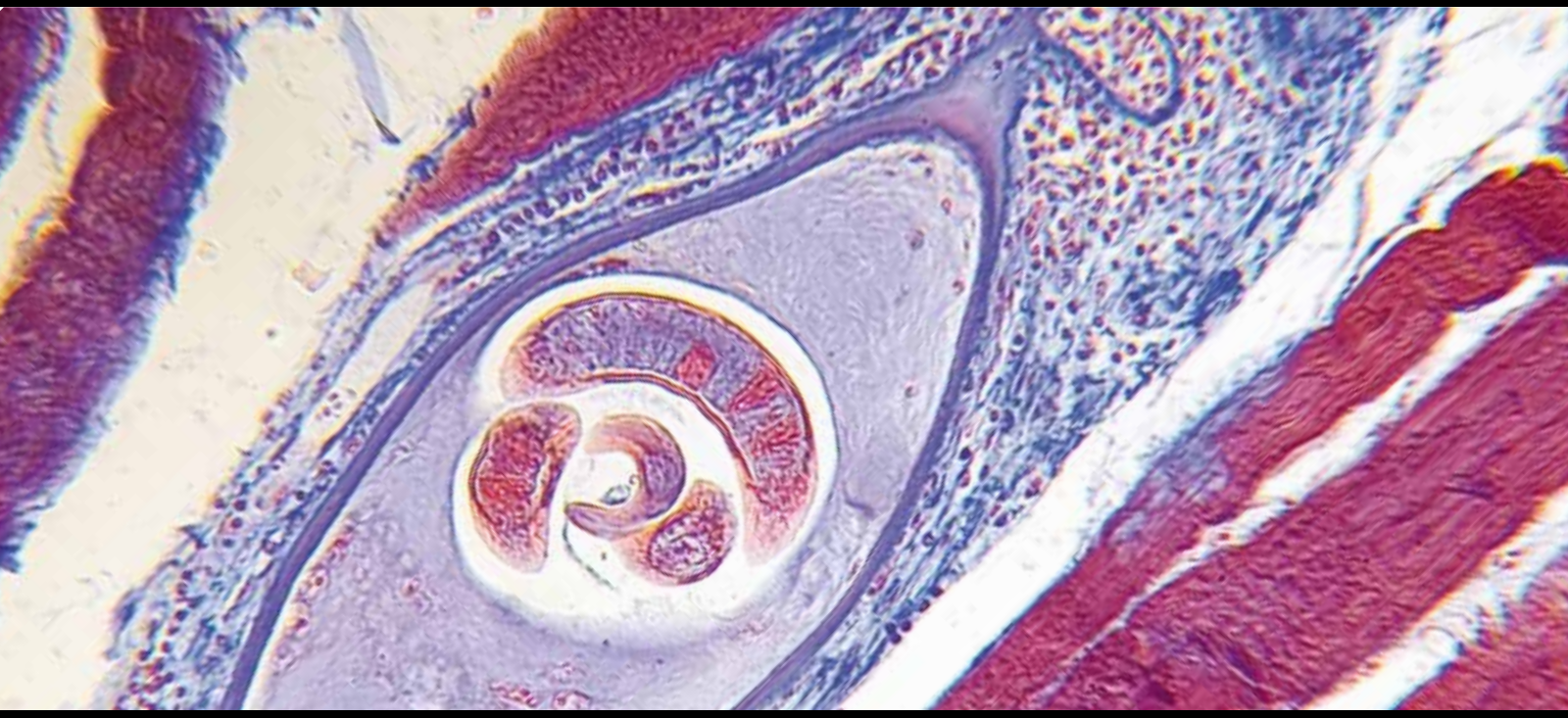
Gastroenterology Research and Practice

Malnutrition and Nutrition–Therapy: Our Neglected Responsibility

Guest Editors: Irit Chermesh, Lubos Sobotka, Corina Hartman, and Rémy Meier



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Editorial Board

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Editorial

Malnutrition and Nutrition-Therapy: Our Neglected Responsibility

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Around 30% of hospitalized patients in Europe are malnourished, and the figures for the community are also alarming. In certain diseases the proportion of malnourished patients can go up to 60%. The consequences of malnutrition are still neglected. The levels of knowledge and awareness of nutritional problems are low among all caregivers. Malnutrition is a heavy burden for the society, leading to increased morbidity, longer hospital stays, increased complications, decreased quality of life for the patients, and higher costs. Interventions to ensure appropriate nutritional care would be cost-effective. The impact of nutritional support is well known from many clinical trials. For each patient group specific nutritional recommendations are published in several reviews and guidelines. Although it is known how to do better, the nutritional support is often not regarded as an important therapeutic tool of the patients.

In this issue several interesting papers summarize different important aspects related to malnutrition and nutritional support.

The first paper describes the mechanism of cancer cachexia and the clinical implication and helps to understand why nutrition should be a central part in the management of cancer patients. It is well known that with an adequate nutritional support an increase of the quality of life can be achieved.

Two further papers are dealing with nutritional aspects in the elderly. A large survey in Germany confirms the high prevalence of malnutrition in nursing homes. A significant number of orally and tube-fed patients were malnourished. The most important factors leading to malnutrition were analysed.

Oropharyngeal dysphagia is a high prevalent problem in the elderly and is a leading factor for malnutrition and aspiration. The paper in this issue gives important information for diagnosing and the treatment for this clinically relevant problem.

Three papers are related to surgical and ICU patients. Too often malnutrition is neglected in surgical patients. The clinical outcome is significantly different in malnourished patients compared to well-nourished controls. The paper on malnutrition in surgery wards confirms the importance of screening all surgical patients. 1/3 of the reported patients were malnourished, and the outcome was not as good compared to the patients not at nutritional risks. Elective surgery should be avoided until the nutritional deficits are corrected. In a further paper the perioperative nutritional support is described.

Enteral nutrition was not given for long time to patients with acute pancreatitis because of the fear of worsening the outcome. This opinion has changed in the last decade. The importance and limits of enteral nutrition are well explained in this issue.

In other three papers more general nutritional items are addressed. In the ICU hyperglycaemia is associated with poor outcome. Several interesting trials were published in the past on this specific problem. Until now the best blood sugar control is still debated. The review in this issue helps the reader to understand this controversial problem in more detail.

In patients with severe malnutrition it is important to know that nutrition support can also be harmful if the refeeding syndrome is not considered. The paper on the refeeding syndrome is therefore very helpful for understanding and avoiding the refeeding problems.

In nutritional practice the placing of a percutaneous endoscopy gastrostomy is very common. This procedure is done more and more on a propofol-based sedation. There are only few data on the safety of propofol-based sedation in the PEG procedure. The paper in this issue shows that propofol is a safe procedure if it is done according to the common guidelines. There is no significant difference in overall complication rates, sedation, and procedure-related complication.

Obesity is also regarded as a form of malnutrition. Controlled weight loss is well recognized as to be beneficial to reduce complications in these patients. One paper in this issue reports data on a specific supplement on the effect on weight loss. The use of green coffee extract shows some promising effects but the available trials are of poor methodological quality. A general recommendation cannot be given now.

The last paper is dealing with the important unhealthy Western diet. This diet is too high in n-6 polyunsaturated fatty acids (PUFA) and too low in n-3 PUFAs. We know that these diets can have negative effects on health. It is extremely important that all efforts should be undertaken to decrease this unhealthy diet in the future. Until now these important recommendations are not sufficiently implemented in the daily practice. This paper is therefore very important for promoting general health.

We hope that the selected manuscripts help the readers to understand more the importance of recognizing the burden of malnutrition and to raise the awareness of the impact of nutritional support for the patients.

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Review Article

Cancer Cachexia: Mechanisms and Clinical Implications

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Cachexia is a multifactorial process of skeletal muscle and adipose tissue atrophy resulting in progressive weight loss. It is associated with poor quality of life, poor physical function, and poor prognosis in cancer patients. It involves multiple pathways: procachectic and proinflammatory signals from tumour cells, systemic inflammation in the host, and widespread metabolic changes (increased resting energy expenditure and alterations in metabolism of protein, fat, and carbohydrate). Whether it is primarily driven by the tumour or as a result of the host response to the tumour has yet to be fully elucidated. Cachexia is compounded by anorexia and the relationship between these two entities has not been clarified fully. Inconsistencies in the definition of cachexia have limited the epidemiological characterisation of the condition and there has been slow progress in identifying therapeutic agents and trialling them in the clinical setting. Understanding the complex interplay of tumour and host factors will uncover new therapeutic targets.

1. Introduction

The etymology of the word cachexia points to its association with poor prognosis: it is derived from the Greek *kakos* and *hexia*—"bad condition" and has long been recognised as a key sign in many cancers. It is a multifactorial condition which comprises skeletal muscle and adipose tissue loss which may be compounded by anorexia, a dysregulated metabolic state with increased basal energy expenditure and is resistant to conventional nutritional support. The pathophysiological mechanisms have begun to be elucidated and this has led to developments in therapeutic avenues [1].

Cachexia correlates with poor performance status, poor quality of life, and a high mortality rate in cancer patients [2]. In a meta-analysis of studies pertaining to patients with advanced cancer and survival of less than 90 days, symptoms including weight loss and anorexia correlated with poor prognosis [3]. Loss of greater than 5–10% of body weight is usually taken as a defining point for cachexia, although the physiological changes may be present long before this cutoff point is reached. Furthermore, the degree of weight loss which significantly impacts on prognosis or performance has not been defined. A longitudinal study has shown that 2.5 kg weight change over 6–8 weeks is sufficient to produce significant changes in performance status [4]. Death usually occurs when there is 30% weight loss [5].

The prominent clinical feature of cachexia is weight loss in adults (corrected for fluid retention) or growth failure in children (excluding endocrine disorders). Anorexia, inflammation, insulin resistance, and increased muscle protein breakdown are frequently associated with cachexia [6]. However, there is no clear consensus definition of this common problem in cancer patients leading to a poor understanding of the aetiology of the condition. Earlier definitions of cachexia described "a wasting syndrome involving loss of muscle and fat directly caused by tumour factors, or indirectly caused by an aberrant host response to tumour presence" [7], however more recent definitions have downplayed the importance of fat loss and describe cachexia as "a complex metabolic syndrome associated with underlying illness and characterised by loss of muscle with or without loss of fat mass" [6], thus highlighting the unique consequences of muscle wasting—the hallmark of cachexia. Without an established definition, future studies in this area will be hampered. A recent consensus definition has been proposed to include further factors to diagnose the cachexia syndrome such as involuntary weight loss, decreased muscle mass, anorexia, and biochemical alterations (*C*-Reactive Protein (CRP), albumin, haemoglobin [8]).

One such study looked at 170 pancreatic cancer patients with weight loss >5% and whether a triad of >10% weight loss, low food intake (<1500 kcal/day), and systemic inflammation (CRP > 10 mg/dL) could better predict adverse functional outcome as well as poor prognosis versus weight loss alone [8]. When two of three of these criteria were present, (representing 60% of the patients) a cohort of patients with adverse function and prognosis were identified [8].

The prevalence of cachexia is thought to be up to 80% of upper gastrointestinal cancer patients and 60% of lung cancer patients at the time of diagnosis [9]. There are no clear figures for the estimated prevalence within specific cancer cohorts. When the electronic medical records of over 8500 patients with a wide variety of malignancies were analysed for the prevalence of cachexia amongst the cohort, the proportion varied according to which standard definition was used: 2.4% using the World Health Organisation's International Classification of Diseases (ICD) cachexia diagnostic code; 5.5% for the ICD diagnosis of cachexia, anorexia, abnormal weight, and feeding difficulties; 6.4% were prescribed megestrol acetate, oxandrolone, somatropin, or dronabinol; 14.7% had >5% weight loss [10]. Despite methodological flaws, there was an interesting lack of overlap between the different criteria pointing to the underdiagnosis of cachexia in clinical practice.

Decreased muscle strength may help distinguish cachexia from other causes of anorexia and fatigue in cancer patients [11]. Decreased muscle strength could be used as a diagnostic criterion with greater sensitivity and specificity for cancer cachexia. Cancer patients who are losing weight and have a systemic inflammatory response have poorer performance status [4]. Until a clear definition with well-defined cut-offs emerges, identification and treatment of cachectic patients as well as research in the area will remain limited. A new consensus definition for diagnostic purposes has been suggested and is outlined in Table 1 [6].

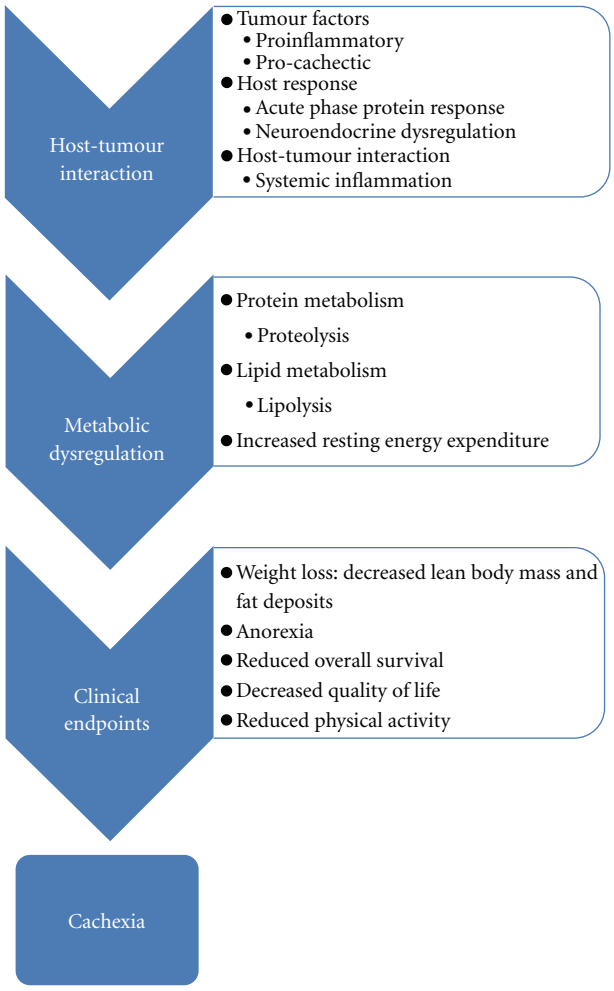

Figure 1: Clinical consequences of cancer cachexia.

2. Pathophysiology

Pathophysiological changes and clinical consequences of cachexia are summarised in Figure 1.

2.1. Metabolic Changes. The metabolic changes found in cachexia resemble those of infection rather than starvation [12] and are multifactorial and complex. Weight loss of cancer cachexia is due to loss of both skeletal muscle and adipose tissue mass, whereas weight loss is mainly from adipose tissue stores in starvation [13]. In cachexia there is an increase in muscle protein catabolism leading to net loss of muscle mass. The ATP ubiquitin-dependent proteolytic pathway is the greatest contributor to proteolysis in cachexia [14, 15]. Other proteolytic pathways such as lysosomal cathepsins B, H, D, and L [16] and activity of the calcium/calpain pathway have also been implicated [17]. Increased intracellular proteolytic activity usually manifests as loss of body weight. This proteolysis has been shown to occur even in the absence of weight loss in cancer patients. Activation of proteolysis is an early event during tumour growth and it may be present for a long time prior to its clinical manifestation. Protein synthesis may be increased or unchanged [18].

Loss of adipose tissue mass is due to lipolysis [5]. This process is driven by lipid mobilising factor (LMF) and tumour (and host) factor zinc-alpha-2 glycoprotein which has a direct lipolytic effect and sensitises adipocytes to lipolytic stimuli and shows increased expression in cachexia [19]. A further compounding factor is the increased resting energy expenditure due to the dysregulation of energy metabolism. Cancer patients have a higher resting energy expenditure than noncancer controls [20]. It has been speculated that this is due to altered gene expression of mitochondrial membrane uncoupling proteins which uncouple respiration from ATP production resulting in loss of energy as heat [5].

The metabolic changes seen in cachexia are a result of the interplay of tumour factors, host factors, and the interaction between the two.

