply in space missions, which might be deficient in certain nutrients. In addition, we provide evidence that during space missions, inadequate nutrient supply may exacerbate and optimized nutrient supply may ameliorate the physiological adaptation processes in microgravity.

## 2.2 Ground-Based Research

Data pertaining to details of the effects of the space environment on human physiology are limited and difficult to generate. Flying in space is very expensive, and most space agencies and institutes currently have severely limited space life sciences budgets. In addition, space experiments are often technically difficult to devise and perform, as the original researcher is remote from the test subject and the absence of gravity can make the design of experiments quite challenging. Additionally, the number of astronauts and cosmonauts flown each year is small, and the number of experiments each crewmember can participate in is subject to time and other resource constraints. Thus, conclusions must often be drawn from small numbers of data points. Performing a flight analog experiment with human test subjects, such as head-down-tilt bed rest, is also expensive and time consuming; therefore, obtaining a large number of test subjects is difficult in analog studies, although access to test subjects, hardware, and testing is indeed easier than it is in space.

One way to design experiments with small numbers of subjects and still receive statistically sound and reliable results is to standardize study conditions in such a way that the studied effect is not influenced. The European Space Agency (ESA) has developed a standardization plan that will be applied to every study ESA is sponsoring. The same is true for the bed rest studies that were carried out at NASA's Flight Analog Research Unit at the University of Texas Medical Branch at Galveston. The prescribed standards are in particular applied to environmental aspects of the facility in which the trials are taking place and to the constraints on subjects (e.g., sleep, hygiene) as well as to the dietary aspects of the studies. By using this approach and applying the appropriate statistical analyses, researchers can draw conclusions from a set of experiments carried out over several years. This is not only important for gathering sufficient data but also allows researchers to draw conclusions from a sufficient sample size and to publish the data to make them accessible to the public.

### 2.2.1 Food Selection in Spaceflight and Analog Studies

To avoid any impact of inadequate macro- and micronutrient supply on the human body, standards for nutrient intake are defined by respective nutrition experts or expert committees, taking into account particular circumstances in spaceflight and analog studies. These levels of nutrient intake have to be met on either a weekly basis or, depending on experiment requirements, on a daily basis to avoid any effect of dietary intake on experiment results. Ensuring the prescribed standardized and controlled nutrient intake in a lab is quite cumbersome and requires the appropriate expertise of a registered dietitian as well as a metabolic kitchen.

### 2.2.2 Spaceflight

Performing metabolic experiments on board a space station requires standardized nutrient intake. The meals are planned some time in advance by a registered dietitian together with the principal investigator of the experiment. The dietitian will match the preferences of each participant with the experiment requirements. As an example, the 5-day menu of space food for an experiment to investigate the effects of sodium intake on body fluid regulation and bone turnover is shown in Fig. 2.2. The food for the prescribed meals is packed into containers for the experiment, and the containers are labeled accordingly. The astronaut, as planned, will consume the food on the appropriate experiment days (Table 2.1).

### 2.2.3 Analog Studies: Head-Down Tilt Bed Rest

In analog studies such as bed rest, the procedure is different. The food and beverages used are standard commercially available food items. For nutrient intake analysis, data are obtained from the manufacturer's information, from tables of nutrient content, or from direct chemical analysis. The test subjects are asked which kind of food and beverages they are allergic to or very much dislike. This needs to be taken into account since one prerequisite of a metabolic experiment is to have a standardized, day-by-day, relatively constant nutrient intake. To guarantee the appropriate intake, the test subjects need to be able to consume the food and beverages provided. The certified dietitian must therefore define test subjects' diets according to the predefined nutrient needs as well as their respective preferences. The meal plan of each individual test subject has then to be prepared in the metabolic kitchen (Figs. 2.3 and 2.4).

| Meal | DAY L_1 | DAY L_2 | DAY L_3 | DAY L_4 | DAY L_5 |
|---|---|---|---|---|---|
| Breakfast | Vanilla Breakfast Drink (B) FB62 | Chocolate Breakfast Drink (B) FB61 | Chocolate Breakfast Drink (B) FB61 | Chocolate Breakfast Drink (B) FB61 | Chocolate Breakfast Drink (B) FB61 |
| | Orange Drink (B) FB14 | Lemonade (B) FB13 | Orange Drink (B) FB14 | Lemonade (B) FB13 | Orange Juice (B) FB55 |
| | Granola (R) FR15 | Granola (R) FR15 | Granola (R) FR15 | Berry Medley ® FR64 | Oatmeal w/ Brown Sugar FR25 |
| | Blueberry Raspberry Yoghurt (T) FT77 | Fruit Cocktail P (T) FT14 | Fruit Cocktail P (T) FT14 | Blueberry Raspberry Yoghurt (T) FT77 | Fruit Cocktail P (T) FT14 |
| | | | | Granola Bar (NF) FS09 | |
| | | | | | |
| Lunch | Lemonade (B) FB13 | Lemonade (B) FB13 | Apple Cider (B) FB52 | Apple Cider (B) FB52 | Strawberry Drink (B) FB17 |
| | Chicken w/ Corn and Black Beans (T) FT81 | Orange Pineapple Drink (B) FB16 | Beef Stew (T) FT01 | Chicken Fajitas (T) FT44 | Lemonade (B) FB13 |
| | Potato Medley (T) FT87 | Beef Fajitas (I) FT22 | Brown Rice FT83 | Brown Rice FT83 | Beef Steak (I) FW03 |
| | Rhubarb Applesauce (T) FT88 | Brown Rice FT83 | Berry Medley ® FR64 | Peach Ambrosia ® FR27 | Homestyle Potatoes FT86 |
| | Strawberries ® FR38 | Macadamia Nuts (NF) FS25 | Waffles (NF) FE05 | Macadamia Nuts (NF) FS25 | Strawberries ® FR38 |
| | Macadamia Nuts (NF) FS25 | | Macadamia Nuts (NF) FS25 | | |
| | | | | | |
| Dinner | Peach Apricot Drink (B) FB41 | Orange Mango Drink (B) FB30 | Lemonade (B) FB13 | Orange Juice (B) FB55 | Lemonade (B) FB13 |
| | Tuna (T) FK01 | Beef Tips w/ Mushrooms (I) FT60 | Apple Cider (B) FB52 | Tuna (T) FK01 | Beef Tips w/ Mushrooms (I) FT60 |
| | Beef Steak (I) FW03 | Red Beans & Rice FT56 | Chicken Pineapple Salad ® FR63 | Red Beans & Rice FT56 | Brown Rice FT83 |
| | Green Beans & Potatoes (T) FT71 | Brownie (NF) FS22 | Barbecued Beff Brisket (I) FT24 | Brownie (NF) FS22 | Vegetable Quiche ® FR59 |
| | Tapoica Pudding P (T) FT69 | | | | Macadamia Nuts (NF) FS25 |
| | Crackers (NF) FS26 | | | | Brownie (NF) FS25 |
| | Candy Coated Chocolates (NF) FS19 | | | | |
| | | | | | |
| Snack | Lemonade (B) FB13 | Orange Grapefruit Drink (B) FB15 | Lemonade (B) FB13 | Lemonade (B) FB13 | Grape Drink (B) FB07 |
| | Macadamia Nuts (NF) FS25 | Macadamia Nuts (NF) FS25 | Granola (R) FR15 | Bread Pudding (T) FT52 | Crackers (NF) FS26 |
| | Strawberries ® FR38 | Strawberries ® FR38 | Macadamia Nuts (NF) FS25 | Cranapple Dessert (T) FT65 | Candy Coated Chocolates (NF) FS19 |
| | Cranapple Dessert (T) FT65 | Berry Medley ® FR64 | Orange Juice (B) FB55 | Macadamia Nuts (NF) FS25 | |
| | | | | | |

**Fig. 2.2** Menu for an astronaut on a diet with lower sodium intake than the average in-flight diet

**Table 2.1** Content of energy, macronutrients, selected minerals, and fluid of the menu in Fig. 2.2 (day labels include L for low sodium)

| | Day L1 | Day L2 | Day L3 | Day L4 | Day L5 | Mean |
|---|---|---|---|---|---|---|
| Energy (kcal) | 3004 | 2902 | 2999 | 2938 | 2829 | 2934 |
| Protein (g) | 104 | 109 | 107 | 105 | 109 | 107 |
| Fat (g) | 93 | 87 | 98 | 94 | 89 | 92 |
| Carbohydrate (g) | 437 | 429 | 422 | 418 | 396 | 420 |
| Sodium (mg) | 1851 | 1986 | 1882 | 1911 | 1938 | 1914 |
| Potassium (mg) | 3179 | 3083 | 3166 | 3598 | 3247 | 3255 |
| Calcium (mg) | 1100 | 947 | 1036 | 1014 | 1220 | 1063 |
| Water (ml) | 2268 | 2166 | 2103 | 2161 | 2123 | 2164 |

**Fig. 2.3** Metabolic kitchen in the Institute of Aerospace Medicine at the German Aerospace Center, Cologne, Germany, Copyright DLR

### *2.2.4 Facility and Environment*

Environmental conditions such as day and night lighting and sleep cycle; time shifts because of docking of rockets or other reasons; and kind, level, and duration of exercise may affect experiment results in space missions. Similar requirements apply to analog studies in ground-based labs. In the latter, even conditions such as temperature and humidity or gurney use for showering might be predefined and controlled. Adherence to the predefined conditions of experiments with a small n is of utmost importance to be able to conclude that differences are caused only by the effects of microgravity, bed rest, or other stimuli and to avoid an impact of any other factor.

**Fig. 2.4** Weighing of apple juice on a lab scale in a metabolic kitchen, Copyright DLR

## 2.3 Space Food on Space Missions

Crewmembers preparing for spaceflights test the space food and beverages planned for consumption during flight several months before their mission. Usually their final selections of food and beverages during flight depend on availability and certain rules for their food consumption for their respective meals.

At the outset of human spaceflight, it was obvious that food and beverages needed to be provided for the space travelers. The food developed for the early missions in the 1960s was mainly pureed food in squeeze tubes, small cubed food items coated with an edible film to prevent crumbs from escaping, or freeze-dried powdered food (Perchonok and Bourland 2002).

Most of the space food on early ISS missions was of American or Russian origin, reflecting the respective food culture. However, with more and more international participation in spaceflight, other space agencies are supporting space food development. Today we also find European, Japanese, and Canadian food on board the ISS, made with recipes mainly reflecting their food culture. This multicultural menu leads to an increase in food variety and supports a balanced nutrient supply too (Bourland et al. 2000; Smith et al. 1971).

## 2.4 Physiological Changes in Spaceflight

After space travelers launch from a space port, they very rapidly experience microgravity. The musculoskeletal system undergoes dramatic adaptation processes, as do many other systems including the fluid and electrolyte system (Adams et al. 2003; Buckey et al. 1996; Cintron et al. 1990; Convertino 1996; Drummer et al. 2000; Fritsch-Yelle et al. 1996; Leblanc et al. 2007).

With the gravity vector gone, the fluid in the body starts to equally distribute along the body axis, which lead to a fluid shift from the lower part of the body to the upper. Leg volume is lower, and relative blood volume in the upper part of the body increases (Moore and Thornton 1987; Smith et al. 1997b). As an adaptation process, blood volume starts to decrease during the first days in microgravity.

Loss of gravity also influences the mechanical loading of the lower parts of the body. As time goes by, this leads to a reduction in muscle mass and strength, as is observed when a leg is put in a cast after a fracture. Reduction of muscular contraction because of greater mechanical loading also leads to adaptation processes in bone mass (LeBlanc et al. 2000). The bone-resorbing cells, the osteoclasts, are activated by unloading and induce a degradation of bone mass until the strength mandatory in the microgravity environment is reached. Concomitantly, the activity of the bone-forming cells, the osteoblasts, is either reduced or unchanged (Smith et al. 2005a).

Microgravity, however, also seems to affect appetite and as a result nutrient consumption. Although scientific evidence for any change in appetite is missing, anecdotal descriptions from space travelers tell us that they seem to experience fewer smell and taste sensations while they are in microgravity. Smell and taste sensations, however, are very important for eating, and decreases in those might be one reason why most of the space travelers in past missions reduced their food intake.

