The Importance of Nutrition as an Integral Part of Disease Management
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Preface

This book is a reflection of clinical nutrition-related issues taught and discussed during the 12th Nestlé Clinical Nutrition course in New Delhi, India, in 2013. Subjects addressed ranged from basic physiology to the implementation of nutritional practices in the hospital setting as well in the home situation. Although of vital importance, nutrition is still a neglected issue in medical curricula, and inside as well outside hospitals. These interactive courses therefore fill a gap in the knowledge on nutrition. Although reaching front-runners in the nutrition field, continuous efforts are needed to increase awareness and to stimulate nutritional practices. This book, therefore, may expose a larger population to the subjects discussed in an interactive fashion with the course participants and an international group of experts.

Rémy F. Meier (Switzerland) underlines the morbidity and mortality caused by malnutrition and stresses the importance to screen for malnutrition as well as to assess the nutritional state more precisely. Important factors leading to a malnourished state are insufficient up- or intake of nutrition as well as inflammation, together leading to a decrease in muscle, immune and cognitive function, thereby also leading to diminished quality of life and inability to counter disease and heal well from surgical trauma or other types of treatment.

Peter B. Soeters (The Netherlands) provides an introduction to the metabolic events occurring in starved states and situations of illness and trauma. Important viewpoints are the beneficial effects of insulin resistance and the important role of glucose as a building stone in starvation and stress starvation. Amino acids are similarly important but to limit (muscle) protein losses, glucose (in starvation predominantly derived from protein) needs to be utilized only for those purposes that only glucose can fulfill.

B. Ravinder Reddy (India) discusses enteral/oral nutrition and emphasized, apart from covering nutritional requirements, the beneficial effects on the gut. Enteral nutrition activates the intestine stimulating motility, maintains intesti-
nal integrity, and decreases mucosal permeability and inflammation in association with preserving a healthy microbiome.

Another subject, covered by B. Ravinder Reddy, includes the noncaloric benefit of fibers (polysaccharides). Fermentation of soluble fibers can cover as much as 15% of caloric requirements in the presence of an intact colon and rectum but, in addition, fibers promote the absorption of micronutrients, stimulate motility and improve the immune status of the gut probably by influencing the microbiome of the gut and producing butyrate (4-carbon short-chain fatty acid) serving as fuel for the large intestine.

Robert G. Martindale (USA) presented an overview of the different measures that can be taken to improve the nutritional state (= function) before and after operation. A high protein intake, probiotics, immunonutrition, carbohydrate loading, rapid resumption of nutritional intake after operation and exercise contribute to enhanced recovery and improved outcome.

Nutritional practices in critical illness (R.G. Martindale) have shifted from support to treatment. Metabolism can be changed by mitigating the stress-induced immune and hyperdynamic responses by nutritional measures. Many uncertainties still exist, including whom to nourish, what is the best nutritional formula and how to optimize enteral nutrition.

Paula Ravasco (Portugal) emphasizes the increasing number of patients being treated and recovering from cancer. Both cancer and its treatment compromise nutritional intake, which, therefore, needs intensive treatment. This is an often neglected aspect of cancer treatment, despite the reported beneficial effects of continuous and adequate implementation of nutritional support and maintenance of physical fitness before and after different types of therapy.

At a time that there is a substantial increase in the number of aged people, frailty is increasing in prevalence and requires assessment. Bruno Vellas (France) explains that frailty has major negative effects on quality of life and does not only include physical but also mental frailty, which should be distinguished from Alzheimer. A multidisciplinary approach is necessary in which nutrition plays a central role.

In the recent decennia, the metabolic syndrome has become an epidemic all over the world, including South Asia, even more so because the syndrome develops at a lower body mass index than in the Western world. Anoop Misra (India) discusses the management of the metabolic syndrome, including the benefit and harm of drugs, and the crucial role of the prevention of obesity.

Daniel R. Moore (Canada) addresses the dynamics of protein intake and utilization, the role of ‘slow’ proteins like casein and a balanced meal containing whey protein on efficient utilization of protein, minimizing urea formation.
Aged people suffer from ‘anabolic resistance’, requiring more protein per day to maximize muscle protein synthesis due to an increase in the uptake and utilization of protein-derived amino acids in central tissues like liver, spleen, immune system, gut and wounds. This is caused by age-related inflammatory activity related to comorbidity or the aging process itself which utilizes a higher proportion of protein in the meal than in young people, diminishing the amount of amino acids that can be utilized by muscles. The importance of exercise to maintain muscle mass is emphasized.

Stephen J.D. O’Keefe (USA) highlighted the benefits and hazards of parenteral nutrition in patients with intestinal failure. Although lifesaving and adding years of life to these patients, the parenteral route is fraught with infectious, thrombotic and metabolic complications, and substantially inhibits mobility. Apart from optimizing the diet and slowing down motility of the intestine, pharmacological means have been explored to optimize regeneration of the remaining bowel. Especially the glucagon-like peptide-2 teduglutide has been shown to reduce the intravenous caloric need by optimizing gut function.

Mark Nuijten (The Netherlands) explains the modern trend to require the application of the health economic theory to medical nutrition. The role of oral nutritional supplements is discussed as an example. Financial considerations play a role in deciding to treat or to withhold treatment. Costs per quality-adjusted life year play a role in this decision and range in the Western world from 20,000 to 100,000 USD per quality-adjusted life year.

In several parts of the world, endemic malnutrition is still prevalent, and the feeling may arise that attention for sophisticated nutrients and techniques is out of place in such areas. The contrary is true. Expert knowledge is required to make appropriate choices to implement nutritional practices that are of benefit to the population at large as well as to clinical patients. We hope that this book will contribute to spreading this knowledge.

Rémy F. Meier
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Foreword

The last decades have illuminated the important role of nutrition in the prevention and management of diseases. Despite the elaborated knowledge and discussions on the scientific podium, the role of nutrition is often overlooked in clinical practice. Unfortunately, medical nutrition is in most cases not incorporated in the curriculum at medical schools, which might lead to negative attitudes or even total neglect of the nutritional needs of hospitalized patients. Health care providers are often not well informed on the opportunities offered by nutrition to enhance the outcomes of certain treatments to the point that some patients suffer from hospital-related malnutrition. As always, there is also resistance to changes in clinical practice. Even though there are existing nutrition guidelines, their implementation remains suboptimal.

This time the Nestlé Nutrition Institute and Nestlé Health Science, a company aiming to foster the therapeutic role of nutrition in health care, made an effort to propagate the use of science-based, state-of-the-art practices in nutrition as an integrated part of disease management. They organized the 12th Clinical Nutrition Course, which was made available to a wider audience as the 82nd Proceedings of the Nestlé Nutrition Institute Workshop Series. The 5-day theoretical and practical course took place in Gurgaon (New Delhi, India) in October 2013.

The objectives of the course were to promote the education, discussion and exchange of ideas among clinicians globally on medical nutrition practices. The course enables clinicians, including both medical doctors and dietitians, to get a better understanding of medical nutrition, and to connect and share best practices with each other as well as with the course faculty.

The course chairs and the faculty are top leaders and experts in their area of presentation. On behalf of the Nestlé Nutrition Institute and Nestlé Health Science, we would like to thank the Chairmen Prof. Peter Soeters, Prof. Remy Meier and Prof. Ravinder Reddy for their diligent work in establishing a scientific program for yet another successful Clinical Nutrition Course and for assembling
such a distinguished group of experts and clinicians as speakers. Special thanks
go to Prof. Soeters and Prof. Meier for their dedicated and passionate work,
which contributed to the success of the Clinical Nutrition Courses throughout
the years.

We would also like to acknowledge the course faculty for their vigorous ef-
forts in creating such outstanding presentations, preparing related patient cases
for the Problem-Based Learning Sessions and sharing their clinical experiences
with the course participants. The energy throughout the course, the interest
among the participants and the quality of the discussions were all testaments to
the quality of the course and its importance.

Finally, we would like to thank Melanie Pittier, who worked tirelessly in the
background, for her support with all the course preparations, and Lorena
Cheung, Vivek Garg and the team in India for all their support on site in order
to make the course run smoothly and yet another Clinical Nutrition Course suc-
cessful.

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Basics in Clinical Medical Nutrition

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Abstract

Nutrition is a basic requirement for life and plays an important role in health and in disease prevention, but malnutrition is a common event and a cause of increased morbidity and mortality, particularly in patients with disease-related malnutrition showing inflammation and a catabolic state. Malnutrition is often overlooked, and deterioration in the nutritional status following admission to hospital is common. It should be actively pursued by a ubiquitous system of nutrition screening, and full nutritional assessment is required for those found to be at risk. There are simple screening tools which can be used by all health care professionals. Assessment considers body composition, inflammatory status and other aspects of underlying diseases and their functional consequences; it is a more specialist process. It is important to determine the energy and protein needs of each individual patient. Appropriate nutritional intervention can often be offered by the oral route, using food with or without special supplements. When this is insufficient, enteral tube feeding will normally be sufficient, but there is an important subgroup of patients in whom enteral feeding is contraindicated or unsuccessful, and in these patients parenteral nutrition (either total or supplemental) is required. A number of immunonutrients and other special substrates have been shown to be helpful in specific circumstances, but their use is not without potential hazards, and therefore adherence to international guidelines is recommended.

Introduction

Nutrition is a basic requirement for life. Accordingly, nutrition plays an important role in promoting health and preventing disease. Many reasons can lead to a weight change and malnutrition. Malnutrition is a condition resulting from a combination of varying degrees of under- or overnutrition and inflammatory
activity, leading to an abnormal body composition [1]. Several classifications of malnutrition have been proposed in the past. For clinical settings, an etiology-based approach makes most sense. An international consensus committee has proposed the following new terminology:

- Starvation-related undernutrition
- Chronic disease-related undernutrition
- Acute disease- or injury-related undernutrition

In this etiology-based definition of malnutrition and malnutrition risk, the key role of inflammation in disease-related malnutrition is included (fig. 1) [2].

Patients with chronic starvation without inflammation (e.g. patients with anorexia nervosa) belong in the first category. Patients with a mild-to-moderate degree of inflammation can mostly be included in the second category (e.g. cancer, rheumatoid arthritis or sarcopenic obesity). Patients with acute and severe degrees of inflammation are regarded as members to the third category (e.g. patients with major infection, burns, trauma or closed head injury).

Patients with minor nutritional deficiencies and those with overt under- or overnutrition are common in clinical practice. The prevalence of malnutrition (undernutrition) among hospitalized adult patients ranges from 30 to 50%, depending on the criteria used, and in part whether those at high risk as well as those with established malnutrition are included [3, 4]. The EuroOOPS study, which included data from 26 hospital departments from 12 European countries, found that 32.6% of the patients were at risk for undernutrition [5]. Undernutrition should be seen as an additional disease, as well as an important component of comorbidity. The underlying condition and inadequate provision of nutrients (particularly energy and protein) are the main reasons for developing undernutrition. Many patients are already undernourished before they reach the hospital. Those at highest risk for undernutrition are elderly people who are hospitalized or living in care homes, people on low incomes, socially isolated people, patients with chronic disorders and patients recovering from a serious illness or condition, particularly a condition.
that affects their ability to eat. In addition, hospitalized patients often show further deterioration in their nutritional status. One large survey showed that 4 of 5 patients do not consume enough to cover their energy or protein requirements [6]. There are many known reasons to explain this. The underlying disease may directly impair nutrition (e.g. in case of an esophageal stricture) and can induce metabolic and/or psychological disorders which increase the nutritional needs or decrease food intake. In addition, the fasting periods before many examinations and interventions lead to further inadequate food intake. Hospital undernutrition may also aggravate because of inappropriate meal services, inadequate quality and flexibility of the hospital catering, and insufficient aid provided by the care staff.

The consequences of undernutrition are well known. A poor nutritional status leads to an increase in complications, a longer hospital stay, higher mortality, higher costs and more hospital readmissions [5, 7]. The EuroOOPS study, for example, found significant increases in complications, length of stay and mortality in patients at risk for undernutrition [5]. Undernutrition also affects the efficacy of or tolerance to several key treatments, such as antibiotic therapy, chemotherapy, radiotherapy or surgery. Furthermore, it is now clearly demonstrated that undernutrition significantly increases overall health care costs [8].

Undernutrition is undoubtedly a major burden for patients and health care professionals, and active screening for malnutrition should be routinely performed. When undernutrition is diagnosed, it should be treated according to a nutritional care plan tailored to the individual patient. The best outcomes were obtained with supervision by a multidisciplinary nutritional support team.

To improve the overall outcomes from nutritional treatment, it is necessary to select patients with overt undernutrition and those at increased risk of developing nutritional deficiencies during their hospitalization. Ideally, all patients are screened during admission to hospital, followed by a detailed assessment of the nutritional status in those found to be at increased risk. In patients diagnosed with malnutrition or at high risk of malnutrition, an appropriate nutritional intervention should ensue. Unfortunately, although this process is well known and forms part of several national and international guidelines, it is not carried out everywhere. It remains necessary to raise the awareness of undernutrition and to improve the outcomes of treatments by nutritional interventions.

**Nutritional Screening and Assessment**

The identification of patients with nutritional deficiencies or overt undernutrition is the first step in nutritional support. In all patients, the nutritional status should be recorded within 2 days after admission to hospital.
The evaluation of the patient starts with a screening process. If the patient is found to be at increased risk, a detailed nutritional assessment should follow.

**Nutritional Screening**

Nutritional screening uses a tool designed to evaluate rapidly and simply if the patient is malnourished, at risk of malnutrition or if he or she will become undernourished. The screening method should be sensitive enough to detect almost all patients at risk of malnutrition. Several validated screening tools (table 1) are available and recommended by the European Society for Clinical Nutrition and Metabolism (ESPEN).

Recently published guidelines for nutritional screening of individuals in the community, hospitalized patients and elderly patients living in institutions are available (www.espen.org).

Each of the most frequently used screening tools relies to some extent on four principal parameters:

1. Weight loss over time
2. Recent food intake
3. Current body mass index (BMI; kg/m²)
4. Severity of the primary disease

For general screening in the community, the Malnutrition Universal Screening Tool (MUST) is a simple tool for rapid estimation of the grade of the malnutrition risk [9]. Its main disadvantage is that the recent food intake is not included, and calculations of the percent weight loss and BMI have caused problems in some units. The most widely used screening tools in hospital are the Subjective Global Assessment (SGA) and the Nutritional Risk Screening (NRS-2002) [9–11].

For the SGA, first the patient’s history is taken, followed by a physical examination [10]. The difficulty with the SGA is that it needs great experience in order to obtain reliable and reproducible results. The screener has to integrate all the information to make an overall judgement on the patient’s nutritional status.

The NRS-2002 is a simpler and well-validated screening tool [11]. The NRS-2002 starts with questions about the four items listed above for an ‘initial’ screen-

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**Table 1. Screening tools**

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<td>Malnutrition Universal Screening Tool (MUST)</td>
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<td>Subjective Global Assessment (SGA)</td>
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<tr>
<td>Nutritional Risk Screening (NRS-2002)</td>
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<tr>
<td>Mini-Nutritional Assessment (MNA) (elderly)</td>
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ing. If any of the questions is answered with ‘yes’ and a marked difference from normal values is observed, a ‘final’ screening follows. The final screening includes documentation of the impairment in the nutritional status and the severity of the disease. For each parameter, a score from 0 to 3 can be given. A final score of 3 or more in this validation process indicates that the patient will benefit from nutritional support.

For patients aged 65 years or more, two specific and well-validated tools are available [12, 13]. The initial long version of the Mini-Nutritional Assessment (MNA) was followed by a simpler one. The short form of the MNA has turned out to be as good as the long version, but it takes less time. The MNA is a combination of screening and assessment tools.

A comparison of the tools for nutritional screening and assessment of patients during hospital admission showed that the NRS-2002 had a higher sensitivity and specificity than the MUST and compared to the SGA. There was a significant association between the length of hospital stay and the nutritional status and risk by the SGA, NRS-2002 and MUST [14]. On admission to hospital, all of these three instruments can be recommended. The most suitable can be chosen according to the preference and experience of the individual unit.

**Nutritional Assessment**

For some patients, screening is not enough, and a more detailed assessment is necessary. A nutritional assessment should be done in those patients found to be at risk during screening, and when metabolic or functional problems prevent the application of a standard plan. For a detailed nutritional assessment, the following three steps are recommended:

1. Measurement of body composition
2. Measurement or evaluation of inflammatory activity and disease activity
3. Measurement of functional parameters

**Measurement of Body Composition**

Body composition describes the body compartments, such as fat mass, fat-free mass, muscle mass and bone mineral mass, in percentage terms depending on the body composition model used. Body composition changes due to starvation, underlying disease and mobility/exercise. Several simple methods to measure body composition are available. Most often, the BMI is calculated by measuring height and body weight (BW). Low and high BMI values are associated with increased morbidity and mortality. The BMI does not, however, reliably indicate the distribution between lean mass and adipose tissue, as there is no linear relationship between BMI and body compartments. Individuals with a low BMI may have an increased fat-free mass; on the other hand, individuals with a high BMI
may have a disproportionately low fat-free mass (e.g. sarcopenic obesity), placing them at an increased risk of failing to overcome disease or trauma.

Anthropometric measurements of limb circumferences and skinfolds represent simple, noninvasive and inexpensive ways of assessing the nutritional status. While mid-arm circumference has been shown to reflect muscle mass, triceps skinfold thickness is considered to be an indicator of subcutaneous fat. Although the measurements appear relatively easy, considerable experience is required to obtain reliable results. There is wide interobserver variability.

Another method of measuring body composition is bioelectrical impedance analysis (BIA). BIA is also a simple, inexpensive and noninvasive method of estimating body composition. It is suitable for routine bedside measurements. It relies on the detection of the body’s conductivity (typically between wrist and ankle), which differs according to the relative proportions of fat, muscle and water. BIA provides reliable data on total body water, body cell mass and fat mass in subjects without significant fluid and electrolyte abnormalities when the appropriate equations (correcting for age, sex and ethnicity) are used. BIA is not recommended in patients with an abnormal hydration state, in subjects with extreme BMI values (<16 or >34) or in the elderly. Extraneous electrical interference also makes BIA measurements less suitable for patients in the intensive care unit (ICU) [15, 16].

A new development in this field is the use of the bioelectrical impedance vector analysis. The position and the length of the vector provide information about the hydration status as well as body cell mass and cell integrity. Both undernutrition and obesity are clearly reflected by the vector analysis, making this approach an attractive bedside method to identify and monitor the patients’ nutritional status, which is less likely than BIA to be confounded by the presence of edema or ascites.

More sophisticated methods for the study of body composition are dual-energy X-ray absorptiometry, magnetic resonance imaging (MRI) and computerized tomography (CT).

Dual-energy X-ray absorptiometry depends on the analysis of radiological density (usually in the hip and spine) and is a useful, indirect method to measure the volume of fat mass, fat-free mass and bone mineral mass (density). It is relatively inexpensive and increasingly used in clinical practice and research. The only drawback is a small radiation exposure. It is currently regarded as the gold standard by many authors.

MRI and CT can also be used for the assessment of body composition. MRI and CT allow not only the quantification of fat mass and fat-free mass, but also give information about the regional fat distribution and enable an estimate of the amount of skeletal muscle. The advantage of MRI over CT is that for MRI
nonionizing radiation is used. These two methods are mainly used in research because of their higher costs, the amount of time needed and their more limited availability [17]. However, it is often possible to obtain nutritional information from scans taken for general diagnostic purposes, and ‘single slice’ techniques reduce the time and costs for review scans. It is probable that MRI will soon be established as the new gold standard for the measurement of body composition.

For research, several other sophisticated methods are available. These include dilution methods, the measurement of total body potassium and in vivo neutron activation analysis. These techniques are demanding and expensive. Therefore, they are not used in clinical practice.

Measurement of Inflammatory Activity and Disease Activity
Inflammation affects both body composition, mainly the muscle mass, and function. Inflammation is characterized by the production and release of proinflammatory cytokines into the circulation; these cytokines are catabolic for muscles. C-reactive protein levels correlate closely with the release of interleukin-6 and can be used as an inflammatory marker. In addition, inflammation reduces albumin levels. Therefore, low albumin levels are not a good indicator for the nutritional status. Serum albumin levels reflect disease severity more closely and can be used as an outcome predictor [18]. Low serum albumin levels are associated with a higher rate of complications and mortality [19, 20]. Extensive laboratory testing is not recommended for the assessment of the nutritional status, but it does play an important role in monitoring nutritional interventions. For short-term outcomes, transferrin, transthyretin (prealbumin) or retinol-binding protein can be used because of their short half-lives. Albumin is more suitable for long-term outcomes because of its longer half-life [18].

Measurement of Functional Parameters
Testing of function is increasingly regarded as important in nutritional assessment, and indeed muscle strength as well as cognitive and immune functions, all influence the quality of life.

Muscle strength is a good functional parameter with which to predict the outcome of both acute and chronic diseases. Both muscle size and muscle inflammation are independent predictors, firstly of muscle strength and secondly of outcome. Typical measurement parameters of muscle strength are hand grip strength, knee extension, hip flexion strength or peak expiratory flow. Impaired hand grip strength has been shown to be a good predictor of increased postoperative complications, increased length of hospitalization, higher rehospitalization rates and a decreased physical status. In addition, it is an excellent predictor not only of short- but also of long-term mortality [21]. For the interpretation of single values,
adequate reference values have to be used. Walking distance in a given time period (e.g. 3 min) can also provide an objective measure of global function.

It is important to include a measurement of cognitive function such as mood, concentration and memory, for example, in a detailed assessment. There is however no established consensus on the tests which can most optimally be used. Only in the elderly and in some patients with liver disease are there simple practicable methods. For the moment, we necessarily rely on the clinical impression in most patient groups.

Immune function has been determined by testing skin reactivity to an array of antigens. The obtained results largely reflect the severity of the disease and, as such, give a crude ‘yes’ or ‘no’ answer to the question as to whether the immune function is compromised. It does not furnish a quantitative measure of immune function. In addition, lymphocyte counts generally indicate the degree of illness and do not reflect malnutrition properly. For the moment, the routine measurement of immune function is not recommended because of the very controversial results in current studies regarding its nutritional significance.

**Nutritional Interventions**

The nature of a nutritional intervention depends on the underlying disease and the nutritional status. When undernutrition is diagnosed or a patient is at risk of undernutrition, a nutritional intervention plan should be started concomitant with the treatment of the underlying disease causing it. Nutritional support is a stepwise process. The choice of an appropriate feeding regimen depends on the clinical situation. Several approaches can be considered. Nutritional counseling and specific oral diets (including oral supplements) can be helpful. In some patients, however, oral nutrition is not possible, so enteral or parenteral nutrition has to be initiated. Regardless of the administration route, the estimation of energy and protein requirements is always a very important issue.

If patients at nutritional risk have appropriate nutritional support, their outcome is improved and rehospitalization rates are decreased. Furthermore, their hospital stay is shorter, and their quality of life is increased [22]. Freely available guidelines (www.espen.org) can help to guide nutrition in specific diseases.

**Oral Nutrition in Hospitals**

Oral feeding should be tried first if there are no contraindications and the gastrointestinal tract is working properly. A variety of menus and diets targeting specific patients’ categories and needs, including diets for vegetarians and different ethnic groups, are available for consideration. In addition, diets for spe-
cific diseases should be available (e.g. lactose- and gluten-free diets, and diets for patients with renal or hepatic diseases). The energy and protein intake can be improved by adding energy- and/or protein-rich supplements to the diet. Furthermore, high-energy snacks between meals can have beneficial effects. Oral intake can be further improved by a protected ‘meal time policy’, which includes three meal times free from avoidable and unnecessary interruptions. Also, the ambience where the meals are served has to be taken into account.

It is very important to monitor nutritional intake. Early detection of reduced nutritional intake is a key factor in the prevention of hospital undernutrition. Dietary protocols and supervision of the tray collection (e.g. four-quarter plate assessment) are useful. If the intake is not enough, oral nutritional supplements (ONS) can be included. ONS are liquid, semisolid or powder products containing the important macro- and micronutrients. ONS are available in a variety of flavors. They are energy dense, and contain 200–300 kcal per serving and 10–20 g protein/300 kcal per serving. ONS should be given in between the regular meals. It has been shown that ONS do not reduce voluntary food intake [23]. The major drawback of ONS is compliance. This has to be carefully considered, and action must be taken if the ONS are not (any longer) consumed in the prescribed amounts.

At present, the best approach seems to be an individual, multifactorial nutritional intervention program. It has recently been shown that such an approach, incorporating (inter alia) counseling, supervised eating and ONS, increases calorie and protein intake, maintains BW, decreases complications and readmission rates, and increases the quality of life [24].

**Enteral and Parenteral Nutrition**
In cases where oral nutrition is not possible for whatever reason, enteral and/or parenteral nutrition should be considered if a significant benefit for the patient can be anticipated.

**Enteral Nutrition**
The classical criteria for enteral nutrition are: preexisting severe undernutrition; oral intake less than 60% of estimated caloric requirements; delay before recovery of oral eating is expected to last more than 5–7 days, and absence of gastrointestinal, metabolic or circulatory contraindications. From the therapeutic, legal and ethical standpoints, enteral nutrition given by a tube is medical treatment.

Several parameters must be considered in the choice of an appropriate feeding tube (nasogastric/nasojejunal percutaneous endoscopic gastrostomy or fine-needle jejunostomy) and in the type of the formula. The type of tube depends on
the integrity of the gut function and the expected duration of feeding. Nasogastric or nasojejunal tubes are recommended for short-term feeding (<3 weeks), and percutaneous endoscopic gastrostomy or fine-needle jejunostomy for longer-term feeding (>3 weeks).

The choice of the formula depends on the underlying disease and the specific demands of the patient. Nutritional support is different in patients with undernutrition without inflammation from that in patients with chronic or acute inflammatory disease.

In patients with undernutrition and no inflammation, e.g. in anorexia nervosa cases, no specific formulae are necessary. Feeding should be started below the target level and slowly advanced to the calculated goal. These patients have a higher risk of the refeeding syndrome [25], so close observation and careful monitoring of electrolytes (particularly phosphate) is mandatory.

Patients with a chronic disease leading to undernutrition can benefit from several special enteral diets. For example, cancer patients need a high-protein diet and may benefit from anti-inflammatory substrates, such as ω-3 fatty acids and antioxidants [26]. Patients with chronic kidney disease who are not on dialysis should have a diet with lower amounts of protein and phosphorus. On the other hand, patients on dialysis benefit from a high-protein and low-phosphorus diet to compensate for the protein loss during dialysis. In patients with gastrointestinal dysfunction or inflammatory bowel diseases, diets with hydrolyzed proteins and medium-chain triglycerides are sometimes better tolerated than normal formulae [27]. Several guidelines showing how nutritional support can be improved in different patient groups have been published (e.g. ESPEN guidelines: www.espen.org).

In patients with acute disease, especially if they have to be treated in the ICU, nutritional support can be a challenge. Acute severe inflammation increases the resting-energy expenditure and nitrogen excretion. There is a strong catabolic drive, which rapidly affects the muscles. The consequent loss of lean body mass has a major influence on outcome. The worst outcomes are seen in acutely ill patients who were already undernourished before hospitalization. In all acutely ill patients, it is important to define the amounts of energy and protein required. Most of these patients are still underfed in the ICU. A global survey showed that calorie and protein administration reached only 44–52% of the amounts prescribed [28].

The gold standard to assess energy requirement is indirect calorimetry. Although it is the most appropriate method to answer this question, it is seldom used. Using the different predictive equations is also possible, but it has to be borne in mind that these equations often underestimate the caloric need. To overcome these problems, the ‘rule of thumb’ formula is often used. In this,
25–35 kcal/kg BW per day are recommended using the ideal BW for calculation. This simple approach has been shown to perform reasonably well in comparison with indirect calorimetry. For obese patients, the adjusted BW should be used. In the ICU, it is crucial not to under- or overfeed the patients. Several studies have shown that a calorie deficit over time increases morbidity and mortality [29, 30]. Equally, hyperalimentation, i.e. the administration of excess energy, predisposes to a fatty liver and also leads to a poorer outcome.

To improve outcome, it is crucial that not only the right amount of energy but also an adequate amount of protein is provided. It is a consistent finding that the amount of protein given to patients is too low, and that this deficit is proportionally greater than the deficit in energy supply. Patients in the ICU usually do not get more protein than 0.8–1.0 g/kg BW per day. Many observational studies have shown that outcomes can be improved by increasing protein supplements. Newer recommendations for protein prescription are accordingly higher, with a typical target value of 1.3–1.5 g/kg BW per day. Allingstrup et al. [31] have nicely demonstrated that patients with a higher protein intake had a significantly better survival than those with a low protein intake. Weijs et al. [32] confirmed their results in another elegant study. They found that the 28-day mortality rate was only decreased in patients reaching both energy and protein goals. Currently, it is recommended that enteral nutrition should start as early as possible. Large studies have confirmed this by showing a significant effect on mortality in the early-fed groups [33, 34].

