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Luboš Sobotka

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INTRODUCTION

In an effort to provide a comprehensive message, ESPEN is proud to present the fourth edition of its well-known book: “Basics in Clinical Nutrition”. The ESPEN faculty under the tireless leadership and the tremendous efforts of its Editor in Chief Lubos Sobotka is proposing this completely revised book giving to the reader an updated information on all the topics covering clinical nutrition, written by the most prominent experts in the field. These messages are in accord with the other ESPEN messages delivered through the education tool named LLL (Life Long Learning virtual university) and the guidelines published recently. The best of the knowledge and expertise of the ESPEN faculty is giving to provide the required tools to the clinicians. In addition, the clinician can complete his knowledge through the web or the live courses of the LLL teaching system, through Clinical Nutrition and eSPEN journals in addition to this outstanding textbook joining utility and practicality to expertise.

This book increased not only in pages but also in quality. The medical students, dietitians, nurses and pharmacists as well as practitioners will find on a daily base the answers to their questions and this book should be present in the medical wards as well as on the desk of health professional practitioners asking for nutritional answers. No surprise if the previous edition of this book has been translated in so many languages and is the messenger of ESPEN through all the world from China to South America.

I am confident that this edition will receive the same warm welcome that the previous editions and will become one of the best sellers in the field. I wish you a pleasant lecture

Pierre Singer
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-three 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, scrutinised, 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 mesmerised, 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, traumatised, 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

During the past decades modern medicine has been molecularised into narrow specialities that often prevent a holistic approach. Clinical nutrition and metabolic care can however bring a major potential for integration in the way it joins almost all disciplines of medicine. The European Society for Clinical Nutrition and Metabolism (ESPEN) accepted this challenge and for more than 30 years has integrated the various medical disciplines through their nutritional and metabolic aspects. Scientific progress in the field is exciting. The latest information transfers and reliable education are essential for the dissemination of novel scientific results and their incorporation into clinical practice. Therefore since the early nineties ESPEN has organised educational activities such as its Basic and Advanced Courses and the ESPEN Life-Long Learning (LLL) Programme.

It is already more than twelve years ago since, after discussions with my colleagues, I decided to edit the manual for the ESPEN Basic Courses, which had been organised since 1994. This became the first edition of *Basics in Clinical Nutrition* and was published exactly 12 years ago.

Very positive reactions, together with creative criticism from readers, led naturally to new editions in 2000 and 2004. Each edition was enhanced and improved by the team of editors and excellent authors. Thanks to their ideas the final quality of the book rose and it became more useful. The popularity and usage of this book has been outstanding and the last two editions are available in no fewer than nine languages.

Three years ago we started to work on the fourth edition that is finished this year. Six associate editors and 99 authors have contributed to this book. Most of them 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. I must also memorialise Prof. Peter Furst and Prof. Xavier Leverve; although they are no longer with us, their ideas and parts of their chapters are still in the book. My great thanks belong also to all the associate editors for their valuable help, and special thanks go to Simon Allison and Alastair Forbes, who were responsible for English corrections of all the chapters.

We tried to keep the unique style of the book and hope we have succeeded. We were not always able to prevent overlaps, and perhaps the occasional apparent contradiction, partially because we do not have firm answers to all questions. However, I hope that this new edition will be valuable for readers.

Future editions written again according to the latest knowledge and covering new elements of clinical nutrition will follow this edition in due course. Therefore,

I would again appreciate all your remarks and criticisms, which will be invaluable in planning for the future versions to be published within the next few years.

I hope that this book will be a useful source of knowledge and of up-to-date information for physicians, dieticians, pharmacists, nurses and students and that it will help to improve practice in clinical nutrition.

Luboš Sobotka
Editor-in-Chief

Hradec Králové, August 2011

1. BASIC CONCEPTS IN NUTRITION

1.1. Energy and protein balance

J Kondrup, M Elia

Learning objectives

- To know 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 lactation.