2.2. Tumour Factors. Tumour cells produce both pro-inflammatory and procachectic factors, which stimulate

Table 1: Diagnostic criteria for cachexia syndrome [6].

	Weight loss of at least 5% in 12 months or less (or BMI <20 kg/m^2)	
AND 3 of 5 From:	Decreased muscle strength	
	Fatigue	
	Anorexia	
	Low fat-free mass index	
	Abnormal biochemistry:	Increased inflammatory markers (CRP, IL-6)
		Anaemia (Hb < 12 g/dL)
		Low serum albumin (<3.2 g/dL)

Note: Fatigue is defined as physical and or mental weariness resulting from exertion; an inability to continue exercise at the same intensity with a resultant deterioration in performance.
Anorexia is defined as limited food intake (total caloric intake less than 20 kcal/kg body weight/day) or poor appetite.
Low-fat-free mass index represents lean tissue depletion (i.e., mid upper arm muscle circumference <10th percentile for age and gender' appendicle skeletal muscle index by DEXA <5.45 (kg/m^2) in females and <7.25 in males).

a host inflammatory response [1]. Tumour produced pro-cachectic factors include proteolysis-inducing [45] and Lipid-mobilising factors [46]. PIF has been identified in the urine of weight losing patients with pancreatic, colon, lung, ovarian, breast, and liver cancers [47]. In animals, PIF signals via NFκB and STAT3 pathways [48]. Stimulation of these pathways, induces proteolysis in muscles via the ubiquitin-proteasome pathway [49] and in hepatocytes, results in production of IL-6, IL-8 and CRP [48]. Tumour xenografts expressing human PIF do not induce cachexia in mice [50]. Further attempts to correlate PIF levels and outcomes have not shown any correlation [51]. Therefore the proposed mechanisms of PIF have not yet been validated in humans. Parathyroid hormone-related peptide (PTHrP), another tumour-derived circulating factor, is associated with higher soluble tumour necrosis factor receptor levels and with lower albumin and transferrin levels [52].

Lipid mobilising factor has been found in cancer patients losing weight but not in those with stable weight [53]. It is thought that LMF sensitises adipocytes to lipolytic stimuli by increasing cyclic AMP production [54]. LMF may bind to beta adrenergic receptors and causes either increased receptor number or increased G protein expression [55].

2.3. Host-Tumour Interaction. Inflammatory cytokine production by the tumour microenvironment in response to tumour cells may drive the cachexia process. Rodent tumour models display increased systemic inflammatory cytokine production, which correlates with the amount of weight loss [56, 57]. The murine model of cancer cachexia associated with systemic inflammation suggests that there is an interplay between IL-1β and IL-6 within the tumour microenvironment, which leads to their amplification [58]. Reduction of IFN-γ by monoclonal antibody treatment reverses cachexia in the Lewis lung carcinoma in mice [59].

Pro-inflammatory cytokines produced include TNF-α, IL-1 and IL-6 [1]. It is not certain whether the cytokine production is primarily from tumour or host inflammatory cells. It has been hypothesised that either tumour cell production of pro-inflammatory cytokines or the host inflammatory cell response to tumour cells is the source of the acute phase protein response seen in many malignancies and in cachexia. One study of oesophagogastric cancers showed cytokine protein concentrations of IL-1β, IL-6 and TNF-α are significantly elevated in tumour tissue. Tumour tissue concentrations of IL-1β protein correlated with serum CRP concentrations ($r = 0.31$, $P = .05$; linear regression) and tumours with diffuse or patchy inflammatory cellular infiltrate were associated with elevated serum CRP [60]. Similarly the production of IL-6 by Peripheral Blood Mononuclear Cells (PBMCs) in pancreatic cancer patients induced an acute phase protein response in another study [61]. Martignoni et al. have suggested that IL-6-overexpression in cachectic pancreatic cancer patients is related to the ability of IL-6 producing tumours to sensitise PBMC and induce IL-6 expression in PBMCs [62].

TNF-alpha and the tumour factor proteolysis-inducing factor are the major contenders for skeletal muscle atrophy in cachectic patient. They both increase protein degradation through the ubiquitin-proteasome pathway and depress protein synthesis through phosphorylation of eukaryotic initiation factor 2 alpha [19]. Studies have shown that proteolysis-inducing factor levels correlate with the appearance of cachexia, but there is some disagreement regarding a correlation between serum levels of TNF-alpha and weight loss. Furthermore, only antagonists to proteolysis-inducing factor prevent muscle loss in cancer patients, suggesting that tumour factors are the most important.

2.4. Host Response Factors

2.4.1. Acute Phase Protein Response. Systemic changes in response to inflammation are denoted the acute phase response [63]. Up to 50% of patients with solid epithelial cancers may have an elevated acute phase protein response [64]. This acute phase protein response (APPR) has been associated with hypermetabolism: in pancreatic cancer patients APPR correlated with elevated resting energy expenditure and reduced energy intake [65]. Other longitudinal studies have found a poorer prognosis in patients displaying this response, independent of weight loss [66]. *C*-reactive protein (CRP) is the most prevalent method used to assess

Table 2: Modified Glasgow Prognostic Score (mGPS): an inflammation-based prognostic score [21].

Biochemical measure	Score
C-reactive protein ≤10 mg/L + Albumin ≥35 g/L	0
C-reactive protein ≤10 mg/L + Albumin <35 g/L	0
C-reactive protein >10 mg/L	1
C-reactive protein >10 mg/L + Albumin <35 g/L	2

the magnitude of the systemic inflammatory response [63]. The modified Glasgow prognostic score (mGPS) (Table 2) combines CRP and albumin concentrations to create a simple scoring system which is a prognostic factor independent of stage and treatment and predicts survival [21, 67].

Raised CRP concentrations at the time of admission to hospital are indicative of an increased risk for all-cause mortality; there is a 22.8-fold increase in cancer mortality in patients with highly elevated CRP concentrations (>80 mg/L) [68]. This response appears to be prevalent amongst cancer patients with elevated CRP measured in almost 80% of 106 patients with inoperable nonsmall cell lung cancer (NSCLC), 40% of whom had >5% weight loss [69]. In patients without weight loss, those who displayed evidence of a systemic inflammatory response reported more fatigue ($P < .05$) [69]. In patients with gastro-oesophageal cancer, the rate of weight loss correlates with serum concentrations of *C*-reactive protein [70]. Elevated CRP levels at the time of diagnosis has been found to be a predictor of poor prognosis in pancreatic, lung, melanoma, multiple myeloma, lymphoma, ovarian, renal, and gastrointestinal tumours [71].

The exact mechanisms linking cachexia, APPR, and poor outcomes is not known. It may be that this systemic alteration in protein metabolism drives the proteolysis of skeletal muscle to fuel the switch to acute phase reactant production. The APPR requires large amounts of essential amino acids: 2.6 g of muscle protein must be catabolised to produce 1 g of fibrinogen [72].

2.4.2. Neuroendocrine Factors. A number of neuroendocrine factors appear to be dysregulated in the cancer state resulting in insulin resistance, reduced anabolic activity, and elevated cortisol [47]. This dysregulation may be driven by the systemic inflammatory response associated with cancer. Inflammatory cytokines such as TNF-α and IL-6 have been implicated in insulin resistance [73]. The endogenous production of or response to anabolic growth factors in patients may be affected either by the tumour or the host response to the tumour and may contribute to cachexia. Testosterone or derivatives have been shown to increase protein synthesis and muscle mass [74]. Emerging evidence implicates reduction in insulin-like growth factor 1 in cachectic states [75].

2.5. Anorexia and Cachexia: An Interdependent Relationship? Whilst loss of appetite and resultant decrease in energy intake undoubtedly contribute to weight loss associated with cancer cachexia, whether anorexia occurs by an independent process or is a result of the inflammatory process of cachexia is not fully understood. Anorexia itself may have a number of components—nausea, altered taste sensation, swallowing difficulties, or depression. The failure of aggressive supplementary nutritional regimes to reverse weight loss in many patients points to primacy of the cachexia disease process [5] and in fact, this disease process may act to establish anorexia. It is thought that lack of appetite is secondary to factors produced by the tumour or the immune response to the tumour. Specifically, cytokines may inhibit the neuropeptide Y pathway or mimic negative feedback action of leptin on the hypothalamus, leading to anorexia [76, 77].

In a study of patients with gastro-oesophageal malignancy ($n = 220$), 83% of whom had weight loss, multiple regression identified dietary intake (estimate of effect: 38%), serum CRP concentration (estimate of effect: 34%), and stage of disease (estimate of effect: 28%) as independent variables in weight loss in these patients [70]. If serum CRP is taken as a proxy measure of systemic inflammation due to cancer cachexia, this indicates that weight loss in cancer is not merely due to reduced calorie intake.

Recently, understanding of the physiological mechanisms of appetite regulation has been increasing. There are two sets of neurons within the arcuate nucleus of the hypothalamus identified to be involved: the melanocortin system and the neuropeptide Y system. Neuropeptide Y stimulates appetite on its own or via release of other orexigenic proteins [78]. Neurons which release α-melanocyte-stimulating hormone (α-MSH) and signal via melanocortin-3 and 4 receptors (MC3R, MC4R) result in decrease in food-seeking behaviour, increased basal metabolic rate and decreased lean body mass [79, 80]. These neurons are constitutively active as mutation in the MC4R results in childhood obesity [81]. Agouti-related protein (AgRP) is produced by neurons (which also produce neuropeptide Y) and counteracts the action of MC4R-stimulating proteins promoting appetite [82]. These "appetite neurons" also express receptors for circulating leptin [83] and interleukin-1β (IL-1β) [84], both of which downregulate appetite and receptors for ghrelin (the orexigenic protein, which increases AgRP) [85].

3. Consequences

Cachexia results in a state of active inflammation whereby tumour-derived factors and the aberrant host response to these factors result in a catabolic state. Whether this catabolic state is the ultimate cause of death in some patients is unknown although a substantial proportion of cancer patients die with symptoms of advanced cachexia [9]. Cachexia directly impacts overall survival, quality of life, and physical activity.

3.1. Survival. Weight loss has been indicated as an important prognostic factor for cancer patients. A classic study by DeWys and colleagues underscores the impact and outcome of weight loss in cancer patients [2]. Using retrospective evaluation in a multicentre study of more than 3000 patients with different tumour types, these researchers reported moderate to severe weight loss in 30% to 70% of patients, depending on the tumor type. The amount of weight loss

depends upon tumor site, size, type, and stage. Age and treatment type also play a role. The greatest incidence of weight loss was seen among patients with solid tumours, for example, gastric, pancreatic, lung, colorectal, and head and neck. Patients with solid tumours are often likely to lose 10% or more of their usual body weight. There is a lower risk of weight loss in patients with breast and hematological cancers. Within each tumour type, survival times were shorter for patients who had experienced weight loss than in those who did not. Not only did weight loss predict overall survival, but it also indicated a trend towards lower chemotherapy response rates.

In more recent studies, similar findings of reduced survival have been reported. Buccheri and Ferrigno (2001) [86] reported in 388 NSCLC cases that total weight loss was the best indicator of prognosis. In ovarian cancer Hess et al. (2007) [87] found a significant relationship between weight change and survival—on multivariate analysis the risk of death increased by 7% for each 5% drop of body weight. In Gastro-oesophageal cancer Deans and Wigmore (2009) [71] reported that patients with the lowest rate of weight loss had a median survival of 30.2 months versus 7.5 months in those with the highest rate of weight loss. Similar findings have also been reported in pancreatic cancer [88].

One proposed mechanism to explain why patients with weight loss have a poorer survival is the increased incidence of complications from surgical, radiotherapeutic, and chemotherapeutic treatments. In a study by Andreyev et al. [89], 1555 patients with a number of different gastrointestinal tumour types were analysed to examine whether weight loss affected prognosis. In patients with weight loss: chemotherapy doses were lower; they developed more frequent and more severe dose limiting toxicity and received, on average, one month less chemotherapy ($P < .001$ in all). Weight loss correlated with shorter failure-free survival, overall survival, decreased response, quality of life, and performance status ($P < .001$ in all) [89]. Whether reduced survival is due to a more aggressive tumour profile in patients with weight loss or due to suboptimal treatment related to weight loss, remains unknown.

3.2. Quality of Life. Cachexia contributes substantially to morbidity in cancer patients. It is associated with symptoms such as fatigue, weakness, poor physical performance, and thus leads to a lower self-rated quality of life. Indeed, when the impact of various factors is related to self-rated quality of life scores, the proportion determined by weight loss is 30% and by nutritional intake 20%, compared to cancer location (30%), disease duration (3%), and stage (1%) [90]. Patients who continue to lose weight while receiving palliative chemotherapy have reduced global quality of life and performance scores when compared to those whose weight loss stabilises [91].

3.3. Physical Activity. Physical activity has been described as a novel, objective, and robust functional outcome measure that is frequently impaired in cachectic states [92]. Activity levels are influenced by several conventional quality of life domains. Measurement of physical activity has long represented a challenge for researchers using time-consuming and expensive tools such as doubly labelled water and indirect calorimetry. However research using these methods has revealed that although resting energy expenditure may be elevated in cachectic patients, total energy expenditure is reduced because weight-losing cancer patients reduce the magnitude of their energy deficit through reductions in physical activity. This reduction in physical activity can be significant—in one study the measured mean physical activity rate was equivalent to that of spinal cord injury patients living at home and greatly reduced versus normal controls [93]. In a more recent study by Dahele et al. (2007) [94] using advanced ambulatory pedometer technology, cancer patients receiving palliative chemotherapy were shown to spend significantly more time lying and sitting, and significantly less time in quiet standing or stepping compared with controls, taking on average 43% less steps than healthy controls. It is known that bed rest leads to a decrease in skeletal muscle mass in healthy patients, due to reduced protein synthesis [95]. Thus, loss of physical function results in decreases in performance status, ability to perform activities of daily living, decreased social interactions, and alterations in body image, all of which manifest as reduced quality of life [96]. Interventions which increase physical activity would be anticipated to be highly beneficial.

Antineoplastic therapies such as surgery, radiotherapy and chemotherapy, may also impact on the development of systemic inflammation and particularly may impact on swallowing difficulties and anorexia due to nausea [97].

4. Therapeutic Approaches

4.1. Goals of Therapy. Clearly since cancer cachexia is associated with a poor prognosis, the aim of management is often to improve symptoms and quality of life. It is noted that a response to chemotherapeutic treatment by shrinkage of the tumour burden often leads to improvement in the cachectic state. The primary endpoints of optimal treatment of cancer cachexia are improvements in lean body mass, resting energy expenditure, fatigue, anorexia, quality of life, performance status, and a reduction in pro-inflammatory cytokines.

A greater understanding of the process of inflammation and its fundamental role in the development of cachexia has led to new avenues opening up in the approach to management of the condition. The hypothesis is that effective treatment of cancer cachexia will improve performance status and quality of life and by inhibiting the process driving cachexia, survival may be improved. In patients who stop losing weight while receiving chemotherapy for gastrointestinal cancers, median survival is improved (15.7 months versus 8.1 months, $P = .0004$) [89]. Animal models are generally unsatisfactory models for assessing the efficacy of intervention due to the larger proportional size and the aggressive doubling rate of tumours: thus the biological behaviour is different to that seen in the clinical setting [98].

There has been recent progress in producing trials of high clinical quality for licensing purposes but these trials may

Table 3: Endpoints for evaluating interventions in cancer cachexia.

Clinical	Functional	Biochemical
Nutritional status	Performance score (ECOG; Karnofsky)	Plasma fatty acid composition
Tolerance of diet	Quality of life scores	Pro-inflammatory cytokines
GI symptoms	Appetite	Acute phase protein reactants
Infections	Fatigue	
Survival	Physical activity as measured electronically [22]	
	Muscle strength	

be beset by difficulties in adequate endpoint analysis due to the numbers lost to followup or patients being unable to comply with therapy due to their poor overall condition, thus limiting their duration, power, or generalisability [99, 100]. In addition there is a degree of heterogeneity in defining relevant end points for analysis of intervention in cancer cachexia. Table 3 summarises the range of endpoints which may be used. One study of 388 nonsmall cell lung cancer patients found that total weight loss was the best predictor of prognosis rather than speed of weight loss [101]. However, weight loss alone does not identify the full effect of cachexia on physical function [8]. It is the loss of fat-free mass (FFM) that is responsible for the reduced functional status, increased mortality, and other negative outcomes associated with malnutrition [102]. Body fat is easier to gain than FFM, so studies that show improved body weight may not translate into reductions in morbidity or improvements in functional status. To improve functional ability and hence quality of life patients need not only to become weight stable but regain the lean tissue lost in the cachectic process. Thus, interventions which lead to improvements in functional status would be expected to cause increases in lean body mass rather than fat mass, however, this distinction is often not reported in interventions.

