



BASICS IN CLINICAL NUTRITION

Fifth Edition

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Associate Editors

Simon P. Allison

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Rémy F. Meier

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The European Society for Clinical
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Publishing House Galén

Na Popelce 3144/10a, 150 00 Prague 5, Czech Republic

Managing Editor Lubomír Houdek, Dr.

Editor-in-Chief Soňa Dernerová, Dr.

Composition Václav Zukal – Galén, Prague

Print FINIDR, s. r. o., Lipová 1965, 737 01 Český Těšín, Czech Republic

www.espenbluebook.org

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Supported by the program PROGRES Q40/12.

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ISBN tištěné verze 978-80-7492-427-9

ISBN e-knihy 978-80-7492-782-9 (1. zveřejnění, 2025) (epub)

ISBN e-knihy 978-80-7492-783-6 (1. zveřejnění, 2025) (mobi)

ISBN e-knihy 978-80-7492-781-2 (1. zveřejnění, 2025) (ePDF)

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INTRODUCTION

I am extremely pleased and proud for the opportunity to introduce, on behalf of ESPEN, the fifth edition of our very well-known and widely used book “Basics in Clinical Nutrition”. ESPEN is particularly proud to present an outstanding team of authors, including most prominent experts for each topic, under the well-proven leadership of Professor Lubos Sobotka. Our gratitude goes to all of them for their expertise and tremendous work in providing a profound revision, that was required to successfully keep track of rapid advances and increasingly recognized importance of clinical nutrition in all medical specialties.

We believe that the effort to create a comprehensive tool, covering and connecting all topics and key questions of clinical nutrition, is quite meaningful and necessary. While focused approaches are allowed by our major ESPEN educational programmes, namely the over-arching Life

Long Learning virtual university (LLL) and the very successful Guidelines, Basics in Clinical Nutrition provides the reference knowledge from everyday practice to unusual situations in our discipline, as well as nutritional advice and consultation for other specialties. Basics in Clinical Nutrition also importantly represents the ideal tool for overall refreshment and update, or indeed for introduction to the field for non-specialists and medical students.

As for all previous editions, the traditional Blue cover contains thoroughly renewed content and knowledge, that I am sure will also renew the success of the book worldwide, as strongly testified by its numerous translations. The Blue book has helped and will continue to contribute connecting the clinical nutrition community. I wish you an excellent reading and studying experience.

Rocco Barazzoni
ESPEN Chairman

COMMENTARY ON THE 4TH EDITION OF BASICS IN CLINICAL NUTRITION

It has been about twelve years and four editions since Professor Lubos Sobotka, with the support of the ESPEN Educational Committee, first undertook the important responsibility to produce “Basics in Clinical Nutrition” as its Editor-in-Chief, and we are all grateful to him for his dedication, talent, leadership, persistence and hard work in continuing to keep us up to date with the state of the art knowledge, information, and data in the broad and vital field of nutrition support. Personally, I am particularly appreciative of his friendship, collegiality, generosity and professional collaboration on multiple projects of mutual interest throughout the years, including invitations to participate as an author in the third and fourth editions of this prestigious tome. We are most fortunate that he has successfully attracted and enlisted the elite group of expert, experienced, talented clinicians, scientists, nutritionists, investigators, innovators, teachers, respected colleagues, and cherished friends to partner with him and his six distinguished Associate Editors in this yeoman effort to summarize and update the current status of clinical nutrition and metabolism. We are also most beholden to the ninety-nine author-scientists from twenty-seven countries throughout the world who have shared their wealth of knowledge, experience, judgment, and wisdom, together with their invaluable efforts, skills, and time, in order to consummate this most commendable and priceless educational contribution to the elite practice of medicine.

Nutrition support is an amalgam of art and science, as is essentially the rest of the broad field of medicine. Both areas of endeavor have had their origins in curiosity; empirical observations; concepts; innovations; experimentations; philosophy;

ideals; and the practical application or translation of newly acquired, accumulated, evaluated, and appraised knowledge and/or experience to clinical use. For millennia, this had formed the basis for the practice of medicine, and advances had been made arithmetically and tediously for hundreds of years until the late nineteenth century and early twentieth century, when discovery, creativity, science, and technology virtually exploded, and has continued to advance logarithmically to the current time. Moreover, this phenomenal increase in knowledge, technology, and expertise is likely to continue in the foreseeable future and to have a significant influence on the application of nutrition support to the practice of medicine, maintenance of health, and achievement of optimal clinical and human performance outcomes. However, in the future, as in the past, it is expected that all new ideas, concepts, proposals, or adjuncts related to improving the quality of health care in general and nutrition support specifically, will be accompanied by ample amounts of doubt, skepticism, criticism, prejudice, controversies, challenges, and resistance to change. Accordingly, the scientific method must be applied consistently, diligently, fairly, dispassionately, honestly, morally, and ethically to allow evaluation of as many aspects of problems, solutions, and situations as possible in order to achieve optimal evaluation, interpretation, and useful applications. Many thousands of studies have been conducted by clinicians, scientists, engineers, and many other investigators and empirical observers throughout the world to validate, refine, and advance the art and science of parenteral and enteral nutrition as well as to translate and apply new knowledge, data, technology, skills, and expertise in the pursuit of

optimal nutrition support and health. This process will continue inexorably and will repeat itself, each time rising to a higher level, while inducing and creating the inevitable and essential changes that will eventually improve the safety, efficacy, efficiency, applicability, and affordability of nutrition support. Ultimately, the risk-benefit, cost-benefit, and outcome data must be accrued, scrutinized, and analyzed to justify the resultant, indicated changes not only to our patients and colleagues, but also to the continuously enlarging numbers of stakeholders in our increasingly enormous and expensive health care systems.

Even after working in this area for a short time, one soon becomes aware of the intricacies, complexities, and precision of the countless phenomenal biochemical interactions that occur continually within the body, the end result of which we interpret as life. The theoretical possibility of modifying these processes to the maximum advantage of the individual is a fascinating, captivating, and motivating idea for many basic and clinical scientists. In trying to learn what the optimal substrates might be for the promotion and maintenance not only of ideal molecular and cellular structure, within the limits of genetic control, but also of optimal cellular and systemic function, one soon becomes aware of the differences in these crucial relationships among the various human age groups. One can also become mesmerized, challenged, and enmeshed by the myriad combinations of disparate factors, including genetics, pathophysiological processes, nutritional status, preventative and therapeutic indications, operative procedures, trauma, immunocompetence, sepsis, and countless co-morbidities, which can significantly alter the inter-relationships among the innumerable individual nutrient substrates and prescribed combinations thereof. If the idealistic, ambitious, and occasionally overwhelming and frustrating goal of providing optimal nutrition to all patients, under all conditions, at all times, could be achieved, patients would be highly likely to enjoy optimal health and quality of life; and perhaps achieve their maximum potentials for performance, accomplishment, satisfaction, happiness, and productive longevity. Contrarily, the extent to which this goal

can not be achieved, thus compromising the patients' ability and capacity to achieve maximum potential of the body cell mass, represents the extent to which the patient is unhealthy, at risk, disordered, diseased, traumatized, compromised, disabled, suppressed, or otherwise sick or infirm. What started as a challenging wonderment to me more than half a century ago, has become a career-long obsession accompanied by periods of elation, creativity, discovery, and successful outcomes; punctuated by frustrations, disappointments, and despair associated with complications, suboptimal results, and failures. Despite how discouraging this may seem, such is the inherent nature of the medical profession, and if practicing the broad field of medicine is a true vocation, privilege, and responsibility, in contrast to a job, or merely a means to make a living, one must continue with persistence, resilience, core values, and purpose toward achieving excellence, if not perfection, in the provision of nutrition support and all other indicated services to all of our patients, but especially to those whose lives may depend upon our proficiency and consistency in providing these services. It is a noble calling; it is *not* for the faint-hearted; and it is *not* for those who lack courage, dedication, strength, persistence, and resilience.

Anyone interested in providing optimal nutrition support to their patients knows that it is essential that knowledge, judgment, proficiency, and competency must prevail in choosing the best nutrient constituents of a feeding regimen and in deciding how these formulations might best be provided for the maximal benefit and safety of the patient under virtually any condition or in any adverse situation. Not to have knowledge, experience, or proficiency with every tool in our clinical tool box detracts from our education and training; our trust, competence, and professionalism; and our morals, ethics, and obligations. Above all, the practice of optimal nutrition support should not be adversely influenced by self-ambition, self-interest, prejudice, financial gain, stature, and other distractions. Practitioners who always treat their patients with enteral nutrition, and those who always treat their patients with parenteral nutrition are both likely to be practicing less than optimal

nutrition support. The judicious use of the most appropriate feeding modality in every conceivable clinical situation requires extensive versatility, experience, judgment, proficiency, wisdom, and equanimity. It bodes well for practitioners of nutrition support to appraise a given clinical situation comprehensively in order to identify and define the goals of nutrition support, and to choose and use the most appropriate nutrition support tools proficiently in the overall comprehensive management of the patient. It would be a most honorable endeavor for all of the members of the health care profession to direct our efforts, talents,

and resources to perfecting nutrition support to the point that we all could nourish our patients by the most efficacious methods and techniques possible to provide substrates sufficient in quality and quantity to support and allow the maximum number of cells in the body cell mass to perform optimally the functions for which they were designed. We owe it to our patients to do so. Mastering the information, knowledge, technology, data, skills, judgment, and wisdom presented in this outstanding volume of the Fourth Edition of "Basics in Clinical Nutrition," will undoubtedly be an invaluable asset in achieving this lofty goal.

Stanley J. Dudrick, MD, FACS

EDITOR'S REMARKS

Metabolic care and clinical nutrition are indispensable areas of contemporary medicine. This is particularly important at the present time when medical care is capable of helping patients in a greater number of complicated conditions than in the past. However, medicine presently consists of many relatively narrow and separated medical specialities with the aim of achieving quick success rather than a deeper understanding of the problem. Proper nutritional and metabolic support requires a holistic approach based on an understanding of the integrative role of metabolism and metabolic pathways and the subsequent provision of comprehensive care.

Reliable education is essential for the dissemination of novel scientific results and their incorporation into clinical practice. The European Society for Clinical Nutrition and Metabolism (ESPEN) has accepted the challenge to organise both research and educational activities in metabolism and nutritional support for almost 45 years. During this time, ESPEN has integrated the various medical disciplines through their shared and unique nutritional and metabolic aspects. ESPEN has organised educational activities such as courses in clinical nutrition and the ESPEN Life-Long Learning (LLL) Programme. It has already been more than twenty years since I edited the first manual for the ESPEN Basic Courses.

The first edition of *Basics in Clinical Nutrition* was published exactly 20 years ago. Very positive reactions, together with constructive criticism from readers and future authors, led naturally to new editions in 2000, 2004, and 2011. Each edition was modernised and enhanced by a team of enthusiastic editors and excellent authors. Thanks to their ideas, the quality of the book rose and it

became even more useful for students, physicians, dietitians, nurses, and pharmacists. The popularity and usage of this book has been outstanding and the last three editions are available in ten different languages.

Unfortunately, during this exciting time, some Blue Book supporters, friends, and excellent editors and authors passed away and are not with us anymore. Therefore, I wish to remember Michael Barnet, Peter Furst, Xavier Leverve, Marek Pertkiewicz, Herbert Lochs, and Keneth Fearon; although they are no longer with us, their ideas are indispensable parts of this book.

Four years ago, we started to work on this fifth edition of the Blue Book that was completed in 2019. Seven associate editors and more than 100 authors from 27 countries have contributed to this edition. Most of authors are leaders in the field and, together, they represent the best of the world's specialists in metabolic care and nutrition. I would like to take this opportunity to thank all of the authors who have provided their scientific knowledge and clinical experience.

My great thanks belong also to the whole team of associate editors for their valuable help, support, and criticism. Very special thanks also go to Sandy Field who was responsible for English corrections and edited each word in the whole book.

We tried to keep the unique style of the book and hope we have succeeded. Of course, we were not able to prevent some overlaps and occasional apparent contradictions; this is because we do not have firm answers to all questions connected with nutrition and metabolism. It should be emphasized that this book is not intended to be merely a collection of guidelines and clinical recommendations, but also as a book that highlights

the pathophysiological context of metabolic pathways and their clinical and nutritional consequences. I hope that this book will be useful, not only as a source of knowledge and of up-to-date information for physicians, dieticians, pharmacists, nurses, and students in that it will help to improve practice in clinical nutrition, but also that the Blue Book will be a provocative inspiration for metabolic research for some readers.

I hope that in the future we will be able to create new editions of the Blue Book written according to the latest knowledge and covering new elements of clinical nutrition. Therefore, I welcome all your remarks and criticisms, which will be invaluable in planning and developing future versions of the Blue Book to be published within the next few years.

Luboš Sobotka
Editor-in-Chief

Hradec Králové August 2019

1. BASIC CONCEPTS IN NUTRITION

1.1. Energy and protein balance

J. Kondrup, M. Elia

Learning objectives

- To understand Basic concepts in energy and nitrogen balance during health and disease
- To be familiar with the terms homeostasis, homeorhesis, adaptation, and accommodation.

Basic concepts

- **Homeostasis** refers to the metabolic regulatory mechanisms that act to keep the body in a constant condition with respect to physiological function and reserves of energy and other nutrients.
- **Homeorhesis** refers to regulatory mechanisms that allow the body to change from one homeostatic, stable condition to another in an organised fashion, e.g. growth during childhood, or the onset of lactation¹.

The concept of homeorhesis can be extended to weight gain after a period of weight loss, and perhaps also to weight loss itself, as long as it follows an organised pattern. Mild disturbances of homeostasis or homeorhesis lead to **adaptation**, without loss of function, e.g. the decrease in resting energy expenditure during starvation, while more severe disturbances lead to **accommodation**, or changes in function, (e.g. the reduction in physical activity during prolonged semi-starvation), with the aim of maintaining other more vital functions.

Although much is known about the homeostatic regulatory mechanisms, which govern the transition between the fasted and fed states, less is known about homeorhetic mechanisms. Short-term experiments or a prolonged mild disturbance lead mainly to adaptation. More severe stimuli lead to breakdown of these mechanisms causing accommodation and resulting in disease or aggravation of disease as a consequence of loss of physiological function.

An important difference between protein and energy balance concerns the effects of increasing intake. With increasing protein intake (in subjects with a constant and adequate energy intake), nitrogen balance becomes more positive as protein is deposited in the body. With further increases, there is little or no further protein retention: nitrogen balance is maintained while the extra protein is oxidized. In contrast, the body has little capacity to oxidize excess energy, so that when extra energy is provided, most of it is deposited. Therefore, in deciding the amount of dietary protein required to maintain nitrogen balance in health, there is a range of intakes to choose from. In contrast, in deciding how much energy is required to maintain energy balance, there is essentially only one intake that applies; for groups of individuals this is the average energy intake producing energy balance.

Components of energy balance

Total energy expenditure (TEE) in healthy subjects consists mainly of resting energy expenditure (REE: about 60% of TEE) and activity-induced energy expenditure (AEE: about 30% of TEE). In addition, diet-induced energy expenditure (DEE) is about 10% of TEE (see chapter 2.2).

REE is the result of homeostatic reactions such as maintaining ion gradients across cell membranes and of substrate cycling, e.g. the constant synthesis and breakdown of protein, glycogen, adipose tissue and intermediates in gluconeogenesis. These cycles serve the purpose of maintaining an alert state of metabolism enabling rapid reactions to external stimuli.

! If a reaction is simultaneously running in the forward direction at a rate of 100 units and backwards at a rate of 99 units, a regulation by 10% in each direction (up- and down-regulation) will have a 210-times larger effect than a 10% stimulation of a single forward reaction running at a rate of one unit.

REE is mainly a product of the metabolism of lean body mass and is, therefore, dependent on variables related to it, e.g. body weight, height, sex, and age. Injury and infection increase REE via neural and cytokine stimuli to the hypothalamus and changes in catecholamine and neurotransmitter secretion. In most cases, the increase is modest and largely offset by immobility. AEE is highly variable, depending on the amount of physical activity, of course, but also on physical capacity since a training paraplegic patient, for instance, may have several-fold higher energy expenditure during a specific activity compared to a healthy person.

A fixed value for TEE, e.g. $30 \text{ kcal} \cdot \text{kg}^{-1}$, is useful for clinical purposes as an initial estimate, but it is clear from the discussion above that this value will vary according to circumstances. One must be prepared, therefore, to adjust the energy intake according to monitoring measures.

The energy content of food ingested is determined by either bomb calorimetric analyses of foods or by measuring its content of fat, nitrogen

(»protein), water, and ashes and obtaining carbohydrate content based on the difference. The calorimetric values for fat, nitrogen, and carbohydrate are then measured in representative samples of pure macronutrients. By subtracting faecal energy, also measured by bomb calorimetry, the absorption of energy from various foods can be obtained; it is usually around 95%.

The metabolizable energy refers to the actual energetic gain by the organism after absorption, but in the case of protein, the energy lost in urine as nitrogenous end products of metabolism is also taken into account. For example, urea has a combustible energy value of 22.6 kJ per gN, in contrast to other end products of metabolism, such as CO_2 and H_2O , which have zero combustible energy values. In the case of fat and carbohydrate metabolism, CO_2 and H_2O are essentially the end products of metabolism (although during fasting, ketones may appear in urine, and in diabetics both sugar and ketones may be excreted in urine).

Details of the principles involved in the calculation of dietary energy using different energy systems can be found elsewhere². The principles associated with the calculation of resting energy expenditure by indirect calorimetry and total energy expenditure by tracer methods can also be found elsewhere³. These are used as part of the process of estimating average energy requirements in health^{4,5}, which in turn acts as a starting point for the estimation of energy requirements in disease⁶. The latter needs to take into account the effect of disease (and stage of disease) and malnutrition on energy turnover.

Components of nitrogen balance

The Reference Nutrient (or Recommended Dietary Allowance) for protein ($0.8 \text{ g} \cdot \text{kg}^{-1}$ per day⁴ or $0.83 \text{ g} \cdot \text{kg}^{-1}$ per day⁷) for healthy subjects is based on long term nitrogen balance studies⁸ and consists of 3 components:

- the average amount of high quality protein needed to maintain nitrogen balance ($0.6 \text{ g} \cdot \text{kg}^{-1}$)
- safety factor to ascertain that 95% of the healthy population is covered ($0.15 \text{ g} \cdot \text{kg}^{-1}$)
- allowance for the usual intake of proteins that are not entirely high quality protein ($0.05 \text{ g} \cdot \text{kg}^{-1}$)

The general acceptance of nitrogen balance as a criterion for adequate intake is only due to the lack of a more specific test. Adequacy for several other essential nutrients is based on treatment or prevention of specific disease states (e.g. scurvy and vitamin C) but such a specific abnormality associated with inadequate protein intake is not known. However, a persistently negative N balance will lead to loss of lean body tissue mass, mainly muscle.

Nitrogen balance is measured by collection of nitrogen losses in urine, faeces, skin and miscellaneous losses (sweat, secretions, etc.) and subtracting these losses from measured nitrogen content of protein intake. For determination of requirements, these balances are measured at several levels of protein intake, from inadequacy to well above estimated adequacy, with the intercept corresponding to zero balance being determined. Each level of intake is tested over several days, often after a period of adaptation to the altered dietary intake level, in order to assure a metabolic steady state at each intake. Due to the technical problems involved, it is understandable that only a few studies are available that have performed such complete analyses, and no *lege artis* studies have in fact been performed in patients. However, a number of modified procedures have been undertaken in various patient groups and have provided useful results, which have formed a basis for estimating protein requirements in these patient groups.