Parenteral Nutrition
Most of the published meta-analyses reported a benefit of enteral nutrition over parenteral nutrition. This is most obvious in respect of infective complication rates. Mortality is generally comparable for enteral and parenteral nutrition except in patients with severe undernutrition, where the parenteral route is more advantageous. Therefore, parenteral nutrition can be recommended in patients with severe undernutrition; in case of contraindications to enteral nutrition, or as a supplement if 60% of the estimated requirements cannot be reached by enteral nutrition by day 3. Therefore, it is very important to monitor energy and protein intake. Supplementation of missing calories by parenteral nutrition is then recommended. Two recently published studies confirmed this approach. In TICACOS (Tight Calorie Control Study), Singer et al. [35] found that providing the target energy requirement based on repeated energy measurements by indirect calorimetry was achievable in a general ICU and that it was associated with lower hospital mortality, although morbidity was increased. In an optimization study of energy provision with supplemental parenteral nutrition in crit-
ically ill patients, Heidegger et al. [36] demonstrated a significant reduction in nosocomial infections in the early supplemented group compared to the non-supplemented group (27 vs. 38%). In addition, the energy and protein intake was significantly higher, and the mechanical ventilation time was reduced (83 vs. 108 h). There was no effect on the length of hospital stay or mortality. These results are however different from the results of a study of early compared with late parenteral nutrition supplementation in critically ill adults. In this study including 4,640 patients, the late initiation of parenteral nutrition was associated with faster recovery and fewer complications than early initiation [37]. This study is controversial and has arguably raised more questions than answers. Major problems in the study design have to be considered. It is clear that some inappropriate patients were included. Many had no nutritional deficits, and after only 3 days, more than 50% of the patients had already been discharged from the ICU. These patients are not usually considered for parenteral nutrition. In addition, the energy intake in the early initiation group was too high as judged by many current guidelines. Moreover, in the first 2 days, patients received only a 20% glucose solution with no amino acids or lipids. This is certainly not a standard form of parenteral nutrition! The claim that early initiation of parenteral nutrition is harmful is also in contrast with the results of a recently published study by Doig et al. [38], who showed that early parenteral nutrition was associated with no more complications.

**Immunonutrition and Special Substrates**

For two decades, attempts have been made to improve the outcome in specific patient groups using specific pharmaconutrients. The usual aim has been to lower inflammation and offset oxidative stress in patients with the systemic inflammatory response syndrome, sepsis, acute respiratory distress syndrome or acute lung injury. The substrates used (e.g. ω-3 fatty acids, glutamine and antioxidants) have been used either alone or combinations thereof. For surgery, burn and trauma patients, enteral nutrition has been productively studied in combination with arginine, ω-3 fatty acids, nucleotides, glutamine and antioxidants in order to enhance the immune response to infection.

The best evidence for this style of immunonutrition can be found with enteral nutrition in surgical patients undergoing major gastrointestinal cancer surgery. It was clearly shown that pre- or perioperative nutrition with an enteral formula including arginine, ω-3 fatty acids and nucleotides reduces complication rates and shortens the length of hospital stay irrespective of the initial nutritional status [39]. In addition, this approach was found to be cost-effective [40]. In surgical patients, it was also shown that parenteral nutrition supplemented with ω-3 fatty acids was more beneficial than standard paren-
teral nutrition. The meta-analysis from Pradelli et al. [41], which included both elective surgery and critically ill patients, demonstrated a 39% reduction in infection rates, a 2-day shorter length of stay in the ICU and a 3-day shorter stay in hospital. There was no difference in mortality. A more recent systematic review and meta-analysis included only critically ill patients [42]. Here, it was found that lipid emulsions containing ω-3 fatty acids may reduce mortality and ventilation days in the critically ill. However, because of the paucity of clinical data, there was inadequate evidence to make a firm recommendation for the routine use of ω-3-fatty acids containing parenteral feeds [42].

Until recently, glutamine supplementation was recommended for all critically ill patients. It was found that low plasma glutamine levels increase mortality and therefore it was considered logical that the supplementation of glutamine should be beneficial [43]. In patients with burns and trauma, enteral nutrition with glutamine has been reproducibly shown to be effective and this can still be recommended. The data pertaining to other conditions are less clear-cut however.

For parenteral glutamine supplementation, quite a number of positive studies have now been published, and initial systematic reviews and meta-analyses indicated beneficial effects, with reductions in infectious complications, mortality and length of hospital stay (www.criticalcarenutrition.com). However, those recommendations are now under very careful scrutiny after the recent publication of two major studies in which the former positive results could not be confirmed. In the SIGNET study from Andrews et al. [44], supplementation with glutamine showed no beneficial effects. In the REDOX study, which included 1,203 patients, supplementation with glutamine with or without antioxidants led to a significantly higher mortality than in the groups without supplementation of glutamine or antioxidants [45]. Clearly, we have to reconsider the use of glutamine. It is quite possible that the negative results of the REDOX study are the consequence of its design. An unusually high dose of enteral and parenteral glutamine (enteral 30 g and parenteral 0.35 g per kilogram BW per day) was given. This generous provision of glutamine was maintained even when feeding was minimal. Furthermore, severely ill ICU patients with failure of two or more organs, and a high proportion of patients with renal failure were included. Previously, these very sick patients with renal failure have generally not been treated with glutamine and certainly not with such high amounts. Accordingly, the real benefit or harm of glutamine is at present unclear. The new findings have to be incorporated into discussions of all the published data on glutamine. There may be subgroups of patients who benefit from glutamine while others will be harmed, and the dose given (and perhaps the route) may also be crucial. The
most recent systematic review from Wischmeyer et al. [46] (which included the SIGNET study but not the REDOX5 study) found significant decreases in hospital length of stay and hospital mortality. Infectious complications were reduced only when glutamine was given enterally. Overall mortality was unchanged in patients receiving enteral and parenteral supplementation. At the moment, most experts in this field still recommend parenteral glutamine supplementation for critically ill patients needing parenteral nutrition. We recommend that the dose to be given and the contraindications for glutamine should be those established in the REDOX5 study.

Conclusion

It has to be kept in mind that an impaired nutritional status affects patient outcome. Therefore, all patients should undergo a screening and assessment process to identify patients at risk. Optimal nutritional support depends on the patient’s underlying disease and the severity of undernutrition. The appropriate provision of nutrients depends on the patient’s condition. Oral nutrition, with or without supplements, or enteral or parenteral nutrition should be used according to the underlying problems. The adequate provision of energy and protein is essential to improve outcomes. Specific diets or nutritional formulae can have a further impact on outcome in specific situations. To determine the best nutritional support currently available, it is useful to consult the guidelines created for specific patient groups. Oral or enteral immunomodulating substrates have been shown to be beneficial in patients with major surgery. For ICU patients, the situation is no longer so clear because of the newly published data on glutamine; further evaluation of all the data is clearly needed but should lead to a more final conclusion in the near future.

Disclosure Statement

Rémy Meier: speaker engagements with honoraria for the following companies with an interest in nutrition: B. Braun (Aesculap), Nestlé, Fresenius-Kabi and Danone, and consulting with honoraria for the following companies with an interest in nutrition: Nestlé, Fresenius-Kabi and Danone.

Alastair Forbes: speaker engagements with honoraria for the following companies with an interest in nutrition: Abbott, Baxter, B. Braun (Aesculap), Nutricia and Yakult.

Rémy Meier and Alastair Forbes are closely involved in the ESPEN educational program with no other conflicts of interest.
References


Abstract
In starvation and to a lesser extent in stress starvation, the loss of protein mass is spared as much as possible. This metabolic arrangement must have developed under the influence of evolutionary pressure in view of the importance of protein mass for function and longevity. Peripheral adipose tissue mass is only limiting when its mass is extremely small. Protein is the predominant precursor of glucose in (stress) starvation and glucose is an essential substrate for the synthesis and maintenance of cells and matrix and for the control of the redox state. To spare protein, glucose should be used efficiently only for those purposes that cannot be achieved by fat. It is suggested that this is achieved by limiting full glucose oxidation and increasing fatty acid and ketone body oxidation, which most likely can also largely cover energy needs of the central nervous system. In stress states, net negative nitrogen balance (catabolism) largely results from net losses of peripheral protein mass, predominantly muscles, whereas central organs (e.g. the liver), the immune system and wound healing are anabolic. A number of factors are responsible for a net negative nitrogen balance which may ultimately lead to death if stress persists. In stress, the amino acid mix derived from peripheral (predominantly muscle) tissues is modified in interplay with the liver and to a minor extent the kidney. This mix is different in non-stressed conditions, containing substantially increased amounts of the nonessential amino acids glutamine, alanine, glycine and (hydroxy)proline. Part of the amino acid skeletons released by muscles are substrates to produce glucose in the liver and kidney. Glucose and the amino acids produced especially serve as substrates for cell proliferation and matrix deposition. The catabolic processes in peripheral tissues cannot be countered completely by adequate nutritional support as long as stress persists. This metabolic arrangement dictates a nutritional mix containing liberal amounts of protein and carbohydrates and addition of lipids to cover energy requirements.
Introduction

In evolution, protein sparing is a first priority of the body, provided that enough energy is present in the form of adipose tissue or diet [1–3]. When this is not the case, the ‘King Penguin syndrome’ develops after which individuals quickly die [4–6].

To limit protein losses, amino acids should be reutilized as much as possible and used for survival purposes but not for purposes that can be achieved by other nutrients. Nevertheless, in starvation, some of the protein-derived amino acid nitrogen and nucleotide-derived base nitrogen is only partly reutilized and partly excreted in the urine as ammonia or urea. This is quantitatively even more important in stress starvation. In this process, peripheral protein (muscle, skin and bone) is lost to a limited degree in starvation and more extensively in stress starvation.

One of the crucial substances to be produced by the body is glucose, which is preferentially used for the synthesis of biomass (nucleotides and cell proliferation) in starvation, stress, inflammation and in situations with rapid growth. To promote these processes, glucose oxidation is inhibited to a major degree [7, 8]. This is achieved by insulin resistance, which in situations of stress and increased cell proliferation persists also in the presence of adequate ingestion of carbohydrates [8, 9].

In view of the priority given to protein sparing and the resulting limitation of the irreversible oxidation of glucose, the body necessarily relies on fat as fuel. Interestingly, predominantly fatty acids derived from peripheral adipose tissues are oxidized, whereas visceral and organ fat is spared or even accumulates.

The extent of fat oxidation is, therefore, predominantly the resultant of the degree of protein and glucose oxidation in all stress and growing states rather than a primary event. On this basis, protein metabolism (flux from peripheral to ‘central’ tissue muscle catabolism; composition of non-essential amino acid produced and how) will be first discussed, subsequently protein-related glucose metabolism and finally a short discussion will be devoted to fat metabolism.

Protein Metabolism

In starvation with or without stress (as a general term for trauma, and infectious and noninfectious inflammation), there is a net flux of amino acids from peripheral tissues (muscle, skin and bone) to ‘central tissues’, which utilize these amino acids predominantly for the synthesis of acute phase proteins, immunocytes, proliferating cells and matrix in healing wounds or growing tissues. In this process, nucleotides are important nitrogen-containing products. Peripheral tissue
release is generally achieved by the increase in protein degradation, whereas protein synthesis remains stable. Nitrogen accrual in the ‘healing tissues’ is achieved by increasing synthesis while degradation is less affected. In the stress states mentioned, this net flux of nitrogen from peripheral tissues to central tissues is an obligatory event and can only be lessened to a modest degree when patients are adequately nourished. However, it has been shown that growth hormone has anticytotic properties, diminishing peripheral release of glutamine in trauma patients [10] and septic pigs [11] while also increasing infectious mortality in critically ill patients [12]. This signifies that the catabolic response is crucial for survival, and the damage caused by growth hormone treatment probably results from the inhibition of the central anabolic synthesis of acute phase proteins [13], immune cells and cells operative in wound healing, which may result from a decrease in the peripheral release of amino acids.

In stress, there is a loss of whole body nitrogen as evidenced by a negative nitrogen balance, which becomes more negative when the stress is more severe. Net nitrogen losses range from 6–7 g of nitrogen in starving adults [14] to approximately 15 g in critically ill patients with extremes up to 30 g in burns or severe infectious states. Simple reasoning might lead to the conclusion that these losses are related to the production of acute phase proteins, matrix proteins, immunocytes and other cells, but these also have a turnover, in which breakdown products may be suitable for reutilization. A process in which protein is definitively lost is the crucial production of glucose derived fatty acid/sterol/phospholipid largely for cell membrane synthesis. Another reason may be related to the influence of ‘cycling.’ Almost all metabolic pathways cycle, implying that in several reactions often in different organs an intermediate branches off from the cycle to produce a building stone for the synthesis of biomass and is later at least to some degree resynthesized. This arrangement may serve to rapidly adapt to changing circumstances or requirements. In nitrogen metabolism, cycling substrates are never regenerated completely because intermediates can branch off to be excreted or to be irreversibly oxidized. This leads to partial losses of intermediates which simultaneously have to be replenished somewhere else in the cycle. In nitrogen cycling, even in stable non-stressed states, the ability to excrete nitrogen into the urine requires a continuous and modest formation of urea in the liver (largely from alanine) and ammonia in the kidney (largely from glutamine). The amounts of urea produced in starving states are low [15] but much higher in stress states. This is comparable with the stationary running motor using little fuel, which can rapidly gear up when under influence of changing requirements substrate/fuel is added to the motor. When tissues grow (cancer or pregnancy) or pus is produced and lost from the body, net peripheral losses in the host (mother or cancer patient) may increase [16]. In conclusion, the causes of catabolism are manifold and are not defined in detail.
Changes in Amino Acid Metabolism as a Consequence of Stress

The net release of amino acids by peripheral tissues in response to stress yields a mixture that does not completely reflect the amino acid composition of muscle protein and that is different from the mixture released in nonstressed states. Specifically glutamine and alanine have been reported to be released in increased amounts. Almost all amino acids released during stress are to a significant extent taken up by the liver. The only amino acid produced in stress by the liver in a net fashion is glutamic acid. Glucogenic amino acids are partly metabolized in the liver producing glucose. Importantly, the kidney participates in the uptake and metabolism especially of glutamine, producing glucose and ammonia. Ammonia is partly excreted in the urine, partly in the venous effluent of the kidney and is in the absence of portal-systemic shunting the only ammonia present in the systemic circulation (fig. 1) [17].

After the release of glucose and glutamic acid by the liver, and of glucose by the kidney, they are partly taken up again in muscle and support the production of glutamine, alanine, glycine and proline far in excess of their composition in muscle protein. A substantial part of the amino nitrogen of glutamine is derived from branched chain amino acids. The central nervous system and possibly the lungs also produce glutamine. Net pulmonary uptake of glutamine has been found in patients having pulmonary inflammatory infiltrates and net release was found when the lungs where not suffering from inflammation [18].

As explained earlier, all these reaction processes branch off from the cycling of these substrates across organs, whereas the turnover of the intermediates in the cycle is far greater than their net utilization. The substantial net formation of the non-essential amino acids glutamine, alanine, glycine and proline takes most likely place in peripheral tissues, besides – to some degree – also in the proliferating cells themselves. They have an increased requirement of these amino acids and glucose for their proliferation and synthesis of matrix. In principle, these amino acids can be considered as conditionally essential amino acids, similar to glutamine, which may be lacking in depleted states or in states with long-standing and severe inflammatory activity. Although the estimation of requirements largely focuses on the synthesis of cells, it is noteworthy that collagen is a substantial part of our tissues and has an amino acid composition with high concentrations of (hydroxy-)proline, glycine and alanine. The turnover of collagen is slow, but a small pool with rapid turnover has been claimed to exist [19, 20].

Another example of cycling is the Cori cycle, in which glycolysis takes place in peripheral tissues and specifically in proliferating cells. Glucose uptake is far greater than lactate production whereas little glucose is fully oxidized. This
supports the view that much of the glucose carbon skeleton is utilized for biosynthesis rather than complete oxidation. The lactate produced is released into the circulation and resynthesized into glucose in the liver and possibly also in the kidney. This happens in inflammatory (stress) states despite normal oxygenation. This increase in apparent senseless cycling plays, however, a similar role, as described earlier for the cycling of glutamine. At several points of the cycle, intermediates (e.g. glucose, glycerol and alanine) can replenish intermediates (anaplerosis) and at other points intermediates branch off and are used for cell
proliferation and maintenance of the redox state [for instance ribose and NADPH in the pentose phosphate pathway and glycereraldehyde-3 phosphate producing serine and subsequently glycine in high amounts also serving the synthesis of the bases of nucleotides (purines and pyrimidines)]. This is again the running motor which is geared up in stress because intermediates are required in increased amounts that can branch off from these cycles and act as substrate for the production of cell components.

Importantly, glucose and glutamine are the main anaplerotic substrates replenishing the intermediates of the Krebs cycle. They serve similar roles as described for the Cori cycle supplying reducing equivalents and supporting the synthesis of cell elements and matrix. Glutamine-derived glutamic acid is crucial in this process either directly or indirectly via aspartic acid serving as one of the substrates contributing to purine and pyrimidine synthesis. Several other glucogenic amino acids can act to a lesser degree in a similar way.

**The Protein-Glucose Connection**

Under the influence of evolutionary pressure, the generally accepted view that protein mass is the limiting factor in long-term survival during (stress) starvation provided normal fat mass is present [1, 2] has led to the preservation of protein mass as much as possible and to the accumulation of fat mass when food is abundant. Glucose is a crucial substrate serving many roles in building cells and matrix, and in maintaining a redox state by promoting the production of reducing equivalents (mainly NADPH). As glucose reserves are very limited in (stress) starvation, new glucose formation is required, which predominantly requires the use of glucogenic carbon skeletons of protein and to a much lesser extent of lipolysis-derived glycerol. To limit the requirements of glucose (and therefore protein breakdown), it should be utilized only for the survival purposes that can only be served by glucose, as mentioned earlier. Complete glucose oxidation is not or only to a very limited degree required, notwithstanding claims in the literature that immunocytes and the central nervous system need glucose for oxidation during critical illness. Referring to H.A. Krebs, Owen et al. [21] report that 100 g of muscle protein yield 57 g glucose. In starvation and stress starvation 7–14 g of net nitrogen loss per day would on the basis of this calculation lead to the net production of 25–50 g of glucose. These amounts would not cover the energy requirements of the brain, which are estimated to range between 100 and 150 g if all this glucose would be oxidized in the brain, which is unlikely and has been shown not to happen in the same report [21]. In fact, a very low respiratory quotient was found (0.62) across the brain, which
should have been much higher when all glucose taken up by the brain would have been oxidized. Consequently, this suggests that significant nonoxidative glucose disposal must have taken place, consistent with synthetic processes. In stress starvation, very limited glucose oxidation by the brain is supported, contrary to other claims, by the demonstration that ketone body formation is also present in septic states [22]. On the basis of indirect calorimetry and isotope technology, glucose oxidation at the whole body level has been estimated to contribute 10–15% of energy requirements. As this glucose is largely derived from amino acids, the contribution of amino acid oxidation is already included in these estimates; 85–90% of energy requirements must therefore be covered by fatty acid oxidation.

**Protein-Glucose Sparing and Insulin Resistance**

In all the stress states earlier mentioned, glucose is specifically channeled into biosynthetic pathways whereas complete glucose oxidation is inhibited. This is achieved by insulin resistance resulting from the activation of pyruvate dehydrogenase kinase which inhibits pyruvate dehydrogenase and catalyzes the dehydrogenation/decarboxylation of pyruvate to acetyl CoA, the fuel of the ‘stove’ of the Krebs cycle. The mechanisms described in this subchapter are supported by the finding that in all situations where food is limited, as well as in all situations where rapid cell proliferation is required, the organism is insulin resistant. Examples are starvation, trauma, infection, periods of growth (puberty, lactation, pregnancy, cancer and obesity), in the fat-loading period before hibernation, estivation and migration as well as during these periods. Longevity has also been shown to require insulin resistance in many other species, including worms, insects and nonhuman vertebrates [23]. The insulin-resistant state, which exists when fat loading occurs before long-term fasts before migration, hibernation and estivation, may have similar characteristics as insulin resistance in obesity. Building and maintaining a large fat mass as well as the pro-inflammatory influence of the ingestion of large amounts of pro-oxidative fat very likely contribute to the insulin-resistant state [9].

**Fat Metabolism**

The views expressed in the previous subchapters lead to the conclusion that in (stress) starvation fatty acid and ketone body oxidation is the predominant source of energy and is part of the integrated changes in protein/glucose/
fatty acid metabolism. High fatty acid levels present in these conditions are necessary to drive oxidation. The special role that has been attributed to high normal and abnormal fatty acid levels in insulin resistance may be questioned. The inhibition of pyruvate dehydrogenase and the subsequent inhibition of pyruvate-derived acetyl-CoA production is a crucial event in the chain of events in metabolism and decreases insulin sensitivity. Its regulation is not completely understood. The FOXO transcription factor family has been suggested to play a role in this respect [24]. However, the potential pro-oxidative effect of high fatty acid levels may secondarily contribute to insulin resistance.

**Nutritional and Metabolic Consequences**

The metabolic response to stress involves protein sparing and is achieved by insulin resistance. The crucial role of glucose in the response to stress and the necessity to utilize glucose efficiently leads to the recommendation to furnish liberal amounts of protein and carbohydrates in stress situations. In addition, the remaining requirement of energy should be covered by the addition of lipids, although slight underfeeding is less risky than overfeeding, provided the individual has normal adipose tissue stores. In view of the important role of insulin resistance, upregulation of insulin sensitivity may be harmful. Tight glucose control has not been discussed in this chapter but maintaining levels between 4 and 6 mmol and limiting glucose ingestion may interfere with an adequate metabolic response in critical illness. In volunteers receiving endotoxin and in septic patients, hyperinsulinemic euglycemic (4–6 mmol) clamp studies have shown that at moderate hyperinsulinemia, requiring low dosages of glucose, most glucose was oxidized and little nonoxidative disposal occurred [25, 26]. When more insulin was given or higher euglycemic levels (10 mmol) were aimed for, nonoxidative glucose disposal increased. Nonoxidative glucose disposal includes glycogen synthesis and biosynthetic pathways described in an earlier part of the chapter. We suggest that glucose levels between 4 and 6 mmol are not physiological in stressed states and interfere with adequate metabolic responses. This may be aggravated when low glucose-containing diets are administered.

**Disclosure Statement**

This author has no conflict of interest to disclose.
References

Noncaloric Benefits of Carbohydrates

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Abstract
Noncaloric benefits of carbohydrates are due to the presence of dietary fibers, which are a heterogeneous group of natural food sources and form an important component of a healthy diet. They differ in physiochemical properties such as solubility, fermentability and viscosity. They have a wide range of physiological effects resulting in gastrointestinal and systemic benefits. These include appetite, satiety, bowel transit time and function, production of short-chain fatty acids and certain vitamins, and effects on gut microbiota, immunity and inflammation, as well as mineral absorption. They also help to control the glycemic status and serum lipid levels, resulting in reduced incidence rates of atherosclerosis, hypertension, stroke and cardiovascular diseases.

Introduction

Carbohydrates (CH) are a major source of nutrients for human beings. The average daily consumption is about 300 g (range from 250 to 800 g). Most of the digestible CH are converted to carbon dioxide, water and energy. CH provide more than 50% of the daily calories. However, the diet also contains low-digestible or nondigestible CH, which are mainly derived from plant sources and constitute the dietary fiber; they are capable of undergoing partial or complete fermentation in the large intestine [1]. There are various types of dietary fibers
which have varying physiological effects. Clinical studies have shown that fibers have a wide range of benefits, depending on their physical and chemical characteristics, e.g. solubility, fermentability and viscosity [2]. This article gives an overview of the noncaloric benefits of such low-digestible and nondigestible CH, which constitute the dietary fiber.

**Definition of Dietary Fibers**

Eben H. Hipsley used the term ‘fiber’ for the first time in 1953, when he reported an increased incidence of pregnancy-related toxemia in Indians living in Fiji Islands who were on a low-fiber diet, compared to a low incidence seen in indigenous Fijians who were on a high-fiber diet [3]. Consequently, a number of diseases were postulated to develop as a result of lack of fiber in the diet, and the term ‘dietary fiber’ was adopted, in keeping with the then ‘dietary fiber hypothesis’ [4]. However, a scientifically sound definition was lacking. In the year 2000, the American Association of Cereal Chemists (AACC) modified the definition based on years of research and inputs from food scientists worldwide [5, 6]. ‘Dietary fiber (DF) is the remnants of the edible part of plants and analogous carbohydrates that are resistant to digestion and absorption in the human small intestine with complete or partial fermentation in the human large intestine’. It includes various substances, such as polysaccharides, oligosaccharides and lignins.

The AACC further classified DF based on their solubility (table 1) [4]. A more practical way of classification is the one that is based on all the physiochemical properties, solubility, fermentability and viscosity (table 2) [2]. The definition was further refined by the Food and Nutrition Board of the Institute of Medicine based on an approach to distinguish between intrinsic and intact components of plants, which is the ‘dietary fiber’ and ‘added fiber’. Together they are called ‘total fiber’ [6]. This last definition is more flexible, as it includes nondigestible CH from animal origin. Therefore, DF is the CH, either of plant or animal source, which is not completely digested in the small intestine and exerts physiological effects which are beneficial.

**Carbohydrates and the Digestive System**

Most of the CH are digested in the small intestine and provide calories. The undigested CH, by their complex effects on the large intestine, provide many noncaloric benefits. They increase the fecal bulk, prevent constipation and undergo
fermentation to provide short-chain fatty acids (SCFA). In addition, they are a source of antioxidants, trace minerals, phenolic compounds and phytoestrogens. They also reduce the risk of diverticulitis, obesity, type 2 diabetes and cardiovascular diseases, and lower serum cholesterol levels [7].

**Table 1. DF constituents according to AACC [4]**

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<th>NSP and resistant oligosaccharides</th>
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<td>Cellulose</td>
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<td>Arabinobiosides</td>
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<td>Arabinogalactans</td>
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<td>Polyfructoses</td>
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<td>Inulin</td>
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<td>Oligofructans</td>
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<td>Galactooligosaccharides</td>
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<td>Pectins</td>
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<th>Analogous CH</th>
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<td>Indigestible dextrins</td>
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<td>Resistant maltodextrins</td>
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<tr>
<td>Synthesized CH compounds</td>
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<td>Polydextrose</td>
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<td>Methyl cellulose</td>
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<td>Hydroxypropylmethyl cellulose</td>
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<td>Indigestible (‘resistant’) starch</td>
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<th>Lignin substances associated with NSP and the lignin complex in plants</th>
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<td>Waxes</td>
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<td>Phytate</td>
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<td>Saponins</td>
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<tr>
<td>Suberin</td>
</tr>
<tr>
<td>Tannins</td>
</tr>
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Carbohydrates in the Small Intestine

Most of the carbohydrate intake is in the form of polysaccharides followed by oligosaccharides. These complex saccharides cannot be absorbed and need to be broken down to monosaccharides, which undergo further enzymatic hydrolysis in the small intestine, resulting in the production of glucose, galactose and fructose. These simple molecules are absorbed via specific transport (sodium-dependent active transport and facilitated diffusion) and nonspecific transport (passive diffusion) systems within the small intestine [1].
Carbohydrates in the Large Intestine
About 85% of CH are absorbed before entering the large intestine. Ten to 30% of the CH remain undigested and enter the colon. These include polymers such as nonstarch polysaccharides (NSP), resistant starches and polysaccharides in structure forms, for example. Bacterial hydrolases convert these complex polymers into smaller molecules, which are further broken down by bacterial amylases into monosaccharides. These monosaccharides undergo anaerobic fermentation by colonic bacteria and are converted to SCFA (acetate, propionate and butyrate), which are a source of energy, and noncaloric substances such as hydrogen, carbon dioxide and methane (fig. 1). This bacterial degradation of nondigestible CH yields an energy salvage of about 62%. The bacteria in the large intestine (there are about 300–500 bacterial species which contain nearly 2 million genes) thus salvage significant energy from the low-digestible and nondigestible CH [8].
Mechanisms of Noncaloric Benefits of Carbohydrates

The components of the low-digestible and nondigestible CH have a variety of actions, which result in various benefits. Most of them slow the gastric emptying time, increase satiety and have a variable mouth-to-fecal transit time. They inhibit the action of pancreatic and other digestive enzymes and reduce the rate of absorption. By their hydrophilic action, they increase the stool weight and volume by 40–100%. They act as nutrients (prebiotics) on the colonic bacteria, which in turn ferment the undigested CH residue, resulting in SCFA production [8]. Soluble fibers are more fermented than insoluble fibers (10 times more) by the huge population of colonic bacteria. SCFA are rapidly absorbed by colonic epithelium, in exchange for bicarbonate, and hydrogen is excreted as a result, which is exchanged for sodium along with water (fig. 2) [9]. The concentration of SCFA is negligible in the jejunum, but progressively increases and is about 10 times higher in the colon. Acetate and propionate control cholesterol to a certain extent [10]. Propionate also acts as a substrate for gluconeogenesis in hepatocytes. Butyrate is the most important SCFA and is the preferred fuel for colonocytes; it accounts for 80% of the energy for colonocytes. It has an immunomodulatory effect and also aids in the growth of jejunal and ileal epithelial cells [11]. An important action of butyrate is its anti-inflammatory effect, which is due to a decreased production of TNF-α, and inhibition of NF-κB activation and cytokine messenger RNA expression [12].
Certain components such as nonstarch fruits and vegetables have a low glycemic index, resulting in reductions in the glycemic load and, thereby, in the incidence of type 2 diabetes [13]. Viscous, soluble fibers (pectin, oat fiber and gums) have a lipid-lowering effect. They form a viscous gel and increase bile salt excretion by preventing their reabsorption in the small intestine. As a result, the liver converts more low-density lipoprotein (LDL) cholesterol to bile acids, resulting in a reduction in total and LDL cholesterol levels [14], and, consequently, exerts a beneficial effect on the incidence of atherosclerosis, cardiovascular diseases and stroke.

The nondigestible bulk, in addition to preventing constipation, also binds luminal carcinogens, thereby reducing their exposure. The presence of vitamins and various bioactive compounds inhibit the molecular pathways which promote carcinogenesis. In addition, butyrate also has an effect on cell differentiation, apoptosis and gene expression on the colonic epithelium [15].