The concept can be extended to weight gain after a period of weight loss, and perhaps also to weight loss itself, as far 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.

Much is known about the homeostatic regulatory mechanisms which govern the transition between the fasted and fed states, although less is known about homeorhetic mechanisms. Short-term experiments or a prolonged mild disturbance lead mainly to an 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 balances 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 whilst the extra protein is oxidised. 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 N 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 1 unit.

REE is a product mainly 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 which may vary between subjects such as a paraplegic and a healthy subject.

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 obvious 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 either by bomb calorimetric analyses of foods, or by measuring its content of fat, nitrogen (\approx protein), water and ashes and obtaining carbohydrate content by difference (if it is not measured). The calorimetric values of 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, account is also taken of the energy lost in urine as nitrogenous end products of metabolism. For example, urea has a combustible energy value ($5.5 \text{ kcal}\cdot\text{gN}^{-1}$), 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 the dietary energy using different energy systems can be found elsewhere.⁽¹⁾ The principles associated with the calculation of resting energy expenditure by indirect calorimetry and total energy expenditure by tracer methods can also be found elsewhere.⁽²⁾ These are used as part of the process of estimating average energy requirement in health,^(3,4) which in turn act as a starting point for the estimation of the energy requirements of disease.⁽⁵⁾ 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 ($0.8 \text{ g}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$ ⁽³⁾ or $0.83 \text{ g}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$ ⁽⁶⁾) for healthy subjects is based on long term nitrogen balance studies⁽⁷⁾ and consists of 3 components:

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

The general acceptance of nitrogen balance as a criterion for adequate intake is only due 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 body lean 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 requirement, 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 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 giving useful results, which 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 $1 \text{ g protein}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$: the nitrogen loss in urine will correspond to approximately $0.85 \text{ g}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$; the loss in faeces will be equivalent to $0.1 \text{ g}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$; and the loss from skin and miscellaneous sources will be equivalent to about $0.03 \text{ g}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$.

With varying intakes, the loss in urine will vary while the losses in faeces and skin, 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. 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 the Net Protein Utilisation (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).⁽⁸⁾ The latter consists of any form of nitrogen that can 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 age.⁽⁶⁾ 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. as suggested for 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 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 (T_3), which is associated with a rise in the inactive reverse T_3 . 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 part 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 postabsorptive state, protein degradation increases while protein synthesis largely remains unaffected. The higher the habitual protein intake, the larger is 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 $1 \text{ g}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$ to $0.4 \text{ g protein}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$, 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 $1\text{--}2 \text{ g}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$ when no protein is given. Immobilisation by itself leads to wasting of muscle tissue. In experimental studies of long-term immo-

bilisation (with intact innervation), the loss of nitrogen from the body corresponds to only $0.05 \text{ g protein}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$ 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 other 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 poorly understood 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 this may correspond to as much as 40% of the intake at an intake of $1.5 \text{ g protein}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$. 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 utilised 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 negative 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 can lead to a positive N balance with repletion of lean tissue but their administration should be guided by clinical and functional effects rather than just the effects on N balance.

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 intakes 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. Body composition and its measurement

KR Westerterp

Learning objectives

- To know the assumptions involved and the application of techniques for the measurement of body composition
- To have knowledge of their precision and limitations
- To be informed 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 by a variety of methods with different assumptions and limitations. All these assumptions stem from the chemical analysis of a limited number of cadavers with a normal body condition until death. The general model for body composition is the two compartment model, i.e. fat mass (FM) and fat-free mass (FFM). Accepted methods for the measurement of body composition are: densitometry, total body water and anthropometry, as described below. Further details can be found in handbooks on the theory⁽¹⁾ and practice⁽²⁾ of human body composition assessment and non-destructive methods for animals⁽³⁾.

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.