From the available N balance studies in healthy subjects, the following values can be derived:

- At an intake of $1 \text{ g protein} \cdot \text{kg}^{-1}$ per day: the nitrogen loss in urine will correspond to approximately $0.85 \text{ g} \cdot \text{kg}^{-1}$ per day; the loss in faeces will be equivalent to $0.1 \text{ g} \cdot \text{kg}^{-1}$ per day; and the loss from skin and miscellaneous sources will be equivalent to about $0.03 \text{ g} \cdot \text{kg}^{-1}$ per day.

With varying intakes, the loss in urine will vary while the losses in faeces and skin, etc., will not vary substantially on an ordinary Western diet in a temperate climate. Faecal loss however, is dependent on the fibre content of the diet, since a high fibre content will increase colonic bacterial

flora and thereby increase the bacterial nitrogen content of faeces and influence nitrogen metabolism⁹. In addition, protein in foods of low digestibility will increase faecal nitrogen losses. Protein of low biological value will also increase urinary nitrogen loss. Digestibility and biological value are combined in Net Protein Utilization (NPU), which is the fraction of protein retained in the body with an increase in intake of a specific dietary protein.

The amount of protein required to maintain nitrogen balance consists of two major components: essential amino acids (EAA) and other forms of nitrogen (mainly provided as non-essential amino acids)¹⁰. The latter consists of any form of nitrogen that can enter ammonium metabolism in the body and be incorporated into amino acids by amination or transamination. The amount of essential amino acids required in healthy adult subjects corresponds to about 27.7% of total protein requirement, while in children it is a little higher (28.6% – 33.5%) depending on age⁷. In the diseased subject, synthetic reactions require yet another pattern of amino acids, e.g. proline for collagen synthesis, aromatic amino acids for synthesis of antibodies and acute phase proteins, and glutamine for rapidly dividing cells. In such conditions, amino acids that are not usually essential can become conditionally essential due to limited synthetic capacity, e.g. glutamine in the severely ill patient. Similarly, in patients with decreased liver function, cysteine may not be produced in sufficient quantities from methionine, and therefore the requirement for sulphur-containing amino acids in these patients may not be covered by provision of methionine alone. In addition, after a period of weight loss, the adult subject may have a requirement for EAA resembling that of a growing child due to the needs for rebuilding of tissue.

The amount and composition of protein required to maintain nitrogen balance in patients may therefore differ substantially from that in healthy subjects. During acute illness, the short-term goals of feeding are to restore and maintain function, while limiting further loss of lean tissue. During the weeks of convalescence, the aim

is to restore lean mass as well as function. Nitrogen balance may be indicative of loss or gain of body protein but is not a goal in itself. Nonetheless, in the absence of specific tests for adequacy of protein intake, some measure of nitrogen balance is useful in various clinical settings, since a prolonged state of negative nitrogen balance is not compatible with life.

Energy loss or gain

In the transition from the fed state to starvation, e.g. an overnight fast, energy requirements will be covered mainly by breakdown of glycogen. This is regulated by decreasing plasma insulin (decreasing glycogen synthesis) and rising glucagon (stimulating glycogenolysis). During a more prolonged period of starvation (2–4 days), glycogen stores fall and gluconeogenesis increases. This is accomplished by hepatic formation of glucose from amino acids originating from skeletal muscle, intestine, and skin. This process is still governed by low insulin and increased glucagon (promoting gluconeogenesis), but is now accompanied by increases in cortisol (stimulating gluconeogenesis and increasing protein breakdown) and growth hormone (increasing gluconeogenesis).

With starvation longer than 72 hours, there is marked increase in the concentration of blood ketones, and the brain adapts to obtaining most of its energy from this source instead of the usual glucose. At the same time, the resting energy expenditure begins to decrease. These changes result not only from the hormonal changes described above, but from a variety of other factors including decreased concentrations of triiodothyronine (T3), which is associated with a rise in the inactive reverse T3. In addition, physical activity is reduced and in more advanced states this is associated with a state of apathy. Muscle function is impaired due to increased relaxation time in neuromuscular function tests, and this is related to decreased electron transport and oxidative phosphorylation in mitochondria.

During long-term weight gain, the cost of adding 1 kg body weight is approximately 7500 kcal while the energy yield from 1 kg body tissue is substantially less. The difference reflects the cost

of building lean body mass and adipose tissue. The proportional formation of lean body mass relative to fat mass is dependent on the initial nutritional status. When an adult subject is underweight without an active catabolic process, the main type of tissue gained is lean tissue. When the subject has a normal healthy weight or is overweight and obese, the main component of weight gain is fat. Since the energy density of fat is ten-fold greater than that of lean tissue, the energy cost of gaining fat mass is much larger than that of gaining lean body mass. Thus, the energy cost of gaining 1 kg body weight depends on the initial body weight and composition, and the presence or absence of a catabolic process, which hinders repletion of lean body mass.

Protein loss or gain

In the transition from the fed to the post-absorptive state, protein degradation increases while protein synthesis largely remains unaffected. The higher the habitual protein intake is, the larger the increase in protein degradation. When no protein is given for a prolonged period, the loss of nitrogen from the healthy subject decreases from approximately $1 \text{ g} \cdot \text{kg}^{-1}$ per day to $0.4 \text{ g protein} \cdot \text{kg}^{-1}$ per day, as an adaptation to insufficient intake. This is in part due to the switch to fatty acid oxidation mentioned above, but it is also due to an adaptive down-regulation of hepatic degradation pathways of amino acids including EAA. After a brief period of starvation, the body reutilises about 60% of the EAA liberated by protein degradation, but the reutilisation increases to about 80% during prolonged starvation. In the patient in intensive care, this loss can be increased to $1\text{--}2 \text{ g} \cdot \text{kg}^{-1}$ per day when no protein is given.

Immobilization by itself leads to wasting of muscle tissue. In experimental studies of long-term immobilization (with intact innervation), the loss of nitrogen from the body corresponds to only $0.05 \text{ g protein} \cdot \text{kg}^{-1}$ per day and therefore the massive loss of nitrogen seen in patients in intensive care, and to lesser extents in other patient categories, is mainly due to the metabolic disturbances associated with disease processes.

Eventually, loss of protein will severely affect the function of a number of organs including muscle, intestine, skin, immune cells, and liver. With the knowledge available, however, the effect of protein deficit per se *versus* the effect of energy and other deficits cannot be distinguished with certainty. From the data available, it appears that immune function is relatively spared compared to physical activity/muscle function, suggesting that unknown regulatory mechanisms are responsible for a programmed loss of function during starvation alone, although such adaptive mechanisms may be impaired in the presence of illness.

During long-term weight gain, the positive nitrogen balance in undernourished subjects without disease may correspond to as much as 40% of the intake at an intake of $1.5 \text{ protein} \cdot \text{kg}^{-1}$ per day. The same data show that nearly 75% of a given increase in protein intake will be retained in the body. This is not very far from the corresponding figures in infants, suggesting that the efficiency of rebuilding lean body mass is close to that of early growth. The regulation of this process is not well understood but sustained high levels of plasma amino acids and insulin may play central roles. This rebuilding is an energy demanding process, since protein degradation as well as protein synthesis is increased during recovery, reflecting constant remodelling of the tissues being restructured. Another manifestation of the anabolic potential in depleted individuals can be considered in terms of both energy and N balances. It is not possible for a healthy adult to have a sustained positive N balance in the face of a sustained negative energy balance. In contrast, it is possible for this to occur in a malnourished individual. The extent to which the anabolic potential of malnourished individuals should be utilized in clinical nutrition deserves consideration.

Implications for clinical nutrition

A key issue in clinical nutrition is whether to aim for N and energy balance or positive/negative balances (changes body composition).

- In overweight/obese individuals without acute disease it is desirable to achieve long-term neg-

ative energy balance. This will almost inevitably be associated with a small negative N balance.

- A long-term goal for depleted individuals is to improve body function by repletion of lean and fat mass, which would mean establishing positive N and energy balances.
- Overfeeding in acute situations, especially in critically ill patients, can cause adverse effects and complications, even in depleted individuals. In such individuals it is important first to establish good oxygenation, acid-base status, and metabolic stability. Establishment of a positive protein balance may have to wait until after the acute phase is over (i.e. until the recovery phase). Animal models of sepsis indicate that overfeeding leads to more positive balances but also to increased mortality. In the intensive care unit (ICU) it is often difficult to achieve a positive N balance due to the catabolic effects of injury and immobility.
- Administration of bioactive substances (e.g. growth hormone) can lead to a positive N balance with repletion of lean tissue but its administration should be guided by clinical and functional effects rather than just the effects on N balance.
- Composition of gut microbes and their metabolites influence the metabolism and energy and protein balance¹¹.

Summary

This opening chapter describes basic principles of energy and nitrogen balances together with principles of homeostatic and homeorhetic changes in the organism. Attempts to establish recommended intakes for protein and energy in various disease states originated from attempts to establish requirements in healthy subjects, where the aim was to preserve a healthy weight by maintaining N and energy balances. However, in disease states there is also a need to consider desirable changes in body composition (changes in N and energy balance), and the phase of disease in which such changes should occur. The special metabolic and nutritional needs of different clinical conditions are considered in specific chapters of this book.

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1.2. Body composition

1.2.1. Measurement of body composition

K. R. Westerterp

Learning objectives

- To understand the assumptions involved and the application of techniques for the measurement of body composition
- To understand the precision and limitations of body composition measurement techniques
- To learn about the two-, three- and four-compartment models for body composition

1.2.1.1. Background

In vivo, body composition can only be measured indirectly. There are a variety of models with different assumptions and limitations. The assumptions stem from the chemical analysis of a limited number of cadavers with a normal body condition until death, the only direct method for measuring body composition. Examples of indirect methods based on assumptions derived from cadaver analysis are densitometry and hydrometry,

as described below. Both methods are based on a two-compartment model, where the body is divided into fat mass (FM) and fat-free mass (FFM). Densitometry is based on density and hydrometry is based on the hydration of FM and FFM as measured by cadaver analysis. Other methods for the measurement of body composition use densitometry, hydrometry, or a combination, without or with additional measures as a reference. For example, the skinfold thickness method was validated by comparison to densitometry and the bio-electrical impedance method was validated by comparison to hydrometry.

A typical three-compartment model is based on the measurement of body weight, body density, and body hydration. A four-compartment model includes total bone mineral content as the fourth measure. Combining techniques reduces the number of assumptions and, thus, increases the accuracy of estimations of FM and FFM. The four-compartment model is currently considered the “gold standard” for assessment of body composition in vivo.

General methods for the measurement of body composition are described below, starting with

densitometry and hydrometry as the two indirect methods, followed by double-indirect methods including methods based on anthropometry, electrical conductance of the body, and body imaging. Further details can be found in handbooks on the theory¹ and practice² of human body composition assessment and non-destructive methods for animals³.

1.2.1.2. Densitometry

Densitometry assumes a constant chemical composition of FM and FFM resulting in a density of 0.90 and 1.10 respectively. The method requires the measurement of body weight and body volume. The most widely used technique for measuring body volume is according to Archimedes' principle, i.e. the volume of an object submerged in water equals the volume of water the object displaces. The difference between weight in air and weight under water, corrected for the density of the water at the temperature at the time of measurement, is the body volume. Body volume has to be corrected for lung volume, ideally by simultaneous measurement of residual lung volume during submersion (Figure 1.2.1.1.). Densitometry has gained widespread use and was, until recently, the gold standard for body composition measurement with other techniques.

The theoretical error of densitometry for predicting FM and FFM is 3%–4%, associated with the uncertainty in the density and chemical composition of FFM. The main variables are water

content and bone density. In practice, additional sources of error are variability in gastrointestinal gas volume and residual lung volume, the latter when lung volume is not measured during but before or after submersion. An error of 0.1 L in one of the two is roughly equivalent to a 1% error in FM and FFM. Usually, errors are not additive and the overall accuracy of densitometry for measuring body composition is 1%–2%

Body volume measurement by submersion in water is not always applicable in adult subjects, i.e. patients and the elderly. A recent development is to measure body volume in air instead of water^{4,5}. The advantage of air measurement is not only in its wider applicability but in the required time for an observation. Underwater weighing in a trained subject takes half an hour while measuring body volume in an air tank is done in 5–10 min.

Body fat can be calculated from body weight and body volume with two equations:

body weight = FFM + FM

– FFM is fat-free mass and FM is fat mass

body volume = FFV + FV

– FFV is fat-free volume and FV is fat volume

With the assumed density for FFM of 1.1 and for FM of 0.9:

body volume = FFM/1.1 + FM/0.9

Solving the two equations with two unknowns we get the Siri equation⁶:

% FM = $(4.95 / D_b - 4.50) \times 100$

where:

D_b – body density = (body weight) / (body volume)

1.2.1.3. Hydrometry

Total body water (TBW) is a measure of body composition assuming a fixed hydration of FFM, usually 73%. Measuring body mass (BM) and TBW allows the calculation of FFM as $TBW/0.73$ and the calculation of FM as BM minus FFM.

TBW is measured with dilution of isotopes of water i.e. isotopes of hydrogen and oxygen: 3H ,



Figure 1.2.1.1. A subject submersed in water during underwater weighing. The subject is lying on a stretcher suspended from a scale while breathing into a spirometer for the simultaneous measurement of lung volume with Helium dilution.

^2H , and ^{18}O . The underlying assumption is that these have the same distribution volume as water.

A subject gets an accurately measured oral or intravenous dose of labelled water, followed by an equilibration period of at least 2 hours and subsequent sampling of the body fluid⁷. Dose, equilibration time, and sampling medium depend on the isotope, the dosing route, and the facilities for sample analysis. Tritium or ^3H is a radioisotope, which is measured with liquid scintillation counting. Deuterium (^2H) and ^{18}O are both stable isotopes, ^2H can be measured in higher concentrations with infrared absorption and both isotopes are measured in low concentrations with isotope ratio mass spectrometry (IRMS). Body fluids for sampling are saliva, blood, and urine. The length of the equilibration period is at least 2 hours with intravenous dosing and taking blood as the sampling medium. Using the less invasive oral dosing and urine sampling requires a minimal equilibration time of 4-6 hours. The calculation of TBW is based on the relationship:

$$C_d \times V_d = (C_1 - C_0) \times \text{TBW}$$

where:

C_d – concentration of the tracer in dose given to subject

V_d – volume of the dose given to subject

C_0 – basal concentrations of the tracer in body fluid

C_1 – concentrations of the tracer after dose consumption in body fluid (Figure 1.2.1.2.).

In practice, using a non-invasive method with stable isotopes at low concentrations, subjects get a dose of labelled water in the post-absorptive state after collecting a background sample, i.e. saliva or urine.

Background levels for ^2H and ^{18}O are around 150 ppm and 2000 ppm, respectively. The minimal excess enrichment to be reached is around 100 ppm. After equilibration, lasting 4–6 hours, a final saliva or urine sample is collected. For urine this should be a sample from at least a second voiding after dosing the labelled water. ^{18}O as a tracer is preferred over ^3H and ^2H as the dilution

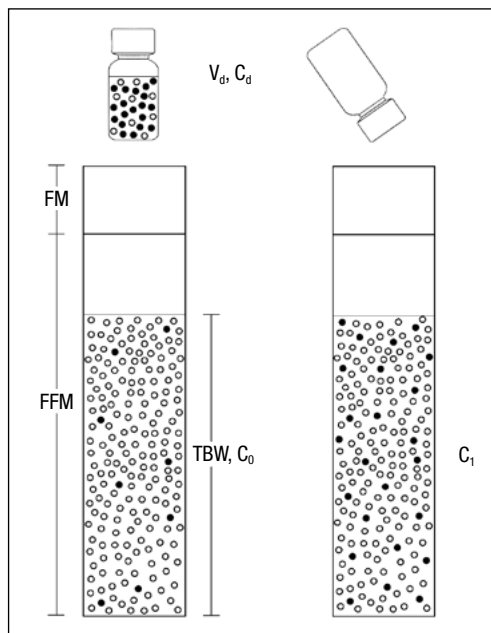


Figure 1.2.1.2. Schematic representation of the measurement of fat mass (FM) and fat-free mass (FFM) with isotope dilution for the measurement of total body water (TBW). The calculation of TBW is based on the relationship: $C_d \times V_d = (C_1 - C_0) \times \text{TBW}$; where: C_d and V_d are the concentration of the tracer and the volume of the dose, respectively, C_0 and C_1 are the concentrations of the tracer in the body water before and after dose consumption.

space of ^{18}O is very close to TBW. The dilution space for the hydrogen isotopes is on average 4% larger and the dilution space for ^{18}O is on average 1% larger than TBW, due to the exchange of the label with non-aqueous substances in the body. On the other hand, the cost of ^{18}O is 100 times higher than the other labels.

1.2.1.4. Anthropometry

Anthropometric methods for the assessment of body composition include the body mass index (BMI), measuring weight and height, and skin-fold thickness measurements. The methods are suitable for clinical practice because of their simplicity, low cost, and fast application. The BMI is the simplest method.

Body mass index (BMI)

Examples of body fat estimation from BMI are the equations of Deurenberg et al⁸. They were de-

rived from a population of more than 500 women and 500 men with an age range from 7–83 years and a BMI range from 14–40 $\text{kg} \cdot \text{m}^{-2}$, using densitometry as a reference.

For children aged 15 years and younger, body fat percentage (BF%) can be predicted by the equation:

$$\text{BF\%} = 1.51 \text{ BMI} - 0.70 \text{ age} - 3.6 \text{ sex} + 1.4$$

(standard error of estimate 4.4% BF)

For adults, the equation is:

$$\text{BF\%} = 1.20 \text{ BMI} + 0.23 \text{ age} - 10.8 \text{ sex} - 5.4$$

(standard error of estimate 4.1% BF)

Where sex is 0 for females and 1 for males.

Thus, the equations show men have a lower BF% than women for a given age and BMI, the difference being, on average, 10% at adult age. The prediction error for BF% is similar to the prediction error obtained with skinfold thickness measurements (as described below) and bio-electrical impedance (as described in the next chapter)

Skinfold thickness

Skinfold thickness is another simple and inexpensive method of measuring body composition. The assumptions forming the basis for the method are:

- The thickness of the subcutaneous FM reflects a constant proportion of the total FM.
- The average thickness of skin folds at selected sites reflects the subcutaneous FM.

Skin folds are usually measured at four sites: triceps, biceps, sub scapula, and iliac crest. The sites are measured at least three times and the sum of the separate measurements is averaged. Equations to predict body fat from the sum of skin folds use a logarithmic transformation of skinfold thickness (as body fat is not linearly related to skinfold thickness) and the age and gender of the subject.

The measurement is made with a caliper, with the skin grasped between thumb and forefinger,

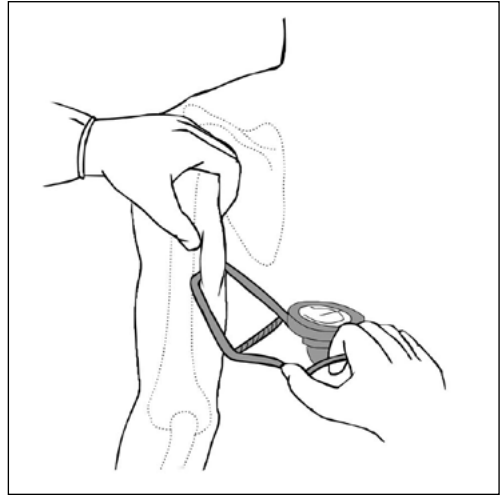


Figure 1.2.1.3. The measurement of triceps skin fold with a caliper

gently shaken to exclude underlying muscle, and pulled away to allow the jaws of the caliper to take over (Figure 1.2.1.3.). The caliper is calibrated to exert a constant pressure. The measurement requires skill to grasp the skin in the right way at the right site. One source of variation is inter-individual differences in compressibility of the subcutaneous tissue. Some people have firm subcutaneous tissue and in others it is very flabby and easily deformable. The method is not applicable in extremely fat subjects where the subcutaneous fat layer gets too large to allow the proper grasping of a skin fold. Errors in skinfold thickness measurement are highly dependent upon the experience of the observer.