Fermentable nondigestible CH ingredients such as inulin and fructooligosaccharides (FOS), which are present in edible fruits, onions, garlic and bananas, selectively stimulate the growth and activity of a limited number of species of bacteria in the colon, such as lactobacilli and bifidobacteria (called prebiotics) [16]. They have a low viscosity, are water soluble and cause a reduction in the pH of the colonic contents. They stimulate the growth of beneficial bacteria,
which inhibit the growth of pathogenic bacteria (e.g. clostridia), are helpful in treating constipation and may be beneficial in inflammatory bowel diseases.

FOS have been shown to have a variety of beneficial properties. They help in the production of SCFA. By reducing the pH, they reduce the ammonium levels and the number of clostridia and other putrefactive bacteria, and also increase calcium and magnesium uptake. They may also reduce serum cholesterol levels, especially in diabetic persons [17].

The nondigestible CH have diverse effects, which can be divided into gastrointestinal benefits and systemic benefits (table 3).

**Table 3.** Noncaloric benefits of CH

<table>
<thead>
<tr>
<th>Gastrointestinal benefits</th>
<th>Systemic benefits</th>
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<tr>
<td>Transit time</td>
<td>Appetite and satiety</td>
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<tr>
<td>Constipation</td>
<td>Weight control</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Glycemic control</td>
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<tr>
<td>Prebiotics and microflora</td>
<td>Hyperlipidemia</td>
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<tr>
<td>SCFA</td>
<td>Cardiovascular disease</td>
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<td>Inflammatory bowel disease</td>
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<td>Irritable bowel syndrome</td>
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<tr>
<td>Gastrointestinal cancer</td>
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**Gastrointestinal Benefits**

*Transit Time.* It depends on the source, type and structure of the dietary fiber, and the effects on the upper gastrointestinal tract can be different from the effects on the colon. Soluble fibers (e.g. pectin and oat fiber) and insoluble fibers (e.g. coarse bran and soy polysaccharides) reduce gastrin emptying time and increase satiety. Pectin, especially in its solid form, is more effective in reducing motility than in its liquid form. The presence of a fiber-rich meal in the ileum has an inhibitory feedback mechanism (ileal brake) and reduces gastric emptying. However, not all fibers have the same effect, as some (guar gum in semi-solid form) have induced conflicting outcomes depending on the form of administration [18–20].

*Constipation.* Nondigested CH increase the stool weight and volume by the physical presence of dietary fiber itself; the hydrophilic effect of the fibers; the increase in gel formation and absorption, and also by the increase in the bacterial mass by fermentation. A systemic review and meta-analysis showed that fiber-enriched diets reduce the incidence of constipation in healthy volunteers and in acute-care settings [2, 21].

*Diarrhea.* Soluble fiber has shown to reduce the incidence of diarrhea by slowing the intestinal transit time and also probably by increasing the
bioavailability and absorption of zinc (zinc is known to reduce the incidence and duration of diarrhea). An earlier meta-analysis did show a reduction in the incidence of diarrhea in hospitalized patients [21, 22].

**Prebiotics and Microflora.** Prebiotics (e.g. FOS, oligofructose and inulin) stimulate the growth of *Bifidobacterium* and *Lactobacillus* species. These bacterial species stimulate fermentation and production of SCFA in addition to inhibiting the growth of pathogenic bacteria (e.g. clostridia). They are also known to produce B vitamins (by bifidobacterial species) and improve bone health by increasing the absorption of minerals [23]. Whelan et al. [24] reported significant increases in bifidobacterial species and SCFA following fiber supplementation.

*Inflammatory Bowel Disease.* It has been proposed that a high-sugar diet and a low-fiber diet are associated with the development of inflammatory bowel disease, but this hypothesis has not been proven [25, 26]. However, a diet rich in hemicelluloses (30 g daily) and glutamine decreased the severity of mild-to-moderate active ulcerative colitis [27]. In a multicenter trial, butyrate enema was shown to reduce inflammation in the distal colon when combined with 5-amino salicylic acid in refractory ulcerative colitis [28].

**Irritable Bowel Syndrome.** The etiology of irritable bowel syndrome is still not clear. Prebiotics, which induce a selective change in microbial species [29] (with or without soluble fibers) may be beneficial in irritable bowel syndrome [30].

**Gastrointestinal Cancer.** DF have a preventive role. The mechanisms depend on the site. In the esophagus and stomach, DF reduce the cancer incidence by their scavenging actions [31]. In the colon, DF sequester potential carcinogens and bile acids, and also increase transit time [32].

**Systemic Benefits**

**Appetite and Satiety.** The presence of a fiber-rich meal in the stomach reduces its motility and induces a sense of satiation, and results in a reduction in the rate of macronutrient delivery to the small intestine. This may have an indirect effect on appetite [18].

**Weight Control.** Body weight results from a complex interplay of many factors. Low-digestible and nondigestible CH have a low density of energy and the potential to prevent weight gain. Previous studies have shown that a diet rich in fibers is associated with a low body weight [33].

**Glycemic Control.** The viscous and gelling nature of soluble fibers results in lower postprandial glucose levels. Insoluble fibers also have an effect on the glycemic status via enhanced insulin sensitivity. The exact mechanism is unclear but may be due to its effect on gut microbiota. A fiber-rich diet reduces
Gram-negative bacteria in the intestines, and experiments have been shown that insulin resistance develops following daily injections of Gram-negative bacterial lipopolysaccharide [34]. A meta-analysis showed a 21% reduction in the development of diabetes with whole-grain consumption [35].

Hyperlipidemia. Soluble fibers reduce total and LDL cholesterol by increasing the fecal loss of bile acids without any alteration in high-density lipoprotein or triglycerides [14]. A meta-analysis has shown a reduction in LDL of 6–15% by DF [36].

Cardiovascular Disease. DF have shown to be beneficial in the prevention and control of hypertension. Probable mechanisms include improvements in hyperinsulinemia and insulin resistance, and a beneficial effect on body weight. This has been confirmed in a meta-analysis [37]. DF also contain biologically active compounds such as phytochemicals and antioxidants, in addition to other natural constituents of fibers, which might contribute to an overall reduction in cardiovascular diseases [38, 39].

Concluding Remarks

Digestible CH are the major source of calories. However, CH also contain low-digestible and nondigestible constituents, which are part of a healthy diet. Physiological effects are varied and depend on the site of the gastrointestinal tract, as well as on the physical and chemical composition of the fiber. They reduce gastric emptying and small bowel transit time, and, by inhibiting the actions of pancreatic and other digestive enzymes, they have a positive effect on the metabolism. By their fermentation effect, they aid in the production of SCFA, which has numerous benefits, e.g. in the absorption of minerals. The various mechanisms of action result in numerous gastrointestinal benefits like managing constipation and diarrhea, and having a prebiotic effect, which results in a change in the composition of gut microflora. They are useful in managing inflammatory bowel disease and irritable bowel syndrome as well as in reducing the incidence of certain colon cancers. The systemic benefits include maintaining a healthy weight, helping in achieving glycemic control and reducing hyperlipidemia, which result in decreased incidence rates of atherosclerosis, stroke and cardiovascular diseases.

Disclosure Statement

None.
References

5. AACC Board holds midyear meeting. Cereal Foods World 2000;45:325.
The Biological Value of Protein

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Abstract
The biological value of a protein extends beyond its amino-acid composition and digestibility, and can be influenced by additional factors in a tissue-specific manner. In healthy individuals, the slow appearance of dietary amino acids in the portal vein and subsequently in the systemic circulation in response to bolus protein ingestion improves nitrogen retention and decreases urea production. This is promoted by slow absorption when only protein is ingested (e.g. casein). When a full meal is ingested, whey achieves slightly better nitrogen retention than soy or casein, which is very likely achieved by its high content of essential amino acids (especially leucine). Elderly people exhibit ‘anabolic resistance’ implying that more protein is required to reach maximal rates of muscle protein synthesis compared to young individuals. Protein utilization in inflammatory or traumatic conditions increases substantially in the splanchnic tissues containing most of the immune system, and in wounds and growing tissues. This happens especially in the elderly, which often suffer from chronic inflammatory activity due to disease, physical inactivity and/or the aging process itself. Consequently, the proportion of protein absorbed in the gut and utilized for muscle protein synthesis decreases in these situations. This compromises dietary-protein-induced stimulation of muscle protein synthesis and ultimately results in increased requirements of protein (~1.2 g/kg body weight/day) to limit gradual muscle loss with age. To optimally preserve muscle mass, physical exercise is required. Exercise has both direct effects on muscle mass and health, and indirect effects by increasing the utilization of dietary protein (especially whey) to enhance rates of muscle protein synthesis.

Introduction
There is still much debate regarding the daily requirements of protein, and consensus conferences have yielded varying results. A general recommendation is to include 0.8 g of protein per kilogram of body weight in adults per day in the
diet, although recent reevaluation of protein requirements with stable isotopes (as compared to the nitrogen balance methodology) suggests that this recommendation is an underestimate [1, 2]. The criticisms regarding the old recommendations are based on the observation that with increasing protein intake, a positive nitrogen balance is generally overestimated leading to an underestimation of protein requirements, which should therefore be 20–30% higher than has been believed. Similarly, defining the biological value of a protein has been subject to long-term debate. One of the problems of proteins is that their actual absorption and incorporation into body proteins has been claimed to be subject to error because it cannot be excluded that amino nitrogen is lost in the stools or metabolized by the bacterial flora. Moreover, the way in which protein quality is scored is an additional point of debate [3] as the biological effect of different proteins in different tissues of the body (e.g. skeletal muscle) is not always consistent despite apparently equivalent biological values [4]. Requirements in absolute numbers/weight/day have generally been defined without taking the different factors that may influence these requirements into account. In part, this is understandable, because this practice has been applied to deliver clear messages to the (political) community regarding protein requirements on a population basis.

Some factors that can influence requirements include the total composition of the protein-containing meal, the specific protein included, the rate of absorption of the protein as amino acids or oligopeptides, their use for incorporation into body proteins, the distribution of the meals, physical activity, the influence of aging and disease, the role of specific amino acids and the presence of growth factors in dietary protein.

The primary purpose of this chapter is to highlight the influence that some of these factors have on muscular mass and function, and to recommend dietary practices to optimize protein accrual and fitness.

**Biological Value of Proteins**

The biological value of a protein has traditionally been defined on the basis of its amino-acid content in relation to human requirements and the suitability for digestion, absorption and incorporation into body proteins. Much debate regarding the method to be used revolves around the question of how much of the protein is actually absorbed as intact amino acids and utilized for the synthesis of protein, bases of nucleotides and other less abundant products. The focus of this debate has especially been to arrive at recommendations for daily protein requirements independent of other factors that may contribute to adequate
utilization of dietary protein. The role of energy in the meal, amounts and amino acid composition of protein, meal distribution over the day and effects of physical activity are important factors determining protein requirements. Moreover, the biological end point and potential tissue of interest (e.g. whole-body protein vs. muscle protein) should be considered when evaluating the biological value or ‘quality’ of a protein for a given population.

Absorption of Protein and Nitrogen Retention

It is well known that the inclusion of oxidizable fuel to a protein meal promotes nitrogen retention. Carbohydrates specifically promote net protein synthesis at the whole-body level (especially when assessed through nitrogen metabolism) primarily due to a reduction in whole-body protein breakdown. Meals completely devoid of glucose need gluconeogenesis from amino acids and to a lesser extent from glycerol to furnish the necessary glucose, which is required for maintenance of the redox state and synthesis of cell elements like membranes, bases, ribose and matrix. Consequently, a meal without carbohydrates but adequate in (fat) calories and protein promotes less nitrogen retention than a meal containing carbohydrate and protein [5]. This is even truer when cell proliferation is stimulated in inflammatory states or in states of growth. In a study in multicatheterized pigs, we found that the addition of maltodextrin to a protein meal diminished urea production compared to pigs only receiving protein [5]. Simultaneously, it was shown that amino acids appeared less abundantly in the portal vein when carbohydrates where added to the meal but that appearance was more prolonged, whereas the area under the curve (representing total uptake of protein-derived amino acids) was similar in both groups. Explanations for these findings include a slower absorption when maltodextrin was added or temporary retention of amino acids in the gut lumen as bacterial protein or inside the portal-drained viscera as rapidly turning over protein [5]. These rapidly turning over proteins should then be synthesized after mucosal absorption of amino acids after digestion of meal-derived protein. It is to our knowledge not precisely established if (and to what extent) dietary-protein-derived oligopeptides are released in the portal vein.

In another in vivo pig experiment, the absorption kinetics of different proteins were studied. Casein-derived amino-acid appearance in the portal vein proved to be less pronounced but more protracted than soy-protein-derived amino acids, which was associated with a greater nitrogen retention [6]. Comparable findings were reported by another group in human studies employing $^{13}$C-leucine-labeled cow’s milk, showing that whey-protein-derived amino acids
were absorbed faster than casein but that whole-body nonoxidative leucine retention (a surrogate marker of protein synthesis that represents the net sum of all anabolic protein pathways in the body, such as splanchnic, kidney, muscle and circulatory) was lower in the whey group than in the casein group in healthy young men [7]. Appearance of the labeled leucine was slower and more protracted in the casein group, and faster and of shorter duration in the whey group. One explanation of these findings may consist of the casein flocculating in the stomach leading to slower gastric emptying and digestion. This is supported by the finding that ingestion of an amino-acid mixture, reflecting the composition of a specific protein, achieves a much lower whole-body postprandial protein balance than with the intact protein [8]. Nitrogen retention at the whole-body level with ingested whey protein improved, however, when the protein was either administered over time using small boluses or when additional macronutrients (i.e. carbohydrates and fat) were included in the meal [9].

A third observation highlighting the importance of the kinetics of protein absorption is the effect of blood in the digestive tract on the appearance of amino acids in the portal vein. A presumed gastric bleed of 1 liter blood of normal composition delivers an estimated 220 g of protein into the gut (150 g of hemoglobin and 70 g of plasma proteins). This protein is severely deficient in isoleucine because hemoglobin contains no isoleucine and the albumin molecule only 1 molecule of isoleucine. Globulins contain modest amounts of isoleucine. Ingestion of blood in a pig model showed rapid appearance of amino acids in the portal vein, which decreased when isoleucine was simultaneously infused. Urea production also decreased with isoleucine infusion. In humans, a pseudo-bleed (ingesting an amino-acid mixture mimicking the composition of blood) showed diminished peripheral protein synthesis in volunteers [10]. With isoleucine supplementation, appearance of amino nitrogen in the portal vein was slower and more prolonged [10]. This may be explained by improved protein synthesis and temporary retention in the intestine achieved by a more balanced amino-acid mixture. In later years, this phenomenon is called the first-pass effect of a meal. Depending on the tracers used mostly in human studies or on multicatheterized animal models, first-pass effects have been found to be located in the total splanchnic area in human studies and in the intestine and liver separately in animal studies.

A final possibility to improve nitrogen retention is to change the habitual practice in many Western countries of having three meals that typically differ in protein quantity and composition (i.e. the majority of daily protein consumed in the evening meal) over a 12-hour fed period followed by 12 h of fasting. It has been suggested that this practice may render protein retention less efficient than when meals would be of equal size and evenly distributed over the day [11].
In conclusion, in healthy young volunteers and pigs, whole-body nitrogen retention is promoted after a meal only containing protein when appearance of amino acids in the portal vein is tapered. This nitrogen retention may be enhanced by such factors as: (i) including carbohydrate in the meal; (ii) optimizing the amino-acid composition of the protein; (iii) including more slowly digested proteins such as casein as compared to soy or whey; (iv) spreading ingestion of meals over time, and/or (v) ingesting full proteins rather than free amino acids. However, it should be noted that whole-body nitrogen retention of whey as part of a complete meal (i.e. containing carbohydrates) is similar or slightly higher than with a casein-containing meal [12].

Protein Ingestion and Muscle Protein Synthesis in Healthy Volunteers

Despite the improvement in in vivo nitrogen sparing at the whole-body level obtained with isolated casein versus soy or whey protein ingestion (i.e. ingested without other meal constituents), the fractional protein synthesis rate in muscles in young volunteers is highest with whey and lowest with casein [13]. These results do not appear to be in line with the earlier reported improved benefit of casein in comparison with whey in in vivo experiments when measured at the whole-body level. This may be explained by the fact that whole-body protein kinetics, which represent an average response of all proteins in the body, do not necessarily reflect what occurs within muscles. Moreover, the high essential amino-acid content of whey (specifically leucine, which promotes muscle protein synthesis more than any other amino acid) and its rapid absorption rate appears to be an important factor for its greater muscle anabolic effect [13]. However, the interpretation of these findings should be tempered as the technique used did not include assessment of protein degradation and because the limited time frame (i.e. 3 h) precludes the assessment of what could happen in the postprandial period. This is highlighted by a study in which different proteins or amino-acid mixtures were administered and $^{13}$C-leucine kinetics were assessed. A rapidly absorbed protein (whey) or an amino-acid mixture led to a greater increase in circulating leucine levels, fractional synthesis rate (FSR) of mixed muscular protein and leucine retention compared with the proteins that are slowly absorbed (casein or whey given in small boluses spread over time) in the first hours [9, 13]. In contrast, whole body net protein balance was more sustained with the slowly absorbed groups, which exhibited after 7 h a greater protein gain than with rapidly absorbed whey or amino-acid mixtures [9]. Ingestion of 6.7 g of essential amino acids containing either 1.7 g (26%) or 2.8 g (41%) leucine in young volunteers stimulated FSR of mixed muscle protein similarly, but only the mix
with a higher leucine content increased FSR in the elderly [8]. A supplement containing carbohydrates and amino acids increased phenylalanine uptake to a greater degree within the 2 h after resistance exercise than when carbohydrates or amino acids were administered alone [14]. As outlined earlier, these findings do not convincingly prove that such supplements should be routinely administered to increase muscle mass and fitness in the elderly. However, the combined results of studies with different designs support the view that elderly people maintain better muscle mass and function when protein intake is augmented to 90 g/day (1.2–1.5 g/kg/day) [15, 16].

Protein Ingestion and Muscle Protein Synthesis in the Elderly

The first-pass extraction in the intestine and the total splanchnic area (portal-drained tissues and liver) is well established, and it is generally accepted that more meal-derived amino acids are retained in the splanchnic tissue in ‘healthy’ elderly than in healthy young volunteers [17, 18]. ‘First-pass extraction’ may, however, be a misnomer because it is not conceivable that a substantial part of the amino acids derived from protein digestion and absorption, and appearing in the portal vein will be completely and instantaneously taken up in a first pass by the splanchnic tissues and utilized for synthetic purposes. It is more likely that the ratio between the utilization rates of amino acids in central and peripheral tissues shifts to the central tissues operative in host response in the elderly, regardless of whether they entered initially enterally or parenterally. It has been well established that in ‘stress’ situations there is an amino acid and (indirectly via the liver) glucose flux from peripheral tissues to central tissues and wounded area, serving as substrates for host response, including protein synthesis (collagen, acute-phase, wound and cellular proteins) and synthesis of RNA, DNA and cell membranes (see paper by Soeters [this vol., pp. 17–26]). Simultaneously, inflammatory illnesses lasting longer than a few days and even moderate-sized (surgical) trauma causes an inevitable and visible loss of muscle mass. Therefore, the different utilization of enterally ingested protein in the elderly compared with the younger volunteers supports the view that aging all by itself is an inflammatory condition influencing metabolism possibly even in the rare cases in which truly elderly people have no evident morbidity. It should be pointed out though that inactivity (even something as ‘benign’ as a reduction in daily step counts for 2 weeks) induces anabolic resistance of muscle protein synthesis, decreases muscle mass and increases markers of chronic low-grade inflammation in otherwise healthy older adults [19]. Therefore, physical (in)activity may have a greater
bearing on ‘biological’ age and its associated negative sequelae than merely the ‘chronological’ age of an individual. It reflects a continuous low-grade host response in the immune system, including the intestine and liver, leading to rapid turnover of proteins and cell elements in that area. In the elderly, a higher percentage of the meal would therefore be utilized for this purpose than in the younger population, being healthier and less subject to continuous inflammatory stress. This has been suggested to be an important cause for the gradual loss of muscle mass (sarcopenia) occurring on a population basis after the age of 30 years.

The typical generation of cytokines, hormones and other modulators that steer the inflammatory response also contribute to muscle loss, which is therefore partly inevitable. Support for this view comes from efforts to inhibit peripheral protein loss by treating intensive-care patients with growth hormone [20]. Growth hormone had been proven to limit nitrogen losses after trauma and burn injuries [21, 22] but at the same time to increase the number of infectious complications and mortality [20]. It therefore supports the view that peripheral tissues should change their metabolism to furnish substrate for the ‘central’ immune response and tissue healing (see chapter paper by Soeters [this vol., pp. 17–26]). Apparently, in this process, peripheral tissues become catabolic. Although beneficial in the short term, in the presence of severe long-standing trauma or disease, this arrangement will lead to such a degree of peripheral protein (muscle) loss that patients cannot survive the event. It is therefore important to understand the kinetics of this response and to find ways to limit nitrogen losses without interfering with their benefit. Evidence will be presented that protein intake and exercise can limit whole-body protein loss in aging and possibly in chronic inflammatory disease.

A decade ago, it was found that whole-body leucine balance (a surrogate measure of protein balance) was greater with an isonitrogenous quantity of whey protein compared to casein in both young and older adults when consumed in a mixed meal [12]. These findings at the whole-body level would generally be in line with the greater fractional synthesis of muscle protein in older adults observed with whey as compared to hydrolyzed and micellar casein, which leads to the suggestion that the digestion rate and peak plasma leucine concentration (whey > hydrolyzed casein > micellar casein) is important to consider when targeting muscle protein remodeling with age [23]. In earlier studies, it was found that splanchnic extraction of leucine after a meal in elderly volunteers was approximately double the extraction compared with young volunteers [17]. The percentage of the leucine ingested that was metabolized in the splanchnic tissues decreased with increased plasma leucine levels but the absolute amount retained may have been similar [17]. It was suggested that a higher splanchnic extraction
of leucine might lead to lower availability of protein in peripheral (muscle) tissues. This implies that the proportion of the meal utilized in the splanchnic region, wound area and immune system increases with decreasing protein intake, in this way leading to a diminished availability of amino acids for peripheral (largely muscle) tissues. However, it has been suggested on the basis of a subsequent study that the delivery of amino acids to muscle is consistent despite a greater splanchnic extraction\[18\]. True or not, it is indisputable that aging is generally associated with morbidity and that the immune system, liver, spleen and inflammatory areas exhibit net protein gain whereas peripheral tissues (predominantly muscles) exhibit net protein loss. In view of these contradictory findings, the kinetics leading to the clinical findings earlier mentioned require further investigation.

Notwithstanding the difficulty to obtain a clear picture on the basis of the type of studies referred to, clinical observation learns that any critically ill patient will lose total body protein. This mainly applies to muscle protein, skin and bone, whereas there is clear evidence that simultaneously anastomoses heal, skin defects are epithelialized, immune cells proliferate and the liver accumulates and produces several types of protein operative in host response. Although never studied in a prospective manner, it is likely that intake of meals containing increased amounts of protein (1.5 g/kg body weight/24 h) limits but does not totally inhibit these protein losses in critically ill patients [24–27]. None of these investigations prospectively studied different protein intakes nor their potential effects on muscle protein gain, which arguably weakens the conclusion that increased protein intake is beneficial. If we accept that aging is associated with low-grade inflammatory activity in a similar but less severe manner compared to critical illness, one of the causes of sarcopenia may be chronic inflammation leading to catabolic but probably beneficial muscle metabolism, occurring despite increasing protein intake.

The ‘anabolic resistance’ of aging mentioned earlier therefore implies that higher doses of amino acids have to be administered to achieve maximal rates of myofibrillar (i.e. contractile) and sarcoplasmic (i.e. noncontractile cellular proteins) protein synthesis, which may [28] or may not [29] reach the same relative levels as in young volunteers. This may be associated with decreased intramuscular expression and/or activation (phosphorylation) of amino-acid-sensing/signaling proteins [29] induced by low-grade inflammation in most elderly people. ‘Anabolic resistance’ may be a misnomer when after a meal more amino acids are utilized in the splanchnic area leading to a decrease in the amount of amino acids available for muscle protein synthesis and when the same muscle FSR can be reached as in younger people when more amino acids are ingested in the elderly.
Inactivity (in the form of immobilization) also has been associated with ‘anabolic resistance’ of muscle protein after ingestion of essential amino acids in both young and older adults [30]. However, recent evidence suggests that even a moderate reduction in habitual physical activity is associated with ‘anabolic resistance’ in skeletal muscle and a marked reduction in lean mass in as little as 2 weeks in otherwise healthy older adults [31]. In contrast, exercise or substantial daily activities can enhance the sensitivity of skeletal muscle to dietary protein. Support for beneficial effects of increasing protein content of the diet in the elderly comes from an observational study in which daily protein intake varied between 54 and 90 g/day [32]. Loss of lean body mass at the 3-year follow-up was (very modestly) diminished in the quintile with the highest protein intake [32]. On the basis of these and other similar studies, it has been concluded that protein requirements in the elderly may be 20–40% higher than in young people, but that additional research employing modern methods has to definitively establish protein requirements [33]. In a very recent epidemiological study, controversy exists regarding the current recommended dietary allowance in young people. A high protein intake was associated with a higher all-cause mortality and mortality from cancer in young people whereas all-cause mortality and mortality from cancer decreased above the age of 65 year [34].

**Protein and Amino-Acid Ingestion and Muscle Metabolism in Exercise**

Whey hydrolysate has been shown to stimulate the synthesis of mixed muscle protein to a greater degree than soy and casein when given to young individuals in the resting state [13]. Exercise increases the muscle protein synthesis rates after ingestion of these proteins [13, 35]. In healthy elderly men, ingestion of isolated whey protein supports greater rates of muscle protein synthesis than micellar casein both at rest and after resistance exercise [36]. These results are probably related to higher arterial plasma amino-acid or leucine levels with whey ingestion, resulting from rapid absorption and the high content of essential amino acids (specifically leucine) of whey [36]. Rapid aminoacidemia after exercise enhances muscle protein synthesis and the activation (estimated via changes in the phosphorylation status) of anabolic signaling molecules that regulate mRNA translation to a greater extent than an identical amount of whey protein fed in small pulses that mimic a more slowly digested protein in young men [37]. This occurred despite the area under the curve of aminoacidemia being similar after bolus or pulse feeding [37]. It appears that a pronounced peak aminoacidemia after exercise enhances muscle protein synthesis in young and elderly subjects. Essential amino acids stimulate myofibrillar protein synthesis. Leucine has been
claimed to have the strongest promoting effects on muscle protein synthesis of all amino acids. In young men, ingestion of 6.25 g of whey supplemented with leucine or a mixture of essential amino acids deficient in leucine stimulated myofibrillar protein synthesis to a similar degree as 25 g of whey in the resting condition, but after exercise this stimulation is only sustained over a longer time period after administration of whey [38]. Mixed muscle protein synthesis at rest and after resistance exercise was similar whether carbohydrates were added or not to a bolus ingestion of whey protein [39]. This is in contrast with another study in which addition of glucose to amino acids augmented the net protein balance (i.e. difference between protein synthesis and protein breakdown) of skeletal muscles 2 and 3 h after resistance exercise [14].

The interpretation of acute measurement of the FSR of muscle after different types of intervention is uncertain because protein degradation is not assessed and the extension of the short duration of the experimental setup to long-term effects may be questioned. However, acute (i.e. ∼3 h) measures of muscle protein synthesis and net protein balance across the leg after exercise and nutrition are rather precisely predicting 24-hour response [40], and may qualitatively predict training outcomes such as muscle hypertrophy and lean mass growth [41]. However, long-term training studies provide more insight in the benefit of protein supplementation on muscle mass and strength. Although resistance training unequivocally increases muscle mass and strength independent of age, a recent meta-analysis concluded that protein supplementation can augment these adaptations in both young and older adults [42]. Additional studies are required to fully elucidate the role that protein type and timing (e.g. when it is consumed in relation to an exercisebout) may have on enhancing training outcomes, especially in older adults, as these outcomes may influence adaptive responses in young adults but were not explicitly covered in the meta-analytical approach.

**Concluding Remarks**

The biological value of protein is dependent on many factors and is arguably related to the specific biological effect and/or tissue of interest. On the basis of the referred literature, whey may be considered to have a high biological value, which is consistent with its high rating on a variety of different scoring systems (e.g. biological value and protein digestibility-corrected amino-acid score). The high absorption rate and content of essential amino acids of whey make it especially suitable for the elderly population who typically present with an ‘anabolic resistance’ to dietary protein, which may be mediated partly by a greater
splanchnic protein turnover that is necessary in host response, and partly by hor-
mones and cytokines steering the inflammatory response. This includes changes
in muscle metabolism producing a substrate mix suitable for the synthesis of
biomass, immune cells and for the regulation of redox balance (see paper by
Soeters [this vol., pp. 17–26]). This effect may also apply to situations of trauma
and illness. However, from a standpoint of skeletal muscle, the ‘anabolic resis-
tance’ of exercise may be mediated by a lack of activity independent of age, which
positions physical activity as being of primary importance to improve the sensi-
tivity of muscle to dietary protein. Moreover, exercise or other forms of substan-
tial physical activity are required to promote protein gain and maintain and/or
enhance muscle function with dietary protein enhancing these adaptations.