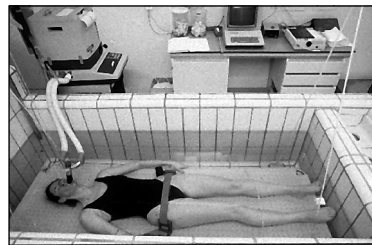


Figure 1.2.1.1. A subject submersed in water during under water weighing. The subject is lying on a stretcher suspended from a scale while breathing in a spirometer for the simultaneous measurement of lung volume with Helium dilution.

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 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⁾. The advantage is not only the applicability but also the required time for an observation. Under water 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 the two equations: body weight = FFM + FM; volume = FFV + FV, where FFV = fat-free volume

and FV = 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 equation⁽⁵⁾:

$$\% \text{ FM} = (4.95 / D_b - 4.50) \cdot 100$$

where:

$$D_b - \text{body density} = (\text{body weight}) / (\text{body volume})$$

1.2.1.3. Total body water

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, ²H, and ¹⁸O. 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 fluid⁽⁶⁾. 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 or ²H and ¹⁸O 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 needs a minimal equilibration time of 4–6 hours. The calculation of TBW is based on the relationship:

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

where:

C_d – concentration of the tracer

V_d – volume of the dose

C_0 – basal concentrations of the tracer

C_1 – concentrations of the tracer after dose consumption (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 ¹⁸O are around 150 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. ¹⁸O as a tracer is preferred over ³H and ²H as the dilution space of ¹⁸O is very close to TBW. The dilution space for the hydrogen isotopes is on average

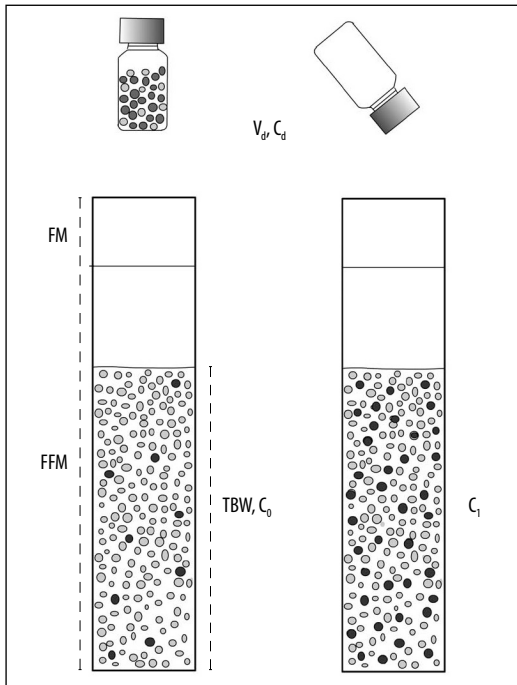


Figure 1.2.1.2. Schematic presentation of the measurement of fat mass (FM) and fat-free mass (FFM) with isotope dilution for the measurement of total body water (TBW). The calculation of TBW is based on the relationship: $C_d \cdot V_d = (C_1 - C_0) \cdot TBW$; where: C_d and V_d are the concentration 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.

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

The quickest and cheapest method of measuring body composition is from skin fold thickness. 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 skin fold thickness, as body fat is not linearly related to skin fold thickness, and the age and gender of the subject.

The measurement is made with a calliper, with the skin grasped between thumb and forefinger, gently shaken to exclude underlying muscle, and pulled away to allow the jaws of the calliper to take over (Figure 1.2.1.3.). The calliper is calibrated to exert a constant pressure. The measurement requires the skill to grasp the skin in the right way at the right site. Other sources of variation are inter-individual differences in compressibility of the subcutaneous tissue. Some people have firm subcutaneous

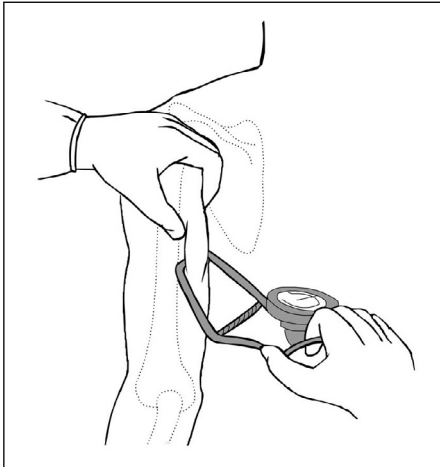


Figure 1.2.1.3. The measurement of triceps skin fold with a caliper

tissue and in others it is very flabby and easily deformable. The method is not applicable in extremely obese subjects where the subcutaneous fat layer gets too large to allow the proper grasping of a skin fold.