Another observation mentioned anecdotally is that stomach fullness is experienced much more rapidly in microgravity and can block a space traveler from continuing to eat. This might also play an important role in reduced food intake during spaceflight.

# Chapter 3
# Energy, Macronutrient Supply, and Effects of Spaceflight

## 3.1 Energy

Our body needs energy to keep up all the major functions of the body such as heartbeat, breathing, metabolism, organ function, and much more. The energy needed for maintaining these functions is called basal metabolism and is the amount of energy needed by the body when it is not performing any physical exercise. The rate at which this energy is used is the basal metabolic rate. The energy expenditure for any physical exercise is added on top of the basal metabolic rate. The sum of these two make up most of the total energy expenditure (TEE). However, for digestion of energy-delivering nutrients (the macronutrients: protein, fat, and carbohydrates), our body also needs energy and produces heat from expending it. The production of heat during digestion is a type of thermogenesis. TEE therefore consists of basal metabolism, any energy expenditure because of physical activity, and thermogenesis.

### *3.1.1 Requirements*

TEE may be calculated using different equations and algorithms derived from several groups (Muller et al. 2004; Schofield 1985).

For astronauts, estimated energy requirements (EER) are calculated before flight and are based on TEE as calculated from the 2002 Institute of Medicine Dietary Reference Intake reports (Institute of Medicine 2002), using an activity factor of 1.25 (active) along with the individual's age, body mass (kg), and height (m) in the following calculations:



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EER for men 19 years and older

$$\mathrm{EER} = 622 - 9.53 \times \mathrm{Age(years)} + 1.25 \times [15.9 \times \mathrm{Mass\ (kg)} + 539.6 \times \mathrm{Height(m)}]$$

EER for women 19 years and older

$$\mathrm{EER} = 354 - 6.91 \times \mathrm{Age(years)} + 1.25 \times [9.36 \times \mathrm{Mass(kg)} + 726 \times \mathrm{Height(m)}]$$

Studies by Lane et al. (1997) have shown that by calculating EER with these equations, one may come, on average, quite close to the individually measured TEEs. Nevertheless, individual specifics of energy needs are not taken into account when using equations, and measurement of individual TEE is desired in order to provide food with adequate amounts of calories to maintain body mass and composition for each of the space travelers. Exercise is a significant factor in TEE during flight, and Stein et al. showed that on some missions TEE was higher during flight than before flight (Stein et al. 1999b).

### *3.1.2 Effects on Physiological Systems*

From the earlier Apollo, Skylab, etc., spaceflights, it has been known that space travelers consume less than the mandatory amount of energy to keep up body mass. Most of them ate less than 80 % of the EER, leading to body mass decreases (Smith et al. 2009). Because of the insufficient energy intake, most of them lost body fat (LeBlanc et al. 2000). Another component of body mass loss seen immediately after landing is due to increased loss of muscle tissue caused by lower levels of physical exercise. Muscle tissue consists mainly of protein and water, which is bound to the protein. Loss of muscle protein therefore leads also to body fluid losses (Fig. 3.1).

Reduced energy intake does not only mobilize fat, the main energy reserves in the human body, and lead to negative energy balances. It also mobilizes protein as an energy-delivering macronutrient. Since the main part of the protein stores in humans is located in the muscle, degradation of protein because of insufficient energy intake may lead to further muscle loss (Stein et al. 1996, 1999b). Care must therefore be taken when recommending physical exercise as a countermeasure to loss of muscle mass. To engage in physical exercise, energy is mandatory. When insufficient energy is supplied, appropriate internal energy stores have to also provide the energy necessary for physical exercise. Physical exercise in this case does not seem to act as a countermeasure anymore because it leads ultimately to further losses of energy stores, which might be muscle protein. When recommending physical exercise as a countermeasure to muscle loss in spaceflight as well as on Earth, it is therefore highly recommended that the appropriate energy intake be checked first to guarantee the desired result of increasing muscle mass.

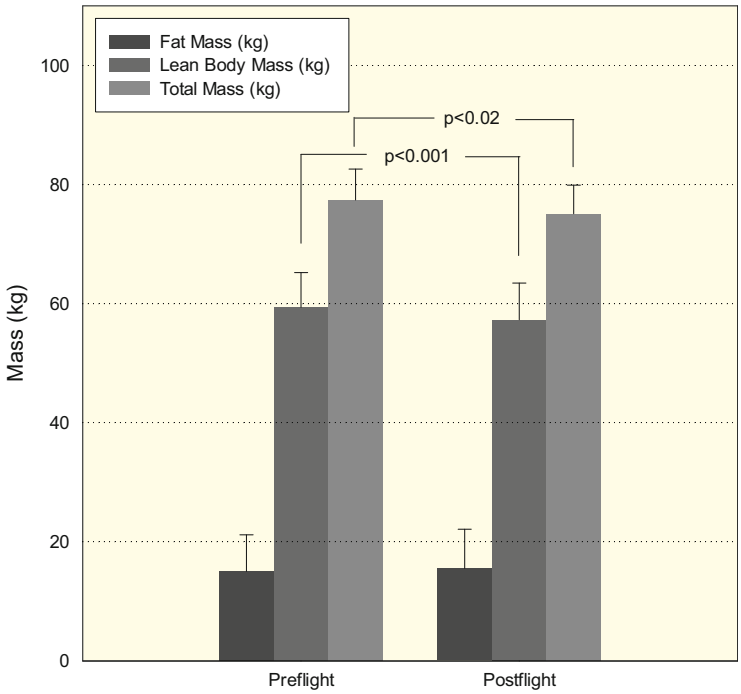


**Fig. 3.1** Changes in body composition after spaceflight [derived from LeBlanc et al. (2000)]

Inadequate energy intake may also induce increased bone resorption processes by higher osteoclasts activity. The reduced mechanical loading of bone in microgravity per se leads to increased bone resorption and maintained or decreased bone formation processes. Decreasing energy intake may foster these processes, as seen in patients suffering from anorexia nervosa, i.e., a dramatic reduction in energy intake (Heer et al. 2002, 2004). Even a certain percentage decrease in energy intake plus exercise might have an impact on bone turnover, as shown by Ihle et al. in exercising women (Ihle and Loucks 2004). However, further studies suggest that adequate calcium supply may play a key role in keeping up bone mass even in calorie restriction programs (Redman et al. 2008). Whether this observation is relevant for spaceflight needs to be confirmed in further studies.

## 3.2 Protein

Protein is a macronutrient and includes molecules that perform many essential physiological functions, serving as enzymes, hormones, transporters, and other important molecules. In an average Western diet, protein represents about 15 % of energy intake per day, which is rather high. The nitrogen in its amino-acid

building blocks makes protein, along with nucleic acids, one of the major nitrogen-containing macromolecules.

### 3.2.1 Effects on Physiological Systems

Protein plays an essential role in the cellular maintenance, growth, and functioning of the human body. It serves as the basic structural molecule of all the tissues in the body (17 % of total body mass). Amino acids are the fundamental building blocks of protein.

The dietary reference intake of protein for adults is 0.8 g/kg body weight/day (Institute of Medicine 2002). Protein is one of the most important limiting factors when the body is deprived of energy, because essential amino acids are not stored in the body. A complete depletion of energy and protein reserves is said to be the cause of death from starvation. It is estimated that when 33–50 % of total body protein is lost, death results (Silber 1984). Loss of more than 40–50 % of initial body mass is not compatible with life (Phillips 1994).

### 3.2.2 Spaceflight

In spaceflight, decreases in muscle mass mainly caused reduced protein synthesis (Stein et al. 1999c). First results from an experiment carried out by Stein et al. on the Russian space station MIR show that whole-body protein synthesis falls by about 45 % (Stein et al. 1999c). Results of bed rest studies largely confirm that muscle unloading is associated with a decreased whole-body protein, synthesis of muscle protein being primarily decreased (Ferrando et al. 1996). Nonetheless, the in-flight reduction of whole-body protein synthesis is usually significantly higher than predicted from ground-based bed rest experiments. During spaceflight, in addition to muscle unloading, other factors may impair protein synthesis. The reduced nutrient intake of astronauts as compared to their requirements may decrease whole-body and muscle protein turnover. Such reduced energy intake may negatively interact with muscle unloading to determine the accelerated wasting of body proteins observed in spaceflight (Stein et al. 1999a). In addition, the hormonal and immune stress response (mainly mediated by cortisol and cytokines) often observed in space may further contribute to protein loss in astronauts. Ferrando et al. investigated the combined effects of hypercortisolemia and prolonged inactivity on muscle protein metabolism in healthy volunteers (Ferrando et al. 1999). They found that inactivity sensitized skeletal muscle to the catabolic effects of hypercortisolemia.

### 3.2.3 Relevance for Life on Earth

Recently the possibility of increasing dietary protein intake to increase thermogenesis, increase satiety, and further metabolic activities, and thereby reduce body mass has been discussed (Bendtsen et al. 2013; Martens et al. 2014; Martens and Westerterp-Plantenga 2014).

However, one disadvantage of high-protein intake is that intake of animal protein in particular, together with low dietary alkalinity (which is usually characterized by a low potassium intake), might affect several physiological systems, which are also affected by microgravity. High-protein diets, for instance, lead to hypercalciuria, which may increase the risk of renal stone formation and may increase fracture risk (Dawson-Hughes 2003). One hypothesis to explain protein-induced hypercalciuria is related to the "acid-ash" hypothesis that excessive intake of animal protein provides excess sulfur-containing amino acids that are metabolized to sulfuric acid and may lead to low-grade metabolic acidosis.

On the one hand, high-protein intake may maintain muscle protein synthesis and insulin sensitivity, but on the other hand, as mentioned above, it may induce low-grade metabolic acidosis. Metabolic acidosis increases muscle protein breakdown as well as glucose levels (Straumann et al. 1992). These data on muscle protein breakdown in humans are also supported by animal experiments in which chronic metabolic acidosis led to a 43 % increase in urinary nitrogen. The protein catabolic effect in rats was caused by stimulation of proteolysis without any effect on protein synthesis (May et al. 1986). When accompanied by inadequate consumption of alkali equivalents, high-protein intake may also contribute to bone loss and may increase fracture risk by increasing bone resorption (Bushinsky 1994; Frassetto et al. 1998; Houillier et al. 1996; Wiederkehr and Krapf 2001; Dawson-Hughes 2003).

In addition, meat, the main source of sulfur-containing amino acids, contains a larger amount of protein per 100 g than protein-rich vegetables and contains lower levels of potassium than fruits and vegetables. Potassium or potassium salts may compensate for metabolically induced low-grade metabolic acidosis caused by animal protein, which explains why similar amounts of protein provided by vegetables or fruits do not lead to low-grade metabolic acidosis. Animal studies have affirmed that correction of metabolic acidosis has a favorable effect on protein metabolism, nitrogen balance, and growth (Bailey and Mitch 2000), suggesting that supplementation of an alkaline salt in combination with a high-protein diet might compensate for the increased breakdown of muscle protein caused by low-grade metabolic acidosis. The same holds true for bone (Frassetto et al. 2005). In bed rest subjects, when high animal protein intake was counteracted by high potassium intake, bone resorption markers were significantly lower (Zwart et al. 2004).

To maintain skeletal muscle mass in adults, the availability of amino acids and adequate energy supply is—in addition to physical activity—a mandatory prerequisite. Insufficient provision of amino acids or energy together with physical inactivity results in muscle wasting, as we see in space missions or analog studies

like bed rest (Ferrando et al. 1996; Biolo et al. 2005; Stein et al. 1999a). Short-term bed rest, for instance, decreases, like spaceflight, mainly muscle protein synthesis (MPS) (Biolo et al. 2004; Paddon-Jones et al. 2004a; Stuart et al. 1990), which might explain all of the loss in muscle mass during inactivity (Rennie et al. 2009). Contributing to this loss is a decreased anabolic response to exercise and feeding. However, supplementation of essential amino acids or whey protein might overcome the decrease in MPS seen in inactivity (Antonione et al. 2008; Paddon-Jones et al. 2004b).