The error in estimating BF% from BMI or skinfold thickness is higher than that with densitometry or hydrometry. However, these anthropometric methods sometimes represent the only opportunity for obtaining information on body composition.

1.2.1.5. Electrical conductance

The most widely used new technique to measure body composition in normal subjects is from electrical conductance of the body. The conductivity of the body is supposed to be a reflection of FFM as FFM contains virtually all of the water

and conducting electrolytes in the body. The two techniques for measuring electrical conductance for determining body composition are total body electrical conductivity (TOBEC) and body impedance (BI). These techniques are less useful in disease due to the effects of disease on fluid and electrolyte distribution.

Total body electrical conductivity (TOBEC)

A TOBEC instrument consists of a solenoid coil to create an oscillating field, inducing a current in any material placed within the coil. The difference between the coil impedance when empty and when a subject is inserted is a measure of body composition.

Body impedance (BI)

A BI instrument creates a current through the body and measures impedance with contact electrodes positioned on the hands and feet. This method is described in the next chapter.

In both situations, with TOBEC and BI, corrections are necessary for conductor length and configuration. For this purpose, TOBEC instruments are usually calibrated with a phantom of known composition. BI results have been validated with simultaneous TBW measurements using isotope dilution. The results from both techniques are good using the appropriate equations for calculation of body composition from body impedance for the population under study. Most laboratories use their own equations because of differences in equipment and methodology.

1.2.1.6. Body imaging

Imaging techniques provide information on body fat distribution. The most widespread body imaging methods for the assessment of body composition are dual energy X-ray absorptiometry (DEXA) and magnetic resonance imaging (MRI).

Dual energy X-ray absorptiometry (DEXA)

Dual energy X-ray absorptiometry was primarily designed to assess total bone mineral mass and mineral density. Thus, it is used to assess total bone mineral content as a parameter for the four-com-

partment model, the current gold standard for assessment of body composition *in vivo*. DEXA is also widely applied to assessment of body fat. It is an imaging technique with minimal radiation dose and is applicable to a wide variety of subjects, including patients. DEXA will differentiate between bone and soft tissue. Subsequently, differentiation within the soft tissue needs to be made between FM and FFM. A limitation of the technique, limiting the accuracy, is that soft tissue behind or in front of bone cannot be assessed. Therefore, the assumption needs to be made that the distribution of FM versus FFM is the same behind or in front of the bone as it is next to the bone. The consequence of this assumption is that the accuracy is lower than that of densitometry or hydrometry and DEXA can certainly not be regarded as a criterion method⁹. However, it can provide estimates of body fat distribution, e.g., upper body, lower body, arms, and legs.

Magnetic resonance imaging (MRI)

Magnetic resonance imaging has the advantage that it can provide more detailed information about body fat distribution, e.g., subcutaneous versus visceral fat and fat within or around muscle and organs. The analysis of the images is prone to error in assessing which part of the image is actually fat mass or other tissue. Measuring total fat mass requires many transversal images, covering the entire body, and calculation of the surface of fat tissue within each image. This can be done with appropriate software or manually but, in either case, accuracy will depend on the ability to determine the actual surface and volume of the tissue. As the resolution of MRI machines is rapidly increasing, the ability to accurately assess different tissues is also increasing. MRI is not likely to replace densitometry or hydrometry for assessment of total body fat but has great potential for answering specific questions related to more detailed assessment of body fat distribution.

1.2.1.7. Discussion

Each body composition method has an uncertainty on the order of magnitude of at least 1.5 kg

FM and FFM. A combination of independent measurements can reduce this measurement bias through adoption of a three- or four-compartment model (Fig. 1.2.1.4.). In a three-compartment model, based on the measurement of body mass, body volume, and total body water, the reported precision is 1.0 kg for FM and 0.7 kg for FFM. A further slight improvement is achieved in a four-compartment model for body composition, subdividing FFM into TBW, protein mass, and total bone or mass. This four-compartment model is now the 'gold standard' for body composition, based on the measurement of four variables: body mass, body volume, and total body water with the 'traditional' methods, and bone mass with DEXA.

The precision of body composition measurement will never reach the level of 0.001 kg for BM with integrated electronic balances. The precision of an average household bathroom scale for the measurement of BM is usually no better than 1.0 kg. Putting the scale in another corner of the

room often results in a difference of 0.5–1.0 kg. Everybody is also familiar with discrepancies of body weight measurements between different scales. Thus, the essential starting point for the measurement of body composition and changes in body composition is an accurate measurement of BM using properly calibrated weighing scales. For comparative studies, subjects should be measured with minimal clothing, minimal gut contents (post-absorptive), and with an empty bladder.

Aging, starvation, and disease violate the general assumptions of the two-compartment model as adopted with densitometry and hydrometry. For example, the decrease in the density of FFM with age-associated bone loss and disease-induced dehydration or edema change the parameters of the measurement. With anthropometry, abdominal fat in male type obesity or Prader Willi syndrome is not accurately measured by the skinfold method, resulting in considerable error. In this situation, a three- or four-compartment model should be used.

Additionally, there are new methods to quantify separate body components including the measurement of total body nitrogen and total body calcium with neutron activation analysis. Unfortunately, none of the more recent developments in the measurement of body composition have resulted in a more direct *in vivo* method, since each method has its own hypotheses and often requires expensive technology.

Summary

In vivo body composition measurements are always indirect and are based on one or more assumptions concerning the nature of the body components, i.e. fat mass and fat-free mass including water, protein, and bone. Examples of indirect methods, based on assumptions derived from cadaver analysis, are densitometry and the measurement of total body water. The other methods are all double-indirect, validated against indirect methods, and, therefore, based on more assumptions. Whatever method is used, the starting point is the measurement of body mass with a calibrated scale. Subsequent subdivision of body mass into components like fat mass and fat-free

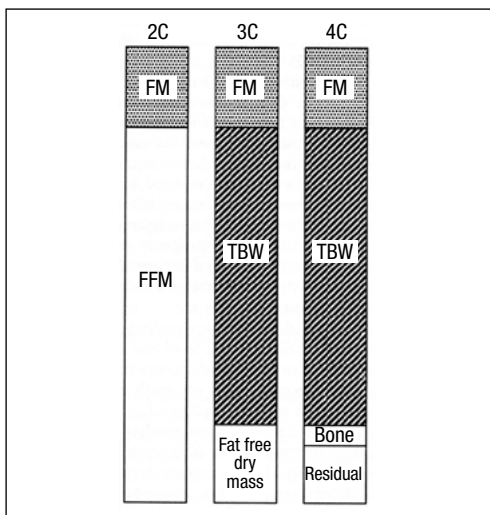


Figure 1.2.1.4. Human body composition models: 2C, two-compartment model where FM and FFM are derived from measurement of body weight and body volume or from body weight and total body water; 3C, three-compartment model where FM and FFM are derived from measurement of body weight, body volume, and total body water; and 4C, four-compartment model where FM and FFM are derived from measurement of body weight, body volume, total body water, and bone mass

mass has an accuracy of 1 kg or less, especially in patients in whom these assumptions are violated by the effects of disease.

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1.2.2. Bioelectrical Impedance Analysis

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Learning objectives

- To understand the basics of bioelectrical impedance analysis
- To understand the indications and contraindications for its use as a method to determine body composition in clinical practice
- To understand how it can be used as a prognostic tool

Introduction

Several methods have been developed for measurement of body composition – see chapter 1.2.1. However, many of them are used almost exclusively for research purposes because they are time consuming and often expensive. During the last twenty years, however, a lot of research has

been done on bioelectrical impedance analysis (BIA) of body compartments. This is a relatively accessible method for measurement of body composition, which is increasingly frequently used in clinical practice. The principles and limitations of this method as well as updated information are the main focus of this chapter.

1.2.2.1. Basic principle of the method

The BIA method is based on the fact that resistance to alternating electric current is dependent on body composition (particularly the content and distribution of water and electrolytes)¹. In the healthy organism, water content is relatively constant in fat-free mass (FFM). Moreover, fat mass (FM) contains low amounts of water and electrolytes and, thus, its resistance is high.

Conductivity to electric current is dependent on the frequency of an alternating current. Low frequency alternating currents pass through the body mainly via the extracellular space, whereas high frequency currents cross the body through both extracellular and intracellular water². Other components, such as bone, or air contained in the lungs or digestive system, are poor conductors and do not need to be taken into account³. Conductivity is, however, influenced by clinical features such as inflammation.

Impedance (Z) consists of two components:

- **Resistance (R)** – opposes the passage of electric current and depends principally on extracellular water.
- **Reactance (Xc)** – is determined by the dielectric properties of cell membranes which behave like condensers and are capable of taking an electric load in an alternating manner and then liberating it after having generated a delay in the passage of the current. This effect depends partly on body cell mass⁴.

Resistance (R) to low frequency (up to 50 kHz) current is mainly proportional to extracellular water, while reactance (Xc) to high frequency (100–200 kHz) current is related to the number of “functioning” cells which facilitate the passage of the high frequency alternating current – Fig-

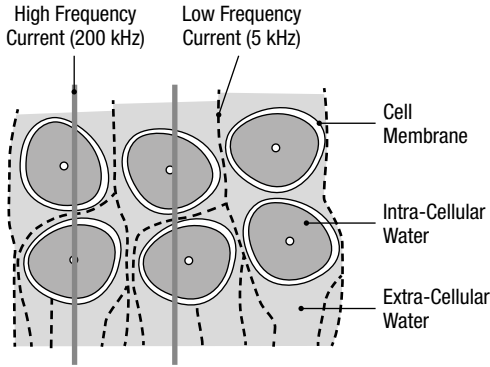


Figure 1.2.2.1. Low frequency electric current passes through extracellular fluid, whereas high frequency electric current passes through both extracellular fluid and intact cells.

ure 1.2.2.1. The higher the frequency of the current is, the lower the resistance and the greater the reactance^{5,6}.

The influence of frequency on R and X_c is shown in Figure 1.2.2.2. At low frequencies, R is high and X_c is almost negligible. In other words, with frequencies up to 50 kHz the impedance Z is practically determined only by R , and the X_c value is less than 10% of the total. At higher frequencies (100–200 kHz), current goes through the cell membranes, reactance increases and resistance decreases.

The phase angle (PA) is not easily explained or understood but is of considerable potential clin-

ical value. At any particular frequency, $PA = (X_c/R) \cdot (180/\pi)$. PA is proportional to body cell mass, but is also greatly affected by disease, which influences membrane potential. At frequencies higher than the critical frequency, the previously rising reactance again decreases, together with resistance. The measured current permeability corresponds to independent oscillation of ions on cell membranes.

The principle underlying the method is most easily understood if we consider the classic example of a cylinder containing a solution of water and electrolytes. The impedance will be proportional to the length of the cylinder, to its cross-sectional area, and to the water content. If half of the water and electrolytes is substituted with oil (fats), the resistance value will double because fat is a low conductivity component with higher impedance. (Figure 1.2.2.3)⁷.

In human applications, it is assumed that the height of the individual is equivalent to the length (L) of the current path. The current has to go through a non-homogeneous (for water and electrolyte content) mixture of different tissues, each with a different cellular composition.

The human body can be considered to be 5 cylinders (corresponding to 2 arms, 2 legs and the trunk) each with its own percentage contribution to the overall impedance. This does not

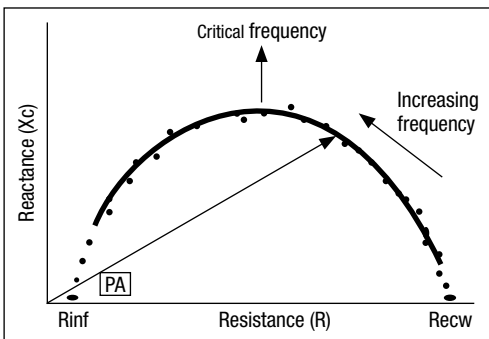


Figure 1.2.2.2. Relationship between reactance and resistance with increasing frequencies in biological systems with capacitive properties. Recw – resistance at zero frequency, Rinf – the resistance at infinite frequency, PA is the phase angle at a specific frequency

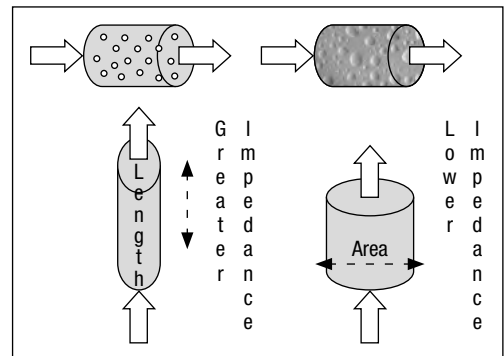


Figure 1.2.2.3. Impedance is dependent on the structure and composition of the measured object.

- Higher impedance (from more fat cells, longer length and/or smaller diameter) – on the left
- Lower impedance (more water and electrolytes, shorter length and/or larger diameter) – on the right.

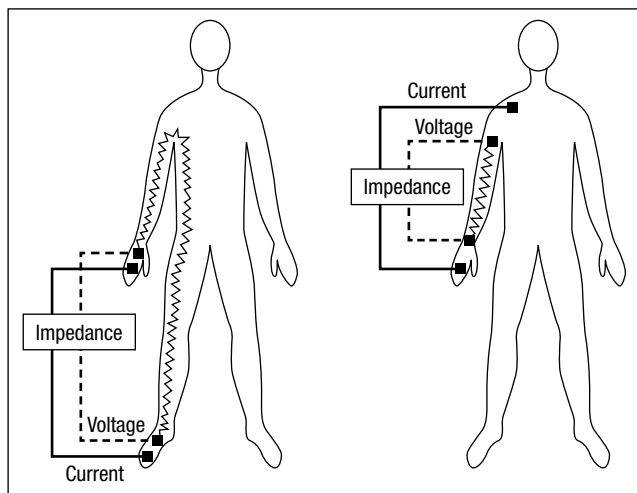


Figure 1.2.2.4. Whole body impedance measurement (left) and segmental impedance measurement of one arm (right).

correspond exactly to its volume because impedance also depends on tissue composition and geometry. Thus, the trunk, notwithstanding the fact that it forms almost 50% of the total body weight, contributes only 10% of the measured total body impedance.

Commercially available BIA devices operate at single (usually 50 kHz) or multiple frequencies (typically 4 or more), and the impedance analysis may be performed on the whole body or as segmental BIA – Figure 1.2.2.4.

It is important to remember that BIA is not a direct method for assessment of body composition. The estimation of body compartments is based on comparison of BIA with a reference method. The predictive equations are the result of regression analysis. Hundreds of such equations have been published, but the two most widely used in Europe and the USA are shown in Table 1.2.2.1.

1.2.2.2. Factors which influence BIA measurement

Unfortunately, it is impossible to have only a single universal equation that can be used in all situations¹. There are several conditions when specific equations are necessary. The most important is the different relationship between trunk and leg length, as seen in different ethnic groups. Situations where the level of lean mass hydration is not the normal 73%, as seen in obese subjects and many disease states, also contraindicate the unadjusted use of general predictive equations – Table 1.2.2.2.

However, even with an optimal equation, we would anticipate errors in body composition analysis as generated from BIA. This occurs because of a lack of standardized measurements, the standard error of the equation, limitations of the reference methods used for validation, deviations in body geometry from that used in equa-

Table 1.2.2.1. Frequently used bioelectrical impedance analysis equations as reported in the literature for the estimation of fat-free mass (FFM).

Equation for FFM estimation	BIA instrument	Criterion method	Ref.
$-4.104 + 0.518 \text{ Ht}^2/\text{R}_{50} + 0.231 \text{ weight} + 0.130 \text{ Xc} + 4.229 \text{ sex}^a$	Xitron	DXA	9[9]
Women: $-9.529 + 0.696 \text{ Ht}^2/\text{R}_{50} + 0.168 \text{ weight} + 0.016 \text{ R}_{50}$ Men: $-10.678 + 0.652 \text{ Ht}^2/\text{R}_{50} + 0.262 \text{ weight} + 0.015 \text{ R}_{50}$	RJL-101	4 compartment model	10[10]

^aSex: male = 1, female = 0

Table 1.2.2.2. The influence of demographic and clinical situations on bioelectrical impedance analysis results⁸

	Influence	Recommendation
Demographic situation		
Race	Different relationship between trunk/limb length and fat-free mass hydration	Use of a race-specific BIA equation
Age	Variation in cross-sectional area and tissue hydration	Use of an age-specific BIA equation
Clinical situation		
States with abnormal hydration (oedema, ascites, dehydration)	Altered measurement accuracy	Use of BIVA or segmental BIA
Obesity	Abnormal hydration, increased fat fraction and altered body shape	Caution when BMI > 35 kg · m ⁻² ; consider segmental BIA
Severe malnutrition (BMI < 16 kg · m ⁻²) or anorexia nervosa	Altered tissue hydration (ECW:ICW ratio)	Caution because of larger prediction errors
Neurological disorders	Altered conductivity due to lean tissue abnormalities	Use of segmental BIA for long-term follow-up

tion development, and because of the biological variability seen in subjects during the examination⁹. A standard error of estimation of 1.8 kg is acceptable for population sampling but not for individual tests or in assessment of specific clinical conditions¹⁰.

1.2.2.3. BIA as marker of tissue health

Beyond its utilization as a body composition method, BIA can be used to obtain information about tissue hydration and cell membrane integrity. BIA measurements yield impedance, resistance and reactance, phase angle (PA), and bioelectrical impedance vector analysis (BIVA). More recently, several factors have been combined to provide a more robust “illness marker”¹¹.

The PA, in particular, is currently considered a global marker of tissue health⁶. It is a reasonably good indicator of body cell mass¹² but is also a marker of cell membrane integrity and function⁶. It should be noted that the PA is modified when there is an alteration in membrane permeability, even when the amount of body cell mass is unchanged⁷. Early papers confirmed PA as a reliable prognostic marker in several clinical situations, including sepsis, HIV infection, intensive care treatment, lung and colorectal cancer, surgery, chemotherapy, and, more recently, in chronic liver disease and transplantation¹³. Other papers

have shown that PA is associated with nutritional status in surgical and elderly patients and can be a sensitive marker in monitoring after nutritional intervention^{14–16}. These papers agree that the prognostic role of PA is not totally explained by the amount of body cell mass, but that PA is an independent predictor. General application of these conclusions is hampered by the fact that different cut-off values were used for each population because of a current lack of PA reference values for healthy populations.

Until 2005, only studies with small samples were available and these were insufficient to show the true PA distribution in healthy populations. More recent studies have shown that PA, like many other biological measurements, is larger in men than women and decreases with aging. Accordingly, PA now has sex- and age-specific reference values. As for other biological variables, normal PA varies according to the population concerned, as shown in a paper comparing PA in the American, Swiss, and German populations^{11,17}. PA values below the 5th sex-, BMI- and age-specific reference values have been shown to be highly predictive of mortality and functional status in cancer patients^{18,19}.