Although the biological value of casein and soy is slightly inferior to whey,
these are still good and acceptable proteins that are generally ‘made better’ (from
a muscle standpoint) by prior contractile activity [13]. Aside from the protein
source, spreading meals of equal size and composition over the day may opti-
mize protein utilization. A recommended daily allowance of protein of 0.8 g/kg
body weight/day has been proposed in the adult population (or an estimated
0.9–1.0 g/kg ideal body weight/day) which recently has been disputed to be an
underestimation and that the recommended daily allowance should be 20–30%
higher. Athletes, elderly and critically ill individuals may require 1.5–2 g/kg ide-
al body weight/day. Ultimately, dietary protein is essential for optimal health
and well-being given its integral role in lean tissue remodeling and immune sur-
veillance. Therefore, not only the absolute amount but also the quality of protein
and the presence of other (macro)nutrients in the meal should be considered
when determining the optimal nutrition for a variety of life conditions.

Disclosure Statement

The authors have no conflict of interest to disclose.

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Abstract
Oral and enteral nutrition affects both the anatomical and physiological integrity of the gastrointestinal tract. It downregulates systemic immune response, reduces overall oxidative stress and limits systemic inflammatory responses. It reduces bacterial translocation, limits pathogenic bacteria in the intestines and enables the production of short-chain fatty acids in the colon. Therefore, it is the most physiologic way of providing nutritional support in all patients. The enteral formulas are available as polymeric, semi-elemental and elemental diets. The beneficial effects on the gastrointestinal tract and systemic organs of ‘early’ enteral nutrition depend on the timing, dose, location and different modalities of enteral delivery. Being familiar with the basic tenets of providing enteral nutrition – the ‘Who, Why, When, Where and What’ – will result in safe nutritional interventions and achieve a positive clinical outcome.

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Introduction
Oral and enteral nutrition (EN) is a physiologic way and an effective means of providing nutritional support and nutritional intervention in all malnourished patients, including perioperative and critically ill patients. Enteral formulas are
available as polymeric (containing whole protein, carbohydrates and fats), semi-
 elemental (containing proteins in the form of small di- and tripeptides, and fats
 in the form of medium chain triglycerides) and elemental (proteins in the form
 of free amino acids) diets. This article gives an overview of the 5Ws of EN –

**Definition of Enteral Nutrition**

According to ASPEN (American Society of Parenteral and Enteral Nutrition),
EN is the provision of nutrients via the gastrointestinal tract (through a feeding
tube, catheter or stoma) and is the preferred route in patients who cannot meet
their nutritional needs through voluntary oral intake [1].

According to ESPEN (European Society for Parenteral and Enteral Nutri-
tion), EN includes oral nutritional supplements as well as tube feeding via naso-
gastric, nasoenteral or percutaneous tubes [2].

**Whom to Feed**

Indications [3]:
(1) In persons with functional gastrointestinal tract in whom oral intake is
impossible, inadequate or unsafe
(2) In malnourished patients and those who are at high risk of developing
malnutrition
(3) In individuals with poor appetite associated with a chronic medical con-
dition
(4) In patients with impaired swallowing function (neurological diseases/
oropharyngeal dysfunction)
(5) In patients with major trauma, burns, wounds and in the malnourished
preoperative patient
(6) In critically ill patients (who are not able to meet their metabolic de-
mands) and those on mechanical ventilation

Contraindications [3]:
(1) Gastrointestinal failure, inflammation and severe postoperative stasis
(2) Complete intestinal obstruction
(3) High-output intestinal fistula
(4) Inability to access the gut: severe burns/multiple trauma
(5) Presence of shock
(6) Hyperlactatemia (>3 mmol/l)
(7) Hypoxia (paO$_2$ <50 mm Hg)
(8) Hypercapnia (pCO$_2$ >75 mm Hg)
(9) Severe acidosis (pH <7.2)

**Why to Feed**

As soon as enteral feeding is commenced, the resultant intestinal responses have a beneficial effect both on the intestines as well as systemic effects [4]. These can be summarized as follows:

- Stimulates intestinal contraction and initiates peristalsis
- Releases trophic substances (digestive enzymes and intestinal hormones) which maintain the enterocytes of the gastrointestinal tract
- Increases the blood flow to the intestinal tract soon after commencing the feeds, which supports the mucosa-associated lymphoid tissue
- Increases IgA production in response to the antigen associated with the feeds. IgA coats the microorganisms and prevents their adherence; it also proliferates and migrates via the systemic circulation to the lungs, liver and kidneys
- Increases the processing of naïve CD4 cells (due to the antigenic stimulus) and these lymphocytes are incorporated in the gut-associated lymphoid tissue. In turn, these lymphocytes gain access to the systemic circulation and are incorporated in the mucosa-associated lymphoid tissue at different sites (lungs, liver and kidneys). Feeding also generates CD4 cells towards the Th2 pathway, resulting in a systemic anti-inflammatory effect
- Feeding also promotes the role of commensal bacteria and also reduces the colonization of pathogenic bacteria and their toxins. In addition, the constituents of the diet promote the production of short-chain fatty acids, which act as fuel to the colonocytes and also result in antioxidant and anti-inflammatory effects

**When to Feed**

EN should commence [5, 6]:

1. Within 12–24 h of an acute event (operation/trauma)
2. After stabilization of vital functions (e.g. hemodynamics/volume status)
3. After resuscitation
What to Feed

There are various types of commercially available EN supplements available in either ready-to-use, liquid or powdered form, which has to be reconstituted. They provide from 1.0 up to 2.0 kcal/ml; their pH ranges from 5.5 to 7.0 and their osmolality from 300 to 600 mosm/l (table 1).

These supplements are available as whole protein (with or without fiber), modified protein, e.g. semi-elemental (di-/tripeptides) and elemental, and disease-specific formulations, such as formulations for patients with respiratory (altered carbohydrate:fat ratio), renal (low in proteins and electrolytes for predialytic patients and protein-rich feeds for patients on dialysis), cardiac (low in sodium) and hepatic diseases (rich in branched-chain amino acids, and low in standard amino acids and electrolytes), diabetes (low in carbohydrates and rich in monounsaturated fatty acids), milk intolerance (soy-based) and for those with HIV/AIDS (modified fat/peptides), for example, and as immunonutrition (rich in arginine, fish oil and nucleotides, which are useful for patients in the perioperative period and with metabolic stress and impaired immunity).

Polymeric feeds are available as standard, high-protein, energy-dense and high-fiber supplements. Standard polymeric feeds have the standard distribution of macronutrients and are for those with a normal gastrointestinal function.

(4) After assessment
(5) After planning
(6) After confirming the position of the respective tubes
High-protein supplements have a protein content of 15% or more of the total energy and are useful in various catabolic states and for wound healing. Energy-dense formulations provide 2.0 kcal/ml and are useful in those with fluid-restricted intake and with dyselectrolytemia. High-fiber supplements with a fiber content of 5–15 g/l are helpful in bowel dysfunction.

Oligomeric enteral formulations are either partially hydrolyzed or peptide based. Monomeric supplements contain free amino acids like glutamine or arginine. Both of these formulations are useful in patients with malabsorption and maldigestion.

The choice of feeds depends on the patient’s condition, availability, local practices and preferences.

**Where to Feed**

The standard routes are oral and through enteral tubes: nasogastric, nasoenteric percutaneous endoscopic gastrostomy (PEG, PEG-J tubes) and feeding jejunostomy (FJ) tubes.

The oral route is preferred in patients who can swallow safely. Nasogastric/nasojejunal tubes can be used for feeding up to 4 weeks, and those requiring long-term feeds will need a PEG, PEG-J or an FJ tube.

Patients can be fed safely, either by gastric or a postpyloric tube placement. A recent meta-analysis has not shown any significant difference in the incidence of aspiration, new-onset pneumonia or mortality. However, postpyloric feeding has shown a decrease in gastric residual volumes and an increase in energy delivery. In patients with severe gastroparesis or acute necrotizing pancreatitis, postpyloric feeding has been shown to be beneficial. Standard protocols should be followed when gastric residual volumes exceed 400 ml, and prokinetic agents might be helpful.

**Enteral Nutrition Protocols [5]**

EN protocols are depicted in figure 1.

- Commence EN in patients who are unable to eat voluntarily
- Commence within 24–48 h
- Withhold EN in patients with severe hemodynamic instability
- Neither presence or absence bowel sounds, nor passage of flatus or stools are necessary to start EN
- Either gastric or small bowel feeds are acceptable
- Determine the target goal at the time of EN initiation
**Is oral nutrition possible within 24 h?**

- **Yes**
  - Diet and/or ONS (250 kcal, 20 g protein)

- **No**
  - Initiation of tube feeds (within 24 h)
    - **Yes**
      - Initial ‘trickle feeds’ (10 ml/h), if:
        - Hemodynamically stable
        - Head-end elevated at 30°
        - Residual volume <250 ml
        - Determine target energy, increase progressively
    - **No**
      - Relative contraindications: Enterocutaneous fistula
      - Absolute contraindications: Acute abdomen (e.g. intestinal ischemia or perforation)
      - Trickle feeds (?)
      - Jejunal feeds (?)
      - Parenteral nutrition

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**Fig. 1. EN protocols. ONS = Oral nutritional supplements.**

- Provide >50–65% calories to achieve clinical benefits over the 1st week
- In critically ill, obese patients, permissive underfeeding is recommended
- Protocols for monitoring and to advance feeds should be adhered to
- All patients should be assessed for the risk of aspiration
- Immune-modulating diets are appropriate for most patients; apply caution in patients with severe sepsis
- Antioxidants, vitamins and trace minerals should be provided to all
- Glutamine should be considered in burn, trauma and mixed intensive care unit patients

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**Conclusion**

Early EN affects both the anatomical and physiological integrity of the gastrointestinal tract. It downregulates systemic immune responses, reduces overall oxidative stress and limits the systemic inflammatory response syndrome. These
benefits alter the course of the patient’s disease significantly. The timing, dose, different aspects of delivery, and their local and systemic effects determine whether the patient benefits from EN. Being familiar with the basic tenets of nutrition intervention is the best way to achieve a positive clinical outcome.

**Disclosure Statement**

None.

**References**


**Further Reading**


Management of the Metabolic Syndrome and the Obese Patient with Metabolic Disturbances: South Asian Perspective

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Abstract

There is an increased prevalence of obesity and the metabolic syndrome (MS) among South Asians. The phenotypes of obesity and body fat distribution are different in South Asians; they have high body fat, intra-abdominal and subcutaneous fat and fatty liver at a lower body mass index compared to white Caucasians; this has led to the frequent occurrence of morbidities related to a higher magnitude of adiposity [e.g. type 2 diabetes mellitus (T2DM), hypertension (HTN) and dyslipidemia]. The increasing prevalence of obesity and related diseases in the South Asian population requires aggressive lifestyle management including diet, physical activity and, sometimes, drugs. For therapeutic interventions, several drugs can be used either as mono- or combination therapy. Drugs like orlistat, which is used for the management of obesity, also reduce the risk of T2DM. Similarly, HMG CoA reductase inhibitors decrease low-density-lipoprotein cholesterol levels and reduce the risk of cardiovascular diseases. However, some drugs used for the treatment of HTN (e.g. β-blockers) may increase the risk of hyperglycemia and therefore need to be used with caution. Finally, to prevent obesity, MS and T2DM among South Asians, it is particularly important to effectively implement and strengthen population-based primary prevention strategies.

Introduction

A rapid increase in obesity and related noncommunicable diseases, including type 2 diabetes mellitus (T2DM), hypertension (HTN), dyslipidemia and cardiovascular diseases (CVD), is occurring in South Asian countries. Insulin
resistance and clustering of proatherogenic, cardiovascular risk factors, also known as the metabolic syndrome (MS), are frequently seen in South Asians, even at a young age [1].

Increasing urbanization, rapid nutrition transition and the consequences of imbalanced nutrition combined with a sedentary lifestyle are the factors contributing to obesity. Persistent obesity dysregulates the metabolic processes, including the action of insulin on glucose, lipids and free fatty acid metabolism, causing hyperglycemia, dyslipidemia, HTN and MS. Obesity and MS are immediate precursors of T2DM and CVD [2].

The purpose of this article is to briefly review obesity and MS focusing on South Asians and then discuss the management of these patients. Literature search was carried out using the terms obesity, insulin resistance, metabolic syndrome, diabetes, dyslipidemia, hypertension, nutrition, physical activity, pharmacotherapy, Asian Indians and South Asians in PubMed from 1980 to March 2014.

Definitions

**Obesity**

Obesity is defined as an excessive accumulation of fat in the body resulting in adverse effects on health of the individual (table 1) [3]. The most widely used method to define thinness and fatness is body mass index (BMI; a ratio of weight in kilograms divided by height in meters squared). Abdominal obesity is defined by waist circumference (WC). As per the consensus statement for the diagnosis of obesity, abdominal obesity and MS for Asian Indians, both BMI and WC should be used together (using Asian Indian-specific cutoffs; table 1) with equal importance for population- and clinic-based metabolic and cardiovascular risk stratification [4]. The cutoffs as defined for Asian Indians are lower than the international criteria in view of the high body fat and occurrence of morbidities with lower BMI values compared with white Caucasians [1].

**The Metabolic Syndrome**

MS is defined as a clustering of cardiovascular risk factors in an individual which predisposes the person to a greater risk of developing T2DM and CVD. According to the consensus statement for the diagnosis of obesity, abdominal obesity and MS for Asian Indians, three out of five factors have to be abnormal for the identification of MS. It includes previously diagnosed patients with HTN, high triglycerides (TG), low high-density-lipoprotein cholesterol (HDL-c), impaired fasting glucose (IFG), impaired glucose tolerance (IGT) or T2DM, and those on
management of MS and obesity in South Asians 63
treatment for the above disorders. This definition is similar to the modified National Cholesterol Education Program, Adult Treatment Panel III definition with ethnic-specific definition of WC (table 1) [4].

**Dyslipidemia**
Dyslipidemia signifies the increased concentration of total cholesterol and low-density-lipoprotein cholesterol (LDL-c), decreased concentration of HDL-c and hypertriglyceridemia present alone or in combination. A combination of lipid abnormalities, elevated serum TG, small LDL-c particles and low HDL-c are metabolically interlinked and have been termed as ‘atherogenic dyslipidemia’ [5].

**Hypertension**
The classification of pre-HTN and HTN as per the criteria of the Seventh Report of the Joint National Committee has been provided in table 1, along with the cutoffs by consensus statement for the diagnosis of obesity, abdominal obesity and MS for Asian Indians [4, 6].

**Hyperglycemia**
Hyperglycemia covers both IFG, IGT as well as diabetes mellitus. IFG and IGT represent intermediate states of abnormal glucose regulation, termed prediabetes. The cutoffs for the diagnosis of these diseases have been explained in table 1 [7].

---

**Table 1. Defining obesity, abdominal obesity, MS, dyslipidemia, HTN and hyperglycemia in Asian Indians**

<table>
<thead>
<tr>
<th>Generalized obesitya</th>
<th>Abdominal obesitya</th>
<th>MSa</th>
<th>Dyslipidemiaa</th>
<th>HTNb</th>
<th>Hyperglycemia [7]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BMI cutoffs</strong></td>
<td><strong>WC cutoffs</strong></td>
<td></td>
<td><strong>Total cholesterol</strong></td>
<td><strong>Pre-HTN</strong></td>
<td><strong>IFG and FPG concentrations</strong></td>
</tr>
<tr>
<td>Normal 18.0–22.9</td>
<td>Men &gt;90 cm</td>
<td></td>
<td>≥200 mg/dl</td>
<td>SBP 120–139 mm Hg</td>
<td>≥100 and &lt;126 mg/dl</td>
</tr>
<tr>
<td>Overweight 23.0–24.9</td>
<td>Women &gt;80 cm</td>
<td></td>
<td>≥150 mg/dl</td>
<td>DBP 80–89 mm Hg</td>
<td>IGT</td>
</tr>
<tr>
<td>Obesity &gt;25</td>
<td>(nonobligatory)</td>
<td></td>
<td>≤100 mg/dl</td>
<td>HTN</td>
<td>Elevated 2-hour FPG</td>
</tr>
<tr>
<td></td>
<td>≥130/≥85 mm Hg</td>
<td></td>
<td>&gt;100 mg/dl</td>
<td>SBP ≥140 mm Hg</td>
<td>≥140 and &lt;200 mg/dl after</td>
</tr>
<tr>
<td></td>
<td>≥150 mg/dl</td>
<td></td>
<td>LDL-c</td>
<td>DBP ≥90 mm Hg</td>
<td>a 75-gram OGTT in the</td>
</tr>
<tr>
<td></td>
<td>HDL-c Males &lt;40 mg/dl</td>
<td></td>
<td>Males &lt;40 mg/dl</td>
<td>Consensus guidelinesa</td>
<td>presence of an FPG</td>
</tr>
<tr>
<td></td>
<td>Females &lt;50 mg/dl</td>
<td></td>
<td>Females &lt;50 mg/dl</td>
<td>SBP ≥130 mm Hg</td>
<td>concentration &lt;126 mg/dl</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>DBP ≥85 mm Hg</td>
<td>Diabetes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>FPG ≥126 mg/dl</td>
<td></td>
</tr>
</tbody>
</table>

SBP = Systolic BP; DBP = diastolic BP; FPG = fasting plasma glucose; OGTT = oral glucose tolerance test.

a As used in the consensus statement for the diagnosis of obesity, abdominal obesity and MS for Asian Indians [4, 6].

b Classification according to JNC VII (Seventh Report of the Joint National Committee) criteria [6].
Management

Therapeutic intervention may benefit persons having obesity, MS, dyslipidemia or T2DM who have an increased risk of developing CVD, with advice on exercise and diet being an essential part of all treatment plans.

Dietary Management
Rapid nutritional transition has resulted in excess consumption of calories, saturated and trans-fatty acids, simple sugars and salt, and low fiber intake in developing countries in South Asia. In combination with a sedentary lifestyle, this has led to an increase in obesity and related disorders. In the following, general guidelines are described, but they need to be tailored to the individual patient.

Energy
The energy requirements suggested are based on the activity profile (sedentary, moderate or heavy), age, gender and physiological status of an individual. Ideally, BMI should be maintained between 18 and 22.9 among Asian Indians [2].

Carbohydrates and Fibers
Carbohydrates form an important component of the diet and are divided into simple and complex carbohydrates. Complex carbohydrates, as consumed by Asian Indians (e.g. whole wheat, brown rice, millets and legumes), should be preferred over refined carbohydrates. Preference should be given to foods with a low glycemic index (e.g. oats, unpolished rice, whole pulses, beans and legumes), while foods with a high glycemic index (e.g. refined flour and root vegetables: yam, potato and tapioca) should be avoided. Simple sugars like crystalline sugar, sugarcane juice, sweetened carbonated beverages, fruit juices and sugar syrups should also be avoided [2].

Fibers
A diet high in natural fibers helps in regulating blood glucose and lowering of cholesterol levels. The total dietary fiber in the daily diet should be at least 25–40 g/day. A minimum of 5–6 servings/day of fruits and vegetables is recommended [2]. Whole grains, cereals, pulses, vegetables and fruits contain high dietary fiber and should be incorporated in the diet.

Proteins
Protein intake should be based on body weight. In conjunction with energy intake, the protein intake should provide 10–15% of the total calories/day in sedentary to moderately active individuals [2]. However, in cases with renal
complications, its consumption needs to be closely monitored under strict medical supervision and modified accordingly. Red meats should be replaced with leaner cuts of meats (chicken/fish). South Asians are predominantly vegetarians, thus high-quality protein is not available to the body; it is therefore required to include low-fat dairy products (milk, buttermilk, cottage cheese or curd) along with other vegetarian sources (soy, pulses or whole grams).

**Fats**
Fats should not provide more than 30% of total energy/day and saturated fatty acids should provide no more than 10% of the total energy/day. For individuals having LDL-c levels ≥100 mg/dl, saturated fatty acids (butter, clarified butter or full-fat dairy products) should be <7% of the total energy/day. Essential polyunsaturated fatty acids (PUFA) such as linoleic acid should provide 5–8% of the total energy/day and α-linolenic acid should be 1–2% of the total energy/day. Cis-monounsaturated fatty acids (olive, mustard, rapeseed, rice bran and groundnut oil) should provide 10–15% of the total energy/day. Trifluoroacetic acids (partially hydrogenated vegetable oils: vanaspati, margarine and reheated oils) are best avoided or should be <1% of the total energy/day. Cholesterol intake should be limited to 200–300 mg/day [2]. Complete dependence on just one vegetable oil does not ensure optimal intake of various fatty acids, therefore use of two or more vegetable oils is recommended.

**Salt**
Dietary sodium content is an important determinant of blood pressure (BP). Regulating salt intake becomes important in case of MS or if obesity is accompanied with HTN [6]. It is recommended that the total salt intake should be <5 g of sodium chloride (or about 2 g of sodium) per day [2]. Dietary intake of sodium from all sources (pickles, chutneys, processed foods/snacks, bakery items, sauces, preserved meat products, other pre-prepared and preserved foods, soups or cheese) should be limited.

**Weight Loss Diets**
The quantity and quality of a diet along with physical activity forms an integral component of approaches dealing with weight loss. Studies have shown the possibility to modulate body weight and composition by changing dietary composition. Numerous studies have been done in the developed countries for weight loss in individuals with obesity using different diets targeted at weight reduction, e.g. the Pritikin Principle, Nutrisystem advanced, Ornish Diet or Weight Watchers Diet; however, the efficacy of these or similar diets is yet to be researched in South Asians [8].
Physical Activity

It is believed that a sedentary lifestyle is an important factor contributing to the development of T2DM and coronary heart disease (CHD) in Asian Indians. Regular physical activity reduces the risk of obesity, dyslipidemia, HTN and T2DM, and has shown to reduce the risk of CHD. Positive outcomes of moderate-intensity physical activity include an increase in HDL-c levels, reduction in BP, long-term maintenance of weight loss and a decreased risk of death from lifestyle-related diseases [9]. The consensus physical activity guidelines for Asian Indians have been summarized in table 2.

<table>
<thead>
<tr>
<th>Disorders</th>
<th>Physical activity guidelines</th>
</tr>
</thead>
</table>
| Obesity   | Moderate-intensity aerobic exercise: 60 min/day  
Vigorous-intensity exercise 60 min 3 or more days/week |
| Coronary heart disease (CHD) | The exercise sessions should be individualized according to the cardiac and physical status of the patient  
Usually, 210 min/week of moderate-intensity physical activity should be achieved  
Depending on the clinical condition, a low-intensity, individualized, supervised exercise program could also be devised |
| Diabetes | Daily physical activity of 60 min in duration including 10–15 min of resistance exercise and work-related activity |

*Definitions of physical activity intensity levels are provided in the box below.*

---

**Box**

*Definitions of Physical Activity Intensity Levels [9]*

1. Low-intensity physical activity elicits a slight increase in breathing rate and is relative to a given individual (e.g. strolling <3 km/h on level firm ground, tidying the house, leisurely stationary cycling <50 W or <16 km/h and cooking)

2. Moderate-intensity physical activity elicits a moderate, noticeable increase in depth and rate of breathing while still allowing comfortable talking and is relative to a given individual (e.g. purposeful walking 3–6 km/h on level firm ground, water aerobics, cycling outdoors for pleasure at 19–23 km/h, cleaning the house, hiking and gardening)

3. Vigorous-intensity physical activity elicits a noticeable increase in depth and rate of breathing and will not allow an individual to speak more than a few words without pausing for breath (e.g. walking 1 km in less than 10 min, jogging, cycling outdoors at 23–26 km/h, aerobic dancing and jumping rope)

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Physical Activity

It is believed that a sedentary lifestyle is an important factor contributing to the development of T2DM and coronary heart disease (CHD) in Asian Indians. Regular physical activity reduces the risk of obesity, dyslipidemia, HTN and T2DM, and has shown to reduce the risk of CHD. Positive outcomes of moderate-intensity physical activity include an increase in HDL-c levels, reduction in BP, long-term maintenance of weight loss and a decreased risk of death from lifestyle-related diseases [9]. The consensus physical activity guidelines for Asian Indians have been summarized in table 2.
Cautions Regarding Physical Activity

(1) For all patients, all decisions regarding the initiation of exercise programs should be taken in consultation with a physician/diabetologist after undergoing a pre-activity evaluation.

(2) Sudden commencement or acceleration of physical activity or any high-intensity exercises should be avoided.

Therapeutic Management

Individuals with obesity, MS, dyslipidemia, HTN or T2DM have an increased risk of developing CVD and can therefore benefit from therapeutic interventions. Since these conditions typically coexist in an individual, a multidrug therapy may be needed.

Obesity

Treatment of obesity needs to be quite specific according to BMI category (table 3). There are few drugs available for weight loss although research is ongoing and there may be more options in the future. It is important to note that the weight loss associated with medication use is not continuous and drug withdrawal may be associated with weight gain.

Orlistat

Orlistat acts by inhibiting pancreatic lipase resulting in the partial blocking of intestinal digestion and absorption of dietary fat. It can result in a modest weight loss, but major limitations are the associated gastrointestinal

<table>
<thead>
<tr>
<th>Treatment</th>
<th>25–26.9&lt;sup&gt;a&lt;/sup&gt;&lt;br&gt;23&lt;sup&gt;b&lt;/sup&gt;</th>
<th>27–29.9&lt;sup&gt;a&lt;/sup&gt;&lt;br&gt;25&lt;sup&gt;b&lt;/sup&gt;</th>
<th>30–34.9&lt;sup&gt;a&lt;/sup&gt;&lt;br&gt;27&lt;sup&gt;b&lt;/sup&gt;</th>
<th>35–39.9&lt;sup&gt;a&lt;/sup&gt;&lt;br&gt;32.5&lt;sup&gt;b&lt;/sup&gt;</th>
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<td>Diet, exercise, behavior</td>
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<td>Pharmacotherapy</td>
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<td>Bariatric surgery</td>
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+ = Applicable. <sup>a</sup>International guidelines. <sup>b</sup>Consensus guidelines for Indians [4].
symptoms [11]. It is the only drug approved for long-term treatment of obesity in India and the only drug approved for treatment of obesity in children. In addition, it may lower BP and decreases the risk of T2DM development. Gastrointestinal side effects include cramps, fecal urgency and oily spotting/evacuation.

Metformin
Metformin has been shown to cause weight loss [12]. DPPOS (Diabetes Prevention Program Outcomes Study) showed that the weight loss caused by metformin was maintained in the 10-year follow-up study of patients with IGT and these patients also had a lower incidence of diabetes compared to the placebo group [13].

Glucagon-Like Peptide Analogues
Long-acting glucagon-like peptides (GLP-1) receptor agonist, e.g. liraglutide and exenatide, are used for the treatment of diabetes and can cause significant weight loss, approximately 6–8 kg/6 months. These drugs are associated with satiety and decreased gastric emptying [14, 15]. Currently, they are off-label drugs for the treatment of obesity in nondiabetic subjects.

Phentermine
It is an appetite suppressant and has been approved by US Food and Drug Administration for short-term use (up to 12 weeks); however, it has shown to have psychological dependence. Further, rebound weight gain can also occur once drug tolerance develops [16].

A phentermine-topiramate combination pill is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults in the presence of at least one weight-related comorbidity, such as HTN, T2DM or dyslipidemia. The combination of phentermine and topiramate (extended release) results in a mean weight loss of 8–10 kg [11].

Lorcaserin
It is a serotonin-2C agonist also known as an appetite suppressant. It is prescribed for weight loss and can produce a mean weight loss of 4–7 kg [11].

Other Drugs
The following drugs can also be considered as options for the treatment of obesity:

- Diethylpropion (selective norepinephrine-releasing agent)
• Phenylpropanolamine (norepinephrine-releasing agent)
• Bupropion and fluoxetine
• Tesofenasine

Surgical Options
Patients with severe obesity with or at risk of comorbidities should be offered surgical treatment. Surgical options include the following:

* Liposuction. It is the removal of subcutaneous fat through large-volume liposuction.

* Bariatric Surgery. Bariatric surgery is an appropriate treatment for people with T2DM and obesity not achieving recommended treatment targets with medical therapies, especially when there are other major comorbidities. It can be considered for Asian Indians with a BMI above 32.5 with comorbidity and BMI above 37.5 without comorbidity. Many of the MS manifestations have shown potential reversal after bariatric surgery [17].

* Intragastric Balloon. This inflated saline-containing balloon, which is inserted into the stomach, increases the sensation of fullness. However, there is little additional benefit regarding weight loss and its cost should be considered against a program of eating and behavioral modification.

Dyslipidemia and the Metabolic Syndrome
Statins
Statins reduce plasma LDL-c levels and have moderate effects on TG and HDL-c levels. Statins are also thought to raise HDL-c levels by reducing the rate of cholesteryl ester transfer protein-mediated flow of cholesterol from HDL-c. They are highly effective at preventing morbidity and mortality from CVD and can slow the development of atherosclerosis [18]. However, in a meta-analysis of over 90,000 individuals, it was found that statins were associated with a 9% increased risk of developing T2DM (odds ratio 1.09; 95% confidence interval 1.02–1.17), but the benefits of statin therapy clearly outweigh this risk in those with higher baseline risk of CVD [19].

Fenofibrate
These fibric acid derivatives (fibrates) are selective agonists of the peroxisome proliferator receptor-α. They reduce TG levels significantly [20]. Although they are generally well tolerated, there have been concerns about the risk of muscle disorders in patients cotreated with statins and fibrates. Studies indicate that monotherapy with statins or fibrates is associated with a low risk of myopathy and rhabdomyolysis, but this risk increases significantly in combination treatment of statins and fibrates; hence ESC/EAS
(European Society of Cardiology and the European Atherosclerosis Society) guidelines recommend that gemfibrozil and statins should not be coprescribed [21, 22].

Niacin (Nicotinic Acid)
It is a member of the vitamin B complex and exerts its effects by blocking fatty acid flux from adipose tissue and inhibiting the release of VLDL-c, resulting in reduced TG levels and increased HDL-c levels [23]. This class of drugs causes flushing, leading to discontinuation in many patients. Its use for increasing HDL levels to prevent CHD has not been backed up by current research data.