The strong impact that cancer cachexia has on cancer patients' outcome and quality of life suggests that nutritional issues should be taken into consideration from the beginning of the natural history of cancer, a concept termed the parallel pathway [103]. Indeed studies of nutritional intervention that have reported a better weight maintenance in patients are in those who are treated in the "precachexia" phase, that is, prior to loss of >10% of body weight and prior to elevations of CRP. Dietary counselling with or without oral nutritional supplements has proven efficacy in stabilising nutritional status in pre-cachectic patients [104, 105]. A nutritional assessment to seek reversible causes of weight loss is the first step in management in cachectic patients. Approximately 40% of cancer patients eat less than the 34 kcal/kg/day required to maintain weight [106]. The European Society of Parenteral and Enteral Nutrition (ESPEN) report in a consensus statement that there is Grade A evidence for intensive dietary counselling with food plus or minus oral nutritional supplements in preventing therapy-associated weight loss, preventing treatment interruptions and increasing dietary intake in gastrointestinal or head and neck cancer patients undergoing radio- or chemotherapy [107].

For patients with advanced cachexia (>10% weight loss, systemic inflammation and poor appetite) studies seeking to assess the effect of targeted nutritional advice and supplements have generally reported no significant improvement in nutritional status. Standard enteral or parenteral supplements do not appear to result in lean mass weight gain for the typical cancer patient [5, 98, 108]. The largest evaluation of the literature regarding nutritional supplementation (NS) (oral or tube) in cancer patients was the systematic review by Elia et al. (2006) showing no difference in mortality in patients undergoing chemotherapy/radiotherapy (4 RCTs) or surgery (4 RCTs) [109]. A systematic review of parenteral nutrition in cancer patients showed no difference in mortality (19 RCTs), increase in total complication rates in those given parenteral nutrition (8 RCTs), and significantly lower tumour response rate in patients receiving parenteral nutrition (15 RCTs) [110].

This is likely because the inflammatory response of cachexia prevents anabolism. In many cases an attempt is being made to reverse or halt a rapidly advancing catabolic process and it is unrealistic to expect a reversal with calories and protein alone.

The poor results observed with conventional nutrition support in cachectic patients led to the emergence of so-called nutraceuticals or immunonutrition supplements, in an attempt to nutritionally modify the metabolic milieu by providing anti-inflammatory substances, such as eicosapentaenoic acid (EPA), at levels much higher than that typically found in the diet.

4.2. Eicosapentaenoic Acid. Eicosapentaenoic acid (EPA), a long-chain polyunsaturated fatty acid (PUFA) of the omega-3 (n-3) family, has been studies in relation to cancer cachexia for over 15 years. It is of interest in the context of cancer cachexia as it has potential to impact on both the underlying metabolic abnormalities of tumour-induced weight loss, as well as modulation of immune function. When EPA is consumed at levels above that normally found in the diet, it replaces arachidonic acid (AA), an n-6 PUFA, in cell membrane phospholipids. It then acts as a substrate for the production of the 3 series prostaglandins and the 5 series leukotrienes. Eicosanoids synthesized from the n-3 PUFAs (i.e., EPA) rather than the n-6 PUFAs (i.e., AA) have lower potential for promoting inflammation. Modulation of dietary fatty acids can therefore have an impact on many immune processes such as proliferation, phagocytosis, cytotoxicity, and cytokine production [111].

Table 4: Pharmacological options for management of cachexia.

	Agent	Clinical effect (RCT)[#]	Hypothetical mechanism of action
Anabolic agents	Corticosteroids	Improves anorexia and weakness; no improvement in weight or calorie intake [23–25]; well tolerated; effects short lasting	Not established. May inhibit prostaglandin metabolism and central euphoric effect
	Nandrolone decanoate	Decrease in weight loss [26]	Not established. Promote protein nitrogen accumulation
	Oxandrolone	No published randomised clinical trials in cancer cohort	Not established
	Insulin	Increases whole body fat and carbohydrate intake [27]	Not established
	Adenosine Triphosphate (ATP)	Stabilises weight loss and increases energy intake[28]	Not established
Appetite stimulants	Progesterones: Megestrol acetate (MA) Medroxyprogesterone (MP)	Improves appetite, calorie intake and weight (not lean body mass) [29]	MA: may increase the central appetite stimulant neuropeptide YMP: reduces serotonin and cytokine production by PBMCs [30]
	Cannabinoids: Dronabinol	No benefit when added to MA; inferior to MA when used alone [31]. No increase in appetite or QoL [32]	May act on endorphin receptors, reduce prostaglandin synthesis or inhibit IL-1 secretion [33]
Cytokine inhibitors	Cyproheptadine	No improvement in weight gain [34]	Serotonin antagonist with antihistaminic properties
	Thalidomide	Attenuates weight loss, increases lean body mass [35]	Immunomodulatory: downregulates TNF-α (by destabilising mRNA [36]), NFκB, pro-inflammatory cytokines, COX2 [37]
	Pentoxifylline	No improvement in appetite or weight in cachectic patients [38]	Phosphodiesterase inhibitor: inhibits TNF gene transcription
	Eicosapentaenoic acid (EPA)	Cochrane meta-analysis: insufficient evidence to establish whether EPA is better than placebo [39]	*In vitro* attenuates increased cAMP activity and lipolysis by LMF [40]
	Melatonin	Improves cachexia (term not defined) and one year survival increased in advanced NCSC lung cancer [41]	Immunomodulatory [42], Downregulates TNF production [43]
Anti-inflammatories	Non-steroid anti-inflammatory drugs	Reduced inflammatory markers, reduced resting energy expenditure, preservation of total body fat [44]	Not established. May downregulate systemic inflammatory response to tumour

[#] Results from randomised controlled trials (RCTs) are cited.

Despite initial studies showing anabolic effects, principally gains of lean body mass, improvements in grip strength, quality of life, and reductions in IL-6 and PIF could be achieved in a variety of cancers [99], including pancreatic cancer [112, 113], lung cancer [114], and colorectal cancer [115], analysis of RCTs only, using the Cochrane approach, did not show any differences between EPA supplementation and placebo [39]. Whether this is a true representation or a reflection of the advanced cachexia of participants or inherent differences in EPA metabolism between individuals (with only a proportion of patients able to respond to EPA) needs further examination. On subgroup analysis, patients who comply with EPA supplementation seem to have improved lean body mass [116].

EPA-enriched oral nutritional supplements (ONSs) have been compared to megestrol acetate in the North Central Cancer Treatment Group trial of 421 patients with weight loss, poor intake, and anorexia [117]. In a 3-month intervention period, patients were randomized to either EPA-enriched ONS plus placebo liquid suspension, standard ONS plus megestrol acetate suspension, or EPA-enriched ONS plus megestrol acetate suspension. Weight gain was highest in the megestrol acetate group but unfortunately body composition was not assessed and so changes in water

weight cannot be controlled for. There was no difference in survival, appetite, or quality of life scores between the groups, however patients on megestrol acetate reported higher rates of impotence. The fact that an EPA enriched ONS scored as well as drug therapy on certain clinical endpoints (e.g., survival and global quality of life) underscores the limitations of each treatment.

β-hydroxyl β-methyl butyrate (HMB), glutamine, and arginine supplementation have been combined in the hope of a synergistic effect of HMB (a modulator of protein turnover) and the amino acids (immunomodulatory) would increase weight. A phase III RCT of this combination did not show any difference in lean body mass between control and intervention groups [100].

4.3. Pharmacological Agents. Pharmacological options are summarised in Table 4. Among orexigenic agents, megestrol acetate is by far the most widely prescribed and at least 15 randomised controlled clinical trials have demonstrated that this drug, at doses ranging from 160–1600 mg/d significantly improves appetite with respect to placebo [118]. A recent Cochrane meta-analysis reported that it improves weight gain and appetite in cancer patients [29]. Although this increase in appetite is very desirable for both patients and their carers, in most of these trials no definitive improvement in global quality of life was observed [29].

Anti-inflammatory agents (COX inhibitors) can reduce weight loss and aid maintenance of performance status in advanced cancer [119]. The COX-2 inhibitor, meloxicam showed activity against PIF-induced proteolysis, prior to its withdrawal from the market [120]. Beta-adrenoreceptor blockade can reduce resting energy expenditure in patients with cancer ($n = 10$) but have not been trialled in larger-scale studies [121]. They are thought to inhibit proteolysis and lipolysis [122] and have been shown to downregulate catecholamine-induced catabolism in burns patients [123]. Agents which reduced cytokine levels such as thalidomide and pentoxifylline have only shown modest or minimal activity. At RCT, thalidomide has been shown to attenuate weight loss and lead to improved physical function [35]. Pentoxifylline did not have any clinical benefit. Specific antitumour necrosis factor- (TNF-)α agents, etanercept and infliximab, did not show any positive effect on appetite or body weight in RCTs [124, 125]. Corticosteroids, although widely used, have significant side effects including protein breakdown, insulin resistance, water retention, and adrenal suppression and tend to be used during the preterminal phase of patient illness [23, 126]. Anabolic steroid derivatives such as nandrolone and oxandrolone have not been studied in clinical trials in a cancer cohort. Insulin [27], ATP infusions [28], and melatonin [41] have produced modest positive effects in small clinical trials and require further substantiation.

4.4. Combination Therapy. In unresectable cancer cases, there is currently no goal standard treatment that can attenuate catabolism and inflammation, stimulate appetite and intake and consequently promote anabolism (specifically of lean body mass). A multimodal approach has therefore been advocated in the treatment of cancer cachexia. Mantovani (2010) randomised 332 patients with cancer-related anorexia/cachexia syndrome to one of five arms of treatment: (1) medroxyprogesterone 500 mg/d or megestrol acetate 320 mg/d; (2) oral supplementation with eicosapentaenoic acid (EPA); (3) L-carnitine 4 g/d; (4) thalidomide 200 mg/d; (5) a combination of the above for a total of 4 months [127]. Results showed the superiority of arm 5 over the others for all primary endpoints. Significant improvements were observed in arm 5 in LBM, fatigue scores, appetite, and total energy and active energy expenditure with REE decreasing significantly. Toxicity was negligible and comparable between treatment arms.

4.5. Potential Therapeutic Targets. Due to the lack of clinical efficacy of agents which seemed promising in the laboratory setting, ongoing research has continued to explore new therapeutic targets and to develop new agents. Much of this has focussed on manipulation of the melanocortin system of appetite regulation [128]. Activation of the Melanocortin-4-receptor (MC4R) in murine models decreases food-seeking behaviour, increases basal metabolic rate, and decreases lean body mass [80]. Treatment with a MC4R antagonist attenuated these responses [79]. Ghrelin induces the release of growth hormone, regulates appetite, and has anti-inflammatory properties [129, 130]. Initial human studies in Phase I open trials have confirmed safety and show some increase in appetite and body weight [131]. Myostatin is a growth factor involved in the normal regulation of muscle mass [132]. Myostatin inhibitors and IL-6 antagonists are currently at Phase I RCT stage in development [131].

5. Conclusions

A consensus definition incorporating clinical, functional, and biochemical parameters is necessary in order to adequately identify and treat patients with cancer cachexia. A greater understanding of the pathophysiology, particularly in terms of the processes which drive cachexia will lead to new therapeutic target development. A number of issues remain to be resolved including whether inflammation drives the process or is a byproduct of the process. Does reversal of weight loss alone result in improved survival? By improving cachexia (i.e., leading to improved physical and physiological function) in cachexia, can patients become better able to tolerate anticancer therapies such as chemotherapy?

Composite endpoints which measure clinically relevant outcomes such as physical activity and quality of life are required in order to best assess the impact of interventions on cancer cachexia patients. Objective measures of function (as represented by physical activity) using advance ambulatory technology and integrated subjective quality of life parameters are likely to become standard practice in the clinical trial setting.

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Research Article

Prevalence of Malnutrition in Orally and Tube-Fed Elderly Nursing Home Residents in Germany and Its Relation to Health Complaints and Dietary Intake

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Objective. To investigate the prevalence of malnutrition in orally and tube-fed nursing home (NH) residents in Germany and its relation to common health complaints and dietary intake. *Methods*. In 350 NH residents, subjects' characteristics, Mini Nutritional Assessment (MNA), and several health problems were inquired with the nursing staff using standardised interviews. In a subset of 122 residents, dietary intake was assessed by 3-day weighing records. *Results*. 7.7% of the participants were tube fed. 24.1% of orally nourished and 57.7% of tube-fed residents were malnourished (MNA < 17 p.). Malnutrition was significantly related to nausea/vomiting, constipation, pressure ulcers, dehydration, infections, antibiotic use, and hospitalisation. Mean daily energy intake was 1535 ± 413 kcal and mean protein intake was 54.2 ± 0.9 g/d irrespective of the nutritional state. *Conclusion*. In Germany, malnutrition is widespread among NH residents and is related to common health problems. The MNA rather reflects health condition than currently reduced dietary intake.

1. Introduction

Elderly people are at increased risk of malnutrition due to a variety of factors including sensory losses, loss of appetite, chewing and swallowing problems, mobility restrictions, cognitive impairment and depressive mood, acute and chronic diseases, and accompanying multimedication [1]. Due to the frequently reduced physical and mental functioning, nursing home (NH) residents are particularly affected. In previous studies, however, highly differing prevalence rates of malnutrition were reported in institutionalized elderly. In a recent literature review about the nutritional situation of elderly nursing home residents, we found a reduced body-mass index (BMI < 20 kg/m^2) in 10 to 50% of the residents studied; weight loss was reported with prevalence rates between 5 and 41%. According to the Mini Nutritional Assessment (MNA), malnutrition was observed in 2 to 38% and a risk of malnutrition in 37 to 62% [2]. In an Italian [3] and a Swedish [4] study, even 71% of NH residents were found to be malnourished. In Germany, presently about 700,000 elderly are living in institutions and, as in many other countries, an increase is expected due to demographic changes [5]. Nutritional status of this growing population group has not thoroughly been studied before in Germany.

Generally, malnutrition is caused by an ongoing insufficient intake of energy and nutrients. In order to prevent malnutrition in persons who are persistently unable to eat adequate amounts of food, enteral nutrition by means of tube-feeding can be applied. Nutrition via a percutaneous endoscopic gastrostomy (PEG) is an established method for long-term enteral nutrition and is often used in nursing home residents not able to eat adequate amounts of food, although not without controversy [6, 7]. One of the main reasons of controversy may be the fact that enteral nutrition may be used incorrectly to facilitate care or save time instead of spending attention and time to oral feeding. Based on a recent nation-wide mailing survey, it was estimated that about 40,000 NH residents in Germany are living with a PEG

[8]. Our present knowledge about nutritional and health status of nursing home residents who are tube-fed is poor.

Tube-feeding often goes along with gastrointestinal (GI) complaints like nausea and vomiting, constipation or diarrhoea [9], but such symptoms are also frequently reported in orally nourished elderly and may compromise adequate dietary intake and contribute to the risk of malnutrition [1]. On the other hand, malnutrition increases the risk of illness, for example, infections, and may worsen the course of acute and chronic diseases. This association has mainly been reported in the acute-care setting for geriatric patients [10–13]. Little is known about health complaints of nursing home residents and the relation between malnutrition, common health complaints, and dietary intake.

Thus, the *aim* of the present study was to evaluate the prevalence of malnutrition in orally and tube-fed elderly nursing home residents in Germany and the relation between malnutrition, health problems, and dietary intake. We hypothesized that malnutrition and health complaints are widespread and interrelated, and that dietary intake is markedly reduced in malnourished residents.