Measurement of PA is a potentially useful indicator of functional status in patients²⁰, but another interesting way to interpret BIA information was

proposed by Piccoli^{21,22}. It is called bioelectrical impedance vector analysis (BIVA). A bivariate vector is plotted using resistance and reactance at 50 kHz, after standardisation for the patient's height. Individual measurements can then be compared with confidence limits (ellipses) drawn from the healthy population. A displacement of the vector over this ellipse provides a semi-quantitative guide to body composition (more or less soft tissue), and a shortening or lengthening of the vector indicates changes in hydration (more or less fluid).

1.2.2.4. BIA methods used in clinical practice

Single frequency BIA (SF-BIA)

SF-BIA usually measures the impedance at 50 kHz and permits the calculation of TBW and FFM based on empirical regression equations. Usually the resistance index (L2/R50), height, and weight are included in these population-specific equations.

Multifrequency BIA (MF-BIA)

MF-BIA measures the impedance at different frequencies. The number of frequencies used differs between BIA devices. Usually the resistance at a low frequency (< 50 kHz) is used for calculating extracellular water (ECW) and that at high frequencies (> 100 kHz) (where cell membranes are penetrated) for calculating TBW. MF-BIA, like SF-BIA uses empirical regression models. MF-BIA is more accurate for the prediction of ECW than SF-BIA and especially so in critically ill patients¹.

A newer way to evaluate cell membrane function using a multifrequency device is by means of the so-called "illness marker" or impedance ratio. When BIA is done at low frequency, current cannot cross the cell membranes, and impedance is relatively high. When it uses a higher frequency, the current can cross the cell membranes, and the impedance is lower. In normal conditions, the ratio between impedance at 200 kHz and that at 5 kHz is always less than 1. However, when the cell membrane has an alteration/impairment of its function, this ratio approaches unity, as the "sick" membrane offers less resistance to the cur-

rent, even at lower frequencies. Recent studies in ICU patients have shown that the illness marker can be considered as a reliable guide to prognosis. Patients who died in ICU or during that hospitalization had significantly higher illness markers than the patients who survived. Illness marker reference values for the U.S. population were recently published and it was shown that age, gender, and body mass index, but also ethnicity, could influence this measure²³.

Bioelectrical impedance spectroscopy (BIS)

Bioelectrical impedance spectroscopy (BIS) measures the impedance across 50 or more frequencies. The relationship between reactance and resistance at different frequencies is used to extrapolate the resistance at zero and infinite frequency. These values are used to calculate the resistance of the ECW and of intracellular water (ICW). With these resistance values, the size of the fluid compartment can be calculated, based either on empirically-derived predictive equations or on the equations based on the Hanai mixture theory⁵. Because this mixture approach is based on general physical laws, it should be less population specific. However, results show that the individual (and immeasurable) differences in body geometry and specific resistivity of body fluids combine to overturn this assumption^{24,25}.

In conclusion, is it is reasonable to use SF-BIA in healthy people, but applied equations should always be validated in the population studied, with specific values for race, age, and gender. In subjects with altered, or potentially altered, hydration states, MF-BIA or BIS seem more appropriate.

Summary

In conclusion, BIA can be considered a suitable option for body composition assessment so long as some ground rules are respected. These should include use of an equation developed for the specific population concerned, preferably without fluid imbalance or abnormalities in body shape and with a BMI in the range 18 to 34 kg·m⁻². In clinical situations with alterations in fluid distribution, MF-BIA and BIS are more appropriate

than SF-BIA. It has not yet been possible to construct a universally applicable BIA equation.

Phase angle, BIVA, and impedance ratio are obtained directly from resistance, reactance, or impedance, and evidence in the literature indicates that they could be used as prognostic or nutritional markers. They may provide practical ways of using data from BIA in clinical situations when regression equations for body composition assessment are not valid.

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1.3. Diagnosis of malnutrition – Screening and Assessment

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Learning objectives

- To learn the principles and practice of nutritional screening
- To learn the principles of nutritional assessment and to understand the techniques of nutritional assessment
- To understand the limitations of different methods of nutritional assessment

Nutritional risk screening is increasingly practiced in hospitals but is much less frequently conducted in other institutions and in the community. As a consequence, many malnourished individuals remain undiagnosed and untreated. This is mainly due to lack of training and awareness among staff but is also due to lack of validated protocols for screening, assessment, and treatment. There is also a lack of consensus concerning the definition of malnutrition.

1.3.1. Definition of Malnutrition

Several definitions of malnutrition and methods of assessing it have been proposed. ESPEN has, in the past, been mainly concerned with undernutrition but has increasingly accepted that the general term malnutrition should include both overnutrition and undernutrition. Accordingly, in the following paragraphs, we will first discuss “undernutrition”. Next, we will address the role of inflammation as an additive factor that influences body composition and function and, finally, we will discuss the issue of overnutrition.

1.3.1.1 Malnutrition – Undernutrition

ESPEN has recently proposed a definition of *Undernutrition* which not only encompasses physical changes in body composition but also its effects on function and clinical outcomes^{1,2}, defining the point at which point undernutrition interferes with function and impairs clinical outcome, and the level at which nutritional support makes

a difference. This has led to the following definition of clinically significant undernutrition:

“A state resulting from lack of uptake or intake of nutrition leading to altered body composition (decreased Fat Free Mass (FFM) and Body Cell Mass (BCM)) leading to diminished physical and mental function and impaired clinical outcome of disease”.

ESPEN has also suggested parameters which may be used to define the probable presence of undernutrition, with or without inflammatory illness. These are very low body mass index ($BMI < 18.5 \text{ kg} \cdot \text{m}^{-2}$ and/or combination of body weight loss with low BMI or with low index of fat free mass – FFMI (see below).

1.3.1.2. Interaction between undernutrition and inflammation

In clinical practice, both inflammation and undernutrition are usually present in combination and interact in a cumulative manner. Inflammation is associated with increased metabolic demand for energy and protein at the same time as food intake is diminished through loss of appetite and other clinical circumstances. In both these circumstances, there is a vicious cycle between inflammation and undernutrition in which, without adequate intervention, undernutrition and outcome worsen.

The contribution to undernutrition of low intake or uptake of food is readily reversible by nutritional support at all stages of illness. However, the increased energy and protein consumption associated with the catabolic or “flow” phase of injury or inflammation cannot be reversed by nutrition alone, even if macronutrients are supplied in large amounts, as in the now outdated concept of “hyperalimentation”. Only when inflammation-induced catabolism has subsided and the anabolic or convalescent phase of illness

has been reached, can increased food intake result in a complete normalization of nitrogen balance and tissue restoration including the return of lost skeletal muscle.^{3,4}

In a study from Beisel⁵, one-third of the nitrogen lost during experimental infections in healthy volunteers was reported to be due to reduced food intake associated with febrile illness and two-thirds was due to the infection itself. This should not, however, lead to a nihilistic approach, since nutritional support can reverse the effects of low food intake during prolonged illness, supporting an ongoing beneficial host response. However, preserving and rebuilding muscle mass can be achieved only when disease severity has diminished or injury adequately treated. The joint presence of undernutrition and inflammation has led to proposals to include both elements in the definition of malnutrition.

“Malnutrition is a subacute or chronic state of disordered nutrition in which a combination of varying degrees of over- or undernutrition and inflammatory activity has led to a change in body composition and diminished function”⁶.

Nutritional risk assessment should, therefore, not only include static measurements such as BMI or anthropometry but also measures of disease severity/inflammation and bedside measures of function e.g. mood assessment, hand grip dynamometry, and Peak Expiratory Flow Rate.^{7–15}

In 2010, an International Consensus Guideline Committee agreed upon some etiologically-based diagnoses of starvation and disease-related malnutrition in clinical practice.

- (a) Starvation-related malnutrition: chronic starvation without inflammation (e.g. anorexia nervosa)
- (b) Chronic disease-related malnutrition: secondary to chronic mild-to-moderate inflammation (e.g. organ failure, cancer, rheumatoid arthritis, or sarcopenic obesity)
- (c) Acute disease or injury-related malnutrition: when inflammation is acute, causing a severe catabolic state (e.g. major infection, burns, trauma, or closed head injury).^{16,17}

More recently, consensus criteria for the diagnosis of malnutrition were developed in ESPEN consensus meetings in which inflammation and function were not included as primary parameters but were acknowledged as important factors influencing weight, weight loss, and FFM. This resulted in the following diagnostic criteria:

- (a) A Body Mass index (BMI Weight in kg/Height in metres²) < 18.5 kg·m⁻²
- (b) A total weight loss of > 10% or of > 5% over the last 3 months, combined with a low BMI (< 20 kg·m⁻² in those under 70 years old or < 22 kg·m⁻² in those over 70) or Fat Free Mass (FFMI < 15 kg·m⁻² in females or < 17 kg·m⁻² in males)

Whatever definition is adopted, all patients should be carefully assessed to allow an estimate and recording of current nutritional state, likely prognosis, and the indications for nutritional support in the context of an overall treatment plan.¹⁶

1.3.1.3. Malnutrition – Overnutrition

Overnutrition, resulting in obesity, is associated with changes in body composition, function, and individual risks including diabetes, cardiovascular disease, depression, arthritis, cancer, and decreased life expectancy. It is also associated with a low-grade inflammatory state, resulting in an exacerbation of metabolic changes. In early life, obesity, which is becoming increasingly common in childhood and adolescence, is associated with increased muscle mass in response to the mechanical demands of moving an increased bulk. However, the low-grade inflammatory state and decreasing mobility associated with obesity results in a decline in muscle mass in later life, sometimes resulting in sarcopenia. Towards the end of life, fat-free mass continues to decrease but also fat mass shrinks due to anorexia induced by comorbidity and the aging process itself. This course of events explains the obesity paradox.¹⁸ Obese patients that have lost weight have lost both fat mass and fat-free mass (are more sarcopenic) and are functionally more compromised than at an earlier stage when still accumulating weight. Consequently, their cardiovascular sta-

te and other functions will be worse, explaining compromised recovery from illness and trauma.

1.3.2. Screening for malnutrition

The process of identifying patients with nutritional problems should start with a rapid screening procedure, followed by a more detailed assessment in those who are shown, by screening, to be at risk. A good screening instrument should not only be simple, rapid, and easily carried out by non-specialist care givers, but should also meet criteria such as predictive validity, content validity, and reliability, and should lead to appropriate and explicit action.¹⁹ A variety of malnutrition screening tools have been developed in recent years. These usually include simple questions concerning recent involuntary weight loss and food intake. Measurements include height and weight and BMI. Examples of valid, quick, and easy screening instruments are the Malnutrition Screening Tool MST²⁰ and the Short Nutritional Assessment Questionnaire SNAQ.²¹

Some so-called screening instruments also include clinical judgment, physical examination, estimation of disease severity, and nutrient calculations. However, these should really not be considered to be screening tools and are more properly classified as assessments, e.g. the Subjective Global Assessment²² which has been used for over 20 years now and is often used as a reference for the development of new instruments.

The Nutritional Risk Screening (NRS-2002)¹⁴, endorsed by ESPEN, and the Malnutrition Universal Screening Tool (MUST)¹⁵, developed by the British Association for Parenteral and Enteral Nutrition (BAPEN), are widely used instruments in Europe. SGA, NRS-2002, and MUST require simple training for correct use.

Some screening tools are particularly suited to different categories of patients. For adult hospitalized patients, the ESPEN-sponsored NRS-2002 (see Figure 1.3.1.) or the MUST, SNAQ, or MST tools are particularly suitable. In the community setting, MUST has proven its value. For the elderly in the community or in hospital, the MNA²³, or its shorter version MNA-SF²⁴, are suit-

able. Importantly, screening tools are meant to be quick and simple tools to identify patients at risk of malnutrition. However, they are never as good as a thorough assessment. Screening tools underclassify as well as overclassify the risk of malnutrition. Therefore, professional clinical judgement remains essential to correctly assess malnutrition. Recent systematic reviews have highlighted that there is no single, optimal screening tool for malnutrition. In addition, screening tools should be applied only in populations in which they were developed and validated.^{25–27}

1.3.3. Nutritional Assessment

Nutritional assessment is a more detailed and time-consuming process, carried out by staff with nutritional expertise on those found to be at risk on initial screening. This allows a more detailed management plan to be devised, including continuous monitoring and appropriate intervention.

Nutritional assessment should include the following elements:

- Measurement of nutrient balance
- Measurement of body composition
- Measurement of disease severity or inflammatory activity
- Measurement of function (e.g. cognitive, immune function, muscle function)

Nutrient Balance

All potential factors that may lead to malnutrition should be identified and the prognosis of the patient's condition should be estimated. Weight loss, appetite, dietary intake, fluid balance, gastrointestinal symptoms, fever, nutrient losses in excreta, and medical and drug history should all be assessed. Detailed information on food intake and uptake is a critical measure for assessing nutritional status.²⁸

A dietary history should include qualitative as well as quantitative aspects of diet to assess energy, protein, and micronutrient intake and to predict whether the patient's nutritional status is likely to improve or deteriorate by comparison with estimated requirements. Such an assessment is time consuming and requires specific expertise of trained professionals.

Nutritional Risk Screening (NRS 2002)			
Table 1: Initial screening		Yes	No
1	Is BMI < 20?		
2	Has the patient lost weight within the last 3 months?		
3	Has the patient had a reduced dietary intake in the last week?		
4	Is the patient severely ill ? (e.g. in intensive therapy)		
Yes: If the answer is 'Yes' to any question, the screening in Table 2 is performed. No: If the answer is 'No' to all questions, the patient is re-screened at weekly intervals. If the patient e.g. is scheduled for a major operation, a preventive nutritional care plan is considered to avoid the associated risk status.			

Table 2: Final screening			
Impaired nutritional status		Severity of disease (≈ increase in requirements)	
Absent Score 0	Normal nutritional status	Absent Score 0	Normal nutritional requirements
Mild Score 1	Wt. loss > 5% in 3 months or Food intake below 50%–75% of normal requirement in preceding week.	Mild Score 1	Hip fracture* Chronic patients, in particular with acute complications: cirrhosis*, COPD* Chronic haemodialysis, diabetes, oncology
Moderate Score 2	Wt. loss > 5% in 2 months or BMI 18.5–20.5 + impaired general condition or Food intake 25%–50% of normal requirement in preceding week	Moderate Score 2	Major abdominal surgery* Stroke* Severe pneumonia, haematologic malignancy
Severe Score 3	Wt. loss > 5% in 1 month (> 15% in 3 months) or BMI < 18.5 + impaired general condition or Food intake 0%–25% of normal requirement in preceding week in preceding week	Severe Score 3	Head injury* Bone marrow transplantation* Intensive care patients (APACHE > 10).
Score:	+	Score:	= Total score:
Age	if ≥ 70 years: add 1 to total score above	= age-adjusted total score:	
Score ≥ 3: the patient is nutritionally at-risk and a nutritional care plan is initiated Score < 3: weekly rescreening of the patient. If the patient e.g. is scheduled for a major operation, a preventive nutritional care plan is considered to avoid the associated risk status.			

NRS-2002 is based on an interpretation of available randomised clinical trials.

* indicates that a trial directly supports the categorisation of patients with that diagnosis. Diagnoses shown in *italics* are based on the prototypes given below.

Nutritional risk is defined by the present **nutritional status** and risk of impairment of present status, due to increased requirements caused by stress metabolism of the clinical condition.

A nutritional care plan is indicated in all patients who are

- 1) severely undernourished (score = 3),
- 2) severely ill (score = 3),
- 3) moderately undernourished + mildly ill (score 2 + 1), or
- 4) mildly undernourished + moderately ill (score 1 + 2).

Prototypes for severity of disease

Score = 1: a patient with chronic disease, admitted to hospital due to complications. The patient is weak but out of bed regularly. Protein requirement is increased, but can be covered by oral diet or supplements in most cases.

Score = 2: a patient confined to bed due to illness, e.g. following major abdominal surgery. Protein requirement is substantially increased, but can be covered, although artificial feeding is required in many cases.

Score = 3: a patient in intensive care with assisted ventilation etc. Protein requirement is increased and cannot be covered even by artificial feeding. Protein breakdown and nitrogen loss can be significantly attenuated.

Figure 1.3.1. Nutritional risk screening – NRS 2002

A single, 24-hour measure of diet intake (24 h recall) characterizes current intake, whereas a dietary history reflects intake over a longer period of time. Food diaries are useful to obtain an impression of individual intake, but additional inquiry is necessary to obtain a reliable measure. Food frequency questionnaires are often used for studies of diet and health but should not be used in a population other than that for which the questionnaire was developed.

Fluid balance is an intrinsic part of nutritional balance. Physical examination is necessary to detect dehydration or oedema. Daily weight can give an estimate of changes in fluid balance. For this purpose, fluid balance charts should be kept and plasma creatinine, urea, and electrolyte levels should be monitored, as clinically indicated.

Patients' energy requirements are best determined by indirect calorimetry²⁸, although this measurement is not widely available in daily practice. Many equations to estimate energy requirement are available but the majority of them deviate substantially from actual requirements as determined by indirect calorimetry.²⁸

Isolated deficiencies should be identified using laboratory tests. Examples are minerals, e.g., K, Ca, Mg, P, Zn, Fe, and levels of vitamins and trace elements. It should be kept in mind that the acute phase response after trauma and during disease decreases the levels of binding proteins of several trace-elements and electrolytes including Ca, Mg, Zn, and Fe, and increases those of Cu. Measurement of total plasma levels will therefore overestimate, respectively underestimate deficiencies.

Body composition

Body weight, height, and calculated BMI are basic measures that should always be obtained. Other anthropometric measurements, such as BIA, DEXA, CT scanning, and MRI, have not become popular. CT and MRI scans conducted for diagnostic purposes could furnish adequate estimates of fat-free mass but do not take water content of the tissue into account, which increases in inflammatory states. Anthropometric techniques to measure body compartments (FFM, FM, skin folds, MAMC) have been used in a number of studies

and may be particularly useful where weighing is difficult, for instance in patients who are bedridden due to a hip fracture or serious illness.

Disease state and inflammatory activity

Disease state cannot be assessed from only history, clinical examination, and bedside measurements such as temperature, pulse rate, and blood pressure but also requires laboratory tests which reflect the severity of inflammation, including haemoglobin, full blood count, serum albumin, and C-reactive protein. In longstanding disease states, haemoglobin is almost always decreased. It is a sensitive, but not very specific, marker of undernutrition and subacute or chronic inflammation.

Albumin levels are not specific markers of nutritional status but are a reflection of redistribution, due to the increased capillary permeability associated with inflammation, and dilution by the resulting increase in fluid volume. In almost all disease states where albumin synthesis has been measured, the absolute synthesis rate of albumin is normal or increased. Only in end stage liver failure (and possibly in children suffering from kwashiorkor), is synthesis rate decreased. A further contributory cause of hypoalbuminaemia during illness is the decreased half-life of albumin which results in a lower total body albumin mass.

CRP is a sensitive but not precise measure for inflammation that is subject to rapid fluctuations and is not reflective of the degree of inflammation in its later stages.

Functional assessment

Physical dysfunction associated with malnutrition may be identified at the bedside using simple measurements suitable both for defining initial status and for continued monitoring.