ω-3 Polyunsaturated Fatty Acids
A number of studies have shown that highly purified ω-3 PUFA preparations have a beneficial effect on the lipid profile when used at high doses. Several studies have described the successful use of a statin in combination with ω-3 PUFA in patients with mixed dyslipidemia, with a particular benefit observed for TG and VLDL levels [24]. A recent large retrospective ‘real world’ outcome evaluation involving over 12,000 patients in the UK demonstrated 21% lower all-cause mortality in patients treated with 1 g/day of licensed highly purified ω-3 acid ethyl esters within 90 days of a myocardial infarction (p < 0.0001) [25]. In South Asians, the intake of ω-3 PUFA is low, but it is not clear if ω-3 PUFA supplementation would help to ameliorate the metabolic state.

Hypertension
HTN is one of the major components of MS. Effective treatment of HTN includes achieving a normal BMI in patients who are overweight/obese, adopting a DASH (Dietary Approaches to Stop Hypertension) diet, restricting dietary intake of sodium and regular physical activity along with prescribed pharmacotherapy. Treatment with drugs should be started in patients with BP >140/90 mm Hg in whom lifestyle treatments have not been effective [26]. There are a large number of drugs currently available for reducing BP. Most of the patients require two or more antihypertensive agents selected from different drug classes. These multidrug combinations often produce greater BP reduction at lower doses of the component agents, resulting in fewer side effects [27]. Treatment involves thiazide-type diuretics as initial therapy for most patients, either alone or in combination with one of the other classes (e.g. β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and calcium channel blockers). If the initial drug selected is not tolerated or is contraindicated, then a drug from one of the other classes proven to reduce cardiovascular events is usually given instead (table 4) [6].
Conclusions

South Asians are facing growing ‘epidemics’ of obesity and MS. Successful management of obesity includes lifestyle management along with therapeutic interventions. However, some drugs may aggravate other risk factors and therefore need to be used with caution. Evidence is also available for effective intervention programs emphasizing adequate nutrition, physical activity and lifestyle changes starting from childhood for the prevention of obesity, MS and related disorders such as T2DM and dyslipidemia.

Disclosure Statement

The authors declare no conflict of interest.

References


Nutritional Issues in the Short Bowel Syndrome – Total Parenteral Nutrition, Enteral Nutrition and the Role of Transplantation

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Abstract
In this review, I focus on the extreme of the short bowel syndrome where the loss of intestine is so great that patients cannot survive without intravenous feeding. This condition is termed short bowel intestinal failure. The review outlines the principles behind diagnosis, assessing prognosis and management. The advent of intravenous feeding (parenteral nutrition) in the 1970s enabled patients with massive (>90%) bowel resection to survive for the first time and to be rehabilitated back into normal life. To achieve this, central venous catheters were inserted preferably into the superior vena cava and intravenous infusions were given overnight so that the catheter could be sealed by day in order to maximize ambulation and social integration. However, quality of life has suffered by the association of serious complications related to permanent catheterization – mostly in the form of septicemias, thrombosis, metabolic intolerance and liver failure – from the unphysiological route of nutrient delivery. This has led to intense research into restoring gut function. In addition to dietary modifications and therapeutic suppression of motility, novel approaches have been aimed at enhancing the natural adaptation process, first with recombinant growth hormone and more recently with gut-specific glucagon-like peptide-2 analogues, e.g. teduglutide. These approaches have met with some success, reducing the intravenous caloric needs by approximately 500 kcal/day. In controlled clinical trials, teduglutide has been shown to permit >20% reductions in intravenous requirements in over 60% of patients after 6 months of treatment. Some patients have been weaned, but more have been able to drop infusion days. The only approach that
predictably can get patients with massive intestinal loss completely off parenteral nutrition is small bowel transplantation, which, if successful (1-year survival for graft and host >90%) is accompanied by dramatic improvements in quality of life.

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Introduction

It should be noted that the severity of the short bowel syndrome (SBS) varies from mild to severe, and that the degree of severity is directly related to the loss of absorption capacity. For example, the management of mild disease is easy and based on increased oral supplementation to overcome the reduced efficiency of absorption, for example oral B₁₂ supplementation in patients with ileal resection, whilst the management of severe disease includes intravenous supplementation of water, electrolytes and nutrients.

Definition of Severe Short Bowel Syndrome or Short Bowel Syndrome and Intestinal Failure

SBS and intestinal failure (SB-IF) is the most severe form of the syndrome and can only be managed with long-term use of intravenous nutrition, i.e. home (HPN) or total parenteral nutrition (TPN). It is this condition that we will focus on in this article. It has been defined as a condition that results from surgical resection, congenital defects or disease-associated loss of absorption, and is characterized by the inability to maintain protein energy when on a conventionally accepted normal diet [1].

Prediction of Short Bowel Syndrome and Intestinal Failure

Studies performed by Messing et al. [2] in France have indicated that patients with massive intestinal resection or loss can be categorized into those who are likely to become permanently dependent on parenteral nutrition (PN) and those who are not. Measurements suggest that patients with <80 cm of small intestine plus colon are likely to become independent of parenteral support (PS). However, those who have lost their colons as well, i.e. those with end-jejunostomies, will likely need >200 cm of small intestine to remain independent of PS. Of course, this assumes that the remaining small intestine is functionally normal. If it is diseased, as in Crohn’s disease, then greater lengths of small intestine will be required.
Clinical Determination of Short Bowel and Intestinal Failure

The best practical way of assessing whether a patient has SB-IF is to measure 24-hour urine output volumes plus sodium content when they are off all intravenous infusions and eating normally. If the 24-hour urine volume is greater than 1 liter and if urinary sodium is greater than 20 mEq/day, then it is not present. These measurements are also very useful in gauging intravenous fluid and electrolyte requirements in patients requiring TPN or HPN.

Adaptation

The remarkable thing about the intestine is its ability to adapt to the loss of length. Consequently, it is important to reassess absorption in the months following intestinal loss to reassess PS requirements. Some patients might well become independent of intravenous infusions in the 2 years following resection. The process of adaptation begins almost immediately following resection or loss, and can continue for over 2 years [3, 4]. Adaptation is characterized by villous hyperplasia, which increases the absorptive surface 200-fold. In the days before the advent of intravenous feeding, this process allowed some patients to survive with only 15 cm of small intestine [5]. Villous hyperplasia is far more evident in studies in experimental animals than in humans. The hyperplasia is associated with increased digestive enzyme secretion, muscular hypertrophy, delayed food transit through changes in motility and increased blood flow. The net result is increased absorption. These features are illustrated in figure 1. Probably the driving force for adaptation is the increased contact between food and the remaining mucosa resulting from the associated hyperphagia. Studies have shown that adapted patients usually consume 1.5–2.0 times the recommended dietary allowance for protein and calories [6]. Studies of ours have revealed that food-induced pancreatic secretion is also twice normal (fig. 2) [6, 7].

General Principles of Management

(1) It must be remembered that most food digestion occurs in the jejunum and proximal jejunum. Consequently, digestion is rarely a problem and there is no indication for pancreatic enzyme supplementation to improve absorption in SB-IF patients.

(2) The reason why we have an extraordinary long small intestine is to allow for the reabsorption of the massive quantities of fluid (>7 liters/day) and elec-
Electrolytes that are secreted by the upper gastrointestinal tract to ensure optimal enzymatic digestion. Consequently, fluid and electrolyte depletion is the earliest event in SBS.

(3) As mentioned above, digestive function and absorption improves with time because of adaptation, but absorptive capacity must be rechecked over the course of time to reassess basic needs.

(4) As mentioned above, digestion is not the problem, transit is. Consequently, it is important to tailor management to keep food in contact with the remaining intestinal surface for as long as possible.

**Practical Management**

(1) Avoid dietary restriction [8]. Remember hyperphagia is part of the adaptation response.

(2) Prolong nutrient-mucosa contact time. Break down normal meals into small frequent meals, supplement with nutrient-dense liquids and use drugs to reduce motility. Patients need to understand that they have to change the way they eat; they must train themselves to ‘nibble like rabbits’. This reduces the load on the remaining intestine and ensures a longer contact time between food and the absorptive mucosa. The most effective way is to provide continuous slow enteral feeding. This was beautifully illustrated by Joly et al. [9] in their random-
Fig. 2. A randomized crossover study compared absorption between isocaloric tube feeding and OF in 15 SBS patients >3 months after short bowel constitution. An OF period combined with enriched (1,000 kcal/day) tube feeding was also tested. Means ± SD. Net absorption for total calories (a), lipids (b) and proteins (c) during the 3 study periods. In the histograms, intakes (light grey) and losses (in black) are above and below the zero line, respectively, the dark grey being the net absorption (intake losses). Total caloric, lipid and protein intakes (light grey bars) were significantly higher with OF combined with tube feeding (OCEF) than with OF and enteral tube feeding (ETF; \( * p = 0.001 \)). Net absorption for total calories, lipids and proteins (dark grey bars) was significantly higher with ETF and OCEF than with OF (\( ** p 0.001 \)) with permission [9].

ized crossover study of 15 SBS patients; they compared absorption between isocaloric tube feeding and oral feeding (OF), and then a combination of OF and 1,000 kcal/day tube feeding. Figure 2 shows that absorption of calories, lipids and protein was significantly higher with exclusive enteral tube feeding than OF. The combination enhanced absorption further, illustrating the importance of hyperphagia in maximizing absorption in SB-IF patients.
(3) Opiates are the most effective antimotility agents to use in this situation to increase nutrient-mucosa contact time. However, it is best to avoid opiates in the long term and use their derivatives such as Imodium, which have little central side effects. Imodium should be given in much higher quantities, i.e. up to 16 mg 6 hourly, than recommended for people with normal intestines because of the reduced absorption of medications and high therapeutic index.

(4) Studies have shown that with adaptation, colonic bacterial fermentation increases dramatically and can result in a net salvage of up to 1,000 kcal/day in the form of short-chain fatty acids [10]. Consequently, in order to maximize absorption, patients with SB-IF with colons should be given diets enriched with complex carbohydrates.

(5) Previously, patients with SB-IF were encouraged to limit the amount of fat they consumed in order to reduce steatorrhea. However, when formally tested, it was shown that the amounts of calories absorbed were higher when patients consumed a high-fat diet despite the fact that stool fat also increased [11, 12].

(6) One of the key principles of SB-IF management is to restrict water consumption. The reason for this is that the mucosa of the duodenum and jejunum is freely permeable to fluid and electrolytes and cannot maintain a concentration gradient. Thus, in patients with end jejunostomies, the consumption of water will draw electrolytes accompanied by water from the body and exacerbate dehydration and electrolyte deficiencies. In order to prevent this, the use of WHO-type solutions is encouraged. With these solutions, salt and glucose are actively taken up across the mucosa by specific transport mechanisms into the body accompanied by water. Thus, it is always important to encourage patients to take fluids containing sugar and salt in the ratios suggested by the study by Lennard-Jones [13] shown in figure 3. The problem is that patients are tired of drinking these solutions. A pragmatic alternative is to use flavored sport drinks, such as Gatorade. Blenderized soups are also very useful if they contain salt and a carbohydrate source such as pasta, rice or potato.

(7) Another approach is the suppression of secretion. The use of acid suppressants such as H₂ antagonists or proton pump inhibitors is encouraged early following intestinal loss when gastric secretion is increased. Long-term use is, however, contraindicated as acid secretion decreases with time and complete suppression will lead to bacterial overgrowth in the remnant intestine and exacerbation of fluid and electrolyte losses [6, 7]. The most dramatic therapeutic approach to the suppression of secretion is to use octreotide. In a study of 8 well-adapted patients with severe SB-IF, we were able to show that injections of octreotide 50 μg t.i.d. resulted in 50% reductions in stomal fluid and electrolyte losses [6, 7] (fig. 4). Interestingly, while fat absorption was not affected, there was
a significant increase in nitrogen reabsorption, presumably because of the ability of the drug to reduce motility thereby increasing food-mucosa contact time.

We performed studies in this group of patients to examine the effects of octreotide on mucosal growth (fig. 5), using primed continuous 8-hour intravenous infusions of isotope-labeled leucine \[^7\]. The results showed that despite the beneficial effects of the drug, i.e. decreased fluid and electrolyte secretory losses, it had negative effects on mucosal protein synthesis and villous growth, thus countering the physiological adaptation process. Consequently, we only recommend short courses of octreotide to control extremely high secretory stomal losses before adaptation has had time to establish itself.

**Fig. 3.** The physiological basis for WHO rehydration fluids. Sodium balance is only achieved when luminal concentrations exceed 70 mmol/l with glucose concentrations of 140 mmol/l (Lennard-Jones [13]).

**Fig. 4.** The effect of octreotide, a long-acting somatostatin analogue, on end-jejunostomy losses in hyperphagic SB-IF patients [7].
Another approach is to increase adaptation. Much attention has recently been devoted to developing gut hormonal approaches enhancing the natural adaptation process. The first hormone to be used was recombinant growth hormone. Several studies (initially uncontrolled, later controlled) showed that injections of recombinant growth hormone increased electrolyte and energy absorption in SB-IF patients. Perhaps the best of these is the one reported by Seguy et al. [14] (fig. 6). Despite using lower and more physiological doses, their results were very positive, with significant increases in energy, nitrogen, carbohydrate and D-xylose absorption. However, in its marketed form, Zorptive, the drug has been little used in clinical practice primarily because it can only be used during a short time frame and because of its high side effect profile. A Cochrane review [15] of all the controlled trials came up with the following conclusion: ‘The results suggest a positive effect of human growth hormone on weight gain and energy absorption. However, in the majority of trials, the effects are short-lived returning to baseline shortly after cessation of therapy. The temporary benefit calls into question the clinical utility of this treatment. To date, the evidence is inconclusive to recommend this therapy’.

Perhaps the most exciting recent developments in the therapeutic management of SB-IF is the protease-resistant form of glucagon-like peptide GLP-2. GLP-2 is secreted by L-cells in the distal bowel. Many of their properties are those seen in natural adaptation. For example, the peptide slows gastric emptying, reduces gastric secretion, increases mucosal blood flow, stimulates the growth of small and large intestine, increases epithelial proliferation and reduc-

![Fig. 5. Octreotide inhibits mucosal protein synthesis and may have anti-adaptational properties [7].](image-url)
es apoptosis [16]. Thus, unlike growth hormone, its effects are specific to the small intestine. With chemical engineering, the substitution of a glycine molecule for alanine in natural GLP-2 made the product, teduglutide, protease resistant, thus increasing its half-life from minutes to several hours [17]. This is important as it can now be given as a single daily injection.

Two multicenter, multinational randomized controlled trials which verify the potency and efficacy of the drug in reducing intravenous fluid requirements have now been completed. Because the condition is relatively rare, sufficient numbers could only be achieved with international collaborations through 29 sites in 10 countries (USA and Europe). In the first study [18], two dose levels were compared to placebo in 84 patients. Surprisingly, the lower dose (0.05 mg/kg per day) proved more effective in achieving the primary end point of ‘clinically significant’ (≥20%) reductions in intravenous fluid requirements to maintain normal renal function as defined by a stable plasma creatinine and urine volume of 1–2 l/day (46 vs. 6%, p = 0.01). Secondary benefits included increased fasting plasma citrulline, a marker of enterocyte function, and increased lean body mass. In the second confirmatory study, a more simple randomized controlled trial was conducted between placebo and the teduglutide dose of 0.05 mg/kg per day (fig. 7) in 86 patients [19]. Here, 63% achieved >20% reduction in PS

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**Fig. 6.** Three weeks of human growth hormone (HGH) increases intestinal absorption of macronutrients with permission [14]. Lower dose (physiological) recombinant HGH significantly affected energy (440 kcal/day), nitrogen and carbohydrate absorption in 12 SB-IF patients (Crohn’s disease 3/12, residual small intestine mean 43 cm range 0–120 cm, 9/12 had colons, 9/12 colon: study design: randomized double-blind, placebo controlled, cross-over trial GH 0.05 mg/kg/day for 3 weeks placebo controlled, cross-over trial GH 0.05 mg/kg/day for 3 weeks). * p < 0.002, ** p < 0.04, *** p < 0.02, vs. placebo.
compared to 43% on placebo (p = 0.002). Importantly, this translated into more patients being able to drop the frequency of intravenous infusions, and 11 patients were successfully and completely weaned from intravenous therapy during the two studies [20]. Interestingly, the time of weaning varied from 12 to 110 weeks on the drug. There is no doubt about the potent hypertrophic effects of this drug, which can readily be seen with endoscopy and examination of the stoma, which commonly enlarges considerably, as shown in figure 8.

**Fig. 7.** The long-acting protease-resistant modification of the gut peptide GLP-2, teduglutide, reduced intravenous fluid requirements by >20% in 63% of SB-IF patients within 6 months, which translated into a shorter duration of intravenous infusion and total weaning back to normal food in 4 patients (Jeppesen et al. [19]). * p < 0.002, vs. placebo (Cochran-Mantel-Haenszel test).

**Fig. 8.** A common side effect of teduglutide is swelling of the stoma, which indicates the powerful effects the drug has on the residual bowel.
Another interesting fact was the high placebo response. There is no clear explanation, but it is possible that adaptation continues longer than previously thought, or it could be that tighter management in the clinical trial setting allowed further intravenous fluid reductions. The drug has now been marketed. Postmarketing surveillance will be essential to rule out unanticipated long-term side effects, e.g. neoplastic changes bearing in mind its proliferative properties, but to date the safety profile looks good.

**Problems with Home Parenteral Nutrition**

PS is the only life-sustaining form of medical treatment for SB-IF. However, PS is expensive, impairs quality of life (QoL) and is associated with serious complications, such as catheter sepsis, central venous thrombosis and liver failure (table 1) [21, 22].

**Quality of Life**

Many studies have examined this and found that QoL is severely impaired. This is not surprising, as patients lose their freedom as they are tethered to intravenous catheters for the rest of their days. This severely limits social intercourse and the ability to return to a normal occupation and lifestyle. They also have to be vigilant in preserving catheter sterility, as breaks in the line will result in bacteremia, septicemia and repeated hospitalizations.

**Complications of Total Parenteral Nutrition**

It must be appreciated that although TPN has allowed patients to survive without significant gut function and food absorption, feeding into the right side of the heart can never substitute for feeding through the gut and portal

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<th>Table 1. Three-year analysis of the Mayo Clinic HPN Program [21]</th>
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<td><strong>Patients:</strong> 63</td>
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<td>Short bowel: 40</td>
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<td>Chronic obstruction: 23</td>
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<td><strong>Hospitalizations:</strong> 73% <em>(average stay: 11 days)</em></td>
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<tr>
<td>71% were due to catheter infections <em>(Staphylococcus epidermidis: 12, fungi: 8)</em></td>
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<tr>
<td>• 70% of them required catheter replacement</td>
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<tr>
<td>• 2 weeks of intravenous antibiotics</td>
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<td>25% for catheter replacement for thrombosis or damage</td>
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<td>All had intermittent abnormalities in complete blood cell count, urinary excretion, and renal and liver tests</td>
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Nutritional Issues in the Short Bowel Syndrome
vein. Even the freshest of foods is heavily colonized by microbes, which are safe if they stay intraluminal but could be fatal if they enter the systemic circulation. Consequently, the prime function of the gut, other than absorption, is to break down food into a sterile solution that can be absorbed into the portal vein, sensed by the pancreas and assimilated by the liver. To achieve this, microbe quantities are progressively diminished by the action of gastric acid, pancreatic enzymes and bile, and finally sterilized by the action of the gut immune system, which surrounds the lumen and engulfs any remaining bacteria. If you contrast this to TPN, it is easy to understand that the chief complications are septicemia, metabolic instability, liver dysfunction and progressive occlusion of the central veins through trauma of the intima by repeated catheterization. A further problem is that systemically administered nutrients are not as well assimilated and utilized by the liver. Consequently, it is always important to maintain oral intake for hepatic nutrition, even if most is malabsorbed.

Complications are directly related to the quality of catheter care at home (fig. 9). Our analysis showed that some patients never experienced catheter infections, whilst others had to be rehospitalized every few weeks [22]. Other risk factors for catheter infections included the presence of a high-output

Fig. 9. Illustration of the complexity of the management of patients with massive intestinal resection. This elderly patient had suffered thrombosis of his superior mesenteric artery resulting in gangrene of all of the small intestine from the ligament of Treitz. He was managed with gastrostomy with jejunal extension and central feeding via a peripherally inserted central catheter. Massive stomal losses were associated with recurrent bouts of catheter sepsis and progressive liver dysfunction. A small bowel transplant was performed with successful removal of all these tubes and reestablishment of normal eating.
jejunostomy, chronic obstruction and gut stasis leading to bacterial overgrowth and Crohn’s disease.

Perhaps the most life-threatening complication is liver failure. While minor liver function test abnormalities are common and not serious, progressive cholestasis, liver fibrosis and cirrhosis, and eventual liver failure is devastating and uniformly fatal unless a successful liver-small bowel transplant is performed. Luckily, the complication only occurs in ~5% of patients. The etiology is complex and involves repeated infections, absence of oral intake, an extremely short bowel and too many PN calories in the form of fat or dextrose.

**Small Bowel Transplantation**

The efficacy of small bowel transplantation (SBTx) lagged behind that for renal and liver transplantation until recently, when the Intestine Transplant Registry participants announced that ‘a new era has dawned’ as outcome now is very similar to that of liver transplantation, i.e. 1-year survival of graft and host >90% due to improved surgery and immunosuppression [23].

In the USA, Medicare has accepted ‘TPN failure’ as the chief indication for SBTx. The chief criteria are summarized in table 2. It is important to stress that although the novel pharmaceutical approaches to reduce PN requirements certainly contribute to an improved outcome and QoL, only SBTx can predictably get patients off intravenous infusions and make them nutritionally autonomous. We have argued that consideration for SBTx should be made early in patients with risk factors for developing liver failure (e.g. ultrashort bowel <50 cm without colon), as this will preserve the liver and obviate the need for a combined liver-small intestine transplant [24].

To illustrate these points, we conducted a prospective 2-year study of 46 consecutive patients transplanted between June 2003 and July 2004 [25]. PN was stopped completely by day 17 after transplantation. After a mean follow-up time of 21 months, 40/46 (87%) were well with good graft function. Perhaps, most importantly, average QoL, measured with a QoL tool based on a validated self-administered questionnaire containing 26 domains and 130 questions, was

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**Table 2. Indications for TPN failure**

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<th>Medicare indications</th>
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<td>(1) Life-threatening sepsis</td>
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<td>(2) Venous thrombosis – loss of access</td>
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<tr>
<td>(3) Liver disease – progressive fibrosis, cholestasis, cirrhosis</td>
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dramatically improved. A summary of some of the key improvements is shown in figure 10. It should also be noted that we evaluated baseline QoL compared to HPN in patients who declined transplantation and showed that the indices of QoL in transplanted patients prior to transplantation were significantly lower, indicating the gravity of their illness.

Despite these exciting observations, there remains a reluctance to refer patients with Medicare indications for SBTx, as evidenced by the review by Pironi et al. [26] in Europe. They found that only 15% of HPN patients with Medicaid criteria for ‘TPN failure’ and small bowel transplant were referred to a center for transplantation, and only 36% of adults and 43% of children with HPN liver failure were described as needing immediate transplantation [26]. The explanation for the reticence is unclear, particularly since SB-IF-associated liver failure is generally a fatal condition, and also because late referral is associated with poor outcomes [23]. The most likely explanations involve unfamiliarity with the procedure and the paucity of experienced centers offering transplantation because the volume is small and the specific skills needed to perform the surgery, and manage the problems, scarce.

**Conclusion**

There have been significant advances in different approaches to the complex management of patients with SB-IF over the last decade, which have fuelled our armamentarium of therapeutic options and translated into improved quality of
care. However, all these forms of therapy have side effects and potentially serious long-term complications, and so we need to be vigilant in our surveillance, thorough in our multidisciplinary management [27] and continue to seek safer forms of therapy that return QoL towards normal.

Disclosure Statement

Stephen O’Keefe in the past acted as an advisor to NPS pharmaceuticals in the development of their multicenter clinical trials of teduglutide, and has received support from them for investigator-initiated studies.

References

Abstract
In cancer patients, oral nutrition is the preferred route of feeding since it is a significant part of the patient’s daily routine and contributes to the patient’s autonomy. It represents a privileged time to spend with family and friends, avoiding the tendency for isolation in these patients. The acknowledgement that the prescribed diet is individualized, adapted and adequate to individual needs empowers the patient with a feeling of control, and thus it is also a highly effective approach of psychological modulation. All these factors may potentially contribute to improve the patient’s quality of life and may modulate treatment morbidity. The referral to a nutrition professional responsible for the individualized dietary counseling should always be based on evidence-based decision-making plans. The implementation of individualized nutritional counseling should consider the common causes for a poor nutritional intake in elderly cancer patients. A proper approach through counseling requires professionals with specific experience in both nutrition and oncology. Oral nutritional supplements are a simple and practical way to meet nutritional requirements when normal food intake is compromised. Ideally, oral nutritional supplements should be in addition to and not instead of meals. Supplements should be administered at a time which does not interfere with the appetite of the patient. The administration after the meal theoretically potentiates the anabolic effect on protein metabolism. Supplements with high energy density (>1 kcal/ml) or enriched with ω-3 fatty acid are probably the most effective.

Malignancy
The word ‘cancer’ is inclusive and comprises a wide range of different types of malignant tumors, which can develop in virtually every body tissue, thus determining diverse clinical manifestations [1, 2]. Cancer is a major cause of
morbidity and mortality, being the second most frequent cause of death worldwide [2, 3]. However, the advances in early diagnosis and sophisticated treatment modalities increase the possibility of cure or at least may prolong survival. It is thus expectable that most cancer patients will be ambulatory with a desirable ‘good’ quality of life (QoL); the latter requires a patient-centered multiprofessional management in which nutrition plays a central role [4–8].

The Wasting Spectrum in Cancer

Cancer is associated with malnutrition [9–11] that may evolve to cancer cachexia. Cancer cachexia is multifactorial and is defined as ‘a multifactorial syndrome with loss of skeletal muscle mass (with or without loss of fat mass), not fully reversed by conventional nutritional support. Its pathophysiology is characterized by a negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism’ [12, 13], and cachexia is still an unsolved phenomenon. The prevalence of nutritional wasting in cancer ranges from 8 to 84% depending on the cancer site, e.g. 80% in patients with gastrointestinal (GI) cancer [9, 14–18] and 70% in patients with head-neck cancer [19–23]. Cancer wasting is regarded as a physiological adaptation to stress: the body sacrifices large portions of muscle mass to spare immediate critical functions in visceral organs. But there are limitations to this adaptive response: skeletal muscle mass contraction leads to muscle weakness, and decreased work tolerance and functional capacity [24]. The most frequent manifestation of wasting in cancer is weight loss, which when exceeding 10% is of particular clinical and/or prognostic significance, because weight loss of this magnitude in the setting of any illness may lead to significant increases in morbidity and mortality [24, 25]. Some degree of weight loss has been registered in ∼75% of patients before surgery, 57% prior to radiotherapy, 51% prior to chemotherapy and 80% of ambulatory patients [25, 26]. An additional finding is that weight loss is likely to be related to other factors, e.g. cancer aggressiveness (stage and histological characteristics), antineoplastic treatments, age and emotional factors such as depression [5, 8, 27–29].

Tumor Burden, Metabolic Dysfunction and Symptoms

Anorexia is a common contributor to wasting in cancer [30] and the act of eating may incite a variety of adverse symptoms including ‘voluntary anorexia’ due to learned food aversions [27, 31]. In addition, the tumor mass alone may preclude adequate ingestion of food. The underlying factors contributing to reduced food intake include decreased central drive to eat, chemosensory
disturbances (dysgeusia and dysosmia), decreased upper GI motility (e.g. early satiety, nausea and vomiting) and distal tract dysmotility (diarrhea and constipation) [26]. On the other hand, the emotional adjustment associated with dealing with cancer is per se a precipitant of depression and anxiety, which are known contributors to anorexia [32, 33]. Of note, wasting and marked nutritional intake deficits have been associated with advanced disease [34, 35] and cancer aggressiveness [8, 28, 29]; all factors are prone to exacerbate every organ/systemic physiological derangements.

Although anorexia frequently accompanies cachexia, the drop in caloric intake alone cannot account for the body composition changes in cachexia; cachexia can occur even in the absence of anorexia. Norton et al. [36] provided evidence for the parabiotic transfer of cachexia into rats, indicating that cachexia must be mediated by some circulating factors: products of host tissues (e.g. TNF-α, IL-1, IL-6 and IFN-γ) and tumor products with a direct catabolic effect on host tissues (e.g. lipid-mobilizing factor acting on adipose tissue and proteolysis-inducing factor acting on skeletal muscle) [37, 38].

**Acute Phase Responses**

Acute-phase response (APR) refers to various physiologic/metabolic changes in response to tissue injury, infection or inflammation. Liver protein synthesis shifts from synthesizing albumin to producing acute-phase proteins such as C-reactive protein, serum amyloid-A protein, β2-macroglobulin and α1-antitrypsin. APR has been associated with more rapid weight loss and reduced survival in patients with lung or pancreatic cancer, and melanoma [39]. APR is activated and modulated by cytokines [24, 40]; moreover, proteolysis-inducing factor activates the transcription of NF-κB, resulting in increased production of proinflammatory cytokines IL-8, IL-6 and C-reactive protein, and decreased production of transferrin [41]. The mechanism underlying the association between APR, weight loss and survival in cancer is not known, but acute-phase proteins have been suggested to scavenge amino acids leading to muscle protein degradation. Yet, APR alone is not sufficient to produce weight loss.