2. Methods

2.1. Study Design. In this cross-sectional study, all residents from 3 municipal nursing homes (NHs) in Bonn, Germany, were considered for inclusion if they were at least 65 years old, in long-term care, and not in a terminal state (judged subjectively by the responsible nurse). Subjects' characteristics, nutritional status, health complaints, and dietary intake were assessed once in each participant between November 2004 and April 2006. The study was approved by the local ethics committee, and all participating subjects gave a signed consent.

2.2. Subjects' Characteristics. Subjects' characteristics were assessed in standardised personal interviews with the responsible qualified nurse, and included date of birth, gender, length of stay in the nursing home, route of feeding (oral or tube fed), and the following physical and mental aspects. The ability to perform basic *activities of daily living* (ADL) was assessed according to Mahoney and Barthel [14]. Residents were classified as independent (>65 p.), in need of help (35–65 p.), and in need of care (<35 p.). Residents were classified as *mobile* if they were able to walk at least 50 m without personal help, as partly mobile if they were able to walk at least 50 m with help or move independently with a wheel chair, or as immobile if they were unable to move at least 50 m. Kind and number of *chronic diseases* and of prescribed *medications* were gathered from the medical folders. The participants' general *health status* was subjectively judged by the nursing staff as fair, moderate, or poor. *Mental status* (no, mild, severe dementia; no, mild, severe depression) was also rated by the nursing staff by clinical judgment. In tube-fed residents, date of tube-placement and reason for tube-feeding were asked as well as the daily amount of tube-feed and additional oral food intake (no, little, predominant).

2.3. Nutritional Status. The *Mini Nutritional Assessment* (MNA) was used for the assessment of malnutrition. This standardized questionnaire, specifically designed for the elderly, consists of 18 questions with given weighted answers that sum up to a maximum score of 30 points. Patients are classified as well nourished (≥24 p.), at risk of malnutrition (17–23.5 p.), or malnourished (<17 p.) [15, 16]. In tube-fed residents, MNA questions concerning anorexia (A) and quality of diet (J–M) were scored highest, assuming an adequate provision of nutrients due to nutritionally complete tube-feeds and supposed specific nutritional attention for these residents.

Body mass index (BMI) was calculated as weight/(height^2) based on measured weight and height. Residents were weighed with a digital chair scale (Seca, Hamburg, Germany) to the nearest 0.1 kg. Height was measured with a measuring rod to the nearest 0.1 cm with the resident standing without shoes. When patients where unable to stand or had either deformations of the spinal column or osteoporosis, knee height was measured to the nearest 0.1 cm and height calculated according to Chumlea et al. [17]. The prevalence of BMI values below 20 and below 22 kg/m^2 was calculated.

Midarm circumference (MAC) was measured at the midpoint of the relaxed, nondominant arm between the tip of the acromion and the olecranon process.

Calf circumference (CC) was measured at the widest part of the undressed calf.

Both measurements were performed with a plastic tape measure and an accuracy of 0.1 cm and were utilised for the anthropometric questions in the MNA. Values below 21 cm (MAC) and below 31 cm (CC) were considered as reduced, respectively.

2.4. Health Complaints. The presence of nausea/vomiting, constipation, diarrhoea, pressure sores, wound healing problems, and dehydration was assessed in a standardised manner by interviewing the responsible nurse. The frequency of infections, antibiotic treatment, and hospitalisation in the previous three months was collected from the medical folders in cooperation with the responsible nurse.

2.5. Dietary Intake. In a subgroup of 122 orally fed residents, dietary intake was monitored for three consecutive days by precisely weighing all offered food before and all leftovers after each meal, using a digital weighing machine. Due to the high work load related to this method, dietary assessment was restricted to the residents of two nursing units of each of the 3 nursing homes. Foods were coded and analyzed for nutrient composition using the German nutrient database (BLS II.3) [18]. The mean intake of energy and protein was calculated per day and per kg body weight.

All measurements and assessments were performed by the same trained person (LP).

2.6. Evaluation and Statistics. Data analysis was performed using SPSS version 17.0 (SPSS Software, Munich, Germany). Categorical variables are reported as absolute numbers and

percentages. Continuous variables are presented as mean ± standard deviation (SD), median, and 25th and 75th percentiles (P_{25}–P_{75}). Subjects' characteristics and prevalence rates of malnutrition and of health complaints are reported in orally and tube-fed residents; the prevalence of health complaints and dietary intake is reported according to the MNA groups. Chi-square testing was used to detect differences between categorical variables. The normal distribution of continuous variables was tested by Kolmogorov-Smirnov test. Differences in continuous variables between subgroups are analysed by *t*-test or ANOVA and Tukey's post hoc test if normally distributed. Otherwise, Mann-Whitney-*U* and Kruskal-Wallis test were used. Missing values were not considered for statistical analysis. For all tests, *P* values below .05 were considered statistically significant.

3. Results

3.1. Subjects' Characteristics. Out of 382 persons residing in the institutions, 15 had to be excluded. Nine were younger than 65 years, four in a terminal state, and three in short-term care; one person was permanently hospitalized, one removed, and one deceased before data collection. 13 residents refused to participate. 350 residents agreed to take part, 283 women and 67 men with a mean age of 84.8 ± 8.0 years. The median length of stay in the institution was 2.7 years (1.3–4.9 years).

27 residents (7.7%) had a PEG *in situ*. About half of them ($n = 15$) were fed completely via this route and received either 1500 mL ($n = 8$) or 1000 mL ($n = 7$) per day of a standard tube-feed. Four residents were predominantly tube fed (mean 938 mL/day), and seven residents mainly received oral food and some tube-feed in addition (mean 431 mL/d). One resident received only water via the PEG. The reasons for tube-feeding were dysphagia ($n = 13$), refusal to eat ($n = 5$), low food ($n = 3$) or fluid ($n = 3$) intake, in one case a tumor and in one case an oesophagitis. In one case, the reason was unclear. 25 residents were fed continuously and two per bolus. The median duration of tube-feeding was 17.9 months (5.6–26.5 months). Ten residents already had the PEG when they moved to the NH, five received it within one year, one after one year and 11 after more than two years of residence in the NH.

All together, a considerable proportion of the residents were disabled. About one-third was in need of care (37.4%), immobile (34.9%), and/or showed signs of depression (38.0%), respectively. In nearly two-thirds (61.4%), signs of dementia were reported. Most of the participants (55.0%) suffered from 5 or more chronic diseases and nearly three-fourths (70.9%) took 5 or more prescribed medications. Nevertheless, health status of 83.1% of the study population was judged as fair or moderate. The most prevalent medical diagnoses were hypertension (43.3%), dementia (39.8%, as routinely documented by a practitioner), and cardiac insufficiency (32.1%). Diabetes mellitus was prevalent in 24.4%, osteoporosis in 15.8%, and kidney disease in 9.2%. 13.2% suffered from a previous stroke, 7.4% from a tumor and 6.3% from respiratory disease.

Table 1: Characteristics of orally and tube-fed nursing home residents.

	Oral nutrition ($n = 323$)	Tube-feeding ($n = 27$)
Female sex	81.4	74.1
Age, years (mean ± SD (median))	85.0 ± 8.1 (86.0)	81.9 ± 6.2 (82.0)
Age ≥ 85 years (%)	55.1	40.7
ADL, p. (median (P_{25}–P_{75}))	55 (20–85)	0 (0–5) ***
ADL		
Independent (70–100 p.) (%)	41.8	0.0 ***
In need of help (35–65 p.) (%)	26.0	0.0
In need of care (<35 p.) (%)	32.2	100.0
Mobility		
Mobile (%)	59.4	0.0 ***
Moderately mobile (%)	10.8	3.7
Immobile (%)	29.7	96.3
Dementia		
No [%]	40.2	15.4 **
Mild [%]	20.1	11.5
Severe [%]	39.6	73.1
Depression		
No (%)	61.4	69.2
Mild (%)	22.1	7.7
Severe (%)	16.5	23.1
Health status		
Fair (%)	58.2	25.9 ***
Moderate (%)	27.2	29.6
Poor (%)	14.6	44.4
No. of chronic diseases (median (P_{25}–P_{75}))	5 (3–6)	5 (4–7)
≥5 chronic diseases (%)	53.7	70.4
No. of medications (median (P_{25}–P_{75}))	6 (4–8)	5 (4–8)
≥5 medications (%)	70.9	70.4

*** $P < .001$, ** $P < .01$.
ADL = Activities of daily living, SD = standard deviation, P = percentile.

The subjects' characteristics are shown in Table 1 for orally and tube-fed residents separately. Tube-fed residents were significantly more often care dependent, immobile, severely demented, and in a poor health state than residents with oral nutrition. There was no difference in the number of chronic diseases or medications and no difference in the prevalence of specific diseases except stroke, which was reported in nearly half of the tube-fed subjects (48.1%), but only in 10.2% of orally nourished residents ($P < .001$).

3.2. Nutritional Status. According to the MNA, more than one-forth (26.7%) of the total group suffered from malnutrition (MNA < 17 p.) and one-half (52.9%) was at risk (MNA 17–23.5 p.). Malnutrition was significantly more prevalent in tube-fed compared to orally nourished residents ($P <$

.001; Table 2). The mean BMI was 25.5 ± 5.1 kg/m^2 (22.0–28.2 kg/m^2; n = 334) without difference between orally and tube-fed residents. In 13.5%, the BMI was below 20 kg/m^2, and 25.1% had a BMI below 22 kg/m^2. MAC was reduced in 12.9%, again without significant difference between tube- and orally nourished residents. CC was reduced in half of the orally nourished (50.2%) and in three-quarts (76.9%) of the tube-fed residents (P < .001).

3.3. Health Complaints. Constipation was reported in 43.0% of all residents, nausea/vomiting in 13.4%, and dehydration and wound healing problems in 10.6%, respectively. Diarrhoea (6.3%) and pressure sores (3.7%) were less frequent. Constipation and nausea/vomiting were significantly more frequent in tube-fed residents (Table 3). Within the previous three months, 22.3% had an infection, in 16.3% treated with antibiotics, and 14.9% were hospitalised without difference between orally and tube-fed residents. All health problems except diarrhoea and wound healing problems were significantly more often reported in malnourished residents (Figure 1).

3.4. Dietary Intake. The weighing records revealed a mean daily energy intake of 1535 ± 413 kcal (6.42 ± 1.72 MJ) and a protein intake of 54.2 ± 0.9 g/d. Expressed per kg BW the residents consumed 25.5 ± 7.3 kcal and 0.89 ± 0.27 g protein. Dietary intake according to MNA is presented in Table 4. There was no difference between the groups in total intake of energy and protein per day. Expressed per kg BW, both energy (P < .001) and protein (P < .05) intake were significantly higher in malnourished residents compared to well-nourished ones. The difference in energy intake per kg BW between malnourished and those at risk of malnutrition was also significant (P < .05).

Table 2: Nutritional status of orally and tube-fed nursing home residents.

	Oral nutrition (n = 323) mean ± SD (n) median (P_{25}–P_{75})	Tube-feeding (n = 27) mean ± SD (n) median (P_{25}–P_{75})
MNA (p.)	19.9 ± 4.6 (307)	16.0 ± 2.7 (26)
	20.5 (17.0–23.0)	16.0 (14.0–18.0) ***
MNA		
<17 p. (%)	24.1	57.7 ***
17–23.5 p. (%)	53.7	42.3
>23.5 p. (%)	22.1	0.0
BMI (kg/m^2)	25.6 ± 5.2 (308)	24.9 ± 4.9 (26)
	25.3 (22.0–28.4)	25.0 (22.0–28.4)
BMI <20 kg/m^2 (%)	13.6	11.5
BMI <22 kg/m^2 (%)	25.3	23.1
MAC (cm)	25.3 ± 3.9 (315)	24.8 ± 4.2 (27)
	24.8 (22.9–27.6)	24.9 (22.4–27.8)
MAC <21 cm (%)	12.7	14.8
CC (cm)	31.2 ± 4.8 (315)	27.4 ± 4.5 (26) ***
	30.9 (28.0–34.2)	27.8 (25.3–29.8)
CC <31 cm (%)	50.2	76.9 **

*** P < .001, ** P < .01.
MNA = Mini Nutritional Assessment, p. = points, BMI = body mass index, MAC = midarm circumference, CC = calf circumference, SD = standard deviation.

Table 3: Health complaints of orally and tube-fed nursing home residents.

	Oral nutrition (n = 323)		Tube-feeding (n = 27)	
	n	%	n	%
Constipation	133	41.3	17	63.0 *
Nausea/vomiting	38	11.8	9	33.3 **
Diarrhoea	21	6.5	1	3.7
Pressure sore	8	2.5	5	18.5
Wound healing problems	34	10.5	3	11.1
Dehydration	36	11.1	1	3.7
Infection	70	21.7	8	29.6
Antibiotic use	51	15.8	6	22.2
Hospitalization	45	13.9	7	25.9

** P < .001, * P < .01.

4. Discussion

In this cross-sectional study, nutritional status was studied for the first time in a large sample of nursing home residents in Germany. A considerable proportion of the residents were found to be malnourished or at risk of malnutrition.

Prior to that, only two smaller studies addressed the nutritional situation of institutionalized elderly in Germany. One was restricted to 50 apparently healthy women living in two old peoples' homes and reported a generally good nutritional status [19]. The other focused on dietary intake and physical activity of 47 female self-feeding and 20 eating-dependent NH residents [20]. Meanwhile, two large-scale studies with more than 2000 participants in each study were performed—one in 29 German [21], the other one in 30 German and 8 Austrian nursing homes ("nutritionDay") [22]. In both projects, questionnaire-based assessments were performed by local nurses at one specific day. Another regional study recently looked at nutritional and functional status of 200 NH residents in Nuremberg [23, 24].

One strength of the present study is its high participation rate, meaning that the results are representative for the participating institutions. This could be achieved mainly because participation was strongly recommended and supported by the nursing home management. In addition, all information except four anthropometric measurements was collected in cooperation with the nursing staff, implying only minimal burden for the participants. Detailed data were assessed in personal interviews with the responsible nurses. These interviews were scheduled on office days destined for documentation. Thus, enough time was available despite usually high work loads for nursing staff. All nurses were familiar with their dedicated residents and well informed

Table 4: Dietary intake in nursing home residents with malnutrition, at risk of malnutrition and without malnutrition.

	Well-nourished MNA > 23.5 p. (n = 25)	At risk MNA 17–23.5 p. (n = 56)	Malnourished MNA < 17 p. (n = 41)
Energy (kcal/d)	1516.5 ± 431.2	1566.7 ± 420.2	1502.8 ± 398.0
Energy (kcal/kg BW)	21.9 ± 5.3	24.3 ± 7.0	29.3 ± 7.4 ***,§§
Protein (g/d)	56.4 ± 20.3	56.0 ± 19.0	50.4 ± 14.8
Protein (g/kg BW)	0.81 ± 0.23	0.86 ± 0.27	0.98 ± 0.28 *

*** $P < .001$, * $P < .01$ malnourished versus well-nourished.
§§ $P < .01$ malnourished versus at risk of malnutrition.
MNA = Mini Nutritional Assessment, p. = points, BW = body weight.

about their personal characteristics and health situation, so that reliable information could be obtained. For the MNA, it has recently been reported that application by the nursing staff is even superior to direct interviews with the residents, because more complete and detailed, and, especially in demented subjects, more reliable information can be obtained [23]. Nevertheless, it has to be mentioned that categorization of some parameters, especially dementia, depression, and general health status, is affected by subjective perceptions. More detailed assessments were intentionally abandoned in order to keep the burden for the residents as well as total expenses low.

As characteristic for the nursing home population, considerable proportions of the residents were physically and mentally impaired with multiple chronic diseases, multimedication, and a reduced level of self-sufficiency (Table 1). Very similar rates of immobility (30%) and dementia (68%) were reported by Valentini et al. [22] in the above-mentioned "nutritionDay" study from 30 German and 8 Austrian NHs.