The errors estimating FM and FFM from BM and skin fold thickness are higher than the methods mentioned earlier and are reported to be between 3 and 9%, being highly dependant on the experience of the observer. On the other hand this method sometimes represents one of the few opportunities to obtain information on body composition.

1.2.1.5. Other methods for measuring body composition

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 the water and conducting electrolytes in the body. The two techniques for measuring the 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 its effects 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. Results of 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.

Additionally there are new methods to quantify separate body components. 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 needs expensive technology. Examples are the measurement of total body nitrogen and total body calcium with neutron activation analysis, magnetic resonance imaging, and mineral mass with dual energy X-ray absorptiometry. The latter method has also been developed for the estimation of FM but certainly cannot be regarded as a criterion method⁽⁷⁾.

1.2.1.6. Precision of body composition estimates

Each method has an uncertainty of the order of magnitude of at least 1.5 kg FM and FFM. A combination of independent measurements can reduce this measurement bias, adopting 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 claimed precision is 1.0 kg for FM and 0.7 kg for FFM. A further slight improvement is reached in a four compartment model for body composition, subdividing FFM into TBW, protein mass and bone or mineral 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 mineral mass with dual energy X-ray absorptiometry.

The precision will never reach the level of 0.001 kg for BM with integrating electronic balances. On the other hand 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 of 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.

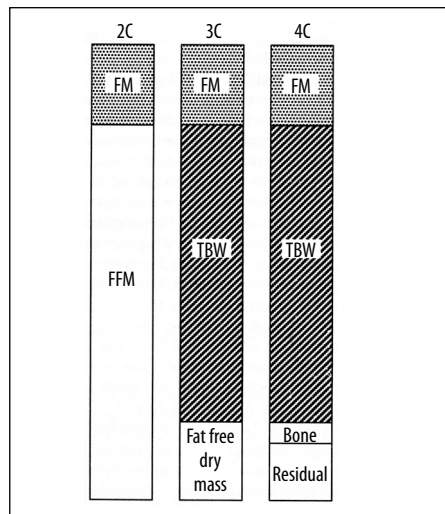


Figure 1.2.1.4. Human body composition models: 2C, two compartment model where FM and FFM are derived from measurement of body weight and body volume or from body weight and total body water; 3C, three compartment model where FM and FFM are derived from measurement of body weight, body volume and total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

Aging, starvation and disease violate the general assumptions of the two compartment models as adopted with the densitometry and the total body water measurement. Examples are the decrease of the density of the FFM with age-associated bone loss and disease induced dehydration or oedema. With anthropometry, abdominal fat in male type obesity or the Prader Willi syndrome is not measured by the skin fold method, resulting in considerable error. In this situation, a three- or even four-compartment model should be used.

Summary

In vivo body composition measurements are always indirect and are based on one or more assumptions concerning the nature of the body components, ie fat mass and fat-free mass including water, protein and bone. Examples of indirect methods, based on assumptions derived from carcass 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 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

MC Gonzalez, LA Nin, PLM Reijven

Learning objectives:

- To know the basics of bioelectrical impedance analysis
- To know the indications and contra-indications 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 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 some newer information, are the main purposes of this chapter.

1.2.2.1. Basic principle of the method

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

The 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 water⁽²⁾. 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 account⁽³⁾. Conductivity is, however, influenced by clinical features such as inflammation⁽⁴⁾.