**Hypermetabolism**

In some studies with malnourished cancer patients, food intake failed to correlate with the degree of malnutrition [31, 42, 43]. The use of appetite stimulants, such as megestrol acetate/medroxyprogesterone acetate (acting by downregulating the synthesis and release of proinflammatory cytokines), may be associated with weight gain in some patients; body composition analysis showed that it is due to increased adipose tissue and possibly also an increase in body fluid, but not in fat-free mass [44, 45].
Higher resting energy expenditure (REE) has been observed in patients with lung and pancreatic cancer [29, 46–49]. However, since energy expenditure decreases with a decrease in food intake, even if there is no increase in REE, this could be considered abnormal in the face of progressive anorexia. In addition, not all changes in energy expenditure are increases in REE. Thus, skeletal muscles of patients with GI cancer with weight loss showed a fivefold elevation in mRNA levels for the mitochondrial uncoupling protein (UCP)-3 versus controls and cancer patients with no weight loss, despite the reported lack of an increase in REE [50, 51]. This suggests that either lipid-mobilizing factor or TNF-α may be responsible for the elevation in UCP-3 mRNA in skeletal muscles of cachectic cancer patients, possibly via an elevation in serum lipid levels.

**Wasting, Protein Metabolism and Skeletal Muscle**

Cachexia is characterized by selective skeletal muscle mass loss, which can be reduced by 75% when weight loss approaches 30% [52]. Skeletal muscle is the body compartment where most of the contraction of lean body mass occurs [50, 53, 54]. Loss of skeletal muscle is characterized by decreased protein synthesis and increased protein breakdown. Protein degradation in muscles results in the release of amino acids, namely alanine and glutamine. The former is channeled to the liver for gluconeogenesis and the synthesis of acute phase proteins, whereas glutamine is taken up by tumor cells to sustain energy and nitrogen demands [46]. Changes in total body protein synthesis are often not observed in weight-losing cancer patients, since hepatic protein synthesis is markedly increased (twofold). However, in weight-losing cancer patients, muscle protein synthesis accounted for only approximately 8% of total body synthesis compared with 53% in healthy controls [46]. A number of studies have reported increased whole-body protein turnover, suggesting that degradation rates are also increased. Intracellular protein breakdown is suggested to be due mostly to the ATP-ubiquitin-dependent proteolytic pathway [55–57]. Low muscle mass in advanced cancer is common and a predictor of immobility and mortality [58, 59]; of note: low muscle mass adversely affects prognosis also in obese patients with advanced pancreatic cancer [60]. Sarcopenic patients are also at higher risk of increased toxicity of antineoplastic treatments [53, 54, 61].

**Wasting, Lipid Metabolism and Adipose Tissue**

Lipids have a high caloric value, and mobilization of lipids is required to meet the increased energy demands of the cachectic patient [11]; as much as 85% of adipose tissue may be lost during the cachectic process [62]. The net efflux of glycerol and fatty acids from adipose tissue in cancer wasting appears to be due to: (1) increased lipolysis apparently mediated by TNF-α and lipid-mobilizing
factor; (2) decreased de novo lipogenesis suggested to be mediated by TNF-α and IL-1 [57, 63], and (3) diminished activity of lipoprotein lipase [11, 64]. The latter enzyme is necessary for the uptake of fatty acids from circulating lipoproteins and the diminished activity in cancer appears to be mediated by TNF-α, IL-6 and IFN-γ [11]. Cancer patients have a high turnover of both glycerol and free fatty acids [65], and the elevated mobilization of lipids is often evident before weight loss becomes established; of note: CT scans showed intra-abdominal fat in cancer patients to be relatively preserved versus intra-abdominal fat in anorexia nervosa patients [66–69].

The Impact of Cancer Wasting

Regardless of the underlying mechanisms, cancer-related wasting is multidimensional and worsens patients’ well-being [39], tolerance to antineoplastic therapies and prognosis [19, 53, 54, 58]. Weight loss decreases immunological responses to tumor cells [70] and resistance to infection [42], enhances susceptibility to postoperative complications [35, 71], and increases disability and overall costs of care [72]. Also, in experimental conditions, both short-term starvation (water only) as well as prolonged semistarvation in healthy volunteers has been reported to reduce physical activity [42, 73, 74]. In the landmark semistarvation study of Keys et al. [75] in which healthy subjects lost 25% of their body weight over 6 months, there was a reduction in both REE and physical activity. Mental function may be further influenced by nutrition in several ways. Starvation and partial food deprivation in adults lead to anxiety, depression and/or other mental changes, which may in part be associated with micronutrient deficiencies. Cognitive function may also be adversely affected. In their study, partial starvation for 24 weeks resulted in loss of 25% of body weight and concomitantly increased their depression score [75].

Nutrition Intervention

Counselling

In clinical practice, oral nutrition is always the priority. In cancer patients, oral nutrition is the preferred route of feeding because it is a significant part of the patient’s daily routine and does contribute substantially to the patients’ autonomy [76]. One has to bear in mind that eating is a source of pleasure and is a privileged time to spend with family and friends, avoiding the tendency for isolation in patients. The referral to a nutrition professional responsible for the
individualized dietary counseling should always be based on evidence-based decision-making plans (fig. 1) [6].

As clinicians, we have to recognize the dimensions that are determinant for patients. An adequate food intake is recognized by the patient as well as by the family and caregivers as essential to maintain the daily activity, energy and functional capacity, and to overcome more successfully the journey of treatment. To be effective, individualized counseling has to be based on a thorough assessment of various nutritional and clinical parameters evaluated in any nutrition consultation [77–80]. A detailed symptom assessment is mandatory (table 1).

Intensive individualized nutritional counseling is the most effective and the most physiologic means of feeding [76–78]. Notwithstanding, one has to acknowledge that this clinical approach requires nutrition professionals specialized in oncology. Due to its worldwide demonstrated efficacy, this integrated intervention should be fostered as the nutritional treatment of excellence in cancer patients.

**Supplementation**

Dietary counseling involves the prescription of therapeutic diets using regular foods; if the patient is unable to achieve his/her nutritional requirements via regular foods, nutritional supplements may be prescribed, the composition of which is based on the dietary deficits detected in the individual and a detailed intake questionnaire. Nutritional supplements can provide energy, protein and nutrients deemed necessary to meet the patient’s needs, and represent a useful
method of support when food intake is a problem. However, the success of supplementation depends on the acceptability of the product by the patient and on patient compliance. Oral supplements, which require an intact and functioning GI tract, can be used as between-meal supplements. If the gut is functioning but oral intake is compromised, tube feeding is often the most feasible means of dietary intervention.

**The Clinical Benefit**

Early individualized nutritional counseling during radiotherapy was the most effective regimen in reducing toxicity, improving nutritional intake and status, as well as QoL [76, 78–80]. After the completion of treatment and nutritional intervention, the efficacy persisted at the 3-month follow-up [78]. Similar results were attained by previous studies, where individualized counseling versus the standard practice did improve the patients’ nutritional status, intake, functional capacity and QoL [6, 78, 79, 81]. Of note: these studies were performed in patients with cancers typically associated with nutritional derangements, e.g. head-neck, colorectal and overall GI tract cancers, in all stages of the disease (stage I–IV), in patients submitted to chemotherapy and/or radiotherapy concomitantly, where chemotherapy regimens included 5-fluorouracil and platinum/irinotecan, for example, and in patients in whom median nutritional status was regular at baseline [80]. Hence, individualized nutritional counseling with regular foods, with or without supplements according to patients’ requirements, has grade A evidence to increase nutritional intake and prevent therapy-associated weight loss and treatment interruptions [76]. Thus, the right time to start nutritional support is as an adjuvant to antineoplastic treatments, as it should be planned along with the scheduled treatments for the cancer patients. Intensive individualized nutritional counseling became the standard recommendation by ESPEN guide-

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**Table 1. Common causes for a poor nutrient intake in cancer patients**

<table>
<thead>
<tr>
<th>Common causes for a poor nutrient intake in cancer patients</th>
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<tr>
<td>Deterioration in taste, smell and appetite as a consequence of the tumor and/or therapy</td>
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<tr>
<td>Altered food preferences/food avoidance/food aversion</td>
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<tr>
<td>Eating problems (teeth/chewing)</td>
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<tr>
<td>Dysphagia, odynophagia or partial/total GI obstruction</td>
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<tr>
<td>Early satiety, nausea and vomiting</td>
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<tr>
<td>Soreness, xerostomia, sticky saliva, painful throat and trismus</td>
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<tr>
<td>Oral lesions and esophagitis</td>
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<tr>
<td>Radiotherapy-/chemotherapy-induced mucositis</td>
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<tr>
<td>Acute or chronic radiation enteritis during and after radiotherapy</td>
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<tr>
<td>Depression and anxiety</td>
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<td>Pain</td>
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lines [76]. This evidence is mostly supported by the results of randomized controlled trials on nutritional therapy, in which a causal pathway between nutritional intervention and functional/clinical outcomes was demonstrated and later confirmed. A comprehensive review of the current literature undertaken by Lis et al. [82] supports the implementation of nutritional screening, assessment and individualized intervention to correct nutritional derangements in cancer patients.

**Timing of Nutrition**

Before Therapy

Individualized counseling with or without supplementation, taking into consideration the patients’ clinical condition and symptoms, did assure that a sustained and adequate diet was able to overcome the predictable deterioration subsequent to radiotherapy. Moreover, such nutritional outcomes concur with what has been proposed as the causal pathway, e.g. optimizing nutritional intake may be the most effective method for treating disease-related malnutrition. There is evidence in a range of conditions to support the hypothesis that enabling the provision of the appropriate nutritional therapy leads to improved body weight and fat free-mass, and that this generally reflects an improvement in the protein energy status. This is of particular concern due to the body composition changes and sarcopenia derived from the disease process. We also demonstrated that the nutritional content of the patient’s diet based on regular foods with appropriate manipulation is the key to improving GI function and other symptomatic manifestations during treatment and in the medium term. In patients who received dietary counseling and education, treatment-related toxicity, symptom incidence and/or disease severity were lower and their improvement in the medium term was faster. Indeed, dietary modifications may alter bowel functions, such as motility, enzyme secretion and nutrient absorption; likewise, nutrition modulates the GI flora whose ecology is central to the pathogenesis of radiation-induced injury severity. Nutrition is also a key determinant of QoL in cancer patients. Dietary counseling significantly improved all QoL function scores in association with an adequate dietary intake and nutritional status in patients that were able to eat and fit enough to comply with an individualized nutritional plan.

These results emphasize that ‘the impairment in structure, function and well-being that form malnutrition, are nutritionally responsive’. Furthermore, the benefits of nutritional intervention on QoL were extrapolated to improved physiological function and overall clinical outcome. In the medium term, in patients that received individualized counseling, all QoL symptom scales reverted to their baseline scores. These results in patients who experience persistent eating difficu-
cultivates support the concept that increased intake of an appropriate mixture of nutrients using regular foods may be of major benefit in modulating outcomes.

Long-term results of prospective randomized controlled trials with a median follow-up of 6.2 years (range: 4–8.2 years) are currently in press, and do provide novel evidence that adjuvant nutritional therapy, provided as early and timely individualized nutritional counseling and education per se, had a sustained effect on outcomes.

After Therapy

Individualized nutritional counseling has been proven to induce positive effects on patients’ nutritional as well as nonnutritional outcomes: improved nutritional intake and status, increased QoL, decreased late morbidity and probably improved prognosis. Additionally, nutritional status and intake, and global QoL scores at the end of treatment had the ability to predict survival and late toxicity. Patients with poorer dietary intake, worse nutritional status and poorer QoL had a significantly shorter survival and increased incidence of symptoms; thus, poor nutritional intake/status and QoL scores had a significant predictive value. Therefore, all patients should receive nutritional counseling with or without supplements according to their intake at the end of any antineoplastic treatment or surgery. Patients must be taught and educated on what to consume at discharge, so that they can maintain their QoL, nutritional and functional status and overall well-being and autonomy.

Disclosure Statement

The author declares that no financial or other conflict of interest exists in relation to the contents of the chapter.

References

Nutrition in Cancer 101


Nutritional Therapy for Critically Ill Patients

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Abstract
Nutritional therapy provided early in the critical care setting has been shown to improve outcome. Appropriate and early nutrition interventions can attenuate the hyperdynamic systemic response and depressed immune reaction to injury, serious illness and major surgery. Controversies limit the uniform application and potential benefits of nutrition, including failure to accurately predict who will ‘need’ nutritional intervention, lack of consensus on what the optimal enteral formulation is, overreliance on parenteral nutrition, failure to maximize the use of early enteral nutrition (EN), and how much and how best to feed the morbidly obese population. Despite challenges and inconsistencies in today’s critical care setting, specialized nutrition has evolved from metabolic ‘support’ during critical illness to a primary therapeutic intervention designed, individualized and focused to achieve metabolic optimization and mitigation of stress-induced immune and hyperdynamic systemic responses. Nutrition should be considered early and commenced after initial resuscitation has taken place. This is most effectively accomplished with the use of protocols that aggressively promote early EN, and will result in lower mortality and a reduction in major complications. Though the complexity of the heterogeneous critically ill population will always be challenging, we are developing a better understanding of immunity, metabolic needs and catabolism associated with intensive care unit admissions.
Introduction

Nutrition therapy provided early in the critical care setting has been shown to improve outcome [1, 2]. Appropriate intervention can attenuate the hyperdynamic systemic response and depressed immune reaction to injury, serious illness and major surgery. Not all intensive care unit (ICU) patients will derive similar benefits, nor tolerate prolonged periods of starvation or underfeeding. One of the main criticisms of aggressive nutritional interventions in the ICU is that not all ICU patients need it. In fact, previously well-nourished patients with a mild degree of critical illness and a relatively short stay in the ICU may derive little or no benefit from nutritional intervention. Most patients admitted at moderate-to-severe nutritional risk, however, should realize benefits from early enteral nutrition (EN) and could be harmed by ongoing prolonged iatrogenic underfeeding [3].

Controversies limit the uniform application of nutritional interventions, including failure to accurately predict who will ‘need’ it, lack of consensus of the optimal enteral formulation, overreliance on parenteral nutrition (PN), failure to maximize use of early enteral feeding, and how much and how best to feed the morbidly obese population. Recent studies on trophic feeding have been misinterpreted to imply that nutrition therapy is not important in the first week of hospitalization following ICU admission [4–6]. Across the globe, most ICUs fail to take steps to identify degrees of nutrition risk, determine the need for nutrition therapy or implement protocols to optimize delivery of the nutrition regimen. There are a number of modifiable factors that will determine whether or not benefits are realized, including the route of delivery, dosing, timing, content of nutrient substrate, interruptions in delivery and efforts to promote patient mobility [3]. Nonmodifiable factors include age, gender and genetics.

Despite challenges and inconsistencies in today’s critical care setting, specialized nutrition has evolved from metabolic ‘support’ during critical illness to a primary therapeutic intervention designed, individualized and focused to achieve metabolic optimization and mitigation of stress-induced immune and hyperdynamic systemic responses.

Enteral Nutrition Therapy

Historically, multiple reports have shown the significant physiologic value of EN over PN delivery (table 1) [7]. EN should be started as soon as possible, i.e. following admission to the ICU, to establish its nonnutritional, immunologic benefits and minimize the protein-calorie debt that frequently occurs during the 1st week of critical illness [8]. Nonnutritional benefits are described as the
physiologic mechanisms that maintain structural and functional gut epithelial integrity [9], attenuate oxidative stress, maintain humoral immunity and modulate the metabolic response [10–12]. By modulating the metabolic response, EN supports optimal carbohydrate utilization thereby decreasing insulin resistance [3].

More obvious nutritional benefits are obtained from the delivery of exogenous nutrients that provide sufficient protein and energy substrates and deliver micronutrients and antioxidants, and other specialized nutrients that aid in the attenuation of metabolic responses to stress. Overarchingly, maintaining lean body mass is the primary goal of successful nutrition intervention (table 1).

Patients receiving early EN versus PN consistently suffer fewer infections and have fewer hospital and ICU days. In some studies, a decrease in mortality has also been reported [13–16]. Randomized controlled trials of early versus delayed EN (e.g. feeding after 72 h) have shown that EN started within the first 24–48 h reduces infection, hospital length of stay (LOS) and mortality [1, 17]. When comparing early EN to ‘standard therapy’ (i.e. no supplemental nutrition) in elective surgical and surgical ICU populations, patients receiving EN initiated

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<th>Table 1. Advantages of EN over PN</th>
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<td><strong>Gastrointestinal benefits of EN</strong></td>
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<tr>
<td>Maintains gut integrity</td>
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<td>Reduced gut/lung axis of inflammation</td>
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<td>Enhances motility/contractility</td>
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<td>Improves absorptive capacity</td>
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<td>Maintains gut-associated lymphoid tissue</td>
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<td>Supports and maintains commensal bacteria</td>
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<td>Reduces virulence of endogenous pathogenic organisms</td>
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<td>Promotes the production of secretory IgA</td>
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<td>Promotes trophic effects on epithelial cells</td>
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<td><strong>Immune benefits of EN</strong></td>
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<tr>
<td>Modulates key regulatory cells to enhance systemic immune function</td>
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<td>Promotes dominance of anti-inflammatory Th-2 over proinflammatory Th-1 responses</td>
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<tr>
<td>Influences anti-inflammatory nutrient receptors in the gastrointestinal tract (duodenal, vagal and colonic butyrate)</td>
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<td>Maintains mucosa-associated lymphoid tissue at all epithelial surfaces (lung, liver, lacrimal, genitourinary and pulmonary)</td>
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<td>Modulates adhesion molecules to attenuate transendothelial migration of macrophages and neutrophils</td>
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<tr>
<td><strong>Metabolic benefits of EN</strong></td>
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<tr>
<td>Promotes insulin sensitivity through stimulation of incretins</td>
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<tr>
<td>Reduces hyperglycemia (advanced glycation end products), and muscle and tissue glycosylation</td>
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<td>Attenuates stress metabolism to enhance more physiologic fuel utilization</td>
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the day after surgery experienced similar results [13–15]. In observational cohort studies, early initiation of feeding prevents an caloric deficit, and improves outcomes in ICU [8, 18]. When a caloric deficit exceeds 4,000–10,000 calories, a rise in complications, including organ failure and infection occur. Other outcomes, including hospital LOS and ICU LOS, also worsen [18–21]. Studies that include protocols to increase the delivery of nutrient and energy to the ICU population improve clinical outcomes, with decreases in infection, shorter hospital LOS and decreased mortality compared to those without an EN protocol [22–26].

Determining patient candidacy for early EN is challenging; not all critically ill patients are appropriate candidates. Patients with minimal metabolic or traumatic stress should not be fed enterally. For example, aggressive, early EN would be inappropriate in patients expected to regain adequate, volitional oral intake within 48–72 h. Additionally, patients with absolute contraindications to EN (e.g. complete bowel obstruction or bowel discontinuity) should not be fed enterally. Nutritionally high-risk patient populations benefit most from early enteral feeds, including those malnourished prior to ICU admission, patients with sepsis, systemic inflammatory response syndrome, persistent inflammatory catabolism syndrome, immunosuppression and catabolism syndrome, and those expected to have a prolonged ICU stay [27–30]. This population should begin enteral feeding as soon as possible after admission. On rare occasions, they may need supplemental PN [31, 32]. If necessary, small bowel feeding should be considered, as well as the use of prokinetic agents to improve tolerance.

While little controversy surrounds the importance of supplemental nutrition for the nutritionally high-risk patient, assessment remains challenging. Nutritional assessment in the ICU population is often inappropriately judged by the use of visceral protein levels, such as albumin and prealbumin [10]. These serum tests are at best surrogate markers and seldom, if ever, of any clinical use in the ICU setting. Alternatively, a number of scoring systems have been developed for nutritional assessment that can be used for more clinically applicable assessment in the ICU population [33]. Nutritional Risk Screening (NRS-2002) [34] and the NUTRIC score [30] are relatively easy to use, and take disease severity and nutritional intake into consideration. The NUTRIC score has been validated in ICU populations [30, 34]. Several other grading systems are useful in hospitalized patients, such as the Mini-Nutritional Assessment, Malnutrition Universal Screening Tool (MUST), Nutritional Risk Index and Subjective Global Assessment, but are much less useful for ICU populations than the NUTRIC score and NRS-2002 [33].

Simple weight-based equations can be used to predict energy expenditure (for example 20–25 kcal/kg per day) and are appropriate for early, rapid determina-
tions of caloric needs; more accurate methods, however, are available. Indirect calorimetry is more accurate in most cases, but requires specialized equipment, and accuracy of the results may be affected at extremes of weight and height [35, 36]. Despite supporting literature, controversy remains regarding optimal timing, reasonable caloric deficits and when to permit underfeeding or ‘trophic feeding’. Significant recent attention has been paid to ‘trophic’ feeding, following a paper by the Vanderbilt Group in 2011 that described it (approximately 20 ml/h) for 5 days in patients with adult respiratory distress syndrome and acute lung injury, and showed outcomes including hospital stay, ventilator-free days and mortality that were essentially equivalent to full feeds [37]. Subsequently, several other studies have reported similar outcomes in a variety of clinical ICU situations [38], including both surgical and medical ICUs [39]. Conceptually, ‘trophic’ or ‘permissive underfeeding’ in the ICU is attractive, since fewer calories and smaller volumes would lessen the concern for hyperglycemia and aspiration; little data, however, support these findings [40, 41].

Once EN is initiated, nutritional therapy should focus on assuring that resuscitation goals continue to be met, risk for aspiration is minimized, and the rate of delivery is safely and swiftly advanced to goal. It is appropriate and safe to provide EN to patients on pressor agents that have been fully resuscitated and are hemodynamically stable [42]. Jejunal feeding-associated ischemic bowel in the patient on enteral feeding is extremely rare and occurs unpredictably and often later in hospitalization when the patient is no longer in the ICU [43]. Gastric feeding is successful and usually well tolerated in the vast majority of ICU patients, particularly when feeding is started early within the first 24 h [44]. A specific enteral access device, the location of infusion within the gastrointestinal tract (e.g. gastric, postpyloric or jejunal feeding) and consideration of need for jejunal feeding with simultaneous aspiration of the stomach are all predicated on the degree of tolerance of gastric feeding.

**What Is the Optimal Formula for the Intensive Care Unit Setting?**

While most patients in the critical care setting will tolerate a standard enteral formula (polymeric at 1.0–1.5 kcal/ml), it is appropriate to consider use of specialty formulas in individual patients in a variety of specific circumstances. Nutrients have traditionally been considered for the delivery of adequate basic energy for cell metabolism and cellular homeostasis. Recently, multiple reports have shown, when selected appropriately, specific nutrients such as eicosapentaenoic (EPA) and docosahexaenoic acid (DHA), arginine, leucine, glutamine and antioxidants given in quantities greater than needed for ‘normal’ cell me-
Tabolism as well as protein synthesis have multiple benefits. Benefits include shortening of ICU LOS, fewer days on mechanical ventilation, attenuation of the hyperdynamic metabolic response to stress, earlier resolution of inflammatory states, fewer systemic and blood stream infections, and decreased mortality in some cases. Despite previous speculation regarding the safety of arginine supplementation in ICU patients with sepsis, it has been shown to be safe from a hemodynamic standpoint, and beneficial in the septic and severely diseased patient [45–48]. In trauma patients and patients undergoing major elective surgery, formulas with arginine, fish oil and nucleotides are highly effective in reducing infection and hospital LOS, but have not proven to be consistently beneficial in the medical ICU population [49, 50]. Data support, however, the use of formulas with supplemental antioxidants and an anti-inflammatory lipid profile delivered by continuous infusion in patients with acute lung injury/adult respiratory distress syndrome on mechanical ventilation [51]. Delivery of EPA and DHA by bolus infusion does not appear to achieve the same physiologic effects or outcome benefits [52, 53]. The addition of supplemental enteral glutamine has shown outcome benefits for patients with burns or trauma, but recent studies do not support its widespread use in patients with multiple organ or renal failure, reporting it is harmful to this population [1]. Many specialty formulas, or so-called ‘organ- or disease-specific’ formulations, exist. They include small peptide, medium chain triglyceride formulas to promote more efficient nitrogen absorption in patients with gut dysfunction [54], a high-protein, low-calorie formula for obese patients [55], and organ failure formulas for patients with liver disease or acute kidney injury. While each is designed with the appropriate physiologic rationale for use in a specific patient population for which they were designed, additional study is needed before routine use in the ICU setting can be recommended. Pulmonary and glucose control formulas, however, lack physiologic validity; the use of these specific formulas is not supported by appropriate outcome data in ICU patients.

Numerous trials have shown a benefit from the provision of antioxidant cocktails to ICU patients on continuous feeding. A recent meta-analysis, including 21 randomized clinical trials, showed a reduction in mortality in patients treated with antioxidant supplements in the ICU [56]. The most effective ‘cocktails’ appear to contain selenium at higher doses, although the optimal dosing regimen, combination of antioxidants and method of administration (bolus vs. continuous infusion) are not clear. Excessive antioxidants can be detrimental, however, so caution with dosing must be taken [57].

The use of probiotics in the ICU setting has shown promise in limiting ventilator-associated pneumonia, antibiotic-associated diarrhea and Clostridium difficile infections. To obtain these benefits, the probiotic product should be ad-
administered per nasogastric tube and swabbed throughout the oropharynx. Used in this fashion, probiotics can reduce ventilator-associated pneumonia and decrease the likelihood of acquiring antibiotic-associated diarrhea, pseudomembranous colitis and overall infections [58–62]. Probiotic benefits appear to be relatively species specific, which should be considered when deciding which product to use or recommend [63].

A number of metabolically active ancillary agents have been proposed for the use in the critically ill patient based on their appropriate physiologic and/or pharmacologic effects [64]. β-Blockers attenuate the hyperdynamic response, and statins have a general pleiotropic effect and several areas of potential benefit, including antioxidant and immune stimulation. Anabolic agents, such as insulin, human recombinant growth hormone and glucagon-like peptide (GLP-2), have been shown to be beneficial in a very select setting to enhance protein synthesis in the muscles and gut. Anabolic steroids have been shown to support lean body mass in highly selective burn populations, but are not consistently helpful in a wide range of ICU patients. Leucine stimulates protein synthesis, citrulline serves as a substrate for arginine synthesis in the kidney and subsequent nitric oxide production, and carnitine may be beneficial in transporting long-chain fatty acids into the mitochondria for β-oxidation. Rigorous, well-designed studies demonstrating a beneficial effect on clinical outcomes with any of these metabolically active ancillary agents, however, are lacking. The use of these agents in the ICU is considered experimental, and should neither be used outside a research protocol setting nor extrapolated for the use in the general heterogeneous ICU patient population [64].

**Impediments to Early Enteral Feeding**

In the ICU setting, patients routinely receive only approximately 50% of the calories and proteins required or recommended [65–67]. Multiple factors impair adequate delivery of EN in the ICU. Frequently, feeds are not initiated early due to difficulty in defining full resuscitation and stabilization. In addition, patients can remain nil per os for diagnostic tests or surgical procedures, or nurses hold feeds for routine care like bathing, line changes, transport to radiologic tests and dislodging of tubes. EN is often withheld or stopped inappropriately for perceived intolerance as assessed by gastric residual volumes. These barriers lead to iatrogenic underfeeding. For these reasons, cessation of delivery of EN is estimated to be inappropriate in up to 66% of the time [66]. Gut dysfunction in critical illness typically involves segmental or diffuse dysmotility, reduced villous height and loss of absorptive surface at the villus tips in addition
to significant alterations in gut microbiota [68]. Typically, patients can be and should be fed through these periods of gut dysfunction, since EN itself can lead to restored gut integrity, enhanced contractility, increases in brush border and glycocalyx enzymes, and restoration of the commensal bacteria [12, 68]. While ileus is a frequent problem in critically ill patients, intensivists should be comfortable with more aggressive feeding strategies [68].

A common misconception in the ICU is that patients with high gastric residual volumes [69], patients with stable hemodynamics on vasopressor therapy [42], patients that are hypoactive or those with absence of bowel sounds with evidence of ileus should not be fed [68]. In prospective trials comparing the assessment of gastric residual volumes versus no assessment, the patients that were not assessed had increased EN delivery without any adverse sequelae while delivering more nutrients [70].

Challenging traditional ICU dogmas is one way to overcome barriers that can prevent positive changes in practice [71, 72]. Approaches to early EN designed to reduce barriers will likely improve abilities to provide optimal nutrition to critically ill medical and surgical patients.

**Strategies to Promote Optimal Nutrition Delivery**

Adopting one or many of the multiple specific strategies available to improve nutrient delivery will improve clinical outcome [73]. ‘Top-down’ or ‘de-escalation’ therapy is a concept widely used in other areas of medicine to manage complex disorders, such as rheumatoid arthritis, hypertension and surgical infection. Overall, this approach may allow more calories to be delivered. In the ICU nutrition arena, a ‘top-down’ protocol represents aggressive therapy with multiple strategies initiated at the start of ICU admission and beginning of enteral feeding, followed by de-escalation of therapy (as was demonstrated in the ‘PEPuP’ protocol) [74]. These assertive EN protocols are based on the principle that most critically ill patients will show a variety of stages of intolerance at the time of initiation of feeds. Rather than wait for patients to demonstrate intolerance (a reactive approach), a number of strategies are initiated simultaneously at the start of feeds to promote tolerance (a proactive approach) [74, 75]. These strategies include starting at goal rate with prokinetic therapy, monitoring the caloric deficit and changing infusion rates accordingly, elevating the head of the bed, not checking gastric residual volumes, and, in selective cases, use of specialty formulations and adding supplemental protein during the first few days of feeding [74]. Development and implementation of a nurse-driven enteral feeding protocol have been shown to increase...
EN delivery [76]. In order to enhance utilization, such protocols should be modified by the individual institution depending on local expertise, culture of the ICU and nursing practice [77].