Regarding dementia, different prevalence rates are noticeable according to the nurses' perception (61.4%) and the diagnosis found in the medical records, routinely documented by a practitioner (39.8%). Presumably, the prevalence was underestimated by physicians, who often miss to diagnose mental impairments [25], and, on the other hand, overestimated by the nursing staff, who might have wrongly interpreted acute or other forms of cognitive impairment (e.g., delirium) as dementia. With respect to malnutrition, however, also mild forms of confusion may be relevant.

As currently recommended [26], malnutrition was assessed by using the MNA, a simple and well-validated instrument, especially designed for the elderly and regarded as the gold standard for nutritional assessment for elderly living in long-term care facilities [27]. The strength of the MNA lies in its multidimensional approach which comprises physical and mental state, health, and self-perception, as well as nutritional status and quality of the diet. The risk of malnutrition may be detected early with this tool, and preventive measures initiated in a timely manner. According to the MNA, we found malnutrition in about one quarter of the residents, and more than half were at risk of malnutrition. Compared to international data, these prevalence rates are in the middle of previously reported ranges [2].

Regarding BMI, about one quarter of the residents showed values below 22 kg/m^2, and a BMI below 20 kg/m^2 was observed in 13.5%—somewhat less frequent than reported in other nursing home populations [22, 23, 28–32].

CC was reduced in more than half of the residents (52.2%). This clearly indicates reduced leg muscle mass and protein stores, caused by disuse of the leg muscles, and reflects the low mobility level in our population. In community-living elderly, a CC below 31 cm was identified as best clinical marker of sarcopenia and associated with disability and reduced leg function [33]. Up to now, CC was measured only in a few studies, all reporting higher mean values [23, 34–36]. Ruiz-López et al. [35] observed reduced values (<31 cm) in 30% of 89 NH residents in Spain. Unfortunately, in all these studies, mobility or activity level were not reported. Importantly, CC was much more often reduced than MAC (13%). All residents with reduced MAC, except one, also had a reduced CC. This difference may be explained by less pronounced muscle mass in upper extremities and less pronounced changes as a result of inactivity.

In tube-fed residents, complete ADL dependence and the high prevalence of immobility and dementia are striking (Table 1). There was no difference in kind and number of chronic diseases, except for stroke, one of the main indications for tube-feeding. However, health status was more often judged to be poor, and these persons likely are in rather advanced disease states.

Regarding tube-feeding of NH residents, there is an ongoing discussion about its benefits and risks. Especially in case of severe dementia the benefit of enteral nutrition is questioned [6]. In our participants, the adequacy of this mode of feeding cannot be judged, since decisions concerning tube-feeding are always very individual—depending on the patients' underlying disease, general condition, and personal preferences. Stated reasons for tube-feeding were dysphagia and low food or fluid intake in most of the cases and, thus, appropriate indications for enteral nutrition [37]. Compared to the recent nation-wide survey of Wirth et al. [8], where 6.6% of all residents of the responding nursing homes were fed via PEG, the prevalence of tube-feeding in our population was very similar. Additional food intake was slightly more common compared to Wirth et al. [8] (44 versus 36%), and a slightly smaller proportion (37 versus 50%) received the PEG before NH admission.

Despite scoring the highest for the five questions regarding appetite and diet quality, a low total MNA score and, thus, a high prevalence of malnutrition were observed in

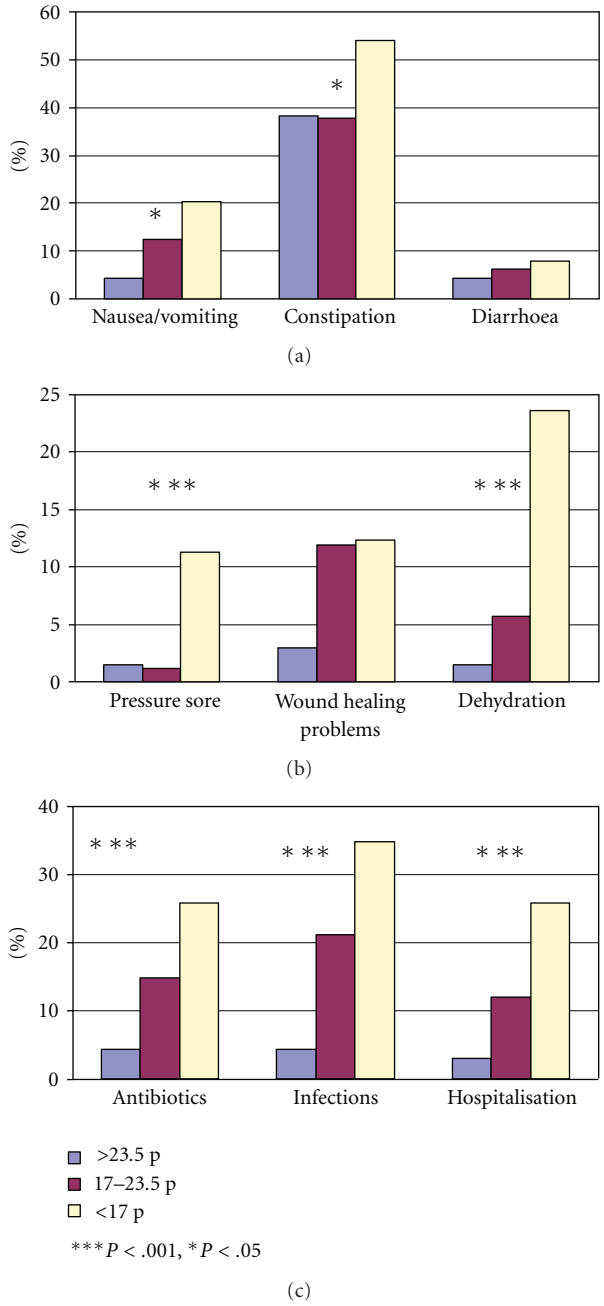

Figure 1: Prevalence of health complaints in well-nourished residents (MNA > 23.5 p.; $n = 68$), residents at risk (MNA 17–23.5 p.; $n = 176$), and malnourished residents (MNA < 17 p.; $n = 89$).

tube-fed residents. This is in line with a number of earlier studies, which have reported a reduced nutritional status in elderly patients at the time of tube placement. These studies, however, referred to low BMI and albumin values [38–42]. In our population, however, BMI was not different in orally and tube-fed residents, and markedly higher than in these studies. Also, MAC did not differ between the two groups (Table 2). These results demonstrate that a normal body mass index can be maintained or achieved by tube-feeding, that is not reflected by the results of the MNA. CC, in contrast, was significantly lower and more often reduced in tube-fed compared to orally nourished residents (Table 2). This reflects the higher proportion of immobility in these subjects and shows that nutritional support alone, without concomitant physical activity, is not effective in improving muscle mass and function.

Gastrointestinal disorders, common in the elderly, may result in complications and can cause major morbidity [43, 44]. With respect to nutrition, they may negatively affect dietary intake and compromise nutritional status.

In our study, *constipation* was by far the most prevalent health complaint—nearly half of our participants were affected. An approximately equivalent prevalence rate was reported in a large Finish NH population [45]. Constipation is favored by age-related changes in gastrointestinal function, for example, weakening of the colonic muscles and changes in anorectal function [43, 46]. It also occurs as an adverse effect of many medications. Thus, the high prevalence may partly be explained by the observed multimedication in our study. Nutritional factors as decreased food, fluid, and fiber intake may also contribute to its development. In our orally nourished participants, with a mean of about 1500 kcal/d food intake was often rather low. Mean fiber intake from food amounted to 12.8 g/d, and thus was also clearly below the recommendation. In only 8 of the 27 tube-fed residents, a fiber-containing feed was used. On the other hand, constipation may lead to discomfort, feeling of fullness, and reduced desire to eat and thus, promoting malnutrition. In a recent Swedish study among older adults in sheltered housing, constipation was identified as one of the strongest risk factors for underweight and weight loss [47]. In agreement and corroborated by Suominen et al. [45], constipation was significantly correlated to malnutrition in our study (Figure 1).

All other health complaints were much less common. *Nausea and vomiting* were reported in 13%. Like constipation, these complaints were more prevalent in tube-fed than in orally nourished residents (Table 3) and significantly related to malnutrition (Figure 1). In contrast, *diarrhoea* was only occasionally reported and neither related to feeding mode nor to malnutrition. Only one tube-fed resident suffered from diarrhea. Obviously, this typical complication of enteral nutrition is avoidable by experienced care. Despite poorer general health, also the other health complaints were not more often observed in tube-fed residents (Table 3); dehydration even tended to be less frequent.

The prevalence of *pressure ulcers* tended to be higher in tube-fed residents, but altogether was very low, despite a high prevalence of immobility and great proportion of bedridden residents in our study—indicating a high quality of care also in this respect. Markedly higher prevalence rates were reported in the above-mentioned German large-scale studies [21, 22]. In accordance with our results, in both of these studies, a close relationship between malnutrition and pressure ulcers is reported, confirming malnutrition as risk factor for this serious health problem [48].

Infections, antibiotic use, and hospitalizations were relatively common in our study population (15–20%; Table 3) and also clearly associated with malnutrition (Figure 1). This

close correlation may partly be explained by the fact that one question of the MNA (question D) asks for acute disease in the past three months and, thus, some overlap in this regard must be admitted.

Interestingly, BMI (neither <20 nor <22 kg/m^2) was not related to health complaints (with the exception of dehydration that was significantly more frequent in subjects with reduced BMI; data not presented), suggesting that the MNA reflects general health condition better than the BMI, again strengthening its usefulness in multimorbid geriatric persons.

Mean dietary intake, assessed by precise weighing of all food for three consecutive days in a subgroup of 122 residents, was 1535 kcal and 54 g protein per day. In several studies in recent years, very similar figures were reported for NH residents [35, 49–52]. This amount of energy is clearly below the recommended amount for healthy elderly [53]; however, its adequacy is difficult to estimate, due to limited knowledge about the exact requirements in this very old, multimorbid, mainly disabled persons. Based on body weight, height, and age, a mean basal metabolic rate (BMR) of 1243 ± 170 kcal was calculated in our population, and an energy intake/BMR ratio of 1.24 ± 0.31. This level is regarded as adequate for immobile elderly, but probably is too low for more active persons. The observed mean protein intake of 0.89 g/kg in fact meets the current recommendation for healthy elderly; however, higher protein needs are suggested for frail and multimorbid elderly. Additional offers of milk-based snacks, food fortification, or nutritional supplements might contribute to improve intake of protein as well as energy and other nutrients.

Unfortunately, nutrient intake of tube-fed residents was not assessed in detail in our study. Those residents who were fed completely by tube received either 1 or 1.5 L of a standard tube-feed, and thus, had at least a basic supply of energy and all essential nutrients. Again, adequacy is difficult to estimate because requirements are not exactly known.

In contrast to our expectations and in contrast to Vellas et al. [54] who reported close correlations between the MNA and dietary intake in 105 geriatric patients and 50 community-living elderly, we found no difference in energy and protein intake between residents with malnutrition, at risk of malnutrition, or without malnutrition. Per kg BW malnourished subjects consumed even more energy and protein than those in better nutritional status (Table 4). Ruiz-López et al. [35] also reported a significantly lower energy intake in 5 malnourished NH residents compared to 56 subjects at risk of malnutrition; however, in accordance with our study, no difference between the MNA groups was found for protein intake per day and per kg BW. Ödlund Olin et al. [52] observed in 80 elderly service flat residents and Murphy et al. [55] in 49 female elderly orthopedic patients no difference in energy intake between the MNA groups. These results suggest that malnutrition evolved from a poor intake in the past, possibly caused by an acute event. After relief of the acute problem, intake may normalize without regaining a well-nourished state. This is consistent with a reported increased energy requirement per kg BW in malnourished compared to normally nourished elderly [56].

In conclusion, malnutrition is widespread among nursing home residents also in Germany and related to common health complaints but not to currently reduced dietary intake. According to the MNA, enterally nourished residents are markedly more often affected by malnutrition than orally nourished residents. On the other hand, our data show that a normal body mass can be maintained or achieved by tube-feeding, indicated by BMI and MAC, that is not reflected by the results of the MNA. Our data suggest that the MNA rather reflects general condition and nutritional risk than current body stores or dietary intake of energy and protein.

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Review Article

Diagnosis and Management of Oropharyngeal Dysphagia and Its Nutritional and Respiratory Complications in the Elderly

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Oropharyngeal dysphagia is a major complaint among older people. Dysphagia may cause two types of complications in these patients: (a) a decrease in the efficacy of deglutition leading to malnutrition and dehydration, (b) a decrease in deglutition safety, leading to tracheobronchial aspiration which results in aspiration pneumonia and can lead to death. Clinical screening methods should be used to identify older people with oropharyngeal dysphagia and to identify those patients who are at risk of aspiration. Videofluoroscopy (VFS) is the gold standard to study the oral and pharyngeal mechanisms of dysphagia in older patients. Up to 30% of older patients with dysphagia present aspiration—half of them without cough, and 45%, oropharyngeal residue; and 55% older patients with dysphagia are at risk of malnutrition. Treatment with dietetic changes in bolus volume and viscosity, as well as rehabilitation procedures can improve deglutition and prevent nutritional and respiratory complications in older patients. Diagnosis and management of oropharyngeal dysphagia need a multidisciplinary approach.

1. Definition and Prevalence

Dysphagia is a symptom that refers to difficulty or discomfort during the progression of the alimentary bolus from the mouth to the stomach. From an anatomical standpoint dysphagia may result from oropharyngeal or esophageal dysfunction and from a pathophysiological standpoint from structure-related or functional causes [1, 2]. The prevalence of oropharyngeal functional dysphagia is very high: it affects more than 30% of patients who have had a cerebrovascular accident; 52%–82% of patients with Parkinson's disease; 84% of patients with Alzheimer's disease, up to 40% adults aged 65 years and older, and more than 60% of elderly institutionalized patients [2, 3]. Increase in the percentage of older persons is one of the principal demographic characteristics of the population of developed countries. In Europe, more than 17% of the citizens are older than 65 years. In the last decade, this group has increased by 28% whereas the rest of the population has only grown 0.8 % [1]. It has been estimated that 16,500,000 US senior citizens will require care for dysphagia by the year 2010 [4]. In spite of its enormous impact on the functional capacity, health, and quality of life of the older persons who suffer it, oropharyngeal dysphagia is underestimated and underdiagnosed as a cause of symptoms

and major nutritional and respiratory complication in older patients. Oropharyngeal dysphagia fulfills most criteria to be recognized as a major geriatric syndrome as its prevalence is very high in geriatric patients and results in multiple diseases, risk factors, and precipitating diseases [5]. The current state of the art with oropharyngeal dysphagia management in older patients aims at identifying patients at risk for dysphagia early, by assessing alterations in the biomechanical events of oropharyngeal swallow response, attempting to prevent and treat the potential complications of dysphagia such as aspiration pneumonia (AP) and malnutrition, and recognizing oropharyngeal dysphagia as a major geriatric syndrome.

Identification of functional oropharyngeal dysphagia as a major neurological and geriatric syndrome will cause many changes in the provision of medical and social services in the near future. Education of health professionals on diagnosis and treatment of dysphagia and its complications, early diagnosis, development of specific complementary explorations in the clinical setting, improvement in therapeutic strategies to avoid aspirations and malnutrition, and research into its pathophysiology are the cornerstones to allow maximal recovery potential for older patients with functional oropharyngeal dysphagia.