Paddon-Jones et al. also studied the effect of essential amino acid (EAA) ingestion on insulin levels (Paddon-Jones et al. 2004b). They found that EAA increased insulin levels in the young but not in the elderly test subjects. In another study, a hypocaloric, high-protein diet increased glucose disposal and glucose oxidation in an euglycemic hyperinsulinemic clamp period significantly compared to a hypocaloric, high-carbohydrate diet (Piatti et al. 1994). High-protein intake might therefore not only overcome reduced MPS but also enhance insulin sensitivity. Even under hypercaloric conditions, high-protein intake seems not to impair insulin sensitivity (Bortolotti et al. 2009).

## 3.3 Fat and Fatty Acids

Fat is the macronutrient with the highest energy content. One gram of fat provides about 9 kcal. Fat consists of different fatty acids, which are either saturated fatty acids or mono- or polyunsaturated fatty acids. Fatty acids are building blocks of cell membranes and play important roles in metabolism. Products of the metabolism of fatty acids also function as hormones and messengers. Fat is stored as triacylglycerol, i.e., esters of glycerol and fatty acids.

### *3.3.1 Requirements*

The current documented spaceflight requirement is for dietary intake of fat to make up 25–35 % of the total daily energy intake, which is also the average intake in space travelers (Smith et al. 2009). Dietary intake of $n-6$ and $n-3$ fatty acids is to be 14 g/day and 1.1–1.6 g/day, respectively. Saturated fat should be $<7$ % of total calories, trans fatty acids $<1$ % of calories, and cholesterol intake $<300$ mg per day.

### *3.3.2 Effects on Physiological Systems*

Only a couple of studies in either microgravity or analogs such as bed rest have focused on fat metabolism. In recent bed rest studies, in both men and women,

Blanc et al. investigated energy metabolism. In these studies, substrate oxidation shifted in short-term bed rest of 7 days from fat to carbohydrate metabolism in men and a net lipogenesis in women (Blanc et al. 2000).

### *3.3.3 Relevance for Life on Earth*

Omega-3 polyunsaturated fatty acids such as eicosapentaenoic acid (EPA) have beneficial effects on bone (Griel et al. 2007; Zwart et al. 2010). The protective effect of EPA has been attributed to its anti-inflammatory actions and inhibition of signaling factors that are associated with inflammation and osteoclasts (Fernandes et al. 2008; Magee et al. 2008).

## 3.4 Carbohydrates

### *3.4.1 Requirements*

The requirement for carbohydrate intake during spaceflight is defined as 50–55 % of the total daily energy intake. In the USA, acceptable daily intake of dietary carbohydrate is defined as intake between 55 % and 75 % of the total dietary energy (Sanders and Lupton 2010). A minimum intake of 140 g/day is required to maintain the needs of organs that require carbohydrate for energy production (MacDonald and Williams 1988). For reference, the daily carbohydrate requirement for male and female astronauts was originally defined in 1991 for missions of 30–120 days as 50 % of the total energy intake (National Aeronautics and Space Administration Johnson Space Center 1993) and in 1995 for missions up to 360 days as 50–55 % of the total energy intake (National Aeronautics and Space Administration Johnson Space Center 1996), with a caveat that most of the carbohydrate should be provided as complex carbohydrates and less than 10 % of the total carbohydrate should be provided as simple sugars.

### *3.4.2 Effects on Physiological Systems*

Early studies documented both increased insulin and glucose at landing in Apollo and Skylab missions. On the Shuttle, studies by German investigators showed no impact of 7 days of flight on glucose tolerance tests (Maaß et al. 1995). Additionally, a Russian study documented a reduction in fasting plasma glucose after 60 or 88 days of flight on a Salyut-Soyuz spacecraft complex and a reduced peak of blood glucose in glucose tolerance tests (Alexandrov et al. 1985). Insulin

resistance (lack of sensitivity to insulin) has been found to result from simulated weightlessness (bed rest) (Biolo et al. 2005; Blanc et al. 2000; Stuart et al. 1988; Vernikos-Danellis et al. 1976). Using C-peptide excretion as a proxy, Stein et al. found evidence of insulin resistance during actual and simulated spaceflight (Stein et al. 1994). Heer et al. documented that after 3 weeks of bed rest, glucose tolerance was altered for more than 4 days after reambulation (Heer et al. 2014). Efforts to maintain muscle mass during spaceflight and bed rest (and presumably correct the insulin resistance) continue, but little research has been done to pursue this as a nutritional issue.

Suboptimal carbohydrate intake before and during spaceflight may have consequences for the crew's productivity and impede their ability to respond in emergency situations (Lane and Rambaut 1994). Deficiency of carbohydrate leads to ketosis. A ketotic state would likely impair performance of crewmembers, as seen in studies conducted by military researchers (Phillips 1994), as well as increase renal stone risk secondary to reduced urinary pH (Pietrzyk et al. 1999, 2007; Zerwekh et al. 2007). Other aspects of the mission would also be at risk (e.g., the life-support systems may not be able to remove exhaled ketones from the air). Toxicity of carbohydrate has not been well studied and would likely be an issue only because it would displace other nutrients (protein and fat) from the diet.

Few data are currently available to assess the impact of spaceflight on carbohydrate metabolism. Observations from spaceflight as well as ground-based bed rest studies show subtle changes in insulin secretion, insulin resistance, and glucose intolerance (Dolkas and Greenleaf 1977; Lipman et al. 1972; Stuart et al. 1988; Vernikos-Danellis et al. 1976). Even subtle changes in such important metabolic processes make it critically important to consider the likelihood, nature, and consequences of altered carbohydrate and insulin metabolism for exploration missions.

### *3.4.3 Relevance for Life on Earth*

Carbohydrates play an important role in the body because they supply the primary source of energy as well as a readily available source. This energy is oxidized and used by various organs and cells in the body, particularly the brain and red blood cells, which depend solely on carbohydrate for energy. The human body stores about 150–500 g of carbohydrate as glycogen, in the liver and skeletal muscle (Levine and Greenleaf 1998). Most of the body's glycogen is in the skeletal muscle. Muscle glycogen stores are used mainly by muscle, whereas the smaller glycogen stores in the liver are used to maintain, store, and export blood glucose. Glycogen stores, especially those in the liver, fluctuate greatly during the day in response to food intake, and these fluctuations may be involved in the regulation of food intake (Stubbs et al. 1998). Liver stores of glycogen are depleted after 12–18 h of fasting (Levine and Greenleaf 1998). In skeletal muscle, glycogen synthesis is triggered by a rise in insulin after the consumption of carbohydrates. De novo synthesis of

glucose from noncarbohydrate precursors can and does occur in the body, if needed. This allows the liver to maintain adequate blood glucose concentrations. Insulin is required for the uptake of glucose into cells, and various transporter systems are found in different types of tissues that utilize glucose.

Requirements for carbohydrate in space are thought to be similar to those on Earth. However, to date, few investigations have been conducted on the effects of microgravity on the metabolism of dietary carbohydrate, and those studies have had conflicting results.

# Chapter 4
# Fluid and Electrolyte Metabolism

## 4.1 Sodium and Chloride

Sodium is the major cation of extracellular fluid (Oh 2011). Together with chloride, sodium is utilized by the body to maintain normal water distribution, osmotic pressure, and anion–cation balance in the extracellular fluid compartment (Tietz et al. 1994). Electrolyte concentrations in the body are essential for proper cardiovascular function and are under renal and hormonal control (Preuss 2001). Increases in blood sodium levels can be caused by diabetes, renal polyuria, diarrhea, insufficient water intake, excessive sweating, or increased dietary sodium intake. Sodium levels decrease with edema, excessive water intake, vomiting, diarrhea, diuretic therapy, renal tubular damage, hyperaldosteronism, or lower dietary intake.

### *4.1.1 Requirements*

For the normal adult, total body sodium averages about 60 mmol/kg body weight. Forty to 45 % of total sodium resides in the bone, with the balance found in extracellular and intracellular fluid. These sodium stores are classified as either exchangeable (42 mmol/kg body weight) or nonexchangeable, the exchangeable stores being composed of all cellular sodium and less than half of bone sodium (Pitts 1959). Exchangeable sodium becomes available by diffusion when plasma sodium levels become low, and in states of edema, the exchangeable sodium stores absorb sodium.



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### 4.1.2 *Effects on Physiological Systems*

The traditional view of sodium balance derives from experiments introduced by Carl Ludwig, who studied renal salt excretion in humans exposed to extremes (very high versus very low) in salt intake (Ludwig 1861). When urinary output approached input, steady-state regulation of sodium balance was generally assumed in these studies (Ludwig 1861; Strauss et al. 1958). In these classic experiments, a steady state was achieved after transient accumulation or loss of body sodium, which leads to parallel changes in extracellular fluid volume (Fig. 4.1): "If dietary intake is abruptly increased from a low-sodium diet, only about one-half is excreted on the first day. The remainder is retained augmenting sodium stores. This state of affairs elevates the plasma osmolality, stimulating both thirst and secretion of antidiuretic hormone. The increments in water intake and renal water reabsorption produce water retention, resulting in increases in effective circulating volume and weight. After 3–4 days, a new steady state is achieved in which renal sodium excretion matches intake. The same sequence occurs in reverse if sodium intake is reduced" (Rose 1994).

However, not all investigators have corroborated this interpretation. In the MIR 97 space mission, the consumption of an average normal sodium chloride intake of about 200 mmol/day during a 28 day metabolic ward experiment on board the MIR space station led to sodium retention (Drummer et al. 1993). Results were repeated

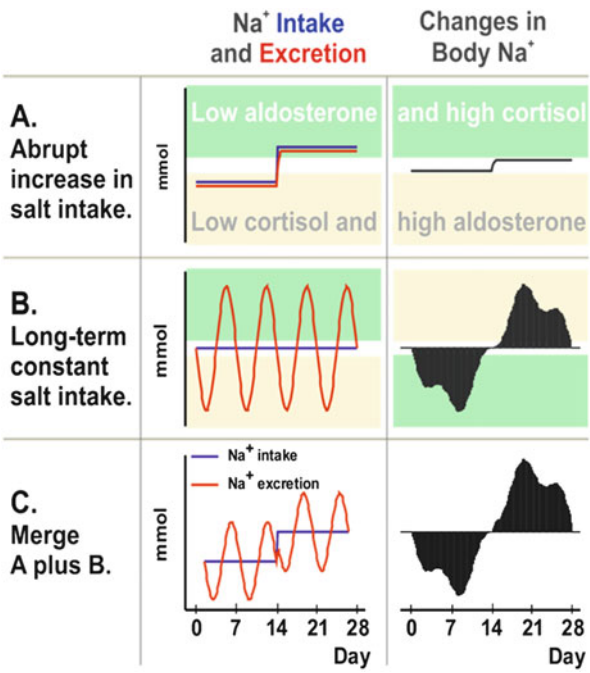


**Fig. 4.1** Sodium regulation in the human body following either abrupt or long-term increase in dietary sodium chloride intake

during detailed ground-based metabolic balance studies in which normal men were given sodium intakes ranging from 50 to 660 mmol/day for up to 10 days (Heer et al. 2000). They found that plasma volume dependently increased with increasing salt intake up to a sodium intake of about 250 mmol sodium per day. With further increases in sodium intake no further fluid was retained. Total body water did not increase, and there was no change in body weight, even though total body sodium content at the end of the study was increased by 1700 mmol. The authors concluded from the results of their two independently conducted studies that in contrast to present opinion, the sodium accumulation did not result in commensurate body water storage but instead induced a relative fluid shift from the interstitial into the intravascular space (Heer et al. 2000).