**What Is the Current Role of Parenteral Nutrition in the Intensive Care Unit Setting?**

PN has a more limited risk/benefit ratio than EN in the critically ill population, and the selection of who of the patients will benefit requires consideration. Although recently the use of PN has been reported to be essentially equivalent in the ICU setting, in general, PN should only be considered when EN is not practical or possible [78]. If a nutritionally ‘low-risk’ patient is admitted to the ICU, then PN should neither be started as an initial procedure nor considered as first-line therapy. If a malnourished or nutritionally ‘high-risk’ patient is admitted, then PN should be started if EN is not feasible or possible [2].

**Future Trends**

A significant and relatively recent interest in combining early EN with aggressive early resistance exercise of axial skeletal muscle and early mobility in the ICU has been shown to promote the uptake and utilization of amino acids with maintenance of muscle mass and enhancement of function [79]. Prospective randomized trials on the effect of exercise in the ICU have shown reduced ICU LOS, duration of mechanical ventilation and total hospital LOS [80, 81]. The use of probiotics is likely on the rise, as manipulation of intestinal microbiota has already been shown to reduce ventilator-associated pneumonia, the likelihood of acquiring antibiotic-associated diarrhea or *C. difficile infections*, and the risk of colonization with vancomycin-resistant enterococci [58–60, 81, 82]. A newly described persistent inflammatory catabolism syndrome exemplifies the long-term adverse metabolic and immune sequelae from prolonged ICU LOS, where a patient continues a pattern of chronic inflammation, catabolism, degradation of lean body mass and a shift from a normal immune response to ineffective production of immature myeloid-derived suppressor cells [83]. These patients are often transferred from the ICU to long-term acute care facilities and cycle between them, never returning to baseline function [83]. Whether aggressive early nutrition therapy attenuates the persistent inflammatory catabolism syndrome, restores bone marrow function and improves long-term outcome has only been postulated and not yet proven.
Conclusions

The concept of nutrition ‘support’ in the ICU is now shifting toward nutrition ‘therapy’. The concept of providing EN and selective PN to attenuate the hyperdynamic response, maintain gut-associated lymphoid tissue and improve systemic immunity is well supported. Pharnaco-nutrition, or immune- and metabolic-modulating nutrition, including specific agents such as EPA and DHA, arginine and antioxidants, should be considered in surgical and select medical ICU populations. Nutrition intervention should be considered early and commenced as soon as initial resuscitation has taken place. This is most effectively accomplished with the use of protocols that aggressively promote early EN, and will result in lower mortality and a reduction in major complications. The evidence to support nutrition therapy as a mainstay in the ICUs has matured as data from cellular models have been translated to human trials. Despite this fact, many questions remain unanswered regarding the optimal dosing and timing, how best to combine EN with supplemental PN and which specialized therapies will improve outcome in the critically ill patient. We are, however, developing a better understanding of immunity, metabolic needs and catabolism associated with ICU admissions. The complexity of the heterogeneous critically ill population will always be challenging. As care in the modern ICU progresses to improve outcome, future nutrition studies will also guide us to answer these questions.

Disclosure Statement

Robert G. Martindale is a member of the advisory board for Nestle Nutrition and Metagenics. There is nothing to disclose for Malissa Warren, Sarah Diamond and Laszlo Kiraly.

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Abstract

As we look forward in 2015, attention to perioperative surgical nutrition continues to play a key role in optimizing outcomes and enhancing surgical recovery. Nutrition therapies for preoperative preparation include high protein intake combined with exercise, immune- and metabolic-modulating nutrients, carbohydrate loading, probiotic therapy and, occasionally, the need for specialized enteral or parenteral nutrition. Early enteral nutrition and probiotic therapy optimize gastrointestinal integrity and function in the postoperative setting. Some questions of who, when and how to optimally feed the surgical patient still exist. Despite these questions, the abundance of evidence supports a determined focus for nutrition optimization prior to major surgery.

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Introduction

The potential role of nutritional intervention to optimize surgical outcomes has yet to become fully realized and nutritional support is clearly underutilized [1]. Recent basic science literature and clinical trials continue to support the multiple benefits of preoperative nutrition therapy, and a recent push to recognize those patients who will benefit from pre- and perioperative nutrition has taken place [1]. In the preoperative period, the use of immune and metabolic
modulation has increased exponentially, while in the postoperative period, early enteral feeding remained a primary recommendation and has moved from theory and animal models to daily practice [2]. To date, the science supporting who to feed, when to feed and how to feed the surgical population continues to be fine-tuned. The benefits of appropriate nutrition both to the patient and the institution are well established, and include decreases in surgical complications, length of hospital stay, use of posthospital skilled nursing care and costs of health care delivery as well as increases in patient satisfaction [3]. In-depth protocols or bundles of interventions to enhance recovery and minimize complications, such as ERAS (Enhanced Recovery after Surgery), are readily available. While the idea of optimization of perioperative nutrition is widely agreed upon, its practice and implementation are not broadly utilized [4]. This article will explore the data that support best practices surrounding perioperative nutrition as we go forward.

**Preoperative Nutrition Preparation**

The preoperative period in the elective surgical candidate is an ideal time to assess and address modifiable risk factors to decrease the risk of surgical complications and poor outcomes. Preoperative preparations 1 month or more prior to surgery, including weight optimization, resistance exercise, improved glycemic control and smoking cessation, now have all been proven to improve postoperative outcomes. Though nutrition sometimes plays an integral role in preoperative preparation, it has yet to gain the attention it deserves. Evidence, however, is solid supporting nutritional preparation prior to surgery [1, 5–7]. A nutrition assessment can aid in identifying the degree of malnutrition and thus the level of preparation needed in the presurgical patient, including whether or not supplemental oral, enteral (EN) or parenteral nutrition (PN) is indicated.

**Preoperative Supplements Modulating Immune and Metabolic Responses**

The most frequent complication in patients undergoing major surgery is infection, the majority being surgical site infection and pneumonia [8]. A substantial body of research has reported improved outcomes in patients undergoing major elective surgery when immunonutrition formulas (IMFs; formulations including arginine and ω-3 fatty acids) have been provided in the perioperative period [5–7, 9, 10]. Beneficial outcomes result in a lower risk of morbidity, including decreased infections and improved wound healing, as well as shorter lengths of
stay and overall cost savings. Despite the significant benefits listed for the preoperative use of IMFs, mortality remains unchanged, as would be expected, due to low mortality rates at baseline in the elective surgery population. In order to show a statistical difference in mortality, a study in elective surgery would require several thousand patients [5]. Arginine is thought to be one of the primary nutrients driving the benefits reported for IMF [5]. In adults, arginine is considered a nonessential amino acid under normal physiologic conditions, but within hours of a major surgical intervention or trauma, plasma arginine levels fall significantly [11]. Providing supplemental arginine in the form of IMF increases arginine availability and promotes the arginine-dependent mechanisms of nitric oxide production, and T lymphocyte function and proliferation that improve the immune response. As a result of arginine metabolism via these processes, there is stimulation of anabolic hormones, such as growth hormone, prolactin and insulin, which enhance recovery, an increase in polyamine biosynthesis and proline synthesis for wound healing and tissue repair, and improved bactericidal action in the macrophage, contributing to decreased infection [12]. The importance of arginine metabolism and the effectiveness of its supplementation in the surgical and trauma population are demonstrated in clinical trials, and arginine supplementation is no longer controversial in these select groups [1, 12, 13].

The use of fish oil [eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)] is at the center of the concept of metabolic manipulation in the perioperative period. Appropriate use of DHA and EPA can partially attenuate the hyperdynamic metabolic response to surgical stress, reverse or stop the loss of lean body tissue, prevent oxidative injury and favorably modulate the inflammatory response [12, 14]. Traditionally, lipids were felt to be important in clinical nutrition but only as a caloric source providing essential fatty acids and supporting the absorption of fat-soluble vitamins via micelle formation in the proximal small bowel. Currently, specific lipids are being used to alter the metabolic response to stress by changes in cell membrane phospholipids, alterations in gene expression and by modulating endothelial expression of ICAM-1, E-selectin and other endothelial receptors regulating vascular integrity and function. Additionally, EPA and DHA derivatives, including resolvins, docosatrienes and neuroprotectins, are potent active effectors of resolution of inflammation [15]. These derivatives are now generally referred to as specialized proresolving molecules [15, 16]; they regulate class differentiation into M1 and M2 to control inflammation in the perioperative period. They also control polymorphonuclear neutrophil transmigration and timing of apoptosis. Docosanoids and neuroprotectins are both derived from DHA and have potent neuroprotective properties. Neuroprotectin decreases neutrophil infiltration, proinflammatory gene
signaling and NF-κB binding. The neuroprotectin NPD1 has been found to reduce neural infarct volume by half in an animal ischemia-reperfusion model [15]. These protective mediators are found to be highly conserved among species, from fish to mammals [15]. With the discovery of these compounds, it is acknowledged that resolution of inflammation is an active process rather than a passive time-dependent process.

When the preoperative period is studied, supplementation with oral IMF for 5–7 days before surgery has been reported to be beneficial in most [17–21] but not all analyses [22–24]. Continuing IMF into the postoperative period strengthens the observed benefits in poorly nourished patients [4, 22]. The most commonly studied surgical populations are patients undergoing major surgery for upper and lower gastrointestinal (GI) malignancies. A few of the more recent studies include Okamoto et al. [22], who evaluated the outcomes of gastric cancer patients receiving IMF supplementation for 7 days compared to those who received isocaloric nutrition. The IMF group demonstrated significantly fewer infectious complications and shorter duration of the systemic inflammatory response syndrome following gastrectomy [21]. IMF has also been studied with positive results in cardiac [25] and hepatobiliary surgery patients [26]. The nutrition status of study groups was divided into well and poorly nourished, or not well defined. Several large meta-analyses that included patients who were well and not well nourished showed that IMF benefitted both groups [7, 9, 27].

In some cases, oral nutrition supplementation in the preoperative period is not feasible. For patients with a decreased ability to take oral nutrition, EN or even PN may be indicated while the patient is being prepared for surgery. Significant weight loss (>10%) in 6 months and a low serum albumin level are correlated with an increased risk of poor outcome [27]. Albumin and prealbumin are only surrogate nutrition markers. Prealbumin and C-reactive protein ratios can help predict the inflammatory state of the host, which can be useful in the postoperative setting if nutrition intervention is now showing benefit.

**Parenteral Nutrition in the Surgical Setting**

The timing of when to use PN in the surgical patient remains controversial. In cases of intestinal obstruction, severe malabsorption, intestinal ischemia or multiple high-output fistulas that preclude the use of EN, evidence supports the use of PN for 7–10 days prior to surgery, delaying it, if possible, as needed to accomplish this. For optimal benefit, preoperative PN should be continued postoperatively until the patient can tolerate EN [28].
Preoperative Carbohydrate Loading

It has been postulated that delivery of an isotonic carbohydrate solution the night before surgery and 3 h preoperatively serves to 'load' the muscles, myocardium and liver with glycogen and is of benefit to surgical patients [29, 30]. The theoretical basis for this intervention is that the patient will deplete glycogen stores by fasting for 12–18 h preoperatively. When carbohydrate stores are depleted, an alternate fuel source for metabolism would be required (either lipid or muscle protein) almost immediately following the start of the surgical procedure [31]. By carbohydrate 'loading', the body can utilize the stored carbohydrate for the first few hours of the catabolic stimulus instead of resorting to muscle protein stores [31]. Carbohydrate 'loading' has been a component of ERAS or fast-track surgical pathways designed to capitalize on the benefits of reduced preoperative fasting [29]. In addition to preserving skeletal muscle mass, carbohydrate loading decreases insulin resistance and improves perioperative glycemic response. In other studies, carbohydrate loading has been reported to promote rapid return of postoperative bowel function and shorten hospital stay [30, 32]. Carbohydrate loading beverages are typically fat free, isotonic and contain about 50 g of carbohydrates in a volume of 300–400 ml per serving. The majority of protocols recommend two servings of the carbohydrate loading beverage for a total of 100 g of carbohydrates the night before surgery (about 8 h prior to surgery), and one serving of 50 g of carbohydrates again the morning of surgery (about 3 h prior to surgery). This dosing practice improves patient comfort, is safe and effective, and has not been shown to increase the aspiration risk of general anesthesia [30].

Postoperative Nutrition: Early Enteral Feeding

Appropriate and timely nutrition therapy in the postoperative setting can reduce infectious and surgical complications, including wound dehiscence and anastomotic leaks. EN or oral feeding within 24 h of surgery can speed recovery, reduce hospital stays and even lower patient mortality. Benefits have been reported over the past 15 years in many studies and a handful of meta-analyses of early EN delivery in the postoperative setting [33–35]. Due to the mounting supportive evidence, early EN has become a mainstay recommendation of fast-track protocols, as previously described [29]. Despite supporting evidence and globally adopted protocols, EN is too often delayed in the postoperative setting due to surgical dogma or common misperceptions regarding the contraindications to feeding [1]. Reasons for delayed EN in the
postoperative setting include lack of bowel function or postoperative ileus, fear of aspiration, fear of bowel ischemia, concern for the integrity of a fresh anastomosis, need to return to the OR and general lack of knowledge concerning its benefits [1].

Evidence-based practices to overcome barriers and maximize the opportunity for early EN postoperatively include obtaining feeding access at the time of the operative procedure, avoiding nasogastric decompression and oral or enteral feeding restriction, considering pharmacotherapy to prevent nausea and vomiting, and early mobility to promote GI function [36].

In a recently published randomized controlled trial, Boelens et al. [37] found that early EN after rectal surgery for malignancy resulted in a lower occurrence of anastomotic leak and shorter hospital stays for patients compared to early PN. In another randomized controlled trial of upper GI surgery patients, Barlow et al. [38] also showed fewer infectious complications, decreased anastomotic leaks and shorter length of hospital stays by 3 days ($p = 0.023$) when EN was initiated within 12 h of surgery compared to the control (nil per os until oral intake could be initiated at approximately 7–10 days postoperatively). The benefits of EN thought to promote improved patient outcomes include preservation of gut integrity and enhancement of gut-mediated immunity [39]. New evidence has emerged describing the mechanisms of these benefits. It is not surprising that maintenance of the microbiome by enteral feeding seems to play an integral role. Luminal nutrient stimulation promotes microbial diversity, improves the integrity of tight junctions and supports epithelial proliferation, resulting in a ‘bioecological control’ of pathogenic bacterial overgrowth [39]. In addition, Lubbers et al. [40] described the activation of the vagal anti-inflammatory reflex stimulated by EN that increases microvascular blood flow to the gut, supporting epithelial barrier function. In another recent publication, Harmanneh et al. [41] described the maintenance of alkaline phosphatase levels in the intestinal brush border by enteral nutrient stimulation. Adequate alkaline phosphatase levels in the intestinal brush border detoxify bacterial toxins, preventing endotoxemia. Heneghan et al. [42] described the beneficial effects on the integrity of the GI tract when Paneth cells are activated by EN. Paneth cells release multiple antimicrobial substances such as defensins, lysosomes, cathelicidins, phospholipase A2, and C-type proteins. Goblet cells, when stimulated by EN, also impact gut integrity by producing mucin that has pathogen-trapping capability [43].

An additional mechanism of benefit to maintain epithelial barrier function with enteral feeding is the reduction in proinflammatory cytokines in the gut wall that leads to epithelial cell apoptosis and contributes to increased intestinal permeability [44].
Role of Parenteral Nutrition in the Postoperative Setting

The American Society of Parenteral and Enteral Nutrition and the Society of Critical Care Medicine provide evidence-based recommendations for the appropriate use of PN in the surgical patient. PN is appropriate in the postoperative setting for severely malnourished patients who require PN preoperatively until adequate EN is achieved after surgery [45]. In addition, PN is appropriate when EN is not feasible, such as in the case of bowel discontinuity and a high-output proximal fistula. If, however, the patient was well nourished prior to surgery, then PN should be delayed for up to 7 days postoperatively if EN is not feasible or attempts at enteral feeding have failed [45].

The use of PN has not been uniformly associated with the same positive outcomes as EN. This is likely related to the lack of luminal nutrient stimulation in the GI tract that results in improved mucosal immunity in addition to the multitude of previously described benefits of EN. Instead, PN is consistently associated with an increased risk of infections in the postoperative setting. In a recent large multicenter randomized trial evaluating early versus late initiation of PN, patients in the late PN group had fewer infections, fewer days on mechanical ventilation and were more likely to be discharged alive than those patients receiving PN early in their ICU stay [46]. Kutsogiannis et al. [47] investigated the use of supplemental PN in a multicenter observational study including nearly 3,000 medical and surgical ICU patients requiring mechanical ventilation. Early supplemental PN improved calorie and protein provision, but was not associated with any clinical benefits. Patients in the early and late PN subgroups experienced longer hospital stays and increased mortality. This study, looking at supplemental PN in addition to EN, confirms that there are other reasons that PN may be associated with an increased risk of infection than just the lack of nutrient stimulation of the GI tract.

Probiotics in the Postoperative Setting

Disruption of the gut barrier function, increased intestinal permeability and immunologic compromise of the patient are unintended consequences of surgery. Probiotics may promote a positive balance and maintenance of the gut microbiota by strengthening intestinal barrier function, increasing numbers of beneficial bacteria and decreasing the number of pathogens. These are important roles for probiotics in the surgical patient, e.g. a beneficial effect on recovery. Recent evidence suggests that pre- and postoperative use of probiotics and synbiotics (prebiotics and probiotics) in the GI surgery patient reduces
infectious complications, decreases the duration of antibiotic treatment and improves GI motility. The meta-analysis by Kinross et al. [48] reviewed 13 randomized studies for the use of probiotics and synbiotics in the elective surgery patient. No complications from the use of these therapies were reported. As in most probiotic research, doses and strains varied across studies. Nineteen different probiotic strains were used across 13 studies [48]. Data published on a more homogenous population showed greater benefit of probiotic therapy. The promising results for probiotic and synbiotic therapy in the elective GI surgery patient are not necessarily translatable to other heterogeneous populations, such as the critically ill. Future studies must define the population, strain and dose to be administered, determine the outcomes to be measured as well as assess issues of safety to appropriately evaluate the effectiveness of probiotics in the clinical setting.

**Conclusion**

Currently, the concept of perioperative surgical nutrition is evolving to become routine practice in major surgery. The heterogeneity of the surgical population makes it very difficult to select a single specific formula, time or route for every patient. Each patient requires an individualized nutrition regimen that considers the severity of their surgical insult, their preexisting nutritional status and ongoing morbidities. By attenuating the metabolic response to stress, the appropriate nutrition regimen can facilitate improved outcomes and decrease health care costs by reducing postoperative morbidities, including deep vein thrombosis, pneumonia, infection, ventilator days, length of stay and mortality. The components of a successful nutrition regimen include IMF (orally and/or enterally) for the duration of 5–7 days preoperatively and in the early postoperative period, carbohydrate loading administered in the immediate preoperative setting and judicious occasional use of PN in the perioperative period. The evidence for probiotics and synbiotics is promising in the surgical setting, though further research is necessary to define the appropriate bacterial species or combinations of species and proper dose.

**Disclosure Statement**

Robert G. Martindale is a member of the advisory board for Nestle Nutrition and Metagenics. There is nothing to disclose for Teresa Hoos and Malissa Warren.
References


Abstract

Rational: The objective of this paper is to describe the applications of health economic theory to medical nutrition. Background: The published literature provides evidence that medical nutrition, e.g. oral nutritional supplements, is an effective treatment for patients with disease related malnutrition. Malnutrition is associated with mortality risk and complication rates, including infections. Malnutrition is not a new problem and with an ageing population it continues to become a major public health concern as increasing age is associated with an increased risk of malnutrition. Findings: This overview shows that in the case RCTs are providing the clinical evidence, there is no methodological difference between a cost-effectiveness analysis for pharmaceutical or nutrition. However, in nutrition the evidence may not always come from RCT data, but will be more often based on observational data. Therefore the clinical evidence of nutrition in itself is not the issue, but the handling of clinical evidence from observational studies. As the link between the consumption of a food product and a resulting health status is often more difficult to establish than the effect of a drug treatment it requires the further development of adapted methodologies in order to correctly predict the impact of food-related health effects and health economic outcomes from a broader perspective.

Rationale

Medical nutrition is a specific nutrition category either covering specific dietary needs and/or nutrient deficiency in patients or feeding patients unable to eat normally. It is exempted from the food regulation in Europe and in the US and regulated by specific rules, as it is dedicated to patients with nutritional deficien-
cies or inability to eat normally. Therefore, it is often not in all countries delivered under medical prescription and supervision by health care professionals.

Although these products have existed for more than two decades, the health economic evidence of medical nutrition interventions tends to be limited. An important reason is that medical nutrition does fall under the coverage requirements for reimbursement, like pharmaceuticals, which often require health economic data. Economic evaluations of pharmaceuticals and other health technologies, including devices, are common practice since the 1990s. Since that time, reimbursement agencies in different countries have developed evaluation guidelines, resulting in a large number of published research papers, comments, letters and editorials on economic evaluations of health technologies and policies [1], although health economic evaluations for medical nutrition are not common yet.

The objective of this paper is to describe the applications of the health economic theory for medical nutrition.

**Background**

**Clinical Background**

Medical nutrition comprises parenteral nutrition, which is regulated in pharmaceutical legislation, as well as all forms of nutritional support that are regulated as ‘foods for special medical purposes’ (FSMP), defined by the European Commission Directive 1999/21/EC independent of the route of application [2]. For the purposes of this article, the term medical nutrition is used only for FSMP, which is a category of dietary foods for particular nutritional uses specially processed or formulated, and intended for the dietary management of patients and to be used under medical supervision. One of the indications for the use of medical nutrition is malnutrition [European Society for Parenteral and Enteral Nutrition (ESPEN) guidelines 2006; Fight against Malnutrition 2012]. The following definition of malnutrition is widely acknowledged, including the ESPEN members: ‘A state of nutrition in which a deficiency, excess or imbalance of energy, protein, and other nutrients causes measurable adverse effects on tissue/body form (body shape, size and composition) and function, and clinical outcome’ [2]. Malnutrition thus includes both overnutrition (overweight and obesity) and undernutrition (insufficient nutrition). Although in some cases improvement in the quality or quantity of food supplied can ameliorate the problem, in many cases the person concerned is simply unable or unwilling to consume sufficient normal food to meet their requirements to manage the malnutrition. Particularly in the case of disease, it is literally of vital importance to
consider other options to improve nutritional intake, such as FSMP products, which include oral nutritional supplements (ONS) as well as enteral tube feeding (ETF) via nasogastric, naso-enteral or percutaneous tubes. Due to the catabolic state, loss of lean body mass leads to weight loss, which is an independent risk factor for mortality in chronically ill patients [3].

The published literature (meta-analyses and systematic reviews) provides evidence that ONS are an effective treatment for patients with disease-related malnutrition (DRM). Without nutritional intake, mortality occurs already after about 28 days in chronically ill patients (approximately 70 days in healthy persons) caused by a 40% weight loss [3]. Mortality rates are significantly lower (odds ratio of 0.61; 95% CI 0.48–0.78) [4]. Similar findings were reported in other reviews [5]. Complication rates, including infections, are significantly reduced (odds ratio of 0.31; 95% CI 0.17–0.56) [6]. Another systematic review showed that nutritional support can significantly reduce the risk of developing pressure ulcers (by 25%) [6]. Therefore, in patients with DRM, or at risk of DRM, the appropriate use of nutritional support can prevent complications arising, produce other clinical, functional and financial benefits, and can be lifesaving in some situations. Stratton and Elia [4] discuss the evidence from systematic reviews and meta-analyses of the effectiveness of nutritional support. The conclusion of this review is that nutritional support, including oral nutritional supplements, ETF and parenteral nutrition, is an important part of the management of any patient.

For the purposes of this article, the term malnutrition is used only for undernutrition in health care, which is caused by changes in the body metabolism due to acute or chronic diseases and/or treatment interventions increasing the daily nutritional needs, also known as DRM.

Economic Impact

Malnutrition is not a new problem, and with an aging population it continues to become a major public health concern as increasing age is associated with an increased risk of malnutrition [7]. It is not confined to developing countries, but is highly prevalent in the European health care system and in other developed regions. In European Union countries, about 20 million patients are affected by DRM (EUR 33 million in Europe), costing EU governments up to EUR 120 billion annually (EUR 170 billion in Europe) [8–10].

To estimate the efficiency (costs in relation to effects) in high-quality economic evaluations of enteral medical nutrition for DRM in adults in the Western world (developed regions), Freijer et al. [11] conducted a systematic review of published studies on this topic. The results showed that managing several patient populations suffering from (or at risk of) DRM in different health care settings with enteral medical nutrition is an efficient intervention from a health
economical perspective. ONS was the most studied form and the duration of using enteral medical nutrition varied from 3 years in patients with a cerebrovascular accident receiving ETF to 17 days of ONS in abdominal surgery patients. The mean duration of using ONS was 3 months. The economic value of enteral medical nutrition was calculated for the Netherlands (63%), Germany (25%) and the UK (12%). In all of the economic evaluations done alongside a clinical trial or survey (62%), the use of ONS or ETF for malnourished patients was part of a protocolized multicomponent nutritional intervention, and the control group received usual or standard care that consisted of no (protocolized) nutritional support including no (standard) use of ONS. In the evaluations using the modeling technique, the intervention consisted of ONS only versus no use of ONS in the control group [12, 13]. Freijer and Nuijten [12] performed a health economic study to assess the cost-effectiveness of ONS in the Netherlands. The use of ONS reduces the costs with EUR 252 (7.6%) cost saving per patient. The costs of hospitalization reduce from EUR 3,318 to 3,044 per patient, which is a 8.3% cost saving and corresponds to a 0.72-day reduction in the length of stay. The use of ONS would lead to an annual cost saving of a minimum of EUR 40.4 million. This analysis shows that the use of medical nutrition, ONS in this case, is a cost-effective treatment in the Netherlands and is superior to standard care without medical nutrition: it leads to cost savings and a higher effectiveness. A similar study by Nuijten and Mittendorf [13] assessed the health economic impact of ONS in the community setting in Germany. This study shows that the extra costs for ONS (EUR 534) are offset by a reduction in hospitalization costs (EUR 768) leading to total cost savings of EUR 234 per patient. A scenario analysis based on the length of hospital stays and per diem costing instead of diagnosis-related group costs shows that the extra costs for ONS (EUR 534) are also offset by a reduction in hospitalization costs (EUR 791) leading to cost savings of EUR 257 per patient. As a consequence, the use of ONS might be considered cost-effective at a patient and also a population level.

Health Economics

Basic Concepts
Escalating costs have become a major concern for health care professionals, decision-makers and the public, prompting the implementation of new cost containment measures over the last decade, focusing especially on new medical therapies and to a lesser extent on medical devices. The increasing demand results from aging of the population and an increase in new innovative, expensive, medical technologies, which are meant to replace often less expensive standard therapies.
As a consequence, health care decision-makers have been forced to develop new and more stringent criteria in the decision-making process for uptake of innovative therapies in the health insurance package. Instead of only considering the clinical benefits available at registration (traditional data: efficacy, safety and quality parameters) and the price of the new treatment, the decision-makers have taken a broader perspective, including also other related costs in the health care system. Over approximately the last 10 years, we can distinguish various additional data requirements, which especially relate to the use of the medicinal product in real daily practice. The most important new data requirements are effectiveness, cost-effectiveness and budget impact. Other considerations may also be taken into account depending on the specific indication, e.g. equity and social values in case of lifestyle medicinal products or orphan medicinal products.

As a consequence, new treatment options, including preventive treatments, are evaluated from a clinical as well as a broader economic perspective, thereby taking into consideration the overall costs and the impact on quality of life (QoL). The decision of health authorities on coverage of a medicinal product in the health insurance package is based on the value for money of that medicinal product. Health authorities will make a trade-off between the incremental, clinical benefit and the extra costs of the new medicinal product versus standard therapy. Currently, more formal methods of health technology assessment, such as budget impact and cost-effectiveness analysis, and more standardized measures of patient benefit are applied in order to make a value for money decision. The current most important new data requirements for coverage decisions by health authorities are:

- **Effectiveness**, which is the actual health benefit achieved by a medicinal product in daily practice. This contrasts with efficacy, which is the benefit measured under ideal conditions in a homogeneous group of patients.

- **Cost-effectiveness** of a medicinal product is based on the costs that will result from its use, and the potential savings that will be made compared with other products and/or treatments and the health benefits to the patient. The most used measure of this health benefit is the quality-adjusted life year (QALY). The lower the ratio of cost per QALY gained, the more cost-effective a health intervention is said to be. Threshold values are often used in coverage decisions. Medicinal products with ratios above these threshold values are not given coverage under the national health insurance package. These threshold values vary considerably from country to country. Values ranging from USD 50,000 to 100,000 per QALY gained (EUR 37,000–74,000) are sometimes used as a threshold in the US [14], whereas in the UK, the National Institute of Health and Clinical Excellence has adopted a cost-effectiveness threshold range of GBP 20,000–30,000 per QALY gained (EUR 23,800–
35,700). In the case of end-of-life treatment, an incremental cost-effectiveness ratio up to GBP 55,000 (EUR 65,450) may be accepted [15]. Other proposals include a differential threshold value between diverse disease and treatment characteristics; in the Netherlands, for example, recently a range between EUR 20,000 and 80,000 per QALY [16] gained has been suggested depending on the burden of disease for the patient (high burden → high cost per QALY threshold). There is currently an increasing demand for health economic data in the decision-making process in Europe. Several countries now have formal requirements (e.g. England/Wales, Scotland, Sweden, The Netherlands, Belgium, Finland and Portugal).