2. Pathophysiology

Oropharyngeal dysphagia may result from a wide range of *structural alterations* that may impair bolus progression. Most common structural abnormalities include esophageal and ENT tumors, neck osteophytes, postsurgical esophageal stenosis, and Zenker's diverticulum [2]. Dysphagia may also be a side effect in patients with head & neck cancer undergoing radiotherapy. However, oropharyngeal dysphagia in the elderly is more frequently a *functional disorder of deglutition* affecting oropharyngeal swallow response caused by aging, stroke, or associated with systemic or neurological diseases. In biomechanical terms, the oropharyngeal swallow response (OSR) consists of the temporal arrangement of oropharyngeal structures from a respiratory to a digestive pathway, the transfer of the bolus from the mouth to the esophagus, and the recuperation of the respiratory configuration [6, 7] (Figure 1). Sensory input by physicochemical properties of the bolus is required during bolus preparation and trigger and modulate the swallow response. Taste, pressure, temperature, nocioceptive, and general somatic stimuli from the oropharynx and larynx are transported through cranial nerves V, VII, IX and X to the central pattern generator (CPG), within the nucleus tractus solitarius (NTS), where they are integrated and organized with information from the cortex. Swallowing has a multiregional and assymmetrical cerebral representation in caudal sensorimotor and lateral premotor cortex, insula, temporopolar cortex, amygdala, and cerebellum. This observation explains why 30%-50% of unilateral hemispheric stroke patients will develop dysphagia [8]. Once activated, the CPG triggers a swallow motor response involving motor neurons in the brainstem and axons traveling through the cervical spinal cord (C_1-C_2) and cranial nerves (V, VII, IX, to XII) [7].

Duration of the swallow response in healthy humans is in the range of 0.6–1 s [7]. Healthy subjects presented a short reaction time in the submental muscles [9], short swallow response (GPJO-LVO < 740 ms), fast laryngeal vestibule closure (LVC < 160 ms), and fast upper esophageal sphincter opening (UESO < 220 ms) [10]. In contrast, the swallow response is impaired in older people, especially in patients with neurogenic dysphagia [9–11]. Older patients have prolonged reaction time in the submental muscles [9], and overall duration of OSR in these subjects is significantly longer than in healthy volunteers due to delay in the early phase of oropharyngeal reconfiguration from a respiratory to a digestive pathway [10]. We found prolonged intervals to LVC and UESO were the key abnormalities of swallow response, doubling that of healthy subjects and leading to unsafe deglutition and aspiration in neurological older patients (Figure 2) [10, 11]. This delayed swallow response in the elderly can be attributed to an impairment of sensations [12, 13], a decrease in the number of neurons in the brain, and a delay in the synapse conduction in the afferent inputs to the central nervous system (SNC) caused by aging [9] and by other risk factors for dysphagia like neurodegenerative diseases or stroke [1, 14]. Other conditions such as delirium, confusion and dementia, and the effects of sedative, neuroleptic, or antidepressant drugs, can also contribute to impaired swallow response in frail older patients [14]. Transfer of the bolus from the mouth through the pharynx is mainly caused by the squeezing action of the tongue [15]. Older adults present lingual weakness, a finding that has been related to sarcopenia of the head and neck musculature and frailty [16]. Tongue propulsion is assessed by direct measurements with oral sensors [16] or by videofluoroscopic studies which measure the bolus velocity and kinetic energy during swallow [10]. Older adults generate lower maximum isometric pressures than younger adults [16]. We found young healthy adults present high bolus velocity (>35 cm/s) and strong bolus propulsion forces (>0.33 mJ) [10]. In contrast, older people with oropharyngeal dysphagia present impaired tongue propulsion forces (<0.14 mJ) and slower bolus velocity (<10 cms/s) [10]. Therefore, dysphagia in the elderly is associated with impairment in efficacy and safety of swallow caused by weak tongue propulsion and prolonged and delayed swallow response. Pathogenesis of impaired safety is related to a delay in several physiologic protective reflexes in oropharyngeal reconfiguration (mainly laryngeal vestibule closure) caused by a slow neural swallow response and is associated with several risk factors such as aging, neurodegenerative diseases, confusion, dementia, and drugs (Figure 7). Pathogenesis of impaired efficacy is related to alterations in bolus propulsion caused by a weak muscular tongue squeeze associated to sarcopenia and weakness [1].

3. Diagnosis

In many hospitals there is a big discrepancy between the high prevalence, morbidity, mortality, and costs caused by nutritional and respiratory complications of functional oropharyngeal dysphagia and the restricted availability of human and material resources dedicated to dysphagic

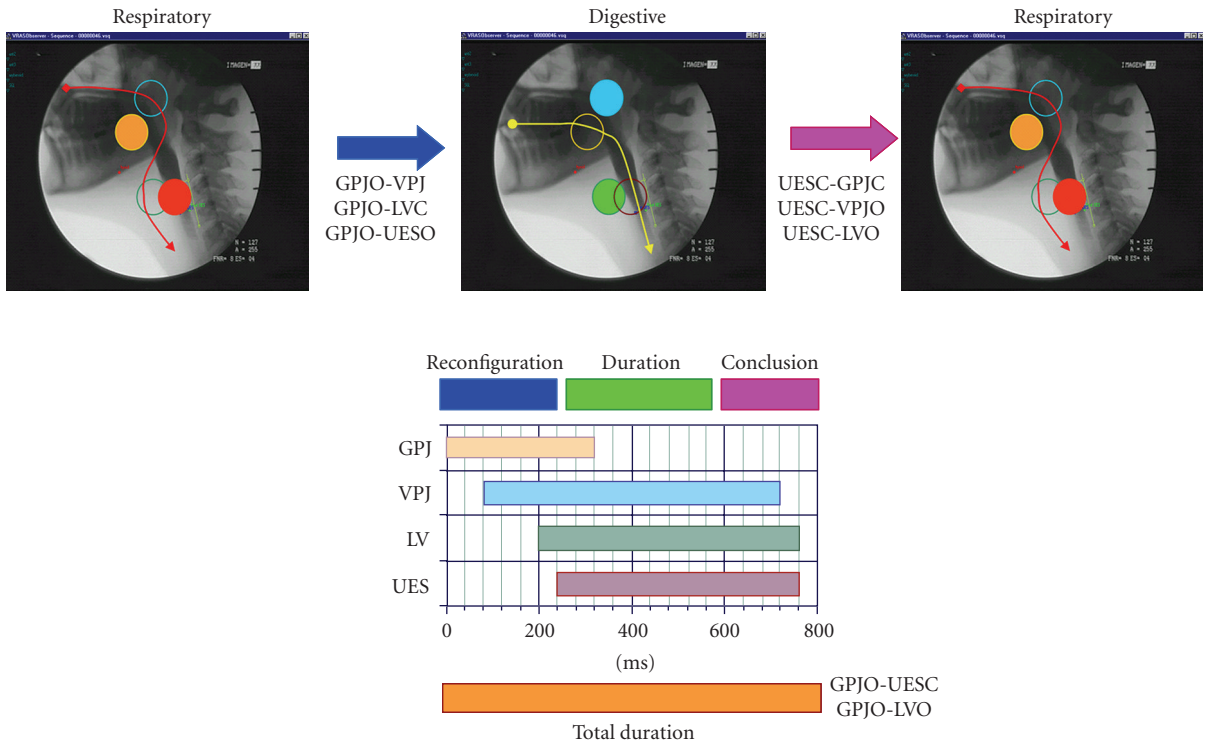

Figure 1: Configuration of the oropharynx during swallow response. Each phase of the response (reconfiguration, duration and conclusion) is defined by opening (O) or closing (C) events occurring at the glossopalatal junction (GPJ), velopharyngeal junction (VPJ), laryngeal vestibule (LV), and upper esophageal sphincter (UES).

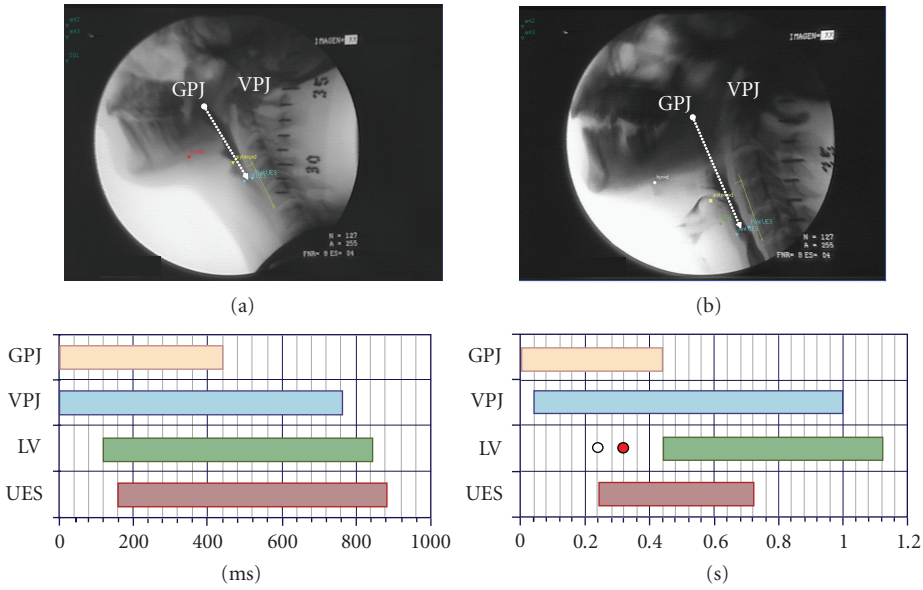

Figure 2: Videofluoroscopic pictures and oropharyngeal swallow response during the ingestion of a 5 mL nectar bolus in: (a) a healthy individual; (b) an older patient with neurogenic dysphagia and aspiration associated with stroke. An increased total duration of the swallow response may be seen, as well as a delayed closure of the laryngeal vestibule and delayed aperture of the upper sphincter. The white dot indicates the time when contrast penetrates into the laryngeal vestibule, and the red dot indicates passage into the tracheobronchial tree (aspiration). GPJ = glossopalatal junction, VPJ = velopalatal junction, LV = laryngeal vestibule, UES = upper esophageal sphincter.

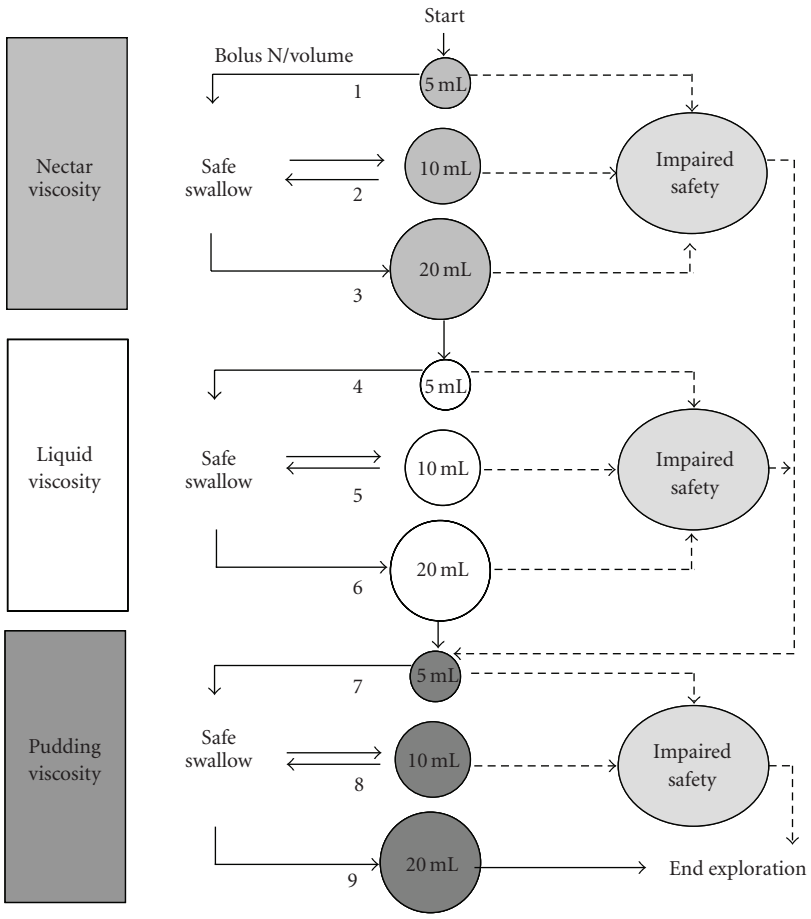

Figure 3: Algorithms of bolus volume and viscosity administration during V-VST. The strategy of the V-VST aims at protecting patients from aspiration by starting with nectar viscosity and volumes were increased from 5 mL, to 10 mL and 20 mL boluses in a progression of increasing difficulty. When patients completed the nectar series without major symptoms of aspiration (cough and/or fall in oxygen saturation ≥3%), a less "safe" liquid viscosity series was assessed also with boluses of increasing difficulty (5 mL to 20 mL). Finally, a more "safe" pudding viscosity series (5 mL to 20 mL) was assessed using similar rules. If the patient presents a sign of impaired safety at nectar viscosity, the series is interrupted, the liquid series is omitted, and a more safe pudding viscosity series is assessed. If the patient presents a sign of impaired safety at liquid viscosity, the liquid series is interrupted and the pudding series is assessed (Figure 1(C)).

patients. Dysphagia with oropharyngeal aspiration is not usually considered an etiologic factor in older patients with community-acquired pneumonia [17, 18] or with malnutrition [19]. Diagnosis and management of oropharyngeal dysphagia needs a **multidisciplinary approach**. A *dysphagia multidisciplinary team* should include several professional domains: nurses, speech-swallow therapists, gastroenterologists, ENT specialists, neurologists, surgeons, rehabilitation physicians, dietitians, radiologists, and geriatricians. The goals of a multidisciplinary dysphagia team include: (a) early identification of older patients with dysphagia; (b) diagnosis of any medical or surgical etiology for dysphagia that may respond to specific treatment; (c) characterization of specific biomechanical events responsible for functional dysphagia in each patient; and (d) the design of a set of therapeutic strategies to provide patients with safe and effective deglutition, or the provision of an alternative route to oral feeding based on objective and reproducible data [2, 19]. The involvement of patient's family in the diagnostic and therapeutic process is of capital importance. Once a diagnosis of functional oropharyngeal dysphagia has been established, the goal of the diagnostic program is to evaluate two deglutition-defining characteristics: (a) *efficacy,* the patient's ability to ingest all the calories and water he or she needs to remain adequately nourished and hydrated; and (b) *safety,* the patient's ability to ingest all needed calories and water with no respiratory complications [1, 2, 10, 19]. To assess both characteristics of deglutition two groups of diagnostic methods are available (a) *clinical methods* such as deglutition-specific medical history and clinical examination, usually used as screening methods; and (b) the exploration of deglutition using *specific complementary studies* such as videofluoroscopy.