These findings were corroborated in a confinement study as preparation for long-term space missions at the Institute of Biomedical Problems in Moscow, where sodium intake was not fixed, but could be monitored in 3 men for 135 days (Titze et al. 2002). The studies suggested that healthy humans may store large amounts of sodium without fluid retention, a hypothesis that was not in line with textbook explanations (Rose 1994). A simulated spaceflight to Mars has recently allowed reinspection of this theory (Rakova et al. 2013). Healthy subjects were confined to an enclosed, restricted environment in two independent studies for 105 and 520 days, which allowed two ultra-long-term Na+ balance studies in humans. All balance studies except one (Kirkendall et al. 1976) that were used for modeling the kinetics of sodium homeostasis had studied the body's short-term adaptation to extremes in salt intake (Walser 1992). Now for the first time, the reverse was studied during this simulated trip to Mars, namely, sodium homeostasis in response to ultra-long-term constancy in salt intake (Rakova et al. 2013). The subjects received three fixed levels of sodium intake, 12 g salt/day, 9 g salt/day, and 6 g salt/day. Microgravity was not simulated. Actually, the mock spacemen did not upset the steady-state theory. They ate almost 15 kg of salt during the studies and excreted 90–95 % of the dietary salt in their urine. However, the way this steady state was achieved was startling and has been reviewed in detail previously (Titze et al. 2013). When salt intake was fixed for weeks and months, there was considerable day-to-day variability in 24-h Na+ excretion, accompanied by fluctuations of aldosterone, cortisol, and cortisone that peaked with a periodicity of about 1 week. Regular fluctuations of total body Na+ content were also observed, but with longer periodicity of about 1 month. The subjects thereby rhythmically accumulated and released body Na+ independent of daily salt intake, presumably regulated by (neuro)-endocrine rhythmic clocks (Fig. 4.1). This rhythmic accumulation and release of body sodium was not paralleled by changes in body weight, indicating that sodium was stored in the body. These first long-term balance studies did not support the accepted notion that Na+ retention inevitably leads to volume retention and that body Na+ therefore is to be maintained constant within very narrow limits. In contrast, the rather "spooky" Na+ balance studies initiated by the German and European Space program suggested that Na+ is stored in the body (Drummer et al. 1993; Heer et al. 2000; Rakova et al. 2013; Titze et al. 2002).

### 4.1.3 Relevance for Life on Earth

It is speculated that sodium storage might represent a previously undetected cardiovascular risk factor. This hypothesis could be tested in prospective studies only if sodium storage were reversible in response to therapeutic intervention. Titze et al. tested the hypothesis that drug intervention may reduce sodium stores in the body. In line with their initial observation in a patient with hyperaldosteronism (Kopp et al. 2012b), the cross-sectional analysis of tissue sodium content in patients with refractory essential hypertension showed that patients with spironolactone treatment had significantly reduced muscle sodium content (Kopp et al. 2013). They were also surprised to find that correction of hypernatremia in a patient with diabetes insipidus was not attributable to correction of a total body water deficit, but was presumably due to correction of secondary hyperaldosteronism and mobilization of massive sodium stores in the muscle (Kopp et al. 2012a). The most recent evidence, from the first 23Na MRI study in dialysis patients, has shown that 4–5 h of dialysis treatment can reduce sodium and water stored in the muscle and in the skin; however, skin storage of sodium can be excessive in dialysis patients, especially with advancing age (Walser 1985). In younger patients with end-stage renal disease, a single 4- to 5-h hemodialysis treatment without vigorous ultrafiltration was sufficient to reduce elevated tissue sodium content to the levels observed in age-matched, healthy controls. However, excess skin sodium storage, which occurred in older dialysis patients or in patients with an anti-lymphangiogenic serum profile, was difficult to correct with the same hemodialysis treatment regime. Whether sodium stores could be mobilized in these patients with more vigorous ultrafiltration during the treatment session is unclear.

## 4.2 Potassium

### 4.2.1 Requirements

The current documented spaceflight requirement for potassium is 4.7 g/day, the same as the US recommendation for adequate intake of potassium for men and women aged 19–70 years (Institute of Medicine 2004).

### 4.2.2 Effects on Physiological Systems

As the most plentiful intracellular cation, potassium has a significant role in several physiological processes (Preuss 2001). It is crucial to regulation of acid-base balance, energy metabolism, blood pressure, membrane transport, and distribution of fluid in the body. It is also involved in the transmission of nerve impulses and

cardiac function (Kleinman and Lorenz 1984). Potassium metabolism that is disordered because of excessive or deficient circulating levels has negative consequences for cardiac, muscle, and neurological function.

Both serum and urinary levels of potassium decreased after spaceflight in the Apollo program (Jowsey 1971), and there is evidence of a similar decrease on Skylab and Shuttle missions (Leach and Rambaut 1977; Leach-Huntoon et al. 1987; Smith et al. 2009). Potassium loss (both total body potassium and exchangeable potassium) was observed in Apollo crewmembers (Jowsey 1971).

Excess dietary sodium has been shown to be potassium-depleting during bed rest (Heer et al., unpublished observations).

### *4.2.3 Relevance for Life on Earth*

Total body potassium averages 45 mmol/kg body weight, totaling about 3150 mmol (1230 g) of potassium in a reference 70-kg person. Two percent of body potassium (~60 mmol) is distributed in the extracellular fluid, and intracellular fluid levels are typically maintained at 140–150 mmol/L).

Potassium levels cannot be maintained at intakes less than 10–20 mmol/day (Perez et al. 1988). Moderate depletion of potassium in humans is associated with clinically significant impaired active relaxation of the left ventricle (Srivastava and Young 1995). In the referenced study, healthy adults were placed on a potassium-depletion diet for 7 days. At the end of 7 days, isovolumic relaxation time and deceleration time of flow through the mitral valve were significantly increased.

Increased levels of urinary potassium may be related to muscle disuse atrophy and inadequate intake during spaceflight (Lane et al. 2000).

Deficiency of potassium leads to hypokalemia, muscle weakness, constipation, fatigue, or even death. There is no evidence of adverse effects associated with ingestion of excessive amounts of potassium from naturally occurring sources. However, supplemental intake may cause hyperkalemia (and associated weakness, cardiac arrest, and paralysis), metabolic acidosis, decreased neuromuscular functions, or even death.

# Chapter 5
# Fat-Soluble Vitamins

For a compound to be considered a vitamin, it has to be an essential component of the diet, a dietary essential. The elimination of a vitamin from the diet must result in a more or less clearly defined deficiency disease (Bender 2009). Vitamins are classified as either fat soluble or water soluble. In light of the astronauts' inadequate dietary intake, the use of vitamin and mineral supplements is often debated (Smith et al. 2001). However, the deficient energy intake of the astronauts is clearly the issue having highest priority. If dietary intake increases, the intake of all nutrients, including the vitamins and minerals, will increase. Fat-soluble vitamins (A, D, E, and K) are soluble in lipids and are usually absorbed in fat globules.

## 5.1 Vitamin A

Vitamin A comprises a family of fat-soluble compounds that are structurally similar to retinol and have the same biological activities. The term "vitamin A" or "retinoids" includes retinol, α-carotene, β-carotene, and retinyl palmitate. Vitamin A is abundant in some animal-derived foods, whereas provitamin A carotenoids are abundant in darkly colored fruits and vegetables, oily fruits, and red palm oil. β-carotene is the major source of vitamin A for the majority of the world's population. If vitamin A intake is adequate, more than 90 % of total body vitamin A is located in the liver (Raica et al. 1972).

### *5.1.1 Requirements*

The requirement for vitamin A in spaceflight is 700–900 μg retinol activity equivalents (RAE)/day. The actual recommended dietary allowance for vitamin A on Earth is 900 μg REA/day for men aged 19 and older and 700 μg RE/day for women



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aged 19 and older (Food and Nutrition Board 2001). An excess intake of vitamin A, at a level twice the recommended daily intake, leads to an increase in bone resorption and fracture risk (Palacios 2006). Also, β-carotene supplementation should be done with caution, as supplementation was associated with an increased risk of lung cancer in smokers (Virtamo et al. 2014). The upper limit (tolerable upper intake level [UL]) for vitamin A intake is 3000 μg RE/day, and β-carotene supplementation is advised only in situations where there is a risk of vitamin A deficiency. Night blindness is the first ocular symptom to be observed with vitamin A deficiency, and it responds directly to treatment with vitamin A (Christian et al. 1998). Moreover, deficiency leads to loss of appetite, drying and keratinization of membranes, and infection. Headache, vomiting, nausea, blurred vision, and muscular incoordination are acute reactions to toxicity, whereas chronic toxicity leads to a decrease in bone mineral density and liver abnormalities (IOM (Institute of Medicine) 2002a).

Sound evidence exists for a role of vitamin A in the maintenance of humoral antibody response and cell-mediated immunity (Ross 1992; Stephensen 2001). The considerable immune benefits, which would contribute to reducing the risk of various pathogen-mediated diseases, warrant a recommendation to supplement individuals with a poor vitamin A status.

### *5.1.2 Effects on Physiological Systems*

Vitamin A is required for vision, gene expression, reproduction, immune function, and embryonic development. As vitamin A and β-carotene play a role in immune function and protection against infections (Ross 1992; Stephensen 2001), they may play a role in maintaining antioxidant health during spaceflight, during which oxidative stress is increased. But the capacity of vitamin A to function as an antioxidant has not been investigated in spaceflight to date, and the content and stability of vitamin A in the space food supply should be determined. Investigations of Smith et al. (2005b) in 11 astronauts provide no evidence that β-carotene was altered by exposure to microgravity. However, there seems to be an interaction between the effect of landing site and spaceflight on serum levels of retinol and retinol-binding protein (Smith et al. 2005b). This might be due to the fact that blood samples collected in Russia are collected several hours later than blood samples collected in the USA because of the logistics of the landing site. An explanation for this finding might be related to the time delay and to the likelihood that the crewmembers might have consumed food during the time delay. A study in long-duration bed rest shows that no change in retinol or retinol-binding protein occurred during or after bed rest (Zwart et al. 2009b).

### 5.1.3 *Relevance for Life on Earth*

Investigating the relevance of vitamin A and its capacity to function as an antioxidant could help researchers to better understand the role of vitamin A in human nutrition on Earth.

## 5.2 Vitamin D

Vitamin D, also known as calciferol, is now recognized as a prohormone and comprises a group of fat-soluble secosterols. The two major forms are vitamin $D_2$ (ergocalciferol) and vitamin $D_3$ (cholecalciferol). Vitamin $D_2$ is largely human made and added to food‘ whereas vitamin $D_3$ is (a) synthesized in the skin of humans from 7-dehydrocholesterol and (b) consumed in the diet via the intake of animal-based foods. Vitamins $D_2$ and $D_3$ only differ in their side chain structure. The unique aspect of vitamin D that it is synthesized by the human body through the action of sunlight (provided the person has sufficient exposure to ultraviolet [UV] B radiation [290–315 nm]) makes it challenging to develop dietary reference intake values. It is assumed that only 10–15 min of summer sun exposure are sufficient to produce adequate amounts of vitamin D. Since vitamin D does not have to be strictly obtained from the diet, according to the traditional definitions, it is not really a vitamin, although it is essential for life (Autier and Gandini 2007). Vitamin D, in either the $D_2$ or $D_3$ form, is considered biologically inactive until it undergoes two hydroxylation processes. The first step is mediated by 25-hydroxylase (CYP2R1), produces 25-hydroxyvitamin D (25OHD), and takes place in the liver. The second reaction takes place in the kidney and is mediated by 1α-hydroxylase (CYP27B1), which converts 25OHD to the biologically active hormone, calcitriol (1,25-dihydroxyvitamin D (1,25(OH)2D)). Calcitriol synthesis is tightly regulated by two counteracting hormones, with upregulation via parathyroid hormone (PTH) and downregulation via fibroblast-like growth factor-23 (FGF23) (Bergwitz and Juppner 2010; Galitzer et al. 2008).