Measurements of skeletal muscle function are valuable since they are sensitive both to changes in muscle mass and inflammation. Nutrient intake specifically increases muscle strength in the absence or improvement of inflammatory activity. Improvements in muscle strength occur within 2–3 days after the start of nutritional support, i.e. before any increase in muscle mass could have occurred. Conversely, muscle strength deteriorates

rates after the onset of starvation. Muscle function can be assessed qualitatively by the examiner on the basis of the reported or observed changes in the activities of daily living, or quantitatively by measuring handgrip strength. This last measure correlates very well with clinical outcome in surgical patients.^{29,30}

Changes in respiratory muscle strength can be assessed using serial FEV1 measurements, remembering of course that these can also reflect changes in airway resistance. Inspiratory muscle force may therefore also be a useful measure.

Assessment of cognitive function has not been widely practiced but can be helpful. Malnourished patients show deterioration in cognitive function and mood which is reversible by nutritional intervention. Using a validated mental scoring system, e.g., POMS or MMSE³¹, mood status can be quantified and changes with treatment recorded.

Immune function is less easily assessed. Immunological parameters in clinical practice reflect the presence of active inflammatory activity rather than providing a graded measure of immune function.⁶

Assessment in children

In children, growth charts of height and weight are important, as growth velocity is highly sensitive to nutritional status as well as to intercurrent illness and inflammation.

Upper arm circumference has also been used in epidemiological studies of malnutrition in children.

1.3.4. Techniques used in nutritional assessment

1.3.4.1. Anthropometry

Anthropometry furnishes measures of fat and muscle mass and reflects anatomical changes due to nutritional states.

Body weight

Body weight is the most frequently used parameter in clinical practice. However, we are still far from the ideal situation where every inpatient and outpatient has his or her weight recorded.

Weighing scales should be available in all departments and be regularly calibrated. Short-term changes reflect fluid balance and are an adequate indication of water balance. Longer term changes may reflect net changes in real tissue mass but they do not furnish an estimate of compositional changes. Involuntary weight loss over the last 3–6 months is a valuable measure of nutritional status from mild < 5% to severe > 10–15%. Even if there has been weight loss for over a year, this may not reflect malnutrition if there has been recent weight regain. On the other hand, if weight loss is continuing, its causes should be explored.

Measured weight is also valuable in the calculation of metabolic rate from standard equations, the estimation of nutritional requirements, and the calculation of drug dosages. However the prediction error of metabolic equations in an individual may be as high as 28% compared to measurement by indirect calorimetry. In individuals that are substantially overweight or underweight, ideal body weight may be a better reference value for the calculation. Weight divided by ideal weight gives a “percentage of ideal body weight”. Reference tables exist for the North-American population for ideal weight for individuals of the same age and sex. Ideal weights are determined by American health insurance companies based on least health care costs. Weight is the most valuable tool in paediatric practice for assessing growth, particularly when combined with length or height in growth charts in infants.

Body Mass Index (BMI)

BMI (= weight in kg divided by height in metres squared) allows comparison of both sexes and most age groups against a normal range as well as providing a useful monitoring tool to measure changes in nutritional status.

$$BMI = Wt [kg] \cdot Ht^{-2} [m]$$

$$BMI [kg \cdot m^{-2}]$$

> 30	obese
25–30	overweight
20–25	normal weight
18.5–20	possible undernutrition
< 18.5	undernutrition

Survival with a BMI < 10 in women or 12 in men is unusual and values below 20 are well correlated with mortality and outcome. In the elderly who lose height due to osteoporosis, the range moves upwards so that a BMI < 22 is associated with bad outcome, which implies that when BMI falls below 22, elderly people should be considered malnourished. Having a BMI in the normal, or even in the obese range, may still be compatible with malnutrition if a patient has suffered recent involuntary weight loss. When measurement of height is not feasible, for example in ill, old or frail people, or those with scoliosis or kyphosis, gender-specific prediction rules based on age and knee height can be used to calculate height.³²

Midarm circumference (MAC) and Triceps skin-fold thickness (TSF)

MAC is measured using a tape at the midpoint between the acromion and olecranon processes. It is easy to perform and is subject to only small errors. It is a useful surrogate for weight where weighing is impossible. Low levels correlate well with mortality, morbidity and beneficial response to nutritional support. In elderly people, MAC has been shown to be a better predictor of mortality than BMI. MAC measures, of course, the totality of tissue, bone, muscle, fluid and fat, but when combined with measurement of triceps skin fold thickness, useful correlates of muscle and fat mass can be derived. Unfortunately, triceps skin-fold measurement with callipers requires considerable skill and is subject to as much as a 20% inter-observer error. Intra-observer variability is small if the investigator is properly trained. TSF is, therefore, primarily a research tool. Both TSF and MAC are influenced by the state of fluid balance. Upper arm muscle area and upper arm bone-free muscle area (ABMA) can be derived from the following equations modified by Heymsfield³³:

$$\text{AMA (ABMA)} = (\text{MAC} - \pi \text{TSF})^2 / 4\pi$$

For men -10 cm²

For women -6.5 cm²

where:

AMA- arm muscle area (cm²)

ABMA- arm bone-free muscle area (cm²)

MAC- midarm circumference (cm)

TSF- triceps skin fold (cm)

Both MAC and TSF can be related to normal centiles for age and sex:

5–15th centile: moderate undernutrition

< 5th centile: severe undernutrition

1.3.4.2. Advanced measures of function

Direct muscle stimulation involves electrical stimulation of the adductor pollicis muscle and direct measurement of contraction, force, and relaxation, allowing tracing of force frequency curves. Changes can be detected early in starvation and refeeding. Jeejeebhoy and colleagues have popularized this as a useful bedside tool to measure involuntary muscle strength independent of nervous system control and motivation of the patient.^{34,35} At present these techniques are not used anymore, mainly due to the discomfort inflicted upon the patient.

Respiratory function. As well as measuring airway resistance, FEV1 reflects respiratory muscle strength (see above). Expiratory and inspiratory force can also be measured against resistance. Hill has shown a close correlation between these measures and total body protein, with a rapid decline after 20% loss of body protein.³⁶

Immune function. Protein energy malnutrition is associated with a significant impairment of cell-mediated immunity, phagocyte function, complement system, secretory immunoglobulin A antibody concentrations, and cytokine production. Deficiency of single nutrients (e.g. zinc, selenium, iron, and vitamins A, C, E, and B6) also results in altered immune responses.³⁷

1.3.4.3. Laboratory Tests^{38,39}

Serum albumin concentration is a good predictor of surgical risk but reflects disease severity rather than malnutrition, although the rate of return of serum albumin to normal after acute illness may be influenced by energy and protein

intake. As described above, serum albumin is mainly affected by the cytokine response to injury leading to an increased distribution volume and dilution, and a decrease in half-life. This decreases total albumin mass due to an increased albumin escape rate from the circulation which is associated with cytokine responses to injury and due to dilution in an increased extravascular volume.

The shorter half-life proteins, transthyretin (2 days) and transferrin (7 days) are also subject to the same distributional and dilutional influences as albumin. Transthyretin is a more sensitive reflection of recent food intake but is not a good measure of nutritional state. Therefore, these parameters are rarely included as part of nutritional assessment.

Lymphocyte count – A lymphocyte count of $900\text{--}1500\text{ cells}\cdot\text{mm}^{-3}$ is said to indicate moderate malnutrition while $< 900\cdot\text{mm}^{-3}$ indicates severe malnutrition. The proportion and number of T-lymphocytes in the peripheral blood are also reduced by malnutrition but can be restored to normal by refeeding

Creatinine – Both serum concentration and urinary excretion of creatinine reflects muscle mass, being high in muscular weight lifters and low in malnourished patients. Creatinine excretion per 24 hours has been used to calculate a Creatinine height index (CHI):

$$\text{CHI (\%)} = \frac{\text{Measured 24 hr urinary creatinine} \times 100}{\text{Ideal 24 hr urinary creatinine for height}^*}$$

*obtained from standard tables

This has been used to reflect muscle mass. A deficit of 5%–15% may be classified as mild, 15%–30% is moderate, and > 30% is classified as severe depletion.

Nitrogen balance – This is mainly a research tool since, under clinical conditions, intake is nearly

always overestimated and losses in urine, faeces, skin, and wounds are underestimated. The Kjeldahl technique for total nitrogen is better than extrapolation from urinary urea. Although urea contains 80% of urinary nitrogen under normal circumstances, this fraction varies with malnutrition and illness, especially in long-term starving states in which a large proportion of nitrogen in the urine appears as ammonia.⁴⁰ Combustion techniques allow measurement of total nitrogen in liquid as well solid samples. Nonetheless, large changes in urinary urea excretion may be a useful indication of changes in net protein catabolism and it is a simple method to use in the intensive care unit. Starvation with low protein turnover is characterized by a low serum urea concentration if patients are well hydrated.

Bioelectrical impedance⁴¹ – This is based on the conducting properties of different tissues see Chapter 1.2.2. It may be of value as a research tool to study body composition in normal subjects, but it has proved of limited value in clinical practice where large fluctuations occur in fluid balance and body composition. Comparison between day-to-day changes with one technique in a single patient may reliably reveal changes in compartments but comparison between different types of equipment is less reliable.^{42,43}

Other tests – Liver enzyme tests, creatinine (see below), urea, and electrolyte levels, including calcium, phosphate, and magnesium, should all be measured routinely and recorded in serial data charts. Zinc, selenium, and iron are all helpful, particularly in gastrointestinal disease. C-reactive protein is useful for assessment of acute inflammatory activity but is a less reliable parameter for chronic inflammation or recovery from acute inflammatory states.

Recording – It is essential that all data, obtained initially on admission and subsequently during monitoring, are recorded in a serial form, readily accessible either digitally or using serial data charts. This allows any changes in values or trends to be observed immediately and appropriate action tak-

en. The various parameters can also be correlated with each other obtaining a full and accurate clinical picture in a continuous and dynamic form.

Summary

Undernutrition not only causes weight loss and changes in body composition but also impaired physiological function, a higher risk of complications, poor outcome from illness, and shorter longevity. Disease predisposes to malnutrition not only by its effects on food intake, but in the case of trauma and inflammatory disease, by increased metabolic rates and protein catabolism. All patients should undergo nutritional screening on admission using a validated screening tool. Those found to be nutritionally at risk should have a more detailed assessment, combining history, examination, bedside tests of physical and mental function, and relevant laboratory tests reflecting inflammation and potentially deficiencies of vitamins, trace elements, and electrolyte disturbances. All data should be recorded digitally, or on serial data charts in an easily accessible way, so that trends in the different parameters can be readily observed. Screening and assessment should lead to the development of a nutritional management plan, including continued monitoring.

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1.4. The influence of malnutrition on function

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Learning objectives

- To understand the effects of malnutrition on the function of different organs
- To learn about the functional consequences of malnutrition

Introduction

The effects of starvation on the composition and function of organs is considerable. The degree of wasting of various organs was evaluated in Krieger's autopsy study of patients dying from malnutrition¹. The heart and liver lost approximately

30% of their usual weight, but spleen, kidney, and pancreas were also affected. In the Keys study, in which 32 healthy men underwent partial starvation for 24 weeks, each volunteer lost approximately 25% of his initial body weight, fat mass declined to about 30% of baseline value, and fat-free mass declined to about 82% of baseline². The loss of FFM is due, to a large degree, to loss of skeletal muscle. In response to stress, muscle protein supplies not only the precursors for gluconeogenesis but also the amino acids for the synthesis of proteins for repair and for the immune

response. This loss of muscle mass, and the subsequent inability to provide the building blocks for these functions, may be an important reason why malnourished people have a higher risk of developing complications following surgery or in acute illness. In this chapter, the effects of starvation on biological systems and organ function will be discussed.

1.4.1. Cognitive function

Starvation in adults leads to anxiety and depression, which may be linked to specific micronutrient as well as macronutrient deficiencies. This has been clearly demonstrated by Keys, Brozek, and others² in normal subjects and by Hill in patients.³ Various large-scale epidemiological studies have shown associations between quality of diet and prevalence of cognitive impairment^{4–10}. Impaired brain function is likely to be associated with a deficiency of micronutrients arising from a compromised diet, malabsorption, or both, and is mechanistically plausible. In some instances, the presence of hyperhomocysteinemia is quite strongly supported by observational data¹¹.

However, with the possible exception of consuming a Mediterranean diet, there is, as yet, no evidence from randomised controlled trials, that correcting deficiencies through supplementation reduces the incidence of dementia. However, more trials are required¹¹. In children, protein, energy, iron, and iodine deficiencies have been associated with cognitive impairment.

1.4.2. Muscle function

Malnutrition causes a reduction in muscle strength and endurance. In addition to histological changes in muscle (particularly reduction in Type 1 fibres), malnutrition is also associated with a reduction in energy sources and intermediates within skeletal muscle, such as glycogen and creatine. With food deprivation, muscle function is reduced before any change in muscle mass occurs, then worsens further as cell mass is lost¹².

Conversely, function improves by 10%–20% during the first few days of refeeding before any increase in muscle mass. Thereafter, muscle mass is gradually restored in the course of several weeks

to months, while simultaneously, function continues to improve until it reaches the normal state for that individual.

In addition to loss of muscle mass, inflammatory activity also diminishes muscle strength, endurance, and mobility¹³. Muscle strength, therefore, is a composite measure of muscle mass and inflammatory activity and, as such, is a useful risk factor for quality of life and the ability to overcome trauma and illness¹⁴.

Handgrip dynamometry, a measure of voluntary muscle strength, therefore, is a useful clinical tool in nutritional assessment and monitoring, correlating well with outcomes of surgery and with clinical improvement¹⁵. Measurement of involuntary muscle contraction by direct stimulation of the adductor pollicis muscle has provided valuable information in research settings but has not been routinely used. Muscle cell function measured by direct stimulation declines after a few days of fasting, then decreases further as cell mass is lost¹⁶.

1.4.3. Cardiovascular function

Prolonged and severe undernutrition causes loss of cardiac muscle with a decrease in cardiac output, bradycardia, and hypotension. The decrease in heart volume, of which 40% consists of loss of cardiac muscle, is proportional to the loss of body weight¹⁷. A diminished ventricular volume explains the other 60%. Severely depleted individuals have impaired exercise tolerance and may develop peripheral circulatory failure.

Specific deficiencies, e.g., vitamin B1, may cause cardiac failure (wet Beri Beri) and mineral and electrolyte disorders can cause cardiac arrhythmias¹⁸.

1.4.4. Renal function

Malnutrition has been reported to lead to significant alterations in renal hemodynamics, with decreased glomerular filtration rates and renal plasma flow, as well as a lowered capacity to concentrate the urine and excrete an acid load. The capacity to excrete an excess salt and water load is diminished and extracellular fluid volume comprises a higher proportion of body composition than normal¹⁹.

These changes are induced by increased inflammatory activity related to disease, trauma, or other forms of stress. They induce an increase in capillary permeability leading to escape of fluid, proteins, electrolytes, and other plasma components into the extravascular extracellular space (the interstitium) and a decrease of intravascular volume and renal perfusion pressure and function. These abnormalities are less prominent in the presence of undernutrition without inflammation.

1.4.5. Respiratory function

Protein depletion of more than 20% affects respiratory muscle structure and function. It is associated with a decrease in diaphragmatic muscle mass, maximal voluntary ventilation, and respiratory muscle strength²⁰. Impaired neural ventilatory drive also affects ventilation²¹. Depleted persons have an altered response to hypoxia and hypercapnia, an altered breathing pattern, and morphologic changes in the pulmonary parenchyma. Weaning from ventilators is more difficult. Bronchopneumonia is frequent in these patients and is the result of a combination of hypoventilation, inability to cough effectively, and impaired resistance against invading micro-organisms.

1.4.6. Gastrointestinal tract

Enterocytes undergo rapid cell turnover, for which the presence of food in the lumen is the major stimulating factor²². The most obvious effect of acute (and chronic) food deprivation on the small intestine is a reduction in absorptive surface area. In severely depleted people, impaired absorption of lipids, disaccharides, and glucose has been observed. In addition, there is decreased production of gastric, pancreatic, and biliary secretions, which also contributes to malabsorption. As a result of these changes, patients with severe malnutrition often suffer from diarrhoea, aggravating malnutrition and creating a vicious cycle.

Changes in bacterial flora or overt intestinal infections may also increase the severity of malabsorption and diarrhoea²³. All gastrointestinal

changes connected with malnutrition aggravate the risk of inflammation and impaired intestinal barrier function. In chronic conditions, this may lead to liver steatosis (NAFLD) or subsequently to steatohepatitis (NASH) and liver cirrhosis²⁴.

1.4.7. Thermoregulation

Severe weight loss and starvation impair the thermogenic response to cold. Starving for more than 48 hours reduces vasoconstrictor responses. Even when these changes are moderate, they predispose to hypothermia which has important clinical consequences. A drop of core temperature of only 1–2 °C causes impaired cognitive function and confusion as well as poor coordination and muscle weakness, predisposing to falls and injury, particularly in the elderly. During starvation periods or famines, the febrile response is lost and fever may be absent even when life-threatening infection is present^{25,26}. After refeeding, thermoregulation recovers.

1.4.8. Immune system

Malnutrition affects nearly all aspects of immune defense. Particularly impaired are cell-mediated immunity and resistance to infection²⁷. The primary defects in the immune system observed during starvation involve T-lymphocytes and the complement system. The thymus atrophies and lymphocytes in the thymus become depleted. Cytokine responses (e.g. IL-1) are depressed, which may contribute to the low proliferation rate of lymphocytes. Also, phagocytosis, chemotaxis, and intracellular destruction of bacteria are impaired as a result of defects in immune cell function (e.g. monocytes) and the complement system. In the majority of cases, lack of nutritional intake or uptake coincides with the presence of disease which also has an impact on immune status²⁸. Reduced immunity increases the susceptibility to infection and decreases the ability to generate an adequate host response to overcome trauma or other types of stress. Individuals with a BMI below 18.5 kg · m⁻² tend to be ill for longer periods of time per year than the majority of individuals with a BMI above 18.5 kg · m⁻². Similarly, they respond less well following surgery and

during acute illness, prolonging the duration of hospitalization.

1.4.9. Wound healing

Malnutrition, particularly a poor recent nutritional intake, and the presence of inflammation delay wound healing in surgical patients. Low body mass index, low body weight, and reduced food intake have been shown to be independent risk factors for pressure ulcer development. An adequate diet improves wound healing within one week unless patients are suffering from severe infectious or non-infectious inflammation. It is important to realize that any disease, trauma, or infection causes inflammation and when inflammation is more severe, recovery (wound healing, immune response) will be more compromised. There is some evidence that nutritional support is associated with a lower incidence of pressure ulcer development, and that pressure ulcers in patients receiving a high-protein supplement tend to heal better^{29,30}.

1.4.10. Quality of life

Good nutrition promotes quality of life since not only is food a sensory and psychological pleasure in its own right, but mental and physical well-being are dependent on an adequate nutritional state. The consequences of malnutrition include progressive physical, mental, and social disability, as well as an increased predisposition to disease and poor recovery from stressful events³¹.

Summary

Loss of physical integrity develops in parallel with the degree and severity of undernutrition and inflammation. Similarly, cognition and mood are impaired. Changes are also seen in skeletal and cardiac muscle and in respiratory, thermoregulatory, gastrointestinal, immune, and other organ functions.

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1.5. Overnutrition - functional and clinical consequences

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Learning objectives

- To understand the risk of chronic overfeeding
- To understand the nutritional and physiological role of adipose tissue
- To understand the relationship between obesity and the metabolic syndrome
- To briefly summarize the nutritional treatment of obese patients
- To understand the problems of perioperative nutrition and the risks of obesity

Introduction

Overfeeding can be defined as supplying nutrients in excess of requirements leading to increased storage of body stores. Acute and unbalanced overfeeding can lead to gastrointestinal intolerance and metabolic changes represented by hyperglycaemia, hyperlipidaemia, and refeeding syndrome. These consequences will be discussed in respective chapters of the book.