Clinical screening for oropharyngeal dysphagia should be low risk, quick, and low cost and aim at selecting the highest risk patients who require further assessment. Current methods for clinical screening of dysphagia are, for example, the water swallow test [20], the 3-oz water test developed in the Burke Rehabilitation Center [21], the timed

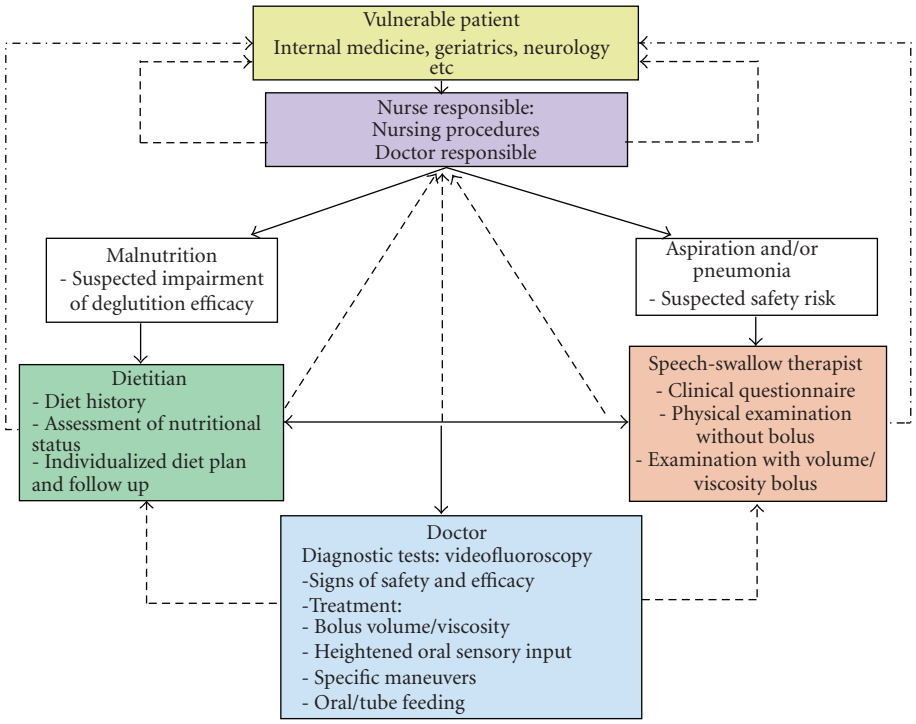

Figure 4: Algorithm for screening, diagnosis and treatment of oropharyngeal functional dysphagia at the Hospital de Mataró. Barcelona. Spain. Note the involvement of several professional domains of the dysphagia multidisciplinary team and the vertical and horizontal flows of information. The continuous black lines indicate the diagnostic screening strategy of patients at risk; the broken lines indicate flow of information on patient status, and broken dotted lines indicate therapeutic interventions.

swallow test [22], and the standardized bedside swallow assessment (SBSA) [23, 24]. Patients are asked to drink 50 mL [25], 3 oz [21], 150 mL [22], or 60 mL [23, 24] water from a glass without interruption. Coughing during or after completion or the presence of a postswallow wet-hoarse voice quality, or swallow speed of less than 10 mL/ are scored as abnormal. These clinical bedside methods can detect dysphagia, although with differing diagnostic accuracy. The Burke's 3-oz water swallow test identified 80% of patients aspirating during subsequent VFS examination (sensitivity 76%, specificity 59%) [21]. The SBSA showed a variable sensitivity (47% to 68%) and specificity (67% to 86%) in detecting aspiration when used by speech swallow therapists or doctors [23, 24]. Note that these screening procedures involve continuous swallowing of quite large amounts of liquid and may place the patient at high risk for aspiration. Furthermore, many of these studies on bedside screening lack methodological quality and, therefore, the psychometric properties of the screening procedure being studied cannot be determined accurately [26]. Our team developed a safer clinical method (the volume-viscosity swallow test, V-VST) using a series of 5–20 mL nectar, liquid and pudding boluses sequentially administered in a progression of increasing difficulty (Figure 3). Cough, fall in oxygen saturation ≥3%, and changes in quality of voice were considered clinical signs of impaired safety, and piecemeal deglutition and oropharyngeal residue, signs of impaired efficacy. The V-VST is a safe, quick, and accurate clinical method with 88.2% sensitivity for impaired safety, 100% sensitivity for aspiration and up to 88.4% sensitivity for impaired efficacy of swallow [2]. Figure 4 shows the algorithm for management (screening, diagnosis, and treatment) of oropharyngeal dysphagia at the Hospital de Mataró, Barcelona, Spain [19]. The V-VST is considered to be a highly adequate instrument for screening for dysphagia and agrees with the recommendations stated in the systematic review on bedside screening for dysphagia by Bours et al. [26] to combine a water test and pulse oximetry using coughing, choking, and voice alteration as endpoints. The use of different viscosities in the V-VST can be considered to be an improvement compared to a simple water test using only liquid.

Videofluoroscopy(VES) is the gold standard to study the oral and pharyngeal mechanisms of dysphagia [2, 27]. If no VFS is available, fiberoptic endoscopic evaluation of swallowing (FEES) may be used as a valuable screening instrument instead [28]. VFS is a dynamic exploration that evaluates the safety and efficacy of deglutition, characterizes the alterations of deglutition in terms of videofluoroscopic symptoms, and helps to select and assess specific therapeutic strategies. Technical requirements for clinical VFS are an X-ray tube with fluoroscopy and a videotape recorder; and there are computed-assisted methods of analysis of images allowing quantitative temporal and spatial measurements [10]. Main observations during VFS are done in the lateral plane while swallowing 3–20 mL boluses of at least three consistencies: liquid, nectar, and pudding. We keep the patient

at a minimal risk for aspiration by starting the study with low volumes and thick consistencies, introducing liquids and high volumes as tolerated [10]. Major signs of impaired efficacy during the oral stage include apraxia and decreased control and bolus propulsion by the tongue. Many older patients present deglutitional apraxia (difficulty, delay, or inability to initiate the oral stage) following a stroke. This symptom is also seen in patients with Alzheimer's, dementia and patients with diminished oral sensitivity. Impaired lingual control (inability to form the bolus) or propulsion results in oral or vallecular residue when alterations occur at the base of the tongue. The main sign regarding safety during the oral stage is glossopalatal (tongue-soft palate) seal insufficiency, a serious dysfunction that results in the bolus falling into the hypopharynx before the triggering of the oropharyngeal swallow response and while the airway is still open, which causes predeglutitive aspiration [2, 29]. Videofluoroscopic signs of safety during the pharyngeal stage include penetrations and/or aspirations. Penetration refers to the entering of contrast into the laryngeal vestibule within the boundaries of the vocal cords. When aspiration occurs, contrast goes beyond the cords into the tracheobronchial tree (Figure 2(b)). The potential of videofluoroscopy regarding image digitalization and quantitative analysis currently allows accurate swallow response measurements in patients with dysphagia (Figure 2). A slow closure of the laryngeal vestibule and a slow aperture of the upper esophageal sphincter (as seen in Figure 2(b)) are the most characteristic aspiration-related parameters [10, 11]. Penetration and aspiration may also result from an insufficient or delayed hyoid and laryngeal elevation, which fail to protect the airway. A high, permanent postswallow residue may lead to postswallow aspiration, since the hypopharynx is full of contrast when the patient inhales after swallowing, and then contrast passes directly into the airway [2, 29]. Thereafter, VFS can determine whether aspiration is associated with impaired glossopalatal seal (predeglutitive aspiration), a delay in triggering the pharyngeal swallow or impaired deglutitive airway protection (laryngeal elevation, epiglottic descent, and closure of vocal folds during swallow response), or an ineffective pharyngeal clearance (postswallowing aspiration) [2].

4. Complications of Oropharyngeal Dysphagia

The severity of oropharyngeal dysphagia varies from moderate difficulty to complete inability to swallow. Oropharyngeal dysphagia may give rise to two groups of clinically relevant complications in older people: (a) malnutrition and/or dehydration caused by a decrease in the efficacy of deglutition, present in up to 25%–75% patients with dysphagia; (b) choking and tracheobronchial aspiration caused by the decrease in deglutition safety and which results in pneumonia in 50% of cases, with an associated mortality of up to 50% [1, 2]. A recent 10-year review found a 93.5% increase in the number of hospitalized older patients diagnosed with AP, while other types of pneumonia in the elderly decreased [30]. Figure 5 summarizes the pathophysiology of complications related to dysphagia in the elderly.

4.1. Malnutrition and Dehydration. Impairment in swallowing efficacy may reduce oral feeding and lead to malnutrition unless nutritional status is monitored and specific dietetic strategies are introduced to enhance caloric intake. Up to 30% of our neurological patients and up to 55% of our frail older patients with dysphagia present or are at risk of malnutrition with a strong relationship between severity of dysphagia and incidence of malnutrition [1, 10]. A recent resolution of the Council of Europe on food and nutritional care in hospitals claimed that undernutrition among hospital patients leads to extended hospital stays, prolonged rehabilitation, diminished Quality of Life, and unnecessary health care costs; and identified functional oropharyngeal dysphagia as a major contributor to malnutrition [31]. Recommendations from this resolution affecting dysphagia included (a) the development of dietary management at national levels as well as national descriptors for texture modification, (b) documentation and assessment of food intake, (c) detailed food service contracts to include texture-modified menus, (d) meal serving system adjusted to patients, and (e) informing and involving patients/families in the process by giving them help and guidance in ordering and consuming food. Recent guidelines on the indications of enteral nutrition in geriatrics also highlighted the role of dysphagia causing undernutrition in older patients [31]. Dehydration is also a frequent complication of dysphagia in elderly patients with oropharyngeal dysphagia [32, 33]. Dehydration and increased plasma osmolarity showed a significant association with mortality in older stroke patients [33]. Figure 5 shows the pathophysiology of complications of dysphagia associated with malnutrition and dehydration. We previously found that malnutrition in patients with neurogenic dysphagia was uniformly marasmic [10]. We believe all older patients with oropharyngeal dysphagia need nutritional assessment to detect those with malnutrition or at nutritional risk. There are several nutritional screening tools developed for assessing different populations. Mininutritional Assessment (MNA) [34] is a reliable tool for evaluating the nutritional status of older people. It is composed of 18 items covering anthropometric assessment (weight, height, and weight loss), general assessment (lifestyle, medication and mobility), dietary assessment (number of meals, food, and fluid intake), and autonomy of eating and is self assessed (self-perception of health and nutrition). In a very recent study using the MNA in older patients with dysphagia and pneumonia we found the prevalence of malnourished patients (36.8%) and patients at risk of malnutrinion (55.3%) was significantly higher than in older patients without dysphagia [35]. If a patient is at nutritional risk or malnourished, nutritional counselling will be given to improve the oral feeding. This is the first nutritional intervention previous to nutritional support. In some circumstances, nutritional counselling is not enough to maintain or recover proper nutritional status and oral nutritional supplements (ONSs) are indicated. Milne [36] reviewed 55 randomized control trials that studied the clinical and nutritional benefits of ONS in older patients on hospital admission, at home, and in nursing homes. The authors concluded that ONS can improve nutritional

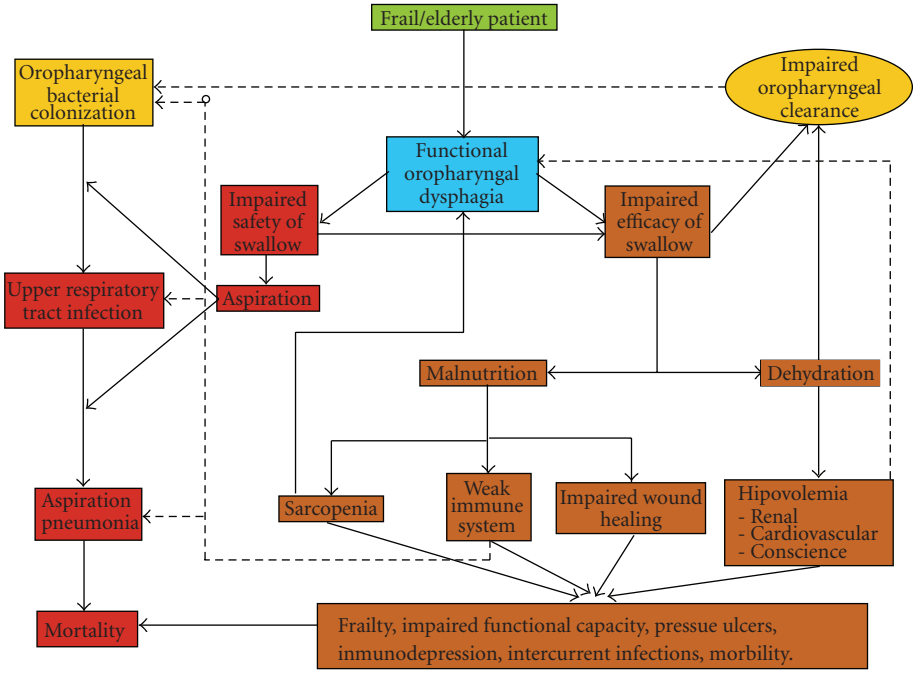

Figure 5: Pathophysiology of nutritional and respiratory complications associated to oropharyngeal dysphagia in elderly patients.

status and reduce morbimortality in malnourished patients during hospital admission. The scientific evidence does not support ordinary supplementation in older people at home or older well-nourished patients in any situation (hospital, home, or nursing home). However, in patients with stroke and dysphagia, the FOOD study [37] evaluated the effect of systematically adding an oral supplement to the hospital diet. These data did not support indiscriminate use of ONS in patients with stroke and it must be prescribed only in malnourished patients on admission or those in whom nutritional status was impaired.

4.2. Respiratory Complications: Aspiration Pneumonia. The incidence and the prevalence of AP in the community are poorly defined. They increase in direct relation with age and underlying diseases. The risk of AP is higher in older patients because of the high incidence of dysphagia [38]. In elderly nursing home residents with oropharyngeal dysphagia, AP occurs in 43%–50% during the first year, with a mortality of up to 45% [27]. We recently studied 134 older patients (>70 yr) consecutively admitted with pneumonia in an acute geriatric unit in a general hospital. Of the 134 patients, 53% were over 84 years old and 55% presented clinical signs of oropharyngeal dysphagia; the mean Barthel score was 61 points, indicating a frail population. Patients with dysphagia were older, showed lower functional status, higher prevalence of malnutrition and comorbidities and higher Fine's pneumonia severity scores. Patients with dysphagia had higher mortality at 30 days (22.9% versus 8.3%, $P = .033$) and at 1 year of follow-up (55.4% versus 26.7%, $P = .001$). Therefore, oropharyngeal dysphagia is a highly prevalent clinical finding and an indicator of disease severity in older patients with pneumonia [35].

The pathogenesis of aspiration pneumonia has been recently revised [17, 18] and presumes the contribution of risk factors that alter swallowing function, cause aspiration and predispose the oropharynx to bacterial colonization. Aspiration observed at VFS is associated with a 5.6–7-fold increase in risk of pneumonia [39]. Up to 45% of older patients with dysphagia presented penetration into the laryngeal vestibule and 30%, aspiration, half of them without cough (silent aspiration); and 45%, oropharyngeal residue [1]. It is accepted that detection of aspiration by VFS is a predictor of pneumonia risk and/or probability of rehospitalization [27]. It is also well known that not all patients who aspirated during VFS develop pneumonia. Impairment in host defenses such as abnormal cough reflex [17, 40], impaired pharyngeal clearance [25], amount and bacterial concentration of aspirate, and weakened immune system also strongly contributed to the development of AP [18]. Impairment of cough reflex increases the risk of AP in stroke patients [40]. Several risks factors contribute to oropharyngeal colonization such as the following (1) Older age, as swallow response, cough reflex, and breathing coordination are impaired in older people. (2) Malnutrition, poor nutritional status is a marker of a population highly susceptible to acquire pneumonia in the elderly as malnutrition depresses the immune system. (3) Smoking status, number of cigarettes smoked per day, and lifetime smoking, and (4) Poor oral hygiene. Probably the most common infectious sequelae of poor oral health in seniors, particularly those who reside in nursing homes, is AP. The oral environment in people who still have teeth is quite different from the flora that thrive in the toothless person but all of them result in oropharyngeal colonization by potential respiratory tract pathogens. (5) Antibiotics, it

has been suggested that inappropriate antibiotic treatment could be a risk factor for pneumonia. In some patients who are smokers or with chronic bronchitis, the use of antibiotics in the previous 3 months may provoke a variety of respiratory flora, predisposing to opportunistic infection with colonization of more aggressive organisms, which could be causative pathogens of AP. (6) Dry mouth, many medications reduce salivary flow or create xerostomia as a side effect. This creates a favourable environment for growth of bacteria that are pathogenic to the lungs if aspirated. (7) Immunity, older adults can have reduced oropharyngeal clearance, reduced numbers of T cells, reduced helper T-cell activity and response to antigens, reduced numbers of B cells and B-cell response to antigens, reduced antibody response, reduced phagocytosis, and reduced Toll-like receptors on phagocytic cells. (8) Feeding tubes, these reduce salivary flow and subsequently alter oropharyngeal colonization in tube-fed patients, but gastroesophagal reflux disease has also been shown to be increased in tube-fed patients and to predispose them to pneumonia. Increased incidence of oropharyngeal colonization with respiratory pathogens is also caused by impairment in salivary clearance [25]. The microbial etiology of AP involves *Staphylococcus aureus*, *Haemophilus influenza,* and *Streptococcus pneumoniae* for community-acquired AP and Gram-negative aerobic bacilli in nosocomial pneumonia [18]. It is worth bearing in mind the relative unimportance of anaerobic bacteria in AP [18]. Surprisingly, in the clinical setting, oropharyngeal dysphagia and aspiration are usually not considered etiologic factors in older patients with pneumonia [17, 18].