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 di-electrical properties of cell membranes, which behave like condensers, which are capable of taking an electric load in an alternating manner, and consequently liberate it having generated a delay in the passage of the current. This effect depends partly on body cell mass⁽⁵⁾.

Resistance (R) to low frequency (up to 50 kHz) current is proportional mainly to the 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 alternate current. The higher the frequency of the current, the less will be the resistance and the greater will be the reactance^(6,7).

The influence of frequency on R and Xc is shown in Figure 1.2.2.1. At low frequencies R is high and Xc is almost negligible. In other words, with frequencies up to 50 kHz the impedance Z is practically determined only by R, and the Xc value is lower 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 clinical value. At any particular frequency $PA = \arctan (Xc/R) \cdot (180/\pi)$.

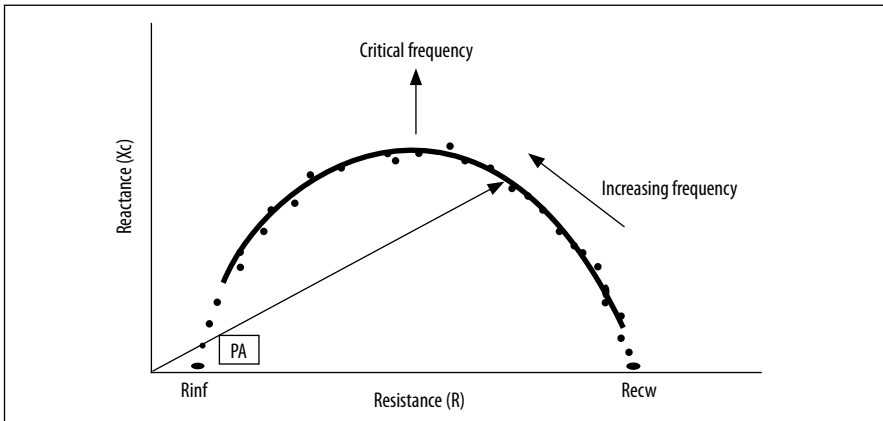


Figure 1.2.2.1. Relationship between reactance and resistance with increasing frequencies in biological systems with capacitive properties. Recw – resistance at zero frequency, Rinf – the resistance at infinite frequency, PA is the phase angle at a specific frequency.

The 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 (50 kHz), the previously rising reactance again decreases, together with the 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 for by oil (fats), the resistance value will increase to about double because fat is a low conductivity component with higher impedance. (Figure 1.2.2.2.)⁽⁸⁾.

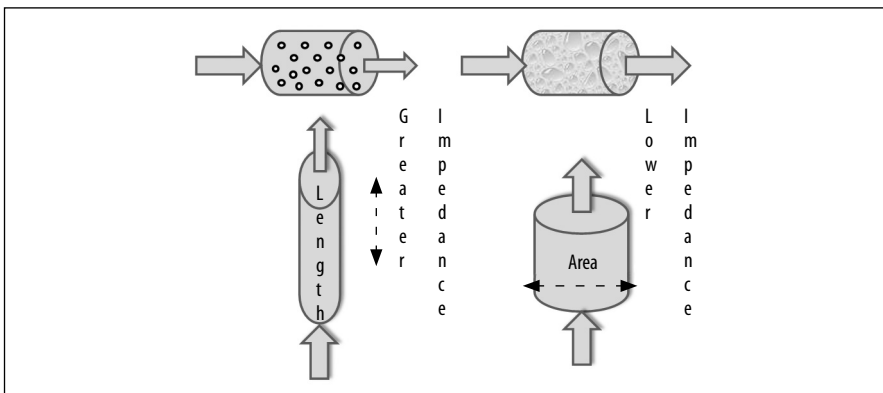


Figure 1.2.2.2. Impedence is dependent on structure and composition of the measured object. Higher impedance (fat cells and longer length and smaller diameter) – the left side, lower impedance (water and electrolytes, shorter length and larger diameters) – the right side.