Long-term excessive intake of energy substrates leads also to accumulation of excessive energy in adipose tissue and subsequent obesity

development. Obesity is growing because the vast majority of the population in the developed world consumes more food than it needs and only a minority do enough exercise to burn off this excess.

1.5.1. Physiology of adipose tissue

It is now generally accepted that adipose tissue is not only a passive energy store but is also a very active organ that produces substances with important regulatory roles elsewhere in the body. Adipose tissue has at least seven such functions (see Table 1.5.1).

The secretory functions of adipose tissue are summarized in Figure 1.5.1. and Table 1.5.2. Many of these hormones, cytokines, and other metabolically active substances contribute to the development of the metabolic syndrome¹.

The most important adipose tissue-derived factors include²:

- ***Leptin*** was the first hormone discovered that is produced primarily by adipose tissue (adipocytes). It acts predominantly on the central

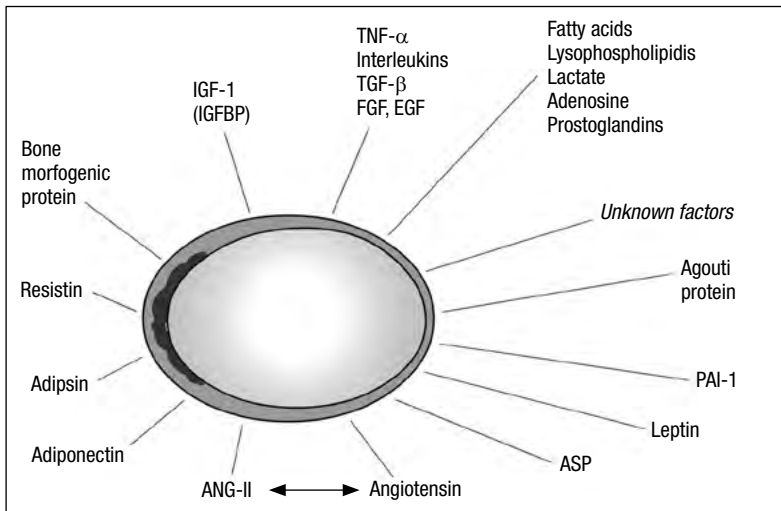
Table 1.5.1. The most important functions of adipose tissue**The functions of adipose tissue:**

Energy storage
 Mechanical protection
 Thermal protection
 Production of hormonal and metabolically active substances
 Protection against fat accumulation in other organs
 Reservoir for immunocompetent cells
 Conversion of inactive hormone precursors to active substances
 Deposition of organic pollutants and endocrine disruptors

nervous system, where it suppresses the feeling of hunger. It also influences reproductive and haemopoietic functions and regulates energy expenditure. Serum leptin levels normal-

ly reflect body fat content, being increased in obese compared to lean subjects. Increased leptin levels in obesity, however, do not decrease food intake and increases in body weight are probably due to decreased central sensitivity to leptin.

- **Resistin and TNF α** are produced primarily by immunocompetent cells but also by adipocytes. They cause insulin resistance by interference with the post-receptor insulin signalling cascade. Their production is usually increased in obesity and both factors could, therefore, be links between obesity, diabetes, and other components of the metabolic syndrome.

**Figure 1.5.1.** Secretory function of adipose tissue (according to Ravussin⁽²⁾)**Table 1.5.2.** The principal products of fatty tissue and their effects

Substance	Role in
Leptin	down-regulation of appetite, influence on reproduction, haemopoiesis and energy expenditure
Resistin	suspected of being connected to insulin resistance, enhances pro-inflammatory cytokines
TNF- α	insulin resistance
Angiotensinogen	hypertension
PAI 1	impairment of fibrinolysis
Interleukin-6 and other cytokines	proatherogenic and procoagulatory effect
Adiponectin	enhances glucose level regulation and insulin sensitivity
Free fatty acids	organ steatosis, insulin secretion impairment
Oestrogens	main female hormones, involved in carcinogenesis of hormone sensitive neoplasms and protection against osteoporosis

- **Angiotensinogen** is secreted by adipose tissue as well as by other tissues. It acts locally to decrease adipocyte differentiation and insulin sensitivity. It can also be released into the circulation and contribute to the rise in systemic blood pressure seen commonly in patients with obesity
- **PAI-1**, an inhibitor of plasminogen activator, is produced in the adipose tissue of obese individuals. The increase in its circulating levels leads to impairment of fibrinolysis.
- **Proinflammatory cytokines** like IL-6 are also produced by adipose tissue and may contribute to atherogenesis and a pro-coagulation state in obese individuals.
- **Oestrogens** are produced in adipose tissue by conversion from less active precursors. Their production is increased in obesity as a result of higher total fat mass, which may be one of the mechanisms linking obesity to the development of cancer and also to sterility.
- **Fatty acid binding protein 4**. Fatty acid binding proteins govern intracellular fatty acid trafficking. They are released into the circulation where they can modulate insulin sensitivity. Increased FABP-4 levels generally accompany obesity and insulin resistance.

In addition to producing these substances, adipose tissue also produces acylation-stimulating protein, adipsin, retinol-binding protein, fibrinogen-angiotensin-related protein and others, including metallothionein, a metalloprotein with a role in stress reactions, which may contribute to the relationship between obesity and cardiovascular disease. Recently, direct production of acute phase C-reactive protein in adipose tissue has been described.

Most adipose tissue-derived substances act as proinflammatory factors. In contrast, myokines, muscle hormones, act as anti-inflammatory factors. There are 4 typical functions of approximately 50 myokines – regeneration, immunosuppression, insulin sensitising effect, and browning of white adipose tissue (brite or beige adipose tissue is formed from white adipocytes by increased number of mitochondria resembling brown adipocytes).

Adipose tissue is also important for normal glucose metabolism, protecting, at least partially, against postprandial oscillations in blood glucose, which may lead to diabetes and other metabolic consequences. This was clearly shown in experiments on transgenic animals which lack white adipose tissue and which develop insulin resistance.

In some clinical situations, the prognosis for obese patients is better than that for normal weight subjects and constitutes the obesity paradox. This is typically observed in people over age 65, in cardiovascular diseases including heart failure and chronic kidney disease, or in physically active obese patients (the so-called “fit fat”).

1.5.2. Acute overfeeding

Acute overfeeding is a problem mainly in patients on total parenteral nutrition which allows administration of unlimited amounts of nutrients (see the chapter devoted to complications of parenteral nutrition). Although refeeding syndrome can also occur with enteral refeeding, the rate of administration is limited by gastrointestinal tolerance.

Acute overfeeding can impair aspects of immune function, increases oxidative load, and causes exacerbation of infections in critically ill patients⁴. Acute unbalanced overfeeding in previously malnourished patients can cause fluid retention, hyperglycaemia, hypophosphatemia, hyperlipidaemia, hypercapnia, heart and liver complications, and the refeeding syndrome. Severe acute refeeding complications can be present even in obese patients who have undergone periods of starvation or hypocaloric intake⁵. Refeeding syndrome is subject of Chapter 7.3.

1.5.3. Chronic overfeeding – Obesity

1.5.3.1. Aetiology of obesity

The fundamental cause of obesity and overweight is an energy imbalance between calories consumed and calories expended.

Globally, there has been:

- an increased intake of energy-dense foods that are high in fat and/or carbohydrates

- high protein intake at early stages of life (first 2–3 years)
- a decrease in physical activity due to the increasingly sedentary nature of many forms of work, changing modes of transportation, and increasing urbanization

In the developed world, more than 40% of the population are overweight, over 20% are obese, and, in some countries, as much as three-quarters of the adult population is overweight. The steep rise in the incidence of obesity in the developed world, when the genetic background has not changed, is due to excess intake of energy and diminishing levels of activity.

It is also probable that the thrifty gene hypothesis plays a part⁶. It has been postulated that individuals who survived as far as the 20th century are the descendants of those who could cope with shortages of food, wars, and famine with highly efficient storage and energy conserving mechanisms. Those from the Indian subcontinent, for example, who migrate from subsistence farming communities to more affluent urban societies, suffer particularly from obesity and its consequences. Mammals have many ways of adapting to low intake of food, including reduced energy expenditure. On the other hand, mechanisms, other than physical activity, for dealing with excess energy intake are limited.

There are known risk factors for obesity that include family history of obesity, low birth weight, and timing/rate of maturation and psychosocial factors. Despite these, chronic overfeeding remains the most important cause of obesity⁷, along with genetic disposition, sedentary lifestyle, and impairment of protective mechanisms like postprandial thermogenesis, non-exercise associated thermogenesis, composition of muscle fibres, and thyroid gland functions.

The human body has important homeostatic mechanism to regulate energy balance but in obese people such mechanisms are impaired, e.g. leptin and insulin sensitivities are reduced, resulting in the ingestion of food intake beyond metabolic needs. On the other hand, reduction of energy intake below metabolic needs triggers an

increase in sympathetic activity, release of peripheral glucose and fatty acids, and decreases in leptin levels. Together, muscle and thermogenic organ activities decrease, resulting in a decrease of resting energy expenditure.

Although obese individuals use fat as their main source of energy, this is also influenced by the pattern of substrate intake. Obese subjects have higher absolute energy expenditure due to their increased lean mass and the work of moving their heavier bodies, although oxygen consumption per kg body weight may be lower than normal, since adipose tissue has a lower metabolic rate than lean tissue. Some obese subjects also have a lower diet-induced thermogenesis.

The progression of obesity can also be augmented by eating disorders⁸. Night-eating syndrome is defined as an intake of more than 50% of the total daily food at night and is associated with an abnormality of the serotonin system and depression and is often associated with sleep apnoea. Binge eating, according to the 'Diagnostic and statistical manual of mental disorders' is defined as uncontrolled periods of overeating, usually in the evening, and is also associated with a central serotonin deficiency.

Studies on animals and volunteers have shown that, after the period of overfeeding is over, body weight usually returns to its original value. Some interesting studies have been carried out on sumo wrestlers, who chronically overfeed but are highly active. When they stop exercising, however, their enlarged muscle mass is quickly replaced by adipose tissue. This is in accordance with recent prospective studies which show that quite obese patients with sufficient levels of physical activity do not have increased mortality⁹. It is actually better to be obese but physically fit (fit-fat) than slim but unfit (unfit-lean).

Recently, it was revealed that gut microbiota might also play an important role in weight management¹⁰. Specific bacterial gut microbiota profiles induced by the Western style diet and characterized by decreased bacteroidetes/firmicutes ratios, or an increase of lactobacillus, *S. aureus*, *E. coli*, and *Faecalibacterium prausnitzii* have been described. These microbiota changes result

Table 1.5.3. Classification of over nutrition

Classification	Sub classification	Criteria
Obesity		$\text{BMI} \geq 30 \text{ kg} \cdot \text{m}^{-2}$
	Obesity grade I	$\text{BMI } 30\text{--}34.9 \text{ kg} \cdot \text{m}^{-2}$
	Obesity grade II	$\text{BMI } 35\text{--}39.9 \text{ kg} \cdot \text{m}^{-2}$
	Obesity grade III	$\text{BMI} \geq 40 \text{ kg} \cdot \text{m}^{-2}$

in more efficient absorption of calories and increased lipid deposition by the digestion and absorption of poorly digestible plant polysaccharides via glycoside hydrolysis and via beta-fructosidase for fructose-containing carbohydrates. Such a microbiota phenotype, which seems to be transmissible by faecal transplantation, has been associated with obesity. Indeed, enteric bacteria contribute, through the elaboration of enzymes not produced by humans, to the fermentation of dietary fibres. Obese patients display increased concentrations of faecal small chain fatty acids (SCFAs) (e.g. butyrate) and/or blood/breath ethanol, produced by a more pronounced bacterial fermentation of indigestible dietary residues (e.g. large polysaccharides, unabsorbed sugars and alcohols) in the colon.

1.5.3.2. Classification of obesity

Generally, obesity is classified using BMI as the sole indicator.

BMI has several limitations, mainly because it does not allow one to distinguish body composition from overall weight. It is well known that visceral fat is metabolically more active than subcutaneous fat and is the fat that counts for cardio-metabolic risk. Therefore, measuring fat distribution is recommended.

Waist circumference (WC) is another possible method to define obesity because it more accurately addresses fat distribution and metabolic risk. World Health Organization recommended cut-off points for waist circumference are defined by the metabolic risk produced, as shown in Table 1.5.4. Waist circumference is better than waist-to-hip ratio as an indicator of visceral fat due to its ease of use in clinical practice. WC can even

Table 1.5.4. Waist circumference and metabolic risk of obesity according to waist circumference

<i>Metabolic risk according to waist circumference</i>		
	Increased	Substantially increased
Women	> 80 cm	> 88 cm
Men	> 94 cm	> 102 cm

be used alone (when weight and height measurements are not feasible) or in combination with BMI.

For further in-depth analysis of body composition, one can measure perimeters and skinfolds of the body. There are several points to measure and equations have been developed in order to estimate body fat that usually require at least 3–4 skinfolds and 1–2 perimeters.

Another tool to screen for obesity is bioelectrical impedance (BIA), this allows measurement of extracellular and cellular compartments of the body, not only fat content.

1.5.3.3. Obesity and metabolic complications

The adipose tissue of a lean individual eating healthy food and exercising regularly consists of small adipocytes secreting a whole spectrum of hormones, such as adiponectin, which protect against insulin resistance and atherogenesis. It also has sufficient reserve capacity to store substrates postprandially. Key metabolic organs such as liver, pancreas, and muscles are thus protected against lipid overload and ectopic lipid storage.

In contrast, the adipose tissue of an obese individual with an unhealthy diet and sedentary life style is associated with metabolic complications and health problems.

– Continuous excessive energy intake leads to hypertrophy of adipocytes due to excessive triglyceride storage. Consequently, the need for triglyceride storage exceeds the storage capacity of adipose tissue and triglycerides and/or other lipid metabolites spill over into non-adipose tissues such as muscle, liver, and pancreas. This phenomenon, referred to as “ectopic lipid storage”, induces insulin resistance in muscle and liver through interference with the in-

sulin signalling cascade and impairs insulin secretion due to increased apoptosis of pancreatic beta cells. Insufficient lipid storage capacity of adipose tissue in obesity also leads to chronically increased free fatty acid levels in the circulation that directly decrease both insulin sensitivity and insulin secretion. A combination of these processes can lead eventually to the development of type 2 diabetes.

- Hypertrophic adipocytes, induced by continuous excessive energy supply, are more prone to apoptosis than “lean” adipocytes. This results in higher infiltration of the adipose tissue of obese patients by immunocompetent cells such as macrophages. Immunocompetent cells, in turn, produce proinflammatory cytokines that further attract and activate immunocompetent cells in adipose tissue. These proinflammatory molecules are also released into the systemic circulation and play an important role in the development of the “sub-clinical inflammation” commonly seen in patients with obesity, type 2 diabetes mellitus, and atherosclerosis.
- Obesity also markedly alters the endocrine production profile of adipose tissue. In general, the adipose tissue of obese subjects produces more proinflammatory factors and insulin resistance-inducing factors (e.g. TNF- α , fatty acid binding protein 4, resistin, interleukin 6) and less anti-inflammatory and insulin-sensitizing factors (e.g. adiponectin). It is important to note that both adipocytes themselves and other non-adipocyte cells in adipose tissue (immunocompetent cells, fibroblasts, endothelial cells) contribute to this unfavourable endocrine profile in patients with obesity.
- Numerous studies have shown that hormone production in adipose tissue differs significantly between subcutaneous and visceral (intra-abdominal) fat depots³. Visceral adipose tissue appears to have a more proinflammatory and metabolically detrimental profile in obesity. Visceral obesity is, therefore, associated with a greater risk of metabolic complications, e.g., type 2 diabetes and cardiovascular disease.
- Increased production of proinflammatory factors by adipose tissue in obesity not only induc-

es insulin resistance but also directly promotes the development of atherosclerosis, since, in addition to proinflammatory molecules, adipose tissue is a direct source of cell adhesion molecules, C-reactive protein, and components of the renin-angiotensin system.

Obesity-related organ changes

Obesity is a disease affecting most organs of the body, since fat cells have important physiological and pathological roles in other tissues. There is special cross-talk between local fat cells and organ cells in organs such as liver, kidney, epididymis, and adrenals. Periadventitial fat produces vasodilating substances under normal physiological circumstances but it has special role in the pathogenesis of hypertension and atherosclerosis. Pericardial fat can influence coronary atherosclerosis and adrenal fat can influence aldosterone secretion. Moderate weight loss of 5%–10% affects predominantly local and organ fat and has important functional effects.

1.5.3.4. Metabolic syndrome

Reaven¹¹ originally defined five components of this syndrome (Table 1.5.6.), but this has now been increased to 80 components that are divided into 7 groups.

The definition of the Metabolic Syndrome¹ by the American National Cholesterol Education Program (ATPIII) requires three key features to be present including abdominal obesity – see Table 1.5.7. This syndrome, also called the insulin resistance syndrome, is caused by both genetic and environmental factors. The latter include intrauterine undernutrition and low birth weight (Barker hypothesis), absence of physical activity, and excessive food intake.

1.5.4. Treatment of obesity

Former attempts to achieve normal weight were unrealistic and unnecessary since even moderate weight loss (5%–10% of the initial weight) decreases the incidence of diabetes by 50%, of some tumours by 50%, and reduces cardiovascular mortality by 20%. These effects are probably associated with fine-tuning of adipose tissue function

Table 1.5.5. The consequences of chronic overfeeding

Metabolic and organ changes connected with chronic overnutrition
– Production of fat, steatosis of liver, muscles, and pancreas
– Obesity
– Excessive secretion of fat cell hormones, fatty acids, and cytokines
– Insulin resistance
– Metabolic syndrome including type 2 diabetes, hypertension and hyperlipidaemia
– Impaired coagulation and fibrinolysis – thrombotic complications
– Sterility and hormonal disorders
– Sleep apnoea syndrome
– Respiratory failure
– Impaired regeneration and wound healing
– Infections
– Atherosclerosis, endothelial dysfunction, cardiovascular diseases
– Oxidative stress
– Systemic inflammation
– Obesity related tumours
– Diabetes mellitus type 2
– Depression
– Cancer (e.g. breast, uterus, kidney, gastrointestinal including pancreas and liver)

and are not improved by further weight loss. Moderate loss of body weight is sufficient to cause a hyposecretory catabolic state with decrease in circulating triglycerides, free fatty acids, insulin, leptin, PAI-1, and other products of the fat cell.