5. Treatment

Treatment of dysphagia in older patients varies greatly among centers. This variability can contribute to some controversy on the effect of swallowing therapy in preventing malnutrition and AP. In addition, there are a limited number of studies addressing these—unresolved—questions. A recent review found that there is insufficient data to determine the effectiveness of treatments for dysphagia in preventing AP in older adults [38]. In contrast, other authors found treatment of dysphagia is cost-effective and the use of dysphagia programs is correlated with a reduction in AP rates [27]. Management strategies for oropharyngeal dysphagia in older patients may be grouped into six major categories and simultaneously applied to the treatment of each patient [41]. During videofluoroscopy, a combination of strategies may be selected to compensate each patient's specific deficiency, and the usefulness of VFS in treating the patient's symptoms thus explored. Swallow therapy aims at improving the speed, strength, and range of movement of muscles involved in the swallow response and at modifying the mechanics of swallow to improve bolus transfer and avoid or minimize aspiration. It should be remarked that the largest body of literature cancers swallow therapy in older patients after strokes [27]. Furthermore, a recent systematic review on the effects of therapy in oropharyngeal dysphagia by speech and language therapists indicated that many questions remain about the actual therapeutic effects, even though some positive significant outcome studies have been published [42]. Many of these studies show diverse methodological problems, and because of the diversity in subject characteristics, therapies, and assessment instruments, the conclusions of most studies cannot be generalized or compared. We believe that management of dysphagia is not an exact science and a combination of clinical expertise and the best available evidence-based medicine is usually needed to manage elderly patients with oropharyngeal dysphagia [1, 27]. Preserved cognitive function is needed to apply some of the strategies. Nutritional and respiratory status should always be monitored in dysphagic patients in order to assess the efficacy of treatments.

5.1. Postural Strategies, Body and Head Positions. Verticality and symmetry should be sought during the patient's ingestion. Attention must be paid to controlling breathing and muscle tone. Postural strategies are easy to adopt—they cause no fatigue—and allow modification of oropharyngeal and bolus path dimensions. Anterior neck flexion (chin tuck) protects the airway [43–45]; posterior flexion (head extension or chin raise) facilitates gravitational pharyngeal drainage and improves oral transit velocity; head rotation (head turn maneuver) toward the paralyzed pharyngeal side directs food to the healthy side, increases pharyngeal transit efficacy, and facilitates UES aperture [44, 46], whereas head tilt to the stronger side prior to the swallow directs the bolus down to the stronger side by utilizing the effects of gravity; and deglutition in the lateral or supine decubitus protects against aspirating hypopharyngeal residues.

5.2. Change in Bolus Volume and Viscosity. In patients with neurogenic dysphagia and also in older patients, reductions in bolus volume and enhancement of bolus viscosity significantly improve safety signs, particularly regarding penetration and aspiration [10]. Viscosity is a physical property that can be measured and expressed in international system units by the name of Pa.s. The prevalence of penetrations and aspirations is maximal with water and thin fluids (20 mPa.s) and decreases with nectar (270 mPa.s) and pudding (3900 mPa.s) viscosity boluses [10]. Systematic videofluoroscopic studies found that increasing viscosity of liquids to pudding viscosity exerted such a dramatic reduction in the prevalence of penetrations and aspirations that routine introduction of dietary modifications in patients considered at risk of AP is logical [10, 27]. In addition, clinical studies also found dietary modifications can reduce the risk of AP [27]. Patients with decreased efficiency of deglutition need dietary adjustments to concentrate their caloric and protein requirements in the low volume of food they can swallow. Modifying the texture of liquids is particularly important to ensure that patients with neurogenic or ageing-associated dysphagia remain adequately hydrated and aspiration-free [2]. This may be easily achieved by using appropriate thickening agents [10].

5.3. Neuromuscular Praxis. The goal is to improve the physiology of deglutition (the tonicity, sensitivity, and

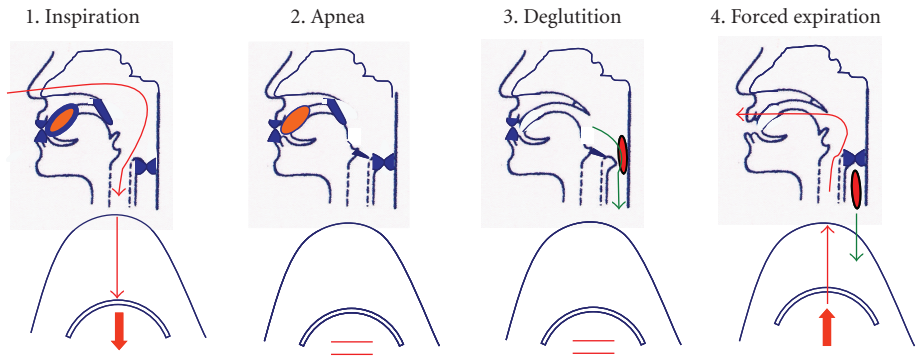

Figure 6: Diagrams showing the four steps of supraglottic swallow to protect the airway from aspiration. Commands for the patient are: (1) Take a deep breath, (2) Hold your breath, (3) Hold your breath while swallowing, (4) Cough immediately after you swallow.

motility of oral structures, particularly the lips and tongue, and pharyngeal structures). Lingual control and propulsion may be improved by using rehabilitation and biofeedback techniques [16]. Improved isometric strength after two months of progressive resistance lingual exercises has proved to correspond with spontaneous increased pressure generation during swallowing in stroke patients, thus showing significant improvement in swallowing function and dietary intake [16]. Of late, the rehabilitation of hyoid muscles with cervical flexion exercises (Shaker exercise) has been shown to improve hyoid and laryngeal elevation, to increase UES aperture, to reduce pharyngeal residue, and to improve dysphagia symptoms in patients with neurogenic dysphagia [47]. The management of patients with impaired UES aperture as a consequence of propulsive deficiencies should be basically oriented to increase bolus propulsion force and to rehabilitate the extrinsic mechanisms of UES aperture, particularly the activity of hyoid muscles [47]. The tongue-holding or Masako manoeuvre is presumed to compensate for the reduction in tongue base-pharyngeal wall contact in swallowing, thus contributing to an increased anterior movement of the posterior pharyngeal wall during swallowing. However, the use of the manoeuvre per se, which inhibits posterior retraction of the base of tongue, results in increasing the pharyngeal residue after the swallow. Another motor treatment for improving muscles strength is neuromuscular electrostimulation (NMES). The first study using NMES in dysphagic patients was performed by Freed et al. [48]. Since then, several studies have been published with controversial therapy outcome [49–52], probably due to the diversity in treatment parameters (frequency, pulse duration, or treatment intensity) and lack of a standard protocol for the use of NMES. However, although NMES as an adjunct to standard treatment is still controversial, a meta-analysis showed a small but significant treatment effect for transcutaneous NMES on patients with dysphagia [53].

5.4. Specific Swallowing Manoeuvres. These are manoeuvres the patient must be able to learn and perform in an automated way. Each manoeuvre is specifically directed to compensate specific biomechanical alterations [1, 41].

Supraglottic and Super Supraglottic Swallow. its aim is to close the vocal folds before and during deglutition in order to protect the airway from aspiration, and by coughing immediately after the swallow to clear any residue. The difference between these related manoeuvres is the degree of effort in the preswallow breath-hold. The super supraglottic swallow requires an effortful breath-hold, whereas the supraglottic swallow requires a breath-hold with no extra effort. It is useful in patients with penetrations or aspirations during the pharyngeal stage or slow pharyngeal motor pattern (Figure 6).

Effortful, Forceful, or Hard Swallow. Its aim is to increase the posterior motion of the tongue base during deglutition in order to improve bolus propulsion. It is useful in patients with low bolus propulsion [1, 41].

Double Deglutition. Its aim is to minimize postswallow residue before a new inspiration. It is useful in patients with postswallow residue [41].

Mendelsohn Manoeuvre. It allows for increased extent and duration of laryngeal elevation and therefore increased duration and amplitude of UES aperture [41].

5.5. Surgical/Drug-based Management of UES Disorders. Identifying an obstructive pattern at the UES allows patient management using a surgical cricopharyngeal section [54] or an injection of botulin toxin [55]. Impaired neural UES relaxation observed in spastic neurological diseases such as Parkinson disease or brain injury is characterized by delayed or absent swallow response, short hyoid motion, weak bolus propulsion, and reduced or even absent neuromuscular relaxation and reduced sphincter compliance on manometry [56]. Treatment must combine treatment of neurogenic dysphagia and improvement of neuromuscular relaxation of the sphincter. Efficacy of cricopharyngeal myotomy in patients with impaired swallow response is fair to poor and injection of botox in the sphincter could be a therapeutic alternative for these patients. Patients with impaired UES opening associated with Zenker's diverticulum or isolated

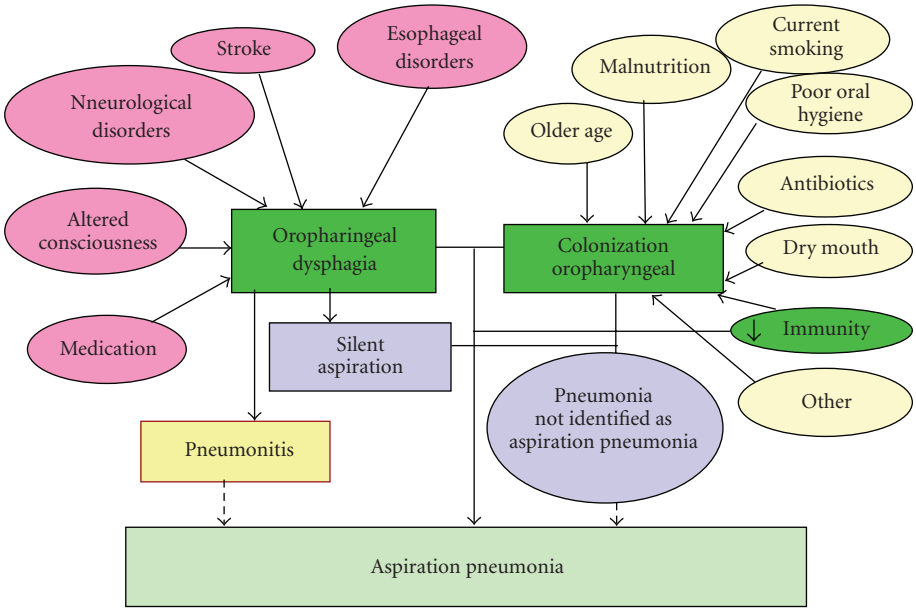

Figure 7: Risk factors for oropharyngeal colonization by respiratory pathogens and aspiration pneumonia in older people.

cricopharyngeal bars show normal swallow response, wide hyoid motion, and strong bolus propulsion and reduced sphincter compliance caused by sphincter fibrosis [57]. Treatment of this group of patients is surgical and combines cricopharyngeal myotomy and resection of the diverticulum. Surgical results in older patients with Zenker's diverticulum and preserved swallow response are excellent [57].

5.6. Sensorial Enhancement Strategies. Oral sensorial enhancement strategies are particularly useful in patients with apraxia or impaired oral sensitivity (very common in older patients) [41]. The aim of these strategies is the initiation or acceleration of the oropharyngeal swallow response. Most sensorial enhancement strategies include a mechanical stimulation of the tongue, bolus modifications (volume, temperature, and taste), or a mechanical stimulation of the pharyngeal pillars. Acid flavors such as lemon or lime [58, 59], and cold substances such as ice cream or ice [60], trigger the mechanism of deglutition, but may not reach clinical or statistical significance even after intense training.

5.7. Pharmacology of Swallow Response in Older People. Several drugs, most centrally acting, can elicit oropharyngeal dysphagia in older people. Neural activity in the nucleus tractus solitarius (NTS) is inhibited by γ-aminobutyric acid (GABA) [61, 62], and benzodiazepine administration can potentiate GABA system at CNS and cause dysphagia [63]. Ethanol also acts in the CNS binding to the $GABA_A$ receptor and alcohol ingestion can predispose to oropharyngeal aspiration [64]. Neuroleptics are widely used in the older demented population for control of aggressive or disruptive behaviour, and doapmine antagonists like phenotiazines and haloperidol can impair swallow function. Moreover, extrapyramidal signs and xerostomia are common adverse effects of these drugs clearly associated with dysphagia [65, 66]. Use of neuroleptics is also associated with a 60% greater risk of pneumonia [67].

Studies using pharmacological stimulant agents also show some promising positive effects [38]. Several types of pharmacological and mechanical stimulation increase the concentration of Substance P (SP) in saliva and improve the swallowing reflex and cough-reflex sensitivity. The increase in serum SP with volatile black pepper oil or capsaicin might be closely related to improvement of the swallow response [68–70]. Capsaicin and piperine (active substance from black pepper) act as transient receptor potential channel vanilloid 1 (TRPV1) agonists. TRPV1 is widely expressed on sensory neurons innervating pharynx and larynx, projecting to NTS and colocalizes with SP [71]. Other stimulants of TRPV1, like heat and acid, have also been reported to improve swallowing [58, 59, 72]. Moreover, intervention with an angiotensin converting enzyme inhibitor also resulted in an increase in serum SP and reduced the incidence of AP [73, 74]. Use of a dopamine agonist such as amantadine and a folic acid supplement known to activate dopaminergic neurons also prevented AP [75]. Higher doses of L-dopa may reduce swallowing abnormalities [76]. The development of physical or drug-based strategies to accelerate the swallow response is a relevant field of research for the management of neurogenic dysphagia and ageing-associated dysphagia [1].

5.8. Percutaneous Endoscopic Gastrostomy. Videofluoroscopy will help in *treatment selection* depending upon the severity of efficacy or safety impairment in each patient: (a) patients with mild efficacy alterations and correct safety may have

a family-supervised restriction-free diet; (b) in patients with moderate alterations, dietary changes will be introduced aiming at decreasing the volume and increasing the viscosity of the alimentary bolus; (c) patients with severe alterations will require additional strategies based upon increased viscosity and the introduction of postural techniques, active manoeuvres, and oral sensorial enhancement; and (d) there is a group of patients with alterations so severe that they cannot be treated despite using rehabilitation techniques; in these patients, VFS objectively demonstrates the inability of the oral route and the need to perform a percutaneous endoscopic gastrostomy (PEG) [2]. However, there is little evidence that nonoral feeding reduces the risk of aspiration [27]. Even though no absolute criteria exist, a number of dysphagia teams have indicated gastrostomy in: (a) patients with severe alterations of efficacy during the oral or pharyngeal stages, or with malnutrition; (b) patients with safety alterations during the pharyngeal stage that do not respond to rehabilitation; and (c) patients with significant silent aspirations, particularly in neurodegenerative conditions. For long-term nutritional support, PEG should be preferred to nasogastric tubes since it is associated with less treatment failure, better nutritional status and may also be more convenient for the patient [40]. In patients with severe neurological dysphagia, tube feeding has to be initiated as early as possible [16]. For most patients requiring gastrostomy a small percentage of food may still be safely administered through the oral route [2].

Competing Interests

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Research Article

Malnutrition in Surgical Wards: A Plea for Concern

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Background. Malnutrition in hospitalized patients is underdiagnosed, with 30 to 60% of patients admitted being malnourished. The objective of this study was to investigate the nutritional status of patients in a general surgery ward and to define the correlation between the risk of malnutrition and the hospital course and clinical outcome. *Study design*. The study group included 100 consecutive patients admitted to a general surgery ward who were ambulant and could undergo the Malnutrition Universal Screening Tool (MUST). *Results*. Thirty-two patients (33%) had aMUST score of 2 or higher, and were therefore defined at high-malnutrition risk. The patients at risk had longer hospitalization and worse outcome. The length of stay of the malnourished patients was significantly longer than that of patients without malnutrition risk (18.8 ± 11.5 vs. 7 ± 5.3 days, $P = .003$). Mortality in the high-risk group was higher overall, in hospital, and after six months and one year of followup. *Conclusions*. Medical personnel must be aware that malnutrition afflicts even patients whose background is not suggestive of malnutrition. Best results are achieved when cooperation of all staff members is enlisted, because malnutrition has severe consequences and can be treated easily.

1. Introduction

In 1859, Florence Nightingale described soldiers in the Crimea hospital