- Budgetary impact data from a financial analysis illustrate the impact of a new medicinal product on the annual national medicinal product budget and total health care budget.

**Quality-Adjusted Life Years**
The cost/QALY is seen as the preferred cost-effectiveness outcome. The QALY gain is calculated by combining the utility gain (QoL gain) with the number of life years gained. QALY gained may therefore be the result of longer life expectancy, utility gain or both. For example, a patient who experiences a survival gain of 4 years at a utility level of 0.4 will achieve the same 1.6 QALY gain as a patient with a survival gain of 2 years at a utility level of 0.8. Therefore, QALY may even be gained without increasing life expectancy. Malnutrition may have a negative effect on QALY through a reduction in life expectancy and a QoL reduction. Meta-analyses on treatment of DRM with medical nutrition show an increased QoL [6, 17]. If the cost per QALY gained is not viewed as the most appropriate outcome, other cost-effectiveness outcomes may be considered, for example, the cost per complication avoided, which reflects the additional costs for the prevention of one complication, e.g. decubitus. As a complication is not only a clinical issue, but also one which may have major economic consequences, this outcome might be relevant for decision-makers.

There are generic QoL scales, e.g. EQ-5D, which are important in the decision-making process, but disease-specific QoL outcomes can be relevant as well. If there is a correlation between the QALY gains and improvement in disease-specific measures, it gives decision-makers more confidence that the effects of the treatment are producing the QALY gains (fig. 1).

**Cost Assessment**
A major issue for cost-effectiveness evaluation is getting good quality costing data (resource use data). Each country has its own rules for costing depending on the decision-making perspective. Ideally, the cost assessment is based on the
so-called opportunity costs of utilizing a technology, which are defined as the benefits to be gained from the best alternative use of the resources. In a system of perfectly competitive markets, price reflects value, and even though health care markets are imperfect, the market price is routinely used to measure the costs of health care goods and services. If a societal perspective is adopted prices paid are an approximate measure of opportunity costs, but with a health system perspective, prices paid reflect opportunity costs to the health sector. The methodological issues for the cost assessment in malnutrition are not much different from other diseases.

The societal perspective is important for malnutrition, as well as for other diseases such as Alzheimer’s disease. Consequently, a study from a third party payer’s perspective, which only includes direct medical costs, may underestimate the true value of a new treatment in malnutrition. Short-term costs may include productivity losses for children caring for their parents, as well as the costs of treatment. Long-term indirect costs may be due to productivity loss as a result of malnutrition. Therefore, the cost assessment in malnutrition should include not only direct medical and nonmedical costs, but also the indirect costs for the patient and caregivers in the short and long term.

In a cost-effectiveness analysis, measuring the extent of costs is an important step. Costs can be broadly divided into two discrete resource categories: direct costs and indirect costs (often labeled productivity costs). Direct costs reflect the monetary burden of the medical care and nonmedical care expenditures made in response to a disease. The cost of medicinal products is one type of direct medical cost. Other types of direct medical costs include costs of hospitalizations, physician visits, tests and procedures, and durable medical equipment. Direct nonmedical costs include the costs to patients, such as travel to obtain treatment, and the value of time spent by family and other nonprofessional caregivers in supporting patients. The main indirect cost is lost produc-
tivity from the patient being absent from work as a result of morbidity or premature mortality induced by the disease or its treatment. Productivity costs are only relevant when studies are conducted from a true societal perspective.

For the collection of data on utilization, a variety of approaches exist. These include subject interviews, subject surveys, provider surveys, medical record reviews, health care utilization diaries and data reviews of insurance claims [18]. Registries and observational studies may also be potential sources for the collection of actual medical costs in daily practice, as well as direct nonmedical costs and indirect costs. In malnutrition, primary cost data collection may be necessary due to the lack of historical databases containing information on the health care utilization costs of current standard care. The prospective collection of cost data might well be achievable.

**Validity**

Clinical trials can have a low external validity because they have strict inclusion and exclusion criteria and treatments are protocol driven, leading to potential overestimation of units of health care utilization. Considering the prospective approach, the concept of validity should be addressed. Internal validity is the extent to which the analytic inference derived from the study sample is correct for the target population. External validity or generalizability is the extent to which the results found in the study sample also apply to the population from which the sample was taken. Randomization is usually applied to balance confounding variables and, with double blinding, helps to support internal validity. However, the external validity of randomized controlled trials (RCT) is more questionable. Inclusion criteria for patients and selection of study sites may mean that the sample is not representative of the potential patient population. In addition, treatment patterns may be determined by the protocol [19]. Therefore, both clinical and economic outcomes may not be typical and do not correspond to usual practice. Hence, it should always be considered that, due to its restriction on external validity, the estimates of efficacy from RCT may not be representative of the effectiveness of the intervention in the target patient population.

The statistical constraints and limitations of external validity may be alleviated by the use of registries. Registries use large, longitudinal, observational studies designed to measure the impact of a particular disease or condition on clinical and patient-specific outcomes, and to document the outcomes associated with different treatments or settings of care. Patients are followed prospectively, and data are collected on disease severity and clinical outcomes as reported by clinicians, as well as resource use, functional status and QoL as reported by the patient. Currently, targeted longitudinal observational databases, or patient registries, are being designed, which reflect the current treatment patterns
without influencing the treatments and without any interference with real practice (e.g. no randomization) being fully naturalistic and having a high external validity.

Observational data, however, may also have important limitations through the nonrandom decisions of clinicians that introduce bias [20]. In observational data, patients would often be treated differently based on the underlying condition [21]. By contrast, in a well-executed RCT, the patients’ condition is independent of treatment, and one can therefore reasonably attribute observed effects to the particular variation in treatment being studied. In observational data, the treatment is not allocated randomly. As a result, the characteristics of those obtaining the treatment will generally differ from the characteristics of those who get standard care (the controls). The differences may be observable characteristics such as age, in which case a regression equation can potentially control for them [22]. However, new methodologies have been developed, which may reduce the dependence of cost-effectiveness analyses on RCT data. For example, Newhouse and McCellan [21] presented an econometric technique (instrumental variables) that can be useful in estimating the effectiveness of clinical treatments in situations when a controlled trial cannot be done. This technique relies upon the existence of one or more variables that induce substantial variation in the treatment variable, but have no direct effect on the outcome variable of interest. The concept was illustrated with an application of aggressive treatment of acute myocardial infarction in the elderly, which showed that some of the differences in observed mortality between patients receiving catheterization and no catheterization could result from differences in the capabilities of the hospitals and physicians treating the two groups of patients, independently of the procedures given to them. For example hospitals with a catheterization unit are more likely to have other sophisticated treatments available to their patients, and their physicians and nurses may be more highly trained. These problems in general mean that while observational data are potentially useful, they must be used with caution, as there are a number of examples where observational data have resulted in conclusions about the effectiveness of therapy which have subsequently been shown to be wrong, such as the prophylactic administration of lidocaine in patients with acute myocardial infarction [23].

**Design**

(1) A health economic evaluation compares at least two alternative medical interventions by examining both their costs and consequences.

(2) Such health economic evaluations can either be performed alongside clinical trials (piggyback study), as observational naturalistic economic evaluations (measured in real-world settings) or on the basis of health economic modeling.
(3) Economic analyses alongside clinical trials are often inconclusive due to a limited time horizon, a possible focus on surrogate end points, a highly selected patient population (low external validity – results are not generalizable) and due to protocol-driven costs.

(4) The major limitations of observational naturalistic economic evaluations are the selection bias (selection among treatment options can be influenced by the clinical and socioeconomic status of the patient) and that they can be conducted only after registration – as they are implemented in real-world settings.

(5) The third type – economic modeling – is routinely used to predict the ‘comparative product value’ for market access and reimbursement purposes. Economic modeling has the advantage that it can handle limitations outlined for piggyback and observational economic evaluations. For example economic modeling may be used to translate efficacy outcomes obtained from RCT into effectiveness outcomes (expected under routine real-world conditions), to simulate long-term therapy effects and to translate surrogate parameters into patient-relevant outcomes. Furthermore, it enables estimating results to specific patient groups or local settings, which is crucial to ensure the relevance of national reimbursement decisions.

**Health Economic Modeling in Medical Nutrition**

The use of models in economic evaluation combines different types of data sources to extend available information. Models can be used to simulate costs of trial modalities, to generalize trial results, to translate evidence from RCT into daily practice or to explore the potential value of additional evidence from empirical research. Several types of models can be used in the area of nutrition. One of them is the decision tree, comparing two or more health strategies. It defines intervention pathways and then links costs and outcomes to all the possible options. Another type of model is the Markov model, which is organized around health states rather than around pathways. In this case, the data input will be based on probabilities of transitions between successive health states, and specific costs and utilities associated with the various health states. Modeling techniques usually extrapolate the available short-term evidence over time in order to estimate outcomes beyond the study period or to link intermediate end points to final outcomes. The need for long-term follow-up, in the general or in a healthy at-risk population, may be solved by extrapolation methods; these are not specifically related to nutrition, but more to underlying available evidence and relationships. The real evidence for the efficacy of a preventive treatment might come from observational studies. For the purpose of illustration, we pres-
ent the linear decision analytic model, which was developed to estimate the health economic impact of ONS in the Netherlands and mentioned in the section Background [12]. The model calculates the medical costs for a virtual population of abdominal surgery patients with ONS and for a virtual population of abdominal surgery patients without ONS. The health economic impact of ONS is calculated using a linear model built in Excel reflecting treatment patterns and associated outcomes. Figure 2 shows the structure of the model for treatment with ONS. The first branch point in a tree is called a decision node because it corresponds to a choice of treatment – ONS or ‘no ONS’ – in patients eligible for ONS due to or at risk of DRM. A decision node is represented as a small square (◻). Subsequent to the decision node, the structure of the decision tree is shown, and it is identical for both treatment options. The other branch points indicate probabilities. Data sources used included published literature, clinical trials and official Dutch price/tariff lists and national population statistics. The assumption of this study was that there were no clinical differences between the treatment arms, except for length of stay. The model shows that the use of ONS is cost-effective, because the additional costs for ONS are more than balanced by a reduction in hospitalization costs due to a reduction in the length of stay.

Discussion

This example shows that in case RCT are providing the clinical evidence, there is no methodological difference between a cost-effectiveness analysis for pharmaceuticals and nutrition. However, in nutrition, the evidence may not always come from RCT data but will be more often based on observational data. Therefore, the clinical evidence of nutrition in itself is not the issue, but the handling of clinical evidence from observational studies. There have been requirements for health
economics for pharmaceuticals for more than a decade, which resulted in formal academic guidelines for the appropriate execution of health economic evaluations. However, these so-called pharmaco-economic guidelines are based on the clinical evidence specifically required for pharmaceuticals. As the link between the consumption of a food product and a resulting health status is often more difficult to establish than the effect of a drug treatment, it requires further development of adapted methodologies in order to correctly predict the impact of food-related health effects and health economic outcomes from a broader perspective.

The definition of standard care is a specific issue in cost-effectiveness analyses for nutrition. The normal daily food intake in the intervention group as well as in the control group can interfere with the medical nutrition intervention, very likely affecting the results. Moreover, randomization between groups as well as within the intervention group might be necessary to cope with the heterogeneity. Heterogeneity in the study population may have a significant bearing on the size of the treatment effect estimated. Another complicating issue is that multiple systems in the body can be affected, which may lead to a high variance in efficacy, contributing to a statistical power problem in RCT.

Finally, we want to address some policy issues. The pharmaceutical world is regulated at all levels starting with the execution of early clinical trials, followed by marketing authorization requirements (e.g. the European Medical Agency) towards the pricing and reimbursement assessment at national, regional and local levels. Furthermore, in most markets (or countries), the user of health care is not the provider and not the payer (‘triangle of health care’), which might have adverse impacts on the utilization and demand of medical care. Nutrition interventions tend to be excluded from these processes, although health care decision-makers have begun to realize that food plays an important role, not only in those already with disease, but also in the onset and evolution of lifestyle-related disorders. Indeed, improving health through better population nutrition may contribute to the cost-effectiveness and sustainability of health care systems. However, cost-effectiveness analyses have been mainly associated with drug and medical device reimbursement decisions, where, in many countries, financial considerations of affordability may be as important as clinical effectiveness and cost-effectiveness. Medical nutrition could improve health, which may contribute to the cost-effectiveness and sustainability of health care systems.

Disclosure Statement

The author declares that no financial or other conflict of interest exists in relation to the contents of the chapter.
References

Abstract

Older adults can be categorized into three subgroups to better design and develop personalized interventions: the disabled (those needing assistance in the accomplishment of basic activities of daily living), the ‘frail’ (those presenting limitations and impairments in the absence of disability) and the ‘robust’ (those without frailty or disability). However, despite evidence linking frailty with a poor outcome, frailty is not implemented clinically in most countries. Since many people are not identified as frail, their treatment is frequently inappropriate in health care settings. Assessing the frail and prefrail older adults can no longer be delayed, we should rather act preventively before the irreversible disabling cascade is in place. Clinical characteristics of frailty such as weakness, low energy, slow walking speed, low physical activity and weight loss underline the links between nutrition and frailty. Physical frailty is also associated with cognitive frailty. We need to better understand cognitive frailty, a syndrome which must be differentiated from Alzheimer’s disease. At the Gérontopôle frailty clinics, we have found that almost 40% of the patients referred to our center by their primary care physicians to evaluate frailty had significant weight loss in the past 3 months, 83.9% of patients presented slow gait speed, 53.8% a sedentary lifestyle and 57.7% poor muscle strength. Moreover, 43% had a Mini-Nutritional Assessment less than 23.5 and 9% less than 17, which reflects protein-energy undernutrition. More than 60% had some cognitive impairment associated with physical frailty.
Introduction

Disability with aging is a clinical issue representing a priority for public health systems. In fact, besides the increased burden on the patient’s quality of life, disability is associated with high health care costs [1]. Assessing the frail and prefrail older adults can no longer be delayed, we should rather act preventively before the irreversible disabling cascade is in place [2].

The Frailty Syndrome: A Common Clinical Situation

During the last two decades, a growing body of literature has been specifically focused on exploring the ‘frailty syndrome’. Frail older adults are at increased risk of negative health-related events, including hospitalization, institutionalization and disability. In particular, frailty is usually considered as a state preceding disability which, in contrast to disability, is still amenable to treatment interventions and reversible [3]. On the basis of this novel concept, the heterogeneous older population was subsequently categorized into three subgroups to be able to design and develop person-tailored interventions. Older persons were then considered ‘disabled’ if needing assistance in the accomplishment of basic activities of daily living (ADL), ‘frail’ if presenting limitations and impairments in the absence of disability, and ‘robust’ if no frailty or disability is present. Frailty has been conceptualized as a physiological syndrome reflecting decreased reserve and resilience, which may lead to a progressive functional decline, vulnerability to stressors and an elevated risk of adverse outcomes, including death. It is a major cause of dependency, yet research suggests that it may be possible to prevent disability and dependency by targeting frail and prefrail older adults with simple screening tools and effective and sustained interventions [2]. A recent consensus conference was convened in Orlando Florida to develop consensus operational approaches along with delegates from IAGG (International Association of Geriatrics and Gerontology), AMDA (American Medical Directors Association), AFAR (American Federation of Aging Research), EUGMS (European Union Geriatric Medicine Society), IANA (International Academy of Nutrition and Aging), SSCWD (Society on Sarcopenia, Cachexia and Wasting Disorders), the EU and GEC (Gateway Geriatric Education Center) [4].

Strong evidence supports the definition of frailty as a syndrome with a distinct etiology consisting of a constellation of signs and symptoms that increase vulnerability to stressors and that, taken together, are better at predicting an adverse outcome than any individual characteristic. Fried et al. [5] have proposed that the signs and symptoms of frailty result from dysregulated energetics
involving multiple molecular and physiological pathways, which lead to sarcopenia, inflammation, decreased heart rate variability, altered clotting processes, altered insulin resistance, anemia, altered hormone levels and micronutrient deficiencies. These physiological impairments result in the five clinical characteristics of frailty: weakness, low energy, slow walking speed, low physical activity and weight loss [5]. The presence of any three of these phenotypes indicates that a person is ‘frail’; one or two phenotypes indicate that the person is ‘prefrail’ and absence of these characteristics indicates the person is ‘robust’.

A systematic review incorporating 31 studies of frailty in persons 65 years or older found a prevalence from 4.0 to 17.0% (mean 9.9%) for physical frailty, with a higher prevalence when psychosocial frailty was also included [6]. While the Fried approach quantifies frailty using five measures, Rockwood et al. [7] have developed a Frailty Index based on the Comprehensive Geriatric Assessment which counts up to 70 items. In a study of community-dwelling older adults in Canada, the Frailty Index-Comprehensive Geriatric Assessment estimated a frailty prevalence of 22.7%, with higher scores predicting an increased risk of death.

Frailty has been linked to longer hospital stays and increased mortality in hospitalized patients [8]. Moreover, in their study of disability trajectories of community-dwelling older persons during the last year of life, Gill et al. [9] found that frailty was the most common condition leading to death, followed by organ failure, cancer, other causes, advanced dementia and sudden death. Yet, despite evidence linking frailty with a poor outcome, frailty is not implemented clinically in most countries. Since many people are not identified as frail, they frequently are treated inappropriately in health care settings. For example, regardless of age, a frail person may be unable to withstand aggressive medical treatment that could benefit a nonfrail person.

**Nutrition and Frailty**

Frailty can be influenced by a number of factors, and nutrition has been identified as a factor influencing the development of frailty. The Orlando Task Force [4] felt that evidence supported three treatments which appeared to be effective in decreasing frailty in the majority of individuals:

- Calorie and protein support
- Vitamin D
- Exercise (resistance and aerobic)

In the Women’s Health and Aging Studies including 599 women aged 70–79 years and a body mass index greater than 18.5, Blaum et al. [10] showed that
being overweight was significantly associated with prefraility, and obesity was associated with prefrailty and frailty. In the English Longitudinal Study of Ageing, Hubbard et al. [11] showed in 3,055 patients aged 65 years and older that the association between body mass index and frailty showed a U-shaped curve. Independent of the body mass index, daily energy intake was lowest in people who were frail, followed by prefrail people, and highest in people who were not frail. Energy-adjusted macronutrient intakes were similar in people with and without frailty. Frail [adjusted odds ratio (AOR): 4.7; 95% confidence interval (CI): 1.7–12.7] and prefrail (AOR: 2.1; 95% CI: 0.8–5.8) people were more likely to report being food insufficient than nonfrail people; serum albumin, carotenoids and selenium levels were lower in frail adults than nonfrail adults [12].

Several observational studies have shown an association between inadequate nutritional intake and frailty. In the Invecchiare (aging) in Chianti (InCHIANTI) study, Bartali et al. [13] found that daily energy intake ≤ 21 kcal/kg body weight was significantly associated with frailty (OR: 1.24; 95% CI: 1.02–1.5). This study also analyzed the association between frailty and nutrients; after adjusting for energy intake, low intakes of protein (OR: 1.98; 95% CI: 1.18–3.31); vitamin D (OR: 2.35; 95% CI: 1.48–3.73), vitamin E (OR: 2.06; 95% CI: 1.28–3.33), vitamin C (OR: 2.15; 95% CI: 1.34–3.45) and folate (OR: 1.84; 95% CI: 1.14–2.98) were significantly and independently related to frailty [13].

Two studies have shown an association between inadequate protein intake and frailty. In the Women's Health and Aging Studies, 24,417 patients aged 65–79 years were included and followed up during 3 years. After adjustment for confounders, results showed that a 20% increase in uncalibrated protein intake (%kcal) was associated with a 12% (95% CI: 8–16%) lower risk of frailty, and that a 20% increase in calibrated protein intake was associated with a 32% (95% CI: 23–50%) lower risk of frailty [14]. In the second study, protein intake below the estimated average requirement (0.7 g/kg per day) was found in 10% of the community-dwelling and frail elderly and 35% of the institutionalized elderly people [15]. Then, dietary protein intake averaged at 1.1 ± 0.3 g/kg per day in community-dwelling, 1.0 ± 0.3 g/kg per day in frail and 0.8 ± 0.3 g/kg per day in institutionalized elderly men.

Finally, two studies showed an association between Mediterranean diet [based on a Mediterranean diet score (maximum 9 points) evaluated by an interview-based food frequency questionnaire] and frailty. In the InCHIANTI study, 690 patients aged ≥65 years were included and followed up during 6 years. Results showed that higher adherence (score ≥6) to a Mediterranean-style diet was associated with lower odds of developing frailty (OR: 0.30; 95% CI: 0.14–0.66) compared with those with lower adherence (score ≤3), and that higher adherence to a Mediterranean-style diet at baseline was also associated with a
lower risk of low physical activity (OR: 0.62; 95% CI: 0.40–0.96) and slow walking speed (OR: 0.48; 95% CI: 0.27–0.86) but not with feelings of exhaustion and poor muscle strength [16]. One other recent study showed that the risk of being frail was significantly reduced in the highest quartile of the Mediterranean diet score (OR: 0.26; 95% CI: 0.07–0.98) [17].

Several studies showed that lower levels of 25-hydroxyvitamin D were associated with a higher prevalence of frailty [18–21].

Observational studies have found an association between serum antioxidants (vitamin E, vitamin C and carotenoids) [22–25], vitamin B₆ and folate [24, 25] and frailty.

In the Gérontopôle frailty screening, approximately 40% of the patients had weight loss and a poor nutritionals status [26].

**Physical Activity and Frailty**

Many studies have shown that physical activity and exercise are beneficial in older adults along the full spectrum of the health status. The demonstrated benefits of exercise in older adults include increased mobility, enhanced performance of ADL, improved gait, decreased falls, improved bone mineral density and increased general well-being. Decreased muscle strength occurs normally with age but is even more pronounced in the frail older adult and more likely to impact adverse outcomes such as disability. Studies suggest that even the frailest oldest adults are likely to benefit from physical activity at almost any level that can be safely tolerated [27]. Regular physical activity has been shown to protect against diverse components of frailty such as sarcopenia, functional impairment and depression [28].

Exercise is believed to be the most effective of all interventions proposed to improve functionality in older adults. In a systematic review, Theou et al. [29] found that 45–60 min of exercise three times a week had positive effects on frailty. Exercise in the frail increases functional performance, walking speed, chair stand, stair climbing and balance, and decreased depression and fear of falling.

A more recent systematic review has been published on the effect of exercise on frail older adults [30]. The authors concluded that the exercise intervention only slightly affected physical function, mainly by increasing gait speed and the Berg Balance Scale score, and improved performance in ADL. Nevertheless, they underlined that participants included in these trials may be not representative of the total frail older adult population because of those who would have benefited from exercise but were excluded from the trial because of age or other comorbidities that prevented them from exercising.
**Multidomain Approach**

Multidomain interventions are currently tested in large programs [31]. This multidomain approach will aim to treat physical and cognitive frailty with a combination of nutrition supplementation and physical and cognitive exercise.

**Implementing Frailty into Clinical Practice**

In order for frailty to be incorporated into the routine practice of primary care physicians, a simple screening test is needed. Several different methods of screening for frailty have been developed and validated. The Fried criteria were operationalized into a screening algorithm for use in the Cardiovascular Healthy Study. Other frailty measures have also been proposed, including the Study of the Osteoporotic Fractures Index [32]. All of these measures count deficits and all of them quantify the degree of frailty and thus the degree of vulnerability to adverse outcomes. Moreover, all of them reflect an aging-associated failure of physiological systems.

Another frailty screening tool that relies on the clinical opinion of the general practitioner has been developed in France. In response to the French government’s policy for preventing disability in older persons, a day hospital was established in 2011, the Gérontopôle of Toulouse (i.e. the geriatric center of Toulouse), for the evaluation of frailty and prevention of disability [26]. Geriatric patients are referred to the center by general practitioners who detect signs or symptoms of frailty, and patients are screened using a simple, quick frailty questionnaire as well as an assessment of gait speed. The frailty screening tool asks six questions regarding living alone, weight loss, fatigue, mobility, memory and slow gait speed. If the physician identifies one of these areas as an area of concern, he/she is asked: ‘In your own clinical opinion, do you feel that your patient is frail and at an increased risk for further disabilities?’ It is this last question that is used to identify patients who are frail (table 1).

The aims of the Gérontopôle frailty clinics are to identify frailty in the early stages through a multidisciplinary evaluation and its cause(s), i.e. underlying diseases or risk factors, and to implement multidisciplinary interventions adapted to each patient’s individual needs. These interventions may include nutrition, physical exercise and/or physical therapy, social support and education. Patients are followed up principally by their general practitioner as well as through phone contact and a structured interview with a nurse from the center to assess the efficacy of the interventional plan.
We recently published the description of the 160 first patients referred for frailty by general physicians to the Gérontopôle frailty clinics, a new clinical facility developed in Toulouse to implement frailty into clinical practice. The mean age of our population was 82.7 years, with a large majority aged 75 years and older. Most patients were women (61.9%). Approximately two thirds of the patients received any kind of regular help. Regarding the level of frailty, 65 patients (41.4%) were prefrail and 83 (52.9%) frail. Near 40% had significant weight loss (more than 4.5 kg in the past 3 months). With respect to the functional status, 83.9% of the patients presented slow gait speed, 53.8% had a sedentary lifestyle and 57.7% had poor muscle strength. Only 27.2% of the patients had a Short Physical Performance Battery score equal to or higher than 10. Autonomy in ADL was quite well preserved (mean ADL score: 5.6 ± 0.8) as expected, suggesting that the study patients had not yet developed disability. Consistently, Instrumental ADL showed a marginal loss of autonomy reporting a mean score of 6.0 ± 2.3. Numerous patients presented vision problems. Finally, it is noteworthy that 9% of the study population presented an objective state of protein-energy malnutrition, i.e. Mini-Nutritional Assessment (MNA) less that 17, and 34% an early alteration of nutritional status with the MNA between 17 and 23.5, while almost everyone (94.9%) had vitamin D deficiency. These results are confirmed in a larger sample with now more than 1,000 patients from the Gérontopôle frailty clinics with similar characteristics.

Table 1. The Gérontopôle frailty screening tool (from Vellas et al. [36], with permission): a questionnaire for the detection of frail older patients by general practitioners

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>Don’t know</th>
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<tbody>
<tr>
<td>Does your patient live alone?</td>
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<td></td>
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<tr>
<td>Has your patient involuntarily lost weight in the last 3 months?</td>
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<tr>
<td>Has your patient been more fatigued in the last 3 months?</td>
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<tr>
<td>Has your patient experienced increased mobility difficulties in the last 3 months?</td>
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<tr>
<td>Has your patient complained of memory problems</td>
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<tr>
<td>Does your patient present slow gait speed (i.e. &gt;4 s to walk 4 m)?</td>
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</tr>
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</table>

If you have answered *yes* to one or more of these questions:

Do you think your patient is frail?  
If *yes*, is your patient willing to be assessed for his/her frailty status at the Frailty Clinic?

Patients aged 65 years and older without both functional disability (ADL score 5/6) and current acute disease.
To have a real impact, the intervention must be strong. To do this, a complete geriatric assessment of the prefrail and frail patients is necessary to be able to diagnose an age-related disease at a prodromal stage, where it is still possible to cure the patient. The evaluation must use specific tools to enable the most accurate diagnosis of potential age-related diseases. The assessment must include also social, health, economic and psychosocial assessments, as well as the evaluation of deficit accumulation. We also need to adapt some of our tools to frailty, e.g. many studies have found that individuals with MNA scores between 17 and 23.5 are more likely to be frail [33, 34].

Due to the aging population, we need long-term and sustained interventions. Physical exercise, cognitive exercise, nutritional interventions and social services will be needed for the detection and treatment of age-related diseases. More standardization of these multidomain interventions is an important area for further research. We have to balance very strong interventions (which will be accepted by few frail older adults) against very weak interventions (which will usually not be strong enough to have a real impact).

**Cognitive Frailty**

To date, most research efforts on frailty have focused on its ‘physical’ aspects, and little work has been done, however, to clarify how the process of frailty itself affects the brain. A brain deemed ‘frail’ and not robust for age may still possess a plastic reserve that could respond to rehabilitative and eventually to preventive strategies to significantly attenuate its functional decline. Considering the current increased interest in the frailty syndrome and aging brain, as well as in the development of strategies to attenuate disability in the elderly, a workshop on cognitive frailty was conducted by an International Consensus Group from the IANA (International Academy on Nutrition and Aging) and IAGG (International Association of Gerontology and Geriatrics) on April 16, 2013, in Toulouse (France) [35]. This report presents current issues related to the relationship between frailty and cognition and results from the Consensus Group. Cognitive frailty, when clearly defined, may represent a novel and more actionable condition to consider in the complex and heterogeneous scenario of cognitive and emotional impairment in older persons. The consensus panel proposed the identification of the so-called ‘cognitive frailty’ as a heterogeneous clinical manifestation characterized by the simultaneous presence of both physical frailty and cognitive impairment. In particular, the key factors defining such a condition include: (1) the presence of physical frailty and cognitive impairment (Clinical Dementia Rating = 0.5) and (2) exclusion of concurrent Alzheimer’s disease or other dementias. Under different circumstances, cognitive frailty may represent a precursor of neurodegenerative processes. A potential for reversibility
may also characterize this entity. A psychological component of the condition is evident and concurs with increasing vulnerability of the individual to stressors.

To identify frail older adults is the future of geriatric medicine and must also be addressed by primary care physicians as well as specialists facing an aging population. Moreover, it is a unique opportunity to prevent further disabilities. All health care professionals play an important role, including dietitians and physical therapists.

Disclosure Statement

Sophie Guyonnet and Marion Secher: None; Bruno Vellas: Research Grant, Consultant: Nestlé, Nutricia.

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