Five different methods are used for the treatment of obesity:

- Diet
- Psychotherapy
- Modification of physical activity
- Pharmacotherapy
- Surgery

Table 1.5.7. Clinical identification of the metabolic syndrome (ATPIII). At least 3 criteria must be present including abdominal obesity

Criterion	Diagnostic value
Abdominal obesity (waist circumference)	
Men	> 102 cm (> 40 in)
Women	> 88 cm (> 35 in)
Triglycerides	> 150 mg · dl ⁻¹ (1.7 mmol · l ⁻¹)
HDL cholesterol	
Men	< 40 mg · dl ⁻¹ (1.04 mmol · l ⁻¹)
Women	< 50 mg · dl ⁻¹ (1.3 mmol · l ⁻¹)
Blood pressure	> 130/85 mmHg
Fasting glucose	> 110 mg · dl ⁻¹ (6.2 mmol · l ⁻¹)

The first three of these are the cornerstones of any weight-reducing program through negative energy balance. These interventions include:

- **Regular food intake.** The daily intake should be divided into 3 to 6 portions. The food conforms to the healthy food rules and has anti-atherogenic properties with sufficient amounts of fibre, vitamins, and minerals. It should be varied and include daily portions of fruit and vegetables, whole grain products, potatoes, and pulses.
- **Reduction in fat intake.** This is the most important part of weight loss. Even patients that have been extensively informed about diet often underestimate its importance. They repeat that they do not use sugar, but while a cube of sugar weighing 5 grams equals 20 kcal, 5 grams of fat spread contains 45 kcal.
- **Change in lifestyle** is accentuated by psychotherapy and includes changes in leisure time pursuits and an increase in overall physical ac-

Table 1.5.6. Components of the metabolic syndrome

Classical definition (Reaven 1988)	Present definition of insulin resistance and about 80 abnormalities in relation to:
Hyperinsulinaemia	Blood glucose levels
High VLDL triglycerides	Blood pressure
Impaired glucose tolerance and diabetes	Blood lipids
Low HDL cholesterol	Hormone levels
Essential hypertension	Coagulation and fibrinolysis Changes in body shape Central nervous system function

tivity. Simple change in dietary habits is seldom successful on its own.

- **Prevention of dietary lapses** with the new life-style has to be encouraged. It is common that, after a single lapse, the patient feels ashamed and, rather than increasing his efforts, stops altogether.
- **Sufficient intake of low-calorie drinks** is important. Alcoholic intake should be reduced (alcohol = 7.5 kcal · g⁻¹).
- **Bariatric surgery** – Morbid obesity and can be significantly reduced by bariatric surgery procedures. To be fully successful, bariatric procedures requires appropriate perioperative nutritional support and dietary education – see chapter 8.26.

The reduction in ingested calories has to be life-long. It is also necessary to modify the whole life-style, including eating and exercise patterns. Short-term dietary measures lasting a few days or weeks, e.g. low calorie diets (600 kcal or 2500 kJ), also known as VLCD (very low calorie diets) are indicated only in very specific situations (Pickwick syndrome, decompensation of diabetes, preparation for surgery). These regimens usually last between 7 and 30 days and have to be supervised by a physician, as they can be dangerous in patients with co-morbidities. With all short- or long-term dietary measures, there is a problem of rebound and weight regain, once motivation is lost. This has to be addressed by repeated long-term education and supervision.

Pharmacological treatment of obesity is also effective and can be administered either intermittently or continuously for many years. The enteral lipase inhibitor – Orlistat impairs the absorption of ingested fats and, thus, significantly reduces insulin resistance induced by overfeeding. The central anorexic Sibutramine was well tolerated and has fewer side effects compared to previously used centrally acting anorexics. Orlistat can be used on a long-term basis for a period of months, or even years, but is usually prescribed intermittently for a few months at a time. Sibutramine distribution was stopped in Europe due to possible cardiovascular side effects in some subgroups of patients in

the SCOUT study¹². Several new centrally acting anorexics have been used in recent years including a fixed combination of naltrexone/bupropione in Europe and the US, and a fixed combination phentermine/ topiramate and lorcaserine in the US. Very effective weight loss can be achieved also by the new antidiabetic drugs – incretin analogues (exenatide and liraglutide) and gliflozins.

Summary

The main complication of chronic overnutrition is obesity which is associated with serious complications including type 2 diabetes, cardiovascular disease, and cancer. These risks can be decreased by losing 5%–10% of weight, thereby reducing insulin resistance, and the production of many atherogenic, pro-coagulatory, diabetogenic, hormonal, and metabolically-active substances. Even with such a small reduction in weight, adipose tissue regains its capacity to protect organs such as liver, pancreas, and muscles from fat accumulation. In catabolic illness, obese patients are just as vulnerable to malnutrition as lean individuals and should be screened and given appropriate nutritional support. The incidence of peri-operative complications is higher in the obese but has been significantly reduced by development of laparoscopic surgery.

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1.6. Prevalence of malnutrition

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Learning objectives

- To understand and define malnutrition
- To be aware of the prevalence of undernutrition and overnutrition
- To learn what the main causes of malnutrition are

1.6.1. Malnutrition

The term ‘malnutrition’ which literally means ‘bad nutrition’, implies that it is a condition that produces unwarranted or detrimental effects. These effects may manifest themselves either clinically, for example by increasing mortality and complications of disease in association with delayed recovery from illness, or functionally, for example by reducing strength and ability to work. In establishing a definition for malnutrition it is important to note the following:

- Malnutrition can be both a cause and a consequence of disease. The term ‘disease-related malnutrition’ encompasses both of these.
- Malnutrition can involve a single nutrient (nutrient-specific malnutrition) or multiple nutrients. Multiple deficiencies are often found in association with chronic protein-energy malnutrition marked by a low body mass index (BMI) (a reduction in the mass of fat-free body and/or a reduction in fat mass) producing detrimental clinical and/or functional effects (discussed in next section).
- Nutrient-specific malnutrition (either deficiency or excess) may exist in the presence of a low, normal, or even increased body mass, fat-

free mass, or body cell mass (see chapter on Indications for nutritional support).

- Malnutrition may affect individuals of all ages, ranging from older adults to children, neonates, and even fetuses, although different criteria are required to identify malnutrition in these diverse populations and circumstances.
- The causes of malnutrition may be numerous, ranging from inadequate nutritional intake (probably the most common cause), excessive losses of nutrients, or high demands imposed by a condition (see chapter on Indications for nutritional support). These causes may co-exist.
- The unwarranted effects of malnutrition are often reversible but they can also be irreversible, as in the case of blindness due to vitamin A deficiency, cretinism due to iodine deficiency, and stunting or reduced height in adult life resulting from prolonged undernutrition during childhood and fetal development.

Because of the multiple dimensions of malnutrition, attempts to define it have varied, some focusing on only certain of the above features, others on the mechanisms producing malnutrition rather than the condition itself, and still others on malnutrition in particular age groups. The following general working definition has been proposed with the above features in mind:

“Malnutrition is a state of nutrition in which a deficiency or excess (or imbalance) of energy, protein and other nutrients causes measurable ad-

verse effects on tissue/body form (body shape, size, composition), body function and clinical outcome”¹.

1.6.2. Identifying malnutrition

Various criteria are available to identify adult malnutrition in clinical practice and in epidemiological studies, one of which is body mass index (BMI; weight (kg)/height (m)²). BMI is a simple anthropometric index which underpins the World Health Organization (WHO) classification of weight status (Table 1.6.1). Among its advantages are that it is a relatively simple, readily available index that easily lends itself to comparisons between different world regions and countries. The WHO has tended to resist attempts to modify the BMI cut-off points, according to age, ethnicity, and gender, at least in part, to facilitate simple comparisons between and within different countries and world regions.

It is well recognized that the use of BMI as an index of weight status and malnutrition has various limitations. These include statistical, medical, and other limitations, such as those due to the confounding effects of body shape and frame size. Nevertheless, BMI is a widely available objective measure of weight status. BMI is related to body composition, since a higher BMI is generally associated with an increase in % body fat (al-

though the relationship is confounded by other factors such as gender, ethnicity, and age) and to body function, since a decline in BMI below ~18.5–20 kg·m⁻² is associated with a progressive decline in function (although the extent varies with the function under consideration). For example, muscle function tends to be affected earlier than lactational performance, while sensory function is hardly affected unless there are concomitant deficiencies of specific vitamins. A high BMI in the overweight and obesity range also has undesirable effects on body function (see other chapters in this book for more information).

Some countries and organizations have favoured the use of alternative BMI cut-off points over those currently used and promoted by WHO. These include lower cut-off points for overweight and obesity (in some Asian countries) and a higher cut-off point for underweight (e.g. in line with an earlier WHO classification) that is currently still in use in various countries where a BMI < 20 kg·m⁻² is taken to represent underweight. Furthermore, although several screening tools align with the WHO classification for BMI, others in developed and developing countries do not. For example, cut-off points between 20 and 24 kg·m⁻² to indicate ‘underweight’ or ‘malnutrition’ (undernutrition) risk, are used in older people ².

In an attempt to establish a better indicator of malnutrition than BMI alone, various screening tools have been developed in various countries. They often include BMI along with other criteria such as recent weight change (or reduction in dietary intake) and the effects of acute disease^{3,4}. However, the many screening tools available for use clinically have been developed for different purposes, for different settings, and for use by different healthcare workers. For example, some tools were developed simply to identify nutritional status, others to identify the need for nutritional support, and still others to predict clinical outcomes or healthcare use (either with or without intervention). As a consequence, different screening tools may not always agree with each other, either with respect to ‘malnutrition’ risk categorization or their ability to predict specific

Table 1.6.1. International Classification of adult underweight, overweight, and obesity according to BMI

Classification	BMI(kg·m ⁻²)
Underweight	< 18.50
Severe thinness	< 16.00
Moderate thinness	16.00–16.99
Mild thinness	17.00–18.49
Normal range	18.50–24.99
Overweight	≥ 25.00
Pre-obese	25.00–29.99
Obese	≥ 30.00
Obese class I	30.00–34.99
Obese class II	35.00–39.99
Obese class III	≥ 40.00

Source: Adapted from WHO 1995, WHO 2000 and WHO 2004

outcomes. Although screening tools for malnutrition have their limitations, it is recognised that screening is an important process that should be a part of routine care. It is also clear that clinical management can be enhanced by a more detailed assessment of nutritional status by a specialist following screening.

In this chapter, the focus is predominantly on undernutrition rather than overnutrition (covered in other chapters), and, unless otherwise stated, the word 'malnutrition' is used to indicate undernutrition. The chapter also focuses on adults rather than children, and it only briefly discusses nutrient-specific malnutrition, which often requires laboratory services to establish or confirm a deficiency or toxicity of a nutrient (e.g.⁵ for details of various types of nutrient deficiencies). In this chapter, use is made of the WHO classification of BMI (weight status) in adults to compare the prevalence of underweight, overweight, and obesity in different world regions and countries. Use is also made of the 'Malnutrition Universal Screening Tool' ('MUST')¹ (www.bapen.org.uk), to illustrate the distribution of malnutrition within a country and within specific care settings within that country (e.g. England and UK). This screening tool was developed by a multidisciplinary group of workers for use in adults of all ages, all types of conditions and in all care settings. Therefore, 'MUST' lends itself to comparisons of the prevalence of malnutrition (medium + high risk) within and between different care settings and can be used to establish an overall prevalence of malnutrition in a country using the same consistent criteria. Therefore, the tool has been used both for clinical and public health purposes, in line with its originally intended design. Furthermore, by incorporating a range of alternative criteria that can be used to establish malnutrition risk in those who are unable to have their weight and height measured, it facilitates the collection of complete datasets¹, which is not possible with a range of other screening tools. However, other commonly used nutritional screening tools can also provide useful information on the prevalence of malnutrition, especially when their use is restricted to the specific setting and purpose

for which they were designed. Such tools include: Nutritional Risk Screening (NRS2002), developed for use in hospitals; Mini-Nutritional Assessment Short Form (MNA-SF), developed for use in older people; and Short Nutritional Assessment Questionnaire (SNAQ), using questions only and avoiding the use of objective weight and height measurements. A more detailed discussion about screening tools can be found elsewhere^{3,4} and later in this book.

Although this chapter focuses only on adults, in paediatrics, the prompt identification and treatment of malnutrition (faltering growth) is essential and more complex than for adults, as growth needs to be considered. Malnutrition in infants and children can encompass both wasting and stunting and studies across developed countries have suggested that both are common across diagnoses (estimates range from 6%–60%), including cardiac disease, cerebral palsy, cystic fibrosis, chronic lung disease, cancer, renal disease, and in children with critical illness cared for in intensive care². More information can be found elsewhere in this book.

1.6.3. Prevalence of malnutrition

1.6.3.1. Underweight and BMI in different countries and world regions

Table 1.6.2 shows the distribution of adult underweight (BMI < 18.5 kg·m⁻², according to WHO classification (WHO Global database on body mass index)). There is considerable variation in prevalence between world regions such as Middle East/Asia/Pacific (1–33%), Africa (9–19%), Europe (0.2–5%), and Americas/Canada (2–7%). The extensive variation in the prevalence of underweight across the countries of the world is not only from those located in different regions of the world (e.g. highest prevalence of underweight in India and Pakistan (~30%), lowest rates in countries such as Australia (1%), USA (2.4%)) but also from countries within some of the same world regions (especially across Asia and Africa). The prevalence of underweight across countries in Europe is less varied, with the highest rate in the UK (5.1%). The prevalence of underweight gen-

Table 1.6.2. Prevalence of 'underweight', 'overweight', and 'obesity' using WHO BMI classification

Country	% underweight (BMI < 18.5 kg · m ⁻²)	% desirable (BMI 18.5–24.99 kg · m ⁻²)	% overweight (BMI 25.0–29.99 kg · m ⁻²)	% obese (BMI ≥ 30.0 kg · m ⁻²)
Australia	1	39.2	39	16.4
Austria	2	56	31	11
Belgium	3.8	55.3	30.2	10.8
Brazil	4	55.4	29.5	11.1
Bulgaria	3.9	50.1	33.6	12.4
Canada	2.6	46.7	36.1	23.1
China	8	58.9	16	2.9
Colombia	3.9	50.2	32.3	13.7
Croatia	0.2	35.4	41.3	22.3
Cuba	7.3	51.8	30.6	11.8
Cyprus	4.3	49.6	33.7	12.3
Czech Republic	2.4	45.9	36.7	15.1
Denmark	2.2	55.3	32.3	11.4
Estonia	4.6	60.1	28.4	14.4
Fiji	6.1	37.6	32.3	23.9
Finland	2.4	52.7	33.1	15.7
France	4.9	53.5	32.4	16.9
Germany			41.1	12.9
Ghana	16.4	72.4	8.1	3.1
Greece			35.2	22.5
Hungary	2	44.8	35.5	17.7
Iceland	2.3	49.4	35.9	12.4
India	32.9	62.5	3.8	0.7
Iran	5.7	51.5	28.6	14.2
Ireland	0.8	42.4	32.7	13
Israel			39.3	22.9
Italy	3.4	52.6	34.2	9.8
Japan	11.5	68.9	20.3	3.1
Kuwait	2.5	33.3	35.4	28.8
Latvia	3.5	51.3	29.6	15.6
Lithuania	2.4	48.6	32.2	19.7
Madagascar	19.2	69.1	9.6	2.1
Malaysia	9.6	49.3	31.6	16.3
Malta	2.6	35.1	41.6	20.7
Mongolia	4.9	66.6	21.8	9.8
Netherlands			29	10
New Zealand	1.3	36.1	36.2	26.5
Norway	5	51	35	10
Pakistan	31.2	54.4	11	3.4
Philippines	12.3	63.7	19.7	4.3
Poland	2.2	45.6	34.2	18
Portugal	2.2	44.2	39.4	14.2
Korea	4.7	63.2	27.4	3.2
Romania	3	55.2	33.1	8.6

Saudi Arabia	7	42.1	36.9	35.6
Singapore	9.2	58.3	25.6	6.9
Slovakia	4.7	48.6	32.4	14.3
South Africa	8.6	46.2	23.5	21.6
Spain	1.8	44.9	37.8	15.6
Sweden	2	52	33	12
Switzerland	3.5	59.2	29.1	8.2
Thailand	19.2	57	19.4	7.8
Turkey	3.5	40.1	40.3	16.1
United Kingdom	5.1	33.9	38.3	22.7
USA	2.4	35.7	32.2	33.9
Vietnam	26.5	68.5	4.5	0.5
Zimbabwe	9.9	53.7	21.6	15.7

Source: WHO Global database on body mass index (<http://apps.who.int/bmi/index.jsp>)

erally seems to be higher in low income countries than high income countries, raising questions about how much of the variation is due to availability of food, social care, disease prevalence and clinical care, and public health factors. In most countries where data are available, the prevalence of underweight is higher in women than men. Data are also lacking from large parts of the world, making it difficult to obtain an overall global average for the prevalence of 'underweight' and the global burden of the condition.

The distribution according to BMI (< 18.5 ('underweight'); 18.5–24.9 ('desirable weight'), 25.0–29.9 ('overweight'), and > 30kg·m⁻² ('obese')) (Table 1.6.2) shows that in several countries (including UK, USA, Australia/New Zealand, France, Portugal, Spain, Czech Republic, Hungary, Turkey), most (> 50%) individuals are not in the 'desirable' weight range. In some countries, such as USA, Canada, New Zealand, Saudi Arabia, and Kuwait, and in many European countries (e.g. UK, Greece, Germany, Spain, Portugal, Poland), most (> 50%) are overweight/obese.

As already indicated, the use of different cut-off points to define underweight and overweight/obesity can have a major effect on the distribution of weight status, although the general trends and ranking order of the prevalence of underweight, overweight, and obesity between countries may be largely unaltered.

1.6.3.2. Prevalence of Malnutrition in a European Country (United Kingdom (UK))

Although data on the prevalence of malnutrition are available from the use of a variety of different screening tools in various countries across the world, for consistency, in this short chapter, 'MUST' is used to summarise the prevalence of malnutrition across different care settings, geographic locations, age, and other criteria in one country (the UK) only. However, the data, trends and some of the principles highlighted below are relevant to other countries and world regions.

Country level prevalence data

Overall, it is estimated that at a given point in time about 5% of the general population of the UK (UK population size of ~65 million, 2017) is at risk of malnutrition (undernutrition) according to 'MUST' (medium + high risk of malnutrition categories)⁶. Malnutrition is at least twice as common in older adults aged 65 years and over than in younger adults. It is likely that the national prevalence of malnutrition in other European countries is similar although such data appears scarce. Therefore, at a national level, the data on the prevalence of underweight based on BMI (see Table 1.6.2) can provide an approximation for most countries.

Distribution of malnutrition between health and social care settings and geographic location

Care setting

More than 90% of malnutrition (for adults and adults + children) in England, UK, is found outside of institutional care in the community (free-living), with hospitals and care homes accounting for only a small proportion of the total (Figure 1.6.1) (6). In adults in the community, medium 'MUST' risk is more common, while in hospitals and care homes high 'MUST' risk is more common^{7,8}. Within institutions, care homes harbour more malnutrition than hospitals, largely because care homes have three-fold more beds than hospitals and partly because the prevalence of malnutrition according to 'MUST' tends to be higher in care homes (about 35%) than hospitals (29%)^{6,8}. Although the distribution of malnutrition may vary in other countries (and may also depend on the number of beds in various types of institutions in different nations), other national surveys on the overall prevalence of malnutrition suggest it is similarly common in both hospitals and care homes (e.g. prevalence using other screening criteria: in the Netherlands, hospitals 25%–40%; care homes 25%, www.fightmalnutrition.eu; in Spain, Predyces study 24% in hospitals⁹).

Most of the malnutrition in hospitals and care homes is present on admission, which means that clinicians and health planners may need to concentrate more on early intervention or pre-

ventive measures in free-living individuals before their admission to these institutions. At the same time there is a need to consider improvements in existing policies for the management of malnutrition within institutions, particularly those involving people that are discharged or transferred to other care settings. Figure 1.6.1 also shows that the distribution of malnutrition within England is not paralleled by the distribution of the public expenditure on malnutrition (i.e. the cost of managing malnutrition and any underlying disease(s) (disease-related malnutrition)). Hospitals account for a disproportionately large proportion of the total public expenditure on health and social care. This raises the question of whether early or preventive measures in the community setting can prevent the rising costs of malnutrition, which are set to rise further with our aging population (see section below on age and malnutrition). Malnutrition is not only a major clinical problem but also a major economic problem since the overall cost of malnutrition in adults and children in England in 2011/12 was estimated to be £19.6 billion (€22.6 billion; £1 = €1.16, Feb 2017) or about 15% of the total public expenditure on health and social care⁶. These costs are due to the poorer clinical outcomes and increased health care use of those with disease-related malnutrition and only a very small proportion of this expenditure is due to the costs of nutritional care⁶. Although often using different methodology, other countries have shown the huge economic burden of malnutrition (e.g. €1.5 billion total cost, Ireland¹⁰, €9 billion total cost, Germany; €1.8 billion *additional* cost, The Netherlands¹¹) and a European assessment in 2009 estimated a cost of €120 billion¹².