The biological actions of 1,25(OH)2D are mediated through binding to the transcription factor vitamin D receptor (VDR) (Jurutka et al. 2001). The most widely known vitamin D actions are related to the musculoskeletal system. Vitamin D action also plays a role in intestinal calcium absorption, serum calcium and phosphate homeostasis, and bone formation and resorption processes. Among the many important cells and tissues in which the VDR has been found are the immune system agents lymphocytes, monocytes, and dendritic cells. Evidence is emerging that calcitriol plays a role in the immune system (Deluca and Cantorna 2001). It has been suggested that calcitriol exerts immunomodulatory and antiproliferative effects through autocrine and paracrine pathways (Adams and Hewison 2008; Arnson et al. 2007; Carvalho et al. 2007; Orbach et al. 2007). Moreover, the cardiovascular system is a target tissue for vitamin D, as VDRs are expressed in

the arterial vessels, heart, and almost all cells and tissues relevant to the pathogenesis of cardiovascular diseases (Bouillon et al. 2008; Pilz et al. 2011). These wide-ranging actions of calcitriol have further been hypothesized to play a potential role in preventive or therapeutic action in cancer (Masuda and Jones 2006) and chronic conditions such as autoimmune conditions (including type 1 diabetes) and infections (Holick 2007).

Vitamin D status can best be assessed by measuring circulating 25OHD concentrations (Zittermann 2010). The cutoff points for defining different vitamin D stages are $<$25 nmol/L for deficiency, 25–49.9 nmol/L for insufficiency, 50–79.9 nmol/L for hypovitaminosis, $\geq$100 to 250–500 nmol/L for adequate status, and $\geq$250–500 nmol/L for intoxication (Zittermann and Gummert 2010). It is now evident that an adequate vitamin D intake is not only necessary to prevent rickets or osteomalacia (National Research Council 2000), it is as well an important determinant for long-latency diseases (Heaney 2003; Trivedi et al. 2003).

For spaceflight vitamin D is a subject of concern because of a lack of exposure to UV light and therewith a reduction of endogenous production of this vitamin. Reduced vitamin D stores of astronauts have been noted during flight and after landing (Smith et al. 1999, 2001).

### *5.2.1 Requirements*

The recommended dietary intake for vitamin D is 15 μg/day for 19- to 70-year-old men and women. For men and women $>$70 years old, the DRI is 20 μg/day (IOM (Institute of Medicine) 2011). The tolerable upper intake level is 100 μg/day for males and females.

Until 2006 the ISS recommendation had been 10 μg vitamin D per day (National Aeronautics and Space Administration Johnson Space Center 1996). However, after a series of publications reported that vitamin D status was associated with many diseases and that much higher vitamin D status than was previously defined was required for optimal health, the spaceflight requirement for dietary intake of vitamin D increased to 25 μg per day (National Aeronautics and Space Administration Johnson Space Center 2005). Data from Smith et al. (2012a) document that this level is adequate to maintain vitamin D status in an environment without sunlight exposure and only few food sources of vitamin D, as the ISS food system provides less than 50 % of this amount (4 μg per day on average) (Smith et al. 2009). Therefore, vitamin D supplementation was initiated for all ISS crews when it was found that on Mir flights, vitamin D status declined as a result of inadequate intake and lack of UV-B light (Smith et al. 1999, 2001, 2012a). It is currently recommended that ISS crewmembers take 20 μg/day (800 IU) of vitamin D during long-duration spaceflight (Smith et al. 2009).

Excess intake of vitamin D—but not sun exposure—can lead to a state of vitamin D "intoxication" or "hypervitaminosis D." Chemically synthesized vitamin D became available late in the third decade of the 20th century; reports of vitamin D

intoxication were first found from 1928 to 1932 and continued throughout most of the twentieth century (Deluca 2008). The condition of hypervitaminosis D leads to hypercalcemia and eventually to soft tissue calcification and resultant renal and cardiovascular damage (Deluca 1974). In spaceflight-related ground-based studies, vitamin D stores were decreased in a 91-day chamber study, whereas they were unchanged in a different 60-day chamber study. The cause of this difference is unknown.

### *5.2.2 Effects on Physiological Systems*

In long-duration spaceflight, most of the astronauts do have low 25OHD levels due to the shielding of crewmembers from the ultraviolet B radiation that forms 25OHD (Rettberg et al. 1998; Smith et al. 2009). Despite the reported use of vitamin D supplements by some of the astronauts ($5.7 \pm 4.0$ supplements), Smith et al. showed that the serum concentration of 25(OH)-D3 for the ISS crewmembers after long-duration flights of 4–6 months was about 25 % less after landing than before launch (Smith et al. 2005b).

For bone and calcium metabolism during spaceflight, vitamin D should not be considered a sole countermeasure, as adequate levels are not expected to protect bone during flight. However, the most recent data give evidence that resistance exercise can prevent bone loss during spaceflight only when combined with an adequate energy intake and vitamin D status (Smith et al. 2012a). The first crews of the ISS used the "interim resistive exercise device" (iRED) with a high load (up to 1337 N), but it had little protective effect on the bone (Schneider et al. 2003). In 2008, the Advanced Resistive Exercise Device (ARED) was launched to the ISS. ARED allows greater absolute loads (2675 N) and provides a constant load throughout the range of motion (Loehr et al. 2011). Only advanced resistive exercise together with adequate energy and vitamin D intake was able to prevent skeletal loss.

In-flight and postflight studies have shown changes in the immune status of the astronauts. Decreased lymphocyte function after spaceflight was shown as decreased mitogenic responsiveness of lymphocytes, altered distribution of circulating leukocytes, altered production of cytokines, decreased activity of natural killer cells, decreased function of granulocytes, decreased activation of T cells, altered levels of immunoglobulins, reactivation of latent viruses, altered virus-specific immunity, expression of Epstein-Barr virus immediate early/late genes, and altered neuroendocrine responses have been observed (Gmunder et al. 1994). Moreover, evidence indicates that a higher vitamin D status in individuals who have high serum cortisol and are wintering over in the Antarctic is related to a lower probability of viral shedding in saliva (Smith et al. 2009; Zwart et al. 2011b). So it might be that a deficient vitamin D status of astronauts during space missions might have an impact on their immune status. As stated before, 25OHD levels typically decrease during spaceflight (Rettberg et al. 1998; Smith et al. 2009), but Zwart

et al. (2009b) could not observe any change in vitamin D status in bed rest, although vitamin D status was positively correlated with vitamin D intake during bed rest.

### *5.2.3 Relevance for Life on Earth*

The discovery that most tissues and cells in the body have a vitamin D receptor has provided new insights into the function of this vitamin (Holick 2007). The role of vitamin D in decreasing the risk of many chronic illnesses, including common cancers, autoimmune diseases, and cardiovascular disease, is of great interest. Regardless of the exact blood ranges used to define deficiency and insufficiency, functional vitamin D deficiency is widespread (Peterlik and Cross 2009), and undiagnosed vitamin D deficiency is not uncommon (Holick 2006; Larsen et al. 2004). Vitamin D insufficiency appears to be highly prevalent among older adults (Barnard and Colon-Emeric 2010). Spaceflight investigations may help nutrition researchers to better understand the role of vitamin D in musculoskeletal diseases as well as in other chronic diseases.

## 5.3 Vitamin E

Of the eight naturally occurring forms of vitamin E (α, β, γ, δ tocopherol), only the α-tocopherol form of the vitamin is maintained in human plasma (Traber 1999).

Vitamin E functions primarily as a chain-breaking antioxidant that prevents the propagation of lipid peroxidation. Unlike the situation for most nutrients, a specific role for vitamin E in a required metabolic function has not been found. Vitamin E has synergistic functions. Together with selenium, it reduces damage to lipid membranes in tissues by the formation of reactive oxygen species (ROS) during infections. Vitamin C and glutathione are involved in reducing oxidized vitamin E back to reusable form. In this form, vitamin E is very potent in scavenging lipid-soluble free radicals.

### *5.3.1 Requirements*

The RDA for men and women is 15 mg (35 μmol/day of α-tocopherol) (IOM (Institute of Medicine) 2000). The values recommended are based largely on induced vitamin E deficiency in humans and the correlation between hydrogen peroxide-induced erythrocyte lysis and α-tocopherol concentrations. The RDA is based on the α-tocopherol form of vitamin E. The current documented spaceflight requirement for vitamin E is the same as the US recommendation. Overt deficiency is very rare (IOM (Institute of Medicine) 2000). However, severe deficiency of

vitamin E leads to neurological disorders, hemolytic anemia, abnormal platelets and lymphocytes, and retinopathy. Intoxication from naturally occurring sources has not been shown to occur. Therefore, no upper limit has been established, as the highest intake is not likely to pose any serious health risks (IOM (Institute of Medicine) 2000).

### *5.3.2 Effects on Physiological Systems*

Space programs are shifting toward planetary exploration. Radiation is considered to be one of the major hazards for space travelers and has emerged as the most critical issue to be resolved for long-term missions, both orbital and interplanetary. The antioxidative properties of vitamin E may help to counteract the free-radical damage caused by high radiation doses during spaceflight.

After long-term spaceflight of 4–6 months, plasma γ-tocopherol was 50 % less than preflight levels, but there was no change in α-tocopherol levels in these astronauts (Smith et al. 2005b). The spaceflight menus provide only about 60 % of the documented requirements for vitamin E, and the stability of vitamin E in space food needs to be determined (Smith et al. 2009). Because of vitamin E's antioxidative capacity, vitamin E intake in spaceflight should be optimized.

### *5.3.3 Relevance for Life on Earth*

The most important role of vitamin E is its antioxidative capacity. But the extent of regeneration and recycling of vitamin E in human tissue is not very well established, and more information is needed about the mechanisms of vitamin E function (IOM (Institute of Medicine) 2000). Spaceflight research could help researchers to better understand the role of vitamin E as an antioxidant in body tissue and in lipid peroxidation processes.

## 5.4 Vitamin K

Two naturally occurring forms of vitamin K exist. Phylloquinone (vitamin $K_1$) is synthesized in plants, whereas menaquinone (vitamin $K_2$) is produced by bacteria. Menadione is a synthetic product that is used as a pharmaceutical but also represents an intermediate in the tissue-specific conversion of vitamin K to menaquinone-4 (Card et al. 2014). The function of vitamin K was originally thought to be strictly limited to involvement in blood coagulation, but evidence suggests that this vitamin is involved in multiple physiological systems. Vitamin K plays a role as a cofactor in the carboxylation of a limited number of proteins. Three

carboxylated proteins—osteocalcin, matrix Gla protein, and protein S—have been identified in the bone. Osteocalcin is synthesized by osteoblasts and in its carboxylated form exhibits strong calcium-binding properties and is related to the bone mineralization process (Shearer 1995). In cases of vitamin K deficiency, undercarboxylated osteocalcin, which lacks some or all of the Gla residues, is synthesized; therefore, blood concentration of undercarboxylated osteocalcin is a sensitive marker for vitamin K nutritional status (Knapen et al. 1989; Sokoll et al. 1997; Vermeer and Hamulyak 1991). The discovery of these vitamin K-dependent proteins in the bone has led to research on the role of vitamin K in maintaining bone health. Epidemiological studies provide evidence for an association between low vitamin K intake and an enhanced osteoporotic fracture risk (Booth et al. 2000; Hart et al. 1985). A higher incidence of femoral neck (Vergnaud et al. 1997) and hip fractures (Szulc et al. 1996) has been observed in patients with high levels of undercarboxylated osteocalcin. Moreover, as a result of vitamin K supplementation, urinary calcium excretion was decreased by 30 % in fast losers (Knapen et al. 1989, 1993).

### 5.4.1 Requirements

Because of the lack of data needed to estimate an average requirement, an adequate intake (AI) is set. The AI for women is 90 μg/day and the AI for men is 120 μg/day (IOM (Institute of Medicine) 2002b). These are the same as the current documented spaceflight requirements. The estimated menu content of vitamin K in the foods provided to astronauts aboard the ISS is $105 \pm 19$ mg/day (Smith et al. 2009), which meets the ISS requirements. As vitamin K is synthesized by the intestinal microflora, deficiency of vitamin K is not common in adults. As no reports about adverse effects in individuals taking higher amounts exist, a tolerable upper intake level (UL) was not established (IOM (Institute of Medicine) 2002b).

### 5.4.2 Effects on Physiological Systems

As bone loss is of major concern during spaceflight, the possibility that vitamin K status plays a role in bone health led to further investigation (Zwart et al. 2011a). The promising results of a vitamin K treatment to protect against bone loss on Earth led to suggestions that such a treatment could also play a role in protecting bone against microgravity-induced mineral loss (Heer 2002; Sugiyama and Kawai 2001). The first investigations of vitamin K metabolism showed a potential benefit in supplementation of vitamin K for bone health (Caillot-Augusseau et al. 2000; Sugiyama and Kawai 2001; Vermeer et al. 1995). Caillot-Augusseau et al. (2000) showed that carboxylation of osteocalcin was decreased in two cosmonauts during both short- and long-duration spaceflight, and it returned to preflight levels soon

after landing. Moreover, in a case study, in-flight supplementation of 10 mg vitamin $K_1$/day (a pharmacological dose) decreased undercarboxylated osteocalcin to preflight levels (Caillot-Augusseau et al. 2000; Vermeer et al. 1995). In a study of plasma phylloquinone in 11 astronauts before and after 4–6 months of spaceflight, an approximate 40 % decrease in plasma phylloquinone after spaceflight was observed (Smith et al. 2005b). Further, uncertainty exists about the efficiency of vitamin K synthesis by the gastrointestinal flora, and the potential for altered absorption, in microgravity (Smith et al. 2009). However, investigations of Zwart et al. (2011a) did not show a change in plasma phylloquinone concentration during or after flight relative to the mean preflight concentration, in samples from 15 crewmembers who had flown on the ISS since 2006. Moreover, they expected to see an increase in undercarboxylated osteocalcin and a decrease in urinary Gla, and neither was observed during or after long-duration spaceflight. These data did not support the idea that a decrease in vitamin K status is induced by microgravity. Therefore, these data do not support the use of vitamin K supplementation as a countermeasure during spaceflight to prevent a vitamin K deficiency or to counteract spaceflight-induced bone loss, because there was no evidence for a decrease in vitamin K status during flight.

Certain evidence exists that synergy occurs between vitamins D and K (Ushiroyama et al. 2002). The connection between these two vitamins might be the vitamin K-dependent (VKD) protein osteocalcin. The gamma-carboxylation of osteocalcin, which is necessary to form hydroxyapatite crystals, is vitamin K dependent. Without a sufficient concentration of vitamin K in blood, osteocalcin remains in part uncarboxylated and thereby is linked to a lower bone density (Booth et al. 2004). Further, the transcription of the osteocalcin gene to messenger RNA is regulated by 1,25(OH)2D and therefore is vulnerable to vitamin D deficiency (Arbour et al. 1995). Another synergy of vitamins K and D is inflammation, which is implicated in both osteoporosis and cardiovascular disease (Bagger et al. 2006). Therefore, vitamin K and D status should be observed during spaceflight, especially during long-duration spaceflight.

### *5.4.3 Relevance for Life on Earth*

This synergy between vitamin D and vitamin K (Ushiroyama et al. 2002) as well as their involvement in calcium homeostasis and in bone and cardiovascular health have significant public health implications.

# Chapter 6
# Water-Soluble Vitamins

The vitamin B-complex group and vitamin C are the so-called water-soluble vitamins, which dissolve in water and are not stored by the body (IOM (Institute of Medicine) Standing Committee on the Scientific Evaluation of Dietary Reference Intakes 1998). As they are eliminated in urine, a continuous daily supply in the diet is required. Eight of the water-soluble vitamins are known as the vitamin B-complex group: folate (folic acid), thiamin (vitamin $B_1$), riboflavin (vitamin $B_2$), niacin (vitamin $B_3$), vitamin $B_6$ (pyridoxine), vitamin $B_{12}$, biotin, and pantothenic acid. B vitamins fall into two categories. They are involved in the reactions of intermediary metabolism related to energy production and redox status, or they are involved in the transfer of single-carbon units (IOM (Institute of Medicine) Standing Committee on the Scientific Evaluation of Dietary Reference Intakes 1998). Moreover, vitamin C is a water-soluble vitamin and it is essential for humans, as we do not have the ability to biosynthesize the compound from glucose due to the lack of gulonolactone oxidase. Vitamin C functions physiologically as a water-soluble antioxidant. It is a matter of concern that water-soluble vitamins are easily destroyed or washed out during food storage and preparation. Despite the presence of fruits and vegetables in the daily diet, nutrient loss is possible during the storage and processing of food. This is also of concern for spaceflight and especially for long-term spaceflight. The space radiation environment is another critical factor that must be controlled for an adequate intake of water-soluble vitamins (Smith and Zwart 2008). Not all water-soluble vitamins are critical or of concern for crewmembers. In the following discussions, only the spaceflight-relevant water-soluble vitamins are pointed out.



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## 6.1 Folate

Folate functions as a coenzyme in single-carbon transfer reactions in the metabolism of nucleic and amino acids. Folate exists in many chemical forms (Wagner 1996). The most oxidized and stable form of folate is folic acid, which occurs rarely in food but is used in vitamin supplements and in fortified food products. There is evidence that folate plays a critical role in reducing the risk of cancer, vascular disease, and psychiatric and mental disorders (IOM (Institute of Medicine) Standing Committee on the Scientific Evaluation of Dietary Reference Intakes 1998).

Inadequate intake of folate leads to a decrease in serum folate concentration, then to a decrease in erythrocyte folate concentration, and a rise in homocysteine concentration in plasma (Finkelstein 1998). Spaceflight affects folate concentration (Smith et al. 2005b). Smith et al. (2005b) detected a decrease in erythrocyte folate of about 20 % ($P < 0.01$). Before launch, the erythrocyte folate of most of the subjects was near the upper limit. After return to Earth, the erythrocyte folate level of these astronauts was at the lower limit of the normal range. As food-processing techniques do not reduce folate availability (Lane et al. 1995), an inadequate folate intake is likely the reason for this decrease. Another reason could be radiation exposure (IOM (Institute of Medicine) Standing Committee on the Scientific Evaluation of Dietary Reference Intakes 1998).

Moreover, there is evidence that the folate and vitamin $B_{12}$-dependent 1-carbon metabolic pathway may be different in crewmembers with and without vision changes during and after spaceflight (Zwart et al. 2012). Crewmembers having ophthalmic changes have an altered metabolic pathway, and this can lead to the buildup of certain intermediates, including homocysteine. Zwart et al. (2012) showed that an association exists between ophthalmic changes and higher concentrations of intermediates of the 1-carbon metabolic pathway (including homocysteine, cystathionine, methylcitric acid, and methylmalonic acid). The authors suggest that differences in this pathway may influence anatomic or physiologic susceptibility to environmental stressors such as fluid shifts or response to cabin $CO_2$.

During short-duration (Zwart et al. 2009a) and long-duration (Zwart et al. 2009b) bed rest, red blood cell folate status did not change. However, folate status may be important during long-term exploration missions because of increases in iron storage during long-duration spaceflight (Smith et al. 2005b).

The spaceflight requirement for folate is 400 μg/day. This is the same as the RDA on Earth. Daily supplementation with folate, vitamin $B_6$, and vitamin $B_{12}$ is associated with a significantly decreased risk for age-related macular degeneration (Christen et al. 2009).

## 6.2 Vitamin $B_6$

The term "vitamin $B_6$" refers to a group of six related compounds: pyridoxal (PL), pyridoxine (PN), pyridoxamine (PM), and their respective 5-phosphates. Vitamin $B_6$ is a coenzyme in the metabolism of amino acids, glycogen, and sphingoid bases (IOM (Institute of Medicine) Standing Committee on the Scientific Evaluation of Dietary Reference Intakes 1998). The clinical symptoms of a vitamin $B_6$ deficiency are seborrheic dermatitis, microcytic anemia, epileptiform convulsions, depression, and confusion (IOM (Institute of Medicine) Standing Committee on the Scientific Evaluation of Dietary Reference Intakes 1998). An excessive intake of vitamin $B_6$ leads to sensory neuropathy (Bassler 1989).

Vitamin $B_6$ is mainly stored in muscle tissue, bound to phosphorylase (Coburn et al. 1988). The major excretory product is 4-pyridoxic acid (Shultz 1981).

During spaceflight, the cross-sectional area of muscle fibers is reduced and a change from type I to type II muscle fibers occurs (Kraemer et al. 2000). This decrease in muscle cross-sectional area could also affect the amount of vitamin $B_6$ that is stored in muscle tissue. During short- (Zwart et al. 2009a) and long-term (Coburn et al. 1995; Zwart et al. 2009a) bed rest, increased excretion of 4-pyridoxic acid could be observed. This excretion may also reflect the loss of vitamin $B_6$ from muscle.

Although there are currently no data showing that vitamin $B_6$ status changes during long-term space missions, the changes observed during bed rest may represent an accurate observation of vitamin $B_6$ status during and after long-duration spaceflight. The stability of the vitamin in the space food supply needs to be determined (Smith et al. 2009).

## 6.3 Vitamin $B_{12}$

Vitamin $B_{12}$, or cobalamin, functions as a coenzyme for two enzymes: methionine synthase and L-methylmalonyl-coenzyme A (CoA) mutase. The latter enzyme catalyzes a methyl transfer reaction in which L-methylmalonyl-CoA is transferred to succinyl-CoA.

Vitamin $B_{12}$ in adequate amounts is essential for normal blood formation and neurological function (IOM (Institute of Medicine) Standing Committee on the Scientific Evaluation of Dietary Reference Intakes 1998); a deficiency of vitamin $B_{12}$ leads to pernicious anemia (van Asselt et al. 1996) and to demyelination of the central nervous system. A deficiency of vitamin $B_{12}$ may lead to an accumulation of folate in serum as a result of slowing of the $B_{12}$-dependent methionine synthase, 5-methyltetrahydrofolate-homocysteine methyltransferase (Oh and Brown 2003). The role of a deficient level of vitamin $B_{12}$ in hyperhomocysteinemia and the promotion of atherosclerosis is under investigation (Zhou et al. 2014). As no adverse effects of an excessive intake of vitamin $B_{12}$ have been reported, no

tolerable upper intake level (UL) exists for this vitamin. Measurement of vitamin $B_{12}$ deficiency is based on serum methylmalonic acid and homocysteine levels, which are increased early in vitamin $B_{12}$ deficiency.

No data currently exist on vitamin $B_{12}$ status during long-duration spaceflight; however, Zwart et al. (Zwart et al. 2012) showed that after spaceflight serum methylmalonic acid concentrations were higher in ISS crewmembers who experienced vision changes (see also the subsection "Folate"). Increased serum homocysteine and low vitamin $B_{12}$ status were independently associated with increased risk for age-related macular degeneration (Christen et al. 2009). As mentioned before, daily supplementation with folate, vitamin $B_6$, and vitamin $B_{12}$ is associated with a decreased risk for age-related macular degeneration (Christen et al. 2009).

## 6.4 Vitamin C

Vitamin C (ascorbic acid) is an essential component of every living cell, to which it provides reducing equivalents for a variety of biochemical reactions (IOM (Institute of Medicine) Standing Committee on the Scientific Evaluation of Dietary Reference Intakes 2000). It is a cofactor for enzymes involved in the biosynthesis of collagen, carnitine, and neurotransmitters. As vitamin C can reduce most physiologically relevant reactive oxygen species (Buettner 1993), it is a very potent antioxidant. Deficiency of vitamin C leads to fatigue, depressed immune function (Schwager and Schulze 1998), and scurvy. The most important concern for spaceflight is the possibility that vitamin C could be degraded in spaceflight foods during long-term space missions when foods are exposed to space radiation. In addition, long-term storage of the vitamin might be a problem. Therefore, vitamin C content and stability in spaceflight food need to be monitored. The spaceflight requirement for vitamin C intake is 90 mg/day. No data are available on the vitamin C intake or vitamin C status of crewmembers.

# Chapter 7
# Minerals

Minerals are inorganic elements, such as calcium, iron, or magnesium, which are essential to the functioning of the human body and are obtained from foods.

For spaceflight issues, some minerals require special attention.

## 7.1 Calcium

More than 99 % of the total body calcium is found as calcium hydroxyapatite in bones and teeth. Bone tissue serves as a reservoir for and a source of calcium. The parathyroid hormone (PTH)-vitamin D endocrine system regulates calcium metabolism, and serum calcium levels are very closely regulated. Maintaining the level of circulating ionized calcium within a narrow range is critical for the human body to function normally. Therefore, calcium needs to be rapidly released from the bone to maintain adequate levels of ionized calcium in serum. High amounts of calcium can be found in dairy products like milk, cheese, and yogurt. Fortification of a number of foods with calcium is becoming more and more common.

### *7.1.1 Requirements*

Calcium is critical for mediating vascular contraction and vasodilatation, muscle function, nerve transmission, intracellular signaling, and hormone secretion.

An inadequate calcium intake leads to a reduced bone mass and osteoporosis. An excess of absorbed calcium leads to kidney stones, hypercalcemia, and ultimately renal insufficiency or even death (IOM (Institute of Medicine) 2011). The requirement for dietary intake of calcium during spaceflight is 1200–2000 mg/day, (National Aeronautics and Space Administration Johnson Space Center 2005) which is higher than the initial ISS requirements (1000–1200 mg/day) (National



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Aeronautics and Space Administration Johnson Space Center 1996). Intakes up to 2500 mg/day are considered safe (IOM (Institute of Medicine) 2011).

### 7.1.2 Effects on Physiological Systems

The immobilization and/or unloading of bones (as in microgravity or bed rest) leads to bone degradation due to the reduction of mechanical stress (Inoue et al. 2000; LeBlanc et al. 2000). Bone loss is a significant health concern for long-term spaceflight (Carmeliet et al. 2001; Holick 2000). The result of skeletal unloading during spaceflight is resorption of bone minerals, which leads to an increase in urinary calcium excretion (Whedon 1984). Negative calcium balance and increased calcium excretion during space missions were documented very early in the Gemini and Apollo flights (Lutwak et al. 1969; Rambaut et al. 1975). Calcium supplementation may seem an obvious choice for a nutritional countermeasure, but this idea has been tested in a number of bed rest studies, without success (Baecker et al. 2010). Disuse-induced bone loss is not efficiently counteracted by high calcium intake alone (Baecker et al. 2010). Moreover, hypercalciuria is an important risk factor for kidney stones (Whiting and Wood 1997). The occurrence of a kidney stone would likely result in the evacuation of the affected crewmember (Smith et al. 2012b). One countermeasure to reduce the renal stone risk is an increase in fluid intake during the mission (Pak et al. 1980).

However, ensuring an optimal and adequate calcium intake is mandatory to avoid exacerbating bone loss in space and under conditions of immobilization. Although it is questionable that the nutritional intake is solely responsible for bone mineral loss, even a moderate protective effect from the diet would benefit crew health.

### 7.1.3 Relevance for Life on Earth

As many health risks are associated with bone and calcium metabolism during space missions, diverse investigations to understand calcium metabolism during spaceflight are undertaken. These investigations and findings will have multiple applications to space travel, and they will probably have implications for bone loss on Earth.

## 7.2 Phosphorus

Phosphorus is most commonly found in nature in its pentavalent form in combination with oxygen, as phosphate ($PO_4^{3-}$). Phosphorus makes up about 0.65–1.1 % of the adult body (Aloia et al. 1984). Eighty-five percent of body phosphorus is found in the form of the calcium phosphate salt hydroxyapatite in bone mineral and other calcified tissues. The acute regulation of blood calcium and phosphorus concentrations is accomplished through the action of PTH and the active form of vitamin D. Deficiency of phosphorus is uncommon and is usually observed only in cases of near-total starvation (Heaney 2012). Symptoms include loss of appetite, muscle weakness, and bone fragility. High serum phosphorus concentration has been shown to impair the synthesis of 1,25(OH)2D in the kidneys, reduce blood calcium, and lead to increased PTH release (Calvo et al. 2014). The increase in PTH then results in a decrease in calcium excretion and increased bone resorption. Hyperphosphatemia occurs in individuals with impaired kidney function. High phosphate concentrations in blood are associated with increased risk of cardiovascular disease. The adverse effects of hyperphosphatemia include reduced calcium absorption and calcification of tissues, particularly the kidneys.

### *7.2.1 Requirements*

The RDA for phosphorus is 700 mg/day in healthy adults. The UL is 4,000 mg/day (IOM (Institute of Medicine) Standing Committee on the Scientific Evaluation of Dietary Reference Intakes 1997).

Concerns exist about high phosphoric acid intakes with the diet (IOM (Institute of Medicine) Standing Committee on the Scientific Evaluation of Dietary Reference Intakes 1997). Suggestions have been made that a low calcium-to-phosphorus ratio (Ca:P ratio) may be detrimental to the bone. Estimates of optimal Ca:P intake ratios have frequently been based on the calcium and phosphorus needs of bone building (Nordin et al. 1976).

### *7.2.2 Effects on Physiological Systems*

Measurements of urinary phosphorus concentration during ISS missions showed a decrease of 45 % after landing relative to before launch (Smith et al. 2005b). Moreover, findings from Skylab experiments showed that plasma phosphate tended to increase during flight (Leach & Rambaut 1977). Excretion of phosphorus in bed rest experiments did not change relative to ambulatory conditions (Zwart et al. 2009a).

As a higher intake of dietary phosphorus, especially relative to calcium intake, can have an effect on the musculoskeletal (Takeda et al. 2014) and cardiovascular systems (Calvo and Park 1996), the calcium:phosphorus ratio should be around 1.0 or higher. For the ISS, the requirements are a calcium:phosphorus ratio higher than 1.0, and it should not exceed 1.5 (National Aeronautics and Space Administration Johnson Space Center 1996, 2005; Smith et al. 2009). However, the diet onboard the ISS provides an excess of phosphorus, leading to a Ca:P ratio of 1.8.

### *7.2.3 Relevance for Life on Earth*

As there are concerns about the increasing amount of phosphates in the Western diet, which is largely attributed to phosphoric acid in some soft drinks and the increasing use of phosphate additives in processed foods (Calvo 2000; Calvo & Park 1996), findings from spaceflight-related research could contribute to understanding the implications of a diet high in phosphorus and the mechanisms by which its effects are manifested.

## 7.3 Magnesium

Fifty to 60 % of the total body magnesium resides in the bone in the adult (IOM (Institute of Medicine) Standing Committee on the Scientific Evaluation of Dietary Reference Intakes 1997). One-third of the skeletal magnesium is exchangeable and may serve as a reservoir for maintaining a normal extracellular magnesium concentration. The kidney is the principal organ involved in magnesium homeostasis (Quamme and Dirks 1986).

Iseri and French (1984) called magnesium "nature's physiological calcium channel blocker." Even mild degrees of magnesium depletion may result in a reduced serum calcium concentration (Fatemi et al. 1991). Magnesium depletion may lead to hypocalcemia (Rude et al. 1976) and to muscle cramps, hypertension, and cerebral vasospasms, as calcium plays an important role in skeletal and smooth muscle contraction.

A nutrient interaction between magnesium and phosphorus also exists. Dietary phytates bind magnesium to phosphate groups on phytic acid (Brink and Beynen 1992). Subjects consuming high-phosphate diets have a decrease in intestinal magnesium absorption. This might be explained by the ability of phosphate to bind magnesium (Hardwick et al. 1991; Reinhold et al. 1991).

No adverse effects are associated with toxicity from naturally occurring sources of magnesium.

### 7.3.1 Requirements

The dietary requirement for magnesium on the ISS is 420 mg/day and 320 mg/day for men and women, respectively (National Aeronautics and Space Administration Johnson Space Center 1996, 2005; Smith et al. 2009). The RDA is 420 mg/day for men aged 31–70 years and 320 mg/day for women aged 31–70 years.

### 7.3.2 Effects on Physiological Systems

A decrease in urinary magnesium that occurs after exposure to spaceflight or bed rest showed that urinary magnesium and phosphorus concentrations were about 45 % less after landing than before launch (Smith et al. 2005b; Zwart et al. 2009b). These results are in accordance with earlier investigations (Leach 1992). This decrease in urinary magnesium and phosphorus might be caused by a suboptimal magnesium intake. Also, data from bed rest showed that urinary magnesium was about 30 % lower after 90 days of bed rest than it was before bed rest. This decrease could be observed in short- and long-duration bed rest (Zwart et al. 2009b). Urinary and dietary magnesium were not significantly correlated.

Decreased urinary magnesium represents a risk in long-duration spaceflight, as magnesium inhibits formation of calcium oxalate renal stones (Su et al. 1991). Whether the decrease observed during spaceflight and bed rest is related to altered dietary intake or to altered bone metabolism needs to be further investigated. Moreover, magnesium has been shown to have effects on the cardiovascular system (Rowe 2010; Volpe 2013). Therefore the decreased magnesium excretion after spaceflight needs to be further investigated, with particular attention to the cardiovascular deconditioning that occurs during and after spaceflight.

### 7.3.3 Relevance for Life on Earth

As mentioned previously, magnesium has been shown to affect the cardiovascular system (Rowe 2010; Volpe 2013). Spaceflight research could give new insights into the effects of magnesium in cardiovascular disease.

## 7.4 Iron

Iron is an essential component of a number of proteins. It is an important element in enzymes, and almost two-thirds of iron in the body is found in hemoglobin, the primary protein found in red blood cells (IOM (Institute of Medicine) Standing

Committee on the Scientific Evaluation of Dietary Reference Intakes 2001). Hemoglobin and myoglobin are heme-containing proteins that are involved in the transport and storage of oxygen. Myoglobin functions in short-term storage and transport of oxygen in muscle cells (Yip 1996). Iron also functions in electron transport and energy metabolism. Cytochromes contain heme as the active site. They act as electron carriers and have important roles in mitochondrial electron transport. Moreover, iron has antioxidant and beneficial prooxidant functions. Peroxidases and catalases are heme-containing enzymes that protect cells against the accumulation of hydrogen peroxide, a potentially damaging reactive oxygen species (ROS).

Iron deficiency is the most common deficiency in the world (Yip 1996). Most of the symptoms of iron deficiency are a result of the associated anemia. The most important functional indicators of iron deficiency are reduced physical work capacity and impaired cognitive function.

As the severity of iron toxicity is related to the amount of elemental iron absorbed, an iron overdose is an emergency situation. Within 1–6 h of ingestion, symptoms may include nausea, vomiting, abdominal pain, tarry stools, lethargy, weak and rapid pulse, low blood pressure, fever, difficulty breathing, and coma. Twelve to 48 h after iron ingestion, symptoms may return and may include serious signs of failure in the following organ systems: cardiovascular, kidney, liver, hematologic (blood), and central nervous systems. Long-term damage to the central nervous system, liver (cirrhosis), and stomach may develop 2–6 weeks after ingestion (IOM (Institute of Medicine) Standing Committee on the Scientific Evaluation of Dietary Reference Intakes 2001).

The content of body iron is about 4 g in the adult human and is determined by dietary supply, physiological iron demands, and adaptation (Cook 1990). Dietary iron is a function of both content and bioavailability of total food iron. The bioavailability of iron is lower in nonheme than in heme iron sources.

### *7.4.1 Requirements*

The spaceflight requirement for intake of dietary iron is 8–10 mg/day for men and women. The RDA is 8 mg/day for men aged 19–70 years, 18 mg/day for women from 19 to 50 years, and 8 mg/day for women over 50 years. The tolerable upper intake limit for adults as defined by the Institute of Medicine is 45 mg/day (IOM (Institute of Medicine) Standing Committee on the Scientific Evaluation of Dietary Reference Intakes 2001). This amount is based on gastrointestinal distress as an adverse effect.

### 7.4.2 Effects on Physiological Systems

Red blood cell (RBC) mass and iron metabolism are altered during spaceflight (Alfrey et al. 1996a; Udden et al. 1995). RBC mass decreases about 10 % because of neocytolysis (Alfrey et al. 1996b, 1997). A consequence of the decreased RBC mass is the transfer of iron from newly synthesized cells into storage proteins and processes. Investigations showed that serum ferritin, an index of iron storage, is increased after spaceflight (Smith et al. 2002, 2005b). Moreover dietary iron content is very high in spaceflight food ($20 \pm 6$ mg/day). The reason for this is that many of the commercial food items in the ISS menu are fortified with iron (Smith et al. 2009). After landing, iron metabolism returns toward normal within a few days, although the replenishment of RBC mass may take several weeks. The repletion of RBC mass occurs after the return of plasma volume. Therefore dilutional "anemia" often occurs (Smith et al. 1997a). However, the efficient postflight recovery of RBC mass suggests that it represents an adaptation to weightlessness (Smith et al. 2009). Iron metabolism is also altered during bed rest (Zwart et al. 2009b). Zwart et al. (2009b) showed that bed rest induces an increase in hemoglobin. However, unlike spaceflight results, no changes were observed in serum ferritin. This shows that for iron metabolism bed rest cannot mimic the complexities of spaceflight.

# Chapter 8
# Supplements

## 8.1 Antioxidants

Oxidative damage has been implicated in the etiology of chronic diseases and acute pathologic states (Stein 2002). Spaceflight (Markin et al. 1997; Stein and Leskiw 2000) and long-term bed rest (Smith et al. 2005a; Zwart et al. 2009b) lead to an increase in oxidative stress. Several in-flight studies have shown changes in cell-mediated immunity (Taylor and Janney 1992), cytokine production (Crucian et al. 2000, 2014; Sonnenfeld 1994), signal transduction (Cogoli 1997), and natural killer cell activity (Kaur et al. 2004). Stein et al. (Stein 2002) showed that long-duration spaceflight is associated with an increase in oxidative stress after return to 1 g. The increased oxidative stress is more pronounced after long-duration spaceflight and lasts for several weeks after landing (Markin et al. 1997).

Oxidative stress, resulting from excessive formation of reactive oxygen species (ROS) or dysfunction of antioxidant defense systems, also leads to an increase in bone resorption processes. Free radicals may affect bone remodeling by regulating osteoclast activity (Mehat et al. 2010). Oxidative stress controls the function of both osteoclasts and osteoblasts (Silverton 1994; Suda et al. 1993).

Antioxidants that can mitigate the damaging effects of ROS have been the focus of recent research. Rivas et al. (2012) showed that bone mineral density was higher in participants defined as high antioxidant consumers in all age groups and also that osteoporotic women have lower serum antioxidant levels relative to controls (Yang et al. 2008). Sendur et al. (2009) observed significantly lower serum antioxidant enzyme activity in postmenopausal women with osteoporosis than in non-osteoporotic healthy controls. This suggests a tight association between oxidative stress and the pathogenesis of osteoporosis in humans.

One example of how dietary patterns (as opposed to discrete nutrients) that include foods rich in antioxidants have been shown to substantially affect bone loss is the protective effect of fruits and vegetables in general on the bone (Boeing et al. 2012; Xie et al. 2013a; Zeng et al. 2013). Fruits and vegetables are rich in



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vitamins C and K, carotenoids, phytochemicals, and flavonoids. Phytochemicals in fruits and vegetables may exert their protective effects on bone by inhibiting bone resorption and stimulating bone formation, as well as by mediating the scavenging of free radicals (Arjmandi et al. 2002). Another possible mechanism is their role in acid-base metabolism and neutralizing acid loads from other components of the diet so that the skeleton is not used as a buffer to resorb and neutralize acid loads (New 2003). Several studies show that greater fruit and vegetable intake is associated with higher bone mineral density (Chen et al. 2010; Hardcastle et al. 2011; Li et al. 2013; New et al. 2000; Rivas et al. 2013). In light of these studies, consuming at least 470 g of fruits and vegetables per day (about 6 servings) is recommended for optimal bone mineral status.

Specific fruits, including dried plums (i.e., prunes, *Prunus domestica* L.), have been shown to have protective effects on bone. Dried plums are rich in flavonoids and have been shown to very effectively prevent and reverse bone loss in both animal and human models. In animals, plum intake increases bone mineral density and restores bone that has already been lost (Bu et al. 2007; Deyhim et al. 2005; Halloran et al. 2010). The mechanism of this recovery is related to the downregulation of osteoclast differentiation and upregulation of osteoblast and glutathione activity (Rendina et al. 2013). In randomized clinical trials with humans, plums also showed effects beneficial for the bone (Arjmandi et al. 2002; Hooshmand et al. 2011; Hooshmand and Arjmandi 2009). One study with postmenopausal women found that daily dried plum consumption (100 g/day) for 3–12 months effectively increased (compared to control subjects provided with similar amounts of dried apple) bone mineral density of the ulna and spine (Hooshmand et al. 2011). In another study with postmenopausal women, 100 g/day of dried plums for 3 months increased bone-specific alkaline phosphatase and IGF-1, reflecting increased bone formation (Arjmandi et al. 2002).

The mechanism of action of flavonoids in protecting the bone varies. The major metabolite of the flavonoid hesperidin in orange juice activates bone morphogenetic proteins, and this activation increases expression of Runx2, which drives osteoblast differentiation from multipotent mesenchymal stem cells (Trzeciakiewicz et al. 2010). Likewise, the anabolic bone action of berries occurs through the upregulation of mitogen-activated protein kinase p38, which ultimately can activate bone cell proliferation and differentiation (Chen et al. 2010), and dried plum extract inhibits increases in RANKL expression in response to TNFα and osteoclast differentiation (Bu et al. 2009).

Another example of specific antioxidants having a protective effect on the bone is an epidemiological study that showed dietary total carotenoids were inversely associated with hip fracture (Dai et al. 2013), and one found a positive association of lumbar spine bone mass with dietary beta-carotene in postmenopausal women (Wattanapenpaiboon et al. 2003). A recent paper providing evidence that lycopene may be beneficial for bone reports the results from a controlled study among postmenopausal women whose diets were lycopene restricted for 1 month (Mackinnon et al. 2011a). Dietary restriction of lycopene significantly increased biomarkers of oxidative stress and bone resorption. In a separate intervention trial,

lycopene supplementation to postmenopausal women for 4 months resulted in decreased bone resorption (Mackinnon et al. 2011a). Animal studies also support a role of lycopene in increasing bone mineral density after 8 weeks of supplementation (Liang et al. 2012).

In further experiments, it was demonstrated that flavonoids increase the expression of genes for osteoblast differentiation proteins such as osteocalcin in isolated mouse marrow-derived mesenchymal stem cells (Srivastava et al. 2013) and the MC3T3-E1 mouse osteoblastic cell line (Kim et al. 2012).

A strong inverse association has also been shown between plasma vitamin C, used as a biomarker for fruit and vegetable intake, and HbA1c (glycated hemoglobin), and between plasma vitamin C and fasting and 2-h blood glucose concentrations, in people at high risk for development of type 2 diabetes mellitus (T2DM) (Carter et al. 2013). One possible mechanism for improving glucose tolerance and/or insulin sensitivity is through mediating the scavenging of free radicals.

For instance, Hosoda et al. (2003) have suggested that green tea and most likely the major catechin epigallocatechin-3-gallate (EGCG) affect glucose regulation by reducing plasma glucose concentrations in T2DM and improve oral glucose tolerance in healthy subjects. In a recently published meta-analysis of 22 randomized controlled trials in humans, green tea catechin consumption significantly reduced fasting blood glucose (Zheng et al. 2013). Green tea catechins also significantly increased glucose tolerance in animals (Shao et al. 2013; Yan et al. 2012), reduced ROS content, attenuated dexamethasone, and TNF-α promoted and increased glucose uptake ability. EGCG also promoted GLUT-4 translocation (Hosoda et al. 2003; Yan et al. 2012).

Resveratrol (3,5,4′-trihydroxystilbene) has been demonstrated to reduce oxidative stress as well as the inflammatory response and to improve insulin sensitivity in T2DM patients and older patients with impaired glucose tolerance (Brasnyo et al. 2011; Crandall et al. 2012; Jimenez-Gomez et al. 2013). Here increased insulin gene expression (Xie et al. 2013b) and more efficient insulin signaling via the protein kinase B (Akt) pathway (Brasnyo et al. 2011) seem to be induced.

The effect of antioxidants on bone could be mediated directly by their acting as free-radical scavengers, preventing oxidation-induced damage to bone cells (Mackinnon et al. 2011b). Moreover, evidence exists that the effect could be mediated indirectly through increasing GH (growth hormone) and IGF 1 (insulin-like growth factor 1).

Up to now, the effects of antioxidants in microgravity have not been tested in humans. However, because of the great potential for improving space travelers' health during long-term missions, this should be one goal for future spaceflights.

## 8.2 Alkaline Salts

As mentioned above, high protein intake may keep up muscle protein synthesis, but on the other hand, it has also been shown to lead to low-grade metabolic acidosis. Metabolic acidosis, as well as inactivity such as in microgravity, increases muscle protein breakdown as well as blood glucose levels (Straumann et al. 1992). The data on muscle protein breakdown in humans are also supported by animal experiments in which chronic metabolic acidosis led to a 43 % increase in urinary nitrogen. Hence, the protein catabolic effect in these animals (rats) was caused by stimulation of proteolysis without any effect on protein synthesis (May et al. 1986). When accompanied by inadequate consumption of alkali equivalents, high protein intake may also contribute to bone loss and may increase fracture risk by increasing bone resorption (Bushinsky 1994; Frassetto et al. 1998; Houillier et al. 1996; Wiederkehr and Krapf 2001).

Low-grade metabolic acidosis can be caused by consuming a high percentage of animal protein, which—among all dietary protein sources—contains the largest amounts of sulfur-containing amino acids. Sulfur-containing amino acids are metabolized to sulfuric acid, which decreases blood pH. In addition, meat has a larger amount of protein per 100 g than protein-rich vegetables and contains less potassium than fruits and vegetables. Consuming potassium or potassium salts may compensate for metabolically induced low-grade metabolic acidosis caused by animal protein, which explains why similar amounts of protein provided by vegetables or fruits do not lead to low-grade metabolic acidosis. Animal studies have affirmed that correction of metabolic acidosis has a favorable effect on protein metabolism, nitrogen balance, and growth (Bailey and Mitch 2000), suggesting that supplementation of an alkaline salt in combination with a high-protein diet might compensate for an increased muscle protein breakdown caused by low-grade metabolic acidosis. The same holds true for the bone (Frassetto et al. 2005). In bed rest, when high animal protein intake is counteracted by high potassium intake, bone resorption markers are significantly lower (Zwart et al. 2004, 2005).

Supplementation of potassium bicarbonate, an alkaline salt, may reduce urinary nitrogen and calcium excretion and thereby save lean tissue (Dawson-Hughes et al. 2008; Frassetto et al. 1997) and potentially bone mass. Consequently, compensation for low-grade metabolic acidosis, together with high protein intake, might enhance the muscle mass-saving effect of high protein intake alone and may counteract increased bone resorption caused by high animal protein intake.

Recent evidence suggests that low-grade metabolic acidosis associated with a protein-rich diet low in organic potassium salts—quantifiable by net acid output in daily urine—can also evoke a modest increase in cortisol production (Maurer et al. 2003; Remer et al. 1998). Since cortisol promotes development of visceral obesity and has a direct negative impact on insulin function throughout the body, even a modest sustained upregulation of cortisol production may have the potential to increase the risk for insulin resistance syndrome and T2DM. This idea is supported by results from animal experiments in which chronic metabolic acidosis

led to an 87 % increase in urinary corticosterone excretion (May et al. 1986). Recently an association between diet-dependent net acid excretion and the sum of the urinary glucocorticoids cortisol and cortisone has been reported in women on their usual diets (Remer et al. 2008a). Urinary free cortisol is regularly analyzed as an integrated measure of blood free cortisol concentrations during the entire day. However, as large amounts of cortisol are reversibly inactivated to cortisone (especially by the kidney) and this cortisone can then be readily reactivated to cortisol in almost all extrarenal tissues, cortisone itself represents a potentially active glucocorticoid (Remer et al. 2008b). Correspondingly, urinary cortisone should be quantified and considered together with urinary cortisol if specific and sensitive analyses of glucocorticoid status are required. The sum of both glucocorticoids has been referred to as potentially bioactive free glucocorticoids, and its level can be expected to rise if the effects of low-grade metabolic acidosis augment those of stress. Supplementing a diet containing a high potential renal acid load with an alkaline salt might therefore prevent bone and muscle loss as well as maintain glucose tolerance in spaceflight.

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