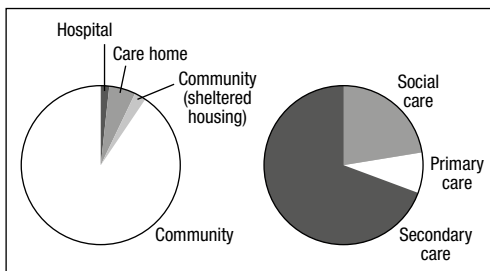


Figure 1.6.1. Estimated distribution of malnutrition (medium + high risk using 'MUST') in England by care setting (left chart). Estimated distribution of costs between primary care (mainly community), secondary care (mainly acute hospitals), and social care (mainly care homes and community) (right chart)⁶

Type of hospital and type of admission

An analysis of 31,637 admissions to UK hospitals⁸ revealed that there was little difference in the prevalence of malnutrition on admission to different types of hospitals (acute, community, and acute/community) but malnutrition was more common in emergency admissions (33%) than elective admissions (20%). The data also suggested a seasonal effect since malnutrition preva-

lence was found to be greatest in winter (34%) and lowest in spring (25%). The BMI distribution of hospital admissions was wider than that of the general population since it was associated with a greater proportion of both underweight and severely obese patients. Patients at both ends of the BMI spectrum need identification and appropriate management.

Type of care home and origin of admission

National surveys in the UK indicate that the prevalence of malnutrition varies significantly according to the type of care home: nursing homes (43%), homes for mentally ill older people (33%), residential homes (30%), and others (38%). The prevalence of malnutrition also varies according to the origin of admission, being higher amongst residents admitted from hospitals (41%) and other care homes (40%) than from their own homes (32%). It is also higher in those that have been admitted to care homes 4–6 months earlier compared to those that have been in the care home for less time (e.g. admitted within 1–2 months (32%))⁷.

Other care settings

Figure 1.6.2 summarises the prevalence of malnutrition within a variety of care settings, including hospital outpatients (where the prevalence

varies according to the age of patients, and their clinical condition), those nursed at home, those living in sheltered housing, and in general practice (using ‘MUST’ across the UK).

1.6.3.3. Geographic location (geographic inequalities)

Malnutrition in older people is estimated to affect about 10% or more of the older population of England and the UK. A secondary analysis of a representative sample of people aged 65 years and over has revealed a malnutrition gradient between northern parts of the UK (with more malnutrition) to southern parts of the UK (with less malnutrition). This gradient is accompanied by a similar gradient in the status of micronutrients, such as vitamin C, carotenoids, and vitamin D (with greater likelihood of deficiencies in the north¹³). This north-south geographic inequality is associated with health inequalities, including mortality, and socioeconomic differences. Specifically, deprivation is linked to malnutrition (see more details below) and more deprived areas are found in northern parts of this particular country. Geographical differences in malnutrition prevalence, alongside other health inequalities, are also likely to exist in other countries. Since the causes of these health inequalities are numer-

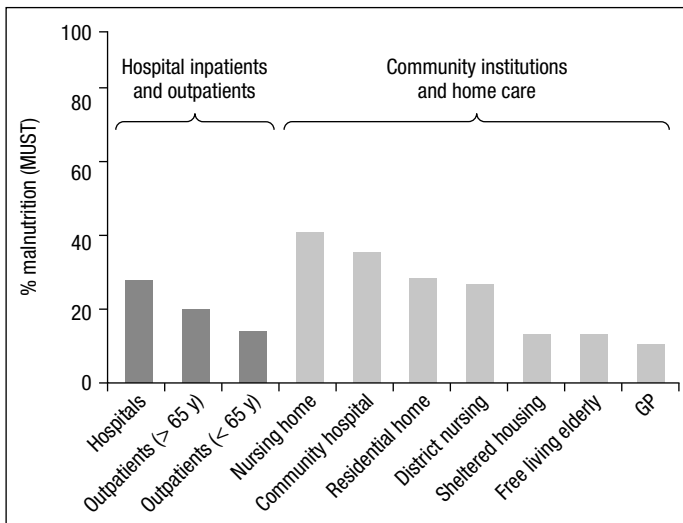


Figure 1.6.2. Prevalence of malnutrition across different health care settings in the UK

ous, it may be more effective to tackle them with a general approach, including a combination of clinical and public health measures.

1.6.3.4. Distribution of malnutrition according to individual characteristics

Age and gender

In most care settings the prevalence of malnutrition increases with age. For example, in care homes in the UK, malnutrition was found to be present in 41% of those aged ≥ 85 years, 36% in those aged 74–84 years, and 27% in those aged < 70 years. Similarly, in care homes, the proportion of residents who are underweight increases steeply with age (and the proportion with obesity decreases), in contrast to the general population. In UK hospitals, the prevalence of malnutrition was found to be greater in older people (32% in those aged ≥ 65 years vs. 24% in those < 65 years).

The prevalence of malnutrition in both hospitals and care homes was found to be greater in women than men (in hospitals 31% v 26%; in care homes 41% v 31%), and only partly accounted for by the older age of women.

Disease category and medical specialty

Malnutrition can occur across acute and chronic diseases and conditions. Table 1.6.3 summarises the prevalence of malnutrition across different diagnostic categories from large national surveys in the UK. Adults with gastrointestinal disease were found to have a prevalence of malnutrition that was consistently higher than the overall mean prevalence.

Deprivation

In a study of a thousand patients admitted to hospital, it was found that malnutrition according to 'MUST' is related to deprivation, assessed from the geographic (residential) location of the patient¹⁴. Malnutrition was related to several of the components of deprivation, such as income, employment, health deprivation and disability, and education, skills and training. All three components of 'MUST' (unintentional weight loss, BMI, and 'acute disease effect') were related to the dep-

Table 1.6.3. Prevalence of malnutrition (medium+high risk, 'MUST') according to the primary diagnostic category in hospitals and care homes in the UK

Diagnostic Category	Hospitals	Care homes ²
Neurological (CNS)	30	39
Gastrointestinal (GI)	42	54
Respiratory	36	44
Cardiovascular Disease (CVD)	20	33
Genito-Renal	26	43
Musculoskeletal	20	37
Cancer	39	50*
'Frail' elderly	-	39
Mental illness	-	25
Sensory impairment	-	16

¹Hospital patients, n 31637⁸, 6% had CNS diseases, 16% had GI diseases, 12% had respiratory diseases, 13% had CVD disease, 8% had genito/renal disease, 16% had musculoskeletal disease, 26% had other diagnoses. Of the total group, 13% had cancer.

²Care home residents, n 3568⁷; Most (56%) residents screened had neurological conditions (e.g. CVA, dementia, Parkinson's disease). Of the total group, 6% had cancer (* from a smaller total sample (n 1957))

rivation. Similar relationships have been found in patients with chronic obstructive pulmonary disease (COPD) attending hospital outpatient clinics, where malnutrition risk was related to deprivation even after adjustment for confounding variables (disease severity, age, and current smoking)¹⁵. Again, a significant relationship was found between malnutrition risk and components of deprivation, such as health deprivation and disability, barriers to housing, crime and living environment, raising issues about how best to tackle these multiple co-existing problems.

1.6.4. Causes of malnutrition (undernutrition) and evidence for treatment

The causes of disease-related malnutrition are numerous and include insufficient food/nutrient intake, impaired nutrient digestion and absorption, and increased requirements for nutrients with increased losses (e.g. from wounds, malabsorption) and catabolism. Principally, insufficient food intake is the main cause of disease-related malnutrition. This can be due to many factors, including anorexia, a common feature of disease,

taste disturbances, nausea and vomiting, and other drug and treatment-induced side effects, eating and swallowing difficulties, problems shopping or preparing meals, or dislike of institutional catering. Other environmental, social, and psychological factors (e.g. anxiety, depression, bereavement, poverty) may also reduce food intake.

Numerous studies across diagnostic groups have documented energy, protein, and micronutrient intakes to be insufficient to meet nutritional requirements, particularly in institutionalised patients, with high wastage of uneaten food. In addition, nutritional support (oral nutritional supplements, enteral tube feeding, parenteral nutrition) is often not used early enough or frequently enough to prevent or treat disease-related malnutrition. This is despite a growing evidence base that suggests benefits to body structure, function (e.g. muscle strength, physical activity), and clinical outcome (e.g. mortality, complication rates) when nutritional support is used. Health care use (e.g. hospital (re)admissions, hospital stays, GP visits) may also be reduced by the appropriate use of nutritional support (see^{2,16–20} for more details). A recent report⁶ has indicated that there are substantial cost savings (approximately £123,530 (€143,295) per 100,000 people, £1 = €1.16 Feb 2017) from implementing screening and treatment of malnourished patients (with oral nutritional supplements, enteral tube feeding, parenteral nutrition, as appropriate; based on National Institute of Health and Care Excellence (NICE) guidance (CG32) and quality standard (QS24), www.nice.org.uk). The treatment and consequences of malnutrition are considered in more detail elsewhere in this book.

Summary

Both undernutrition and overnutrition are major clinical and public health problems that require national and international initiatives to improve their prevention and treatment. Malnutrition (undernutrition), which is mostly disease-related, is a common and costly problem, occurring in individuals with a wide variety of acute and chronic illness, across all ages and settings. Its prevalence is affected by type of care setting, age,

disease category, geography, and deprivation. As malnutrition is widespread, often under-detected and under-treated, routine and regular screening for risk of malnutrition in individuals in hospitals, care homes, and in outpatient clinics and general practice is essential. The screening programme needs to be multidisciplinary and the results of the screening test must be linked to appropriate action including a nutritional care plan. The appropriate management of malnutrition, including the use of nutritional support, can improve function and clinical outcomes, and reduce health care costs for the benefit of patients, the health and social care system, and society.

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1.7. Nutritional requirements for health at rest and upon exercise

1.7.1. Adult subjects

1.7.1.1. Macronutrients

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Learning objectives

- To learn how to estimate the energy requirements of healthy adults
- To determine the macronutrient requirements at rest and during physical activity of healthy adults
- To learn which type of macronutrients are beneficial for health

Energy requirements

In adults of stable weight, energy requirements should balance energy expenditure. Total energy expenditure (TEE) reflects the sum of resting energy expenditure (REE), which is the minimum level of energy required to sustain vital functions, and the energy used for dietary-induced thermogenesis and physical activity (see chapter 2.3). Depending on living areas (low temperature areas Great North, mountains) or activities (winter

sports), thermogenesis to regulate central body temperature should also be taken into account for TEE calculations. Dietary-induced thermogenesis is dependent upon the quantity and type of food eaten and represents ~10% of TEE. However, the energy expenditure due to physical activity is variable, accounting for 15%–50% of TEE. The reference method for REE measurement is indirect calorimetry. REE can be estimated by predictive equations, especially the Harris-Benedict equation, that have the best accuracy in healthy subjects with normal body mass index. Estimation of physical activity-related energy expenditure can be done prospectively or retrospectively using questionnaires, or measured with portable calorimeters, pedometers, devices for heart rate monitoring, or accelerometers. Examples of energy expenditure due to physical exercise are shown in Table 1.7.1.1.1.

Carbohydrates (CHOs)

CHOs are the principal source of energy in a normal diet (particularly during anaerobic exercise), meeting 40%–55% of total energy requirements in the Western diet. For a sedentary subject requiring 2500 kcal per day, the daily recommend-

Table 1.7.1.1.1. Examples of energy expenditure through physical exercise, in $\text{kcal} \cdot \text{minute}^{-1}$, for subjects of 60 kg and 80 kg (adapted from McArdle WD et al.¹)

Body weight	60 kg	80 kg
Mountain climbing	9.4	12.7
Swimming (breast stroke)	9.6	13.0
Ice hockey	9.1	12.5
Handball	8.5	11.5
Horseback riding (galloping)	8.1	11.0
Basketball (practice)	8.1	11.0
Soccer	8.1	10.9
Golf	5.0	6.8
Tennis (recreational)	6.4	8.7
Weight training	5.0	6.8
Running: 300 $\text{m} \cdot \text{min}^{-1}$	17.1	23.1
200 $\text{m} \cdot \text{min}^{-1}$	12.5	16.5
140 $\text{m} \cdot \text{min}^{-1}$	8.0	10.9
Cycling: Racing	10.0	13.5
15 $\text{km} \cdot \text{h}^{-1}$	5.9	8.0
9 $\text{km} \cdot \text{h}^{-1}$	3.8	5.1

ed consumption of CHOs is 300–400 g, although very active individuals may need up to 60% more than this. The intake of CHOs is important to preserve tissue protein. CHOs are also the principal energy substrate for the brain, which utilizes 130–140 g of glucose per day. CHO intake also reduces production of ketone bodies, facilitates storage of triglycerides in fat tissue, and helps to preserve body protein by reducing the need for gluconeogenesis from amino acids. Recommendations for macronutrient intake are summarized in Table 1.7.1.1.2.

CHOs are classified into:

- monosaccharides (glucose, fructose, galactose)
- disaccharides (saccharose, lactose, maltose)
- oligosaccharides (maltodextrins)
- polysaccharides (starch and fibers)

Although starch intake has decreased by 30% over the last century, it is still the most important source of CHO in Western diets. Dietary fibre is also important and provides significant health benefits (see chapter 5.7.).

Table 1.7.1.1.2. Recommendations for macronutrient intake^{4–6}.

Macronutrients	As a percentage of energy intake	As an absolute value (g/day)
Carbohydrates	50–60	> 130
Sugars	≤ 25	
Starches	> 25	30–35
Fibres		
Lipids	20–35	40–60
Saturated fatty acids	as low as possible	
Monounsaturated fatty acids	no recommendation	
Polyunsaturated fatty acids	6–11	10–20
Linoleic acid	3–5	11–17
Alpha-linolenic acid	0.5–2	1.1–1.6
Proteins	10–15	0.6–0.8 $\text{g} \cdot \text{kg}^{-1}$ body weight
Essential amino acids		5–19 $\text{mg} \cdot \text{kg}^{-1}$ protein*

*Depending on the type of amino acid (cf. Table 1.7.1.1.3.)

In contrast to the intake of starch and fibre, intake of mono- and disaccharides has increased by 20% during the last century. A high intake of sugar causes dental caries and, according to some authors, may also be responsible for atherosclerosis, liver steatosis, and dyslipidemia. The latter is characterized by elevated plasma triglycerides and/or low-density lipid (LDL)-cholesterol and reduced high-density lipid (HDL)-cholesterol. Sugar contributes to the excessive intake of energy responsible for obesity and an increased risk of cardiovascular disease². The regular consumption of sugar, a palatable food, could initiate a process that leads to alimentary disorders and food addiction, a vicious cycle for obesity. Sugar can also induce postprandial reactive hypoglycaemia and hypotension, particularly in the elderly. The recommended dietary intake of added sugars (as opposed to natural sugars occurring in fruits and dairy products) should be limited to a maximum of 25% of total energy intake³.

The glycaemic index (GI)

Some authors have argued that the metabolic and long-term health effects of CHOs are dependent

upon their GI rather than their biochemical structure⁷. The GI represents the blood glucose area under the blood glucose curve (AUC) after the ingestion of a defined quantity of a specific type of CHO in the ingested food relative to the same amount of glucose. It is represented by the equation shown below.

$$\text{GI} = (\text{AUC of test food} / \text{AUC of reference food}) \times 100$$

The GI of food is dependent upon the quantity and type of total CHO ingested; the presence of fibre, lipids, and proteins; as well as food processing. The GI of some foods is shown in Figure 1.7.1.1.1. Foods with a low GI (< 50) exhibit reduced elevation of postprandial levels of plasma glucose, triglycerides, and LDL cholesterol, and regulate satiety. The health benefits of low-GI foods need further confirmation before general recommendations can be made. Moreover, the intake of foods with a high GI but a low CHO density (e.g. carrots) is also recommended because they only cause a small increase in plasma glucose per serving.

Caution is required if a large amount of food with a high GI is consumed in the 1-h period before strenuous physical exercise. This can lead to a rapid increase in blood glucose with an excessive release of insulin, causing reactive hypogly-

caemia and inhibition of lipid mobilization when exercise is started. Consumption of foods with a moderate-to-high GI during the recovery period after exercise appears to be more efficient in replenishing glycogen stores. Intake of food with a moderate-to-high GI may also be indicated during intense and prolonged physical activity because it is rapidly absorbed and provides immediate energy and spares glycogen stores in muscles, delaying the onset of fatigue. When its glycogen store is exhausted, muscle must rely almost entirely on fatty acids for fuel, reducing its maximum work capacity by 40% and impairing acceleration in athletes. Marathon runners describe this as 'hitting the wall'. During exercise, high-GI food increases insulin secretion moderately but does not induce hypoglycaemia as it does if eaten in the pre-exercise period.

Lipids

Dietary lipids are ingested as triglycerides, phospholipids, or sterols. Triglycerides are composed of saturated or unsaturated fatty acids. Lipids are an important source of energy, but they are also carriers of fat-soluble vitamins A, D, E and K. Fatty acids are also precursors for the synthesis of modulators of immune function, contribute to the feeling of satiety after eating (partly by slowing gastric emptying), and are substrates for fat formation in subcutaneous adipose tissue (the

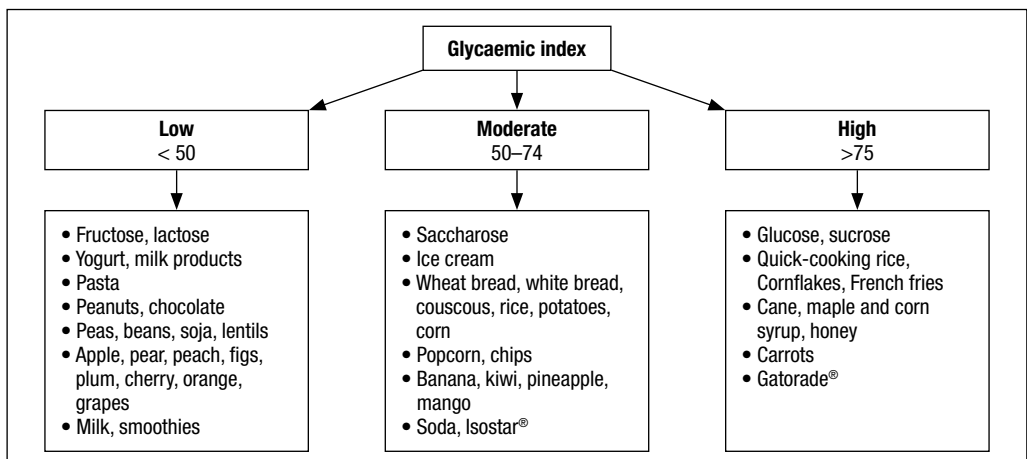


Figure 1.7.1.1.1. Classification of some foods according to their glycaemic index

Vážení čtenáři, právě jste dočetli ukázkou z knihy ***BASICS IN CLINICAL NUTRITION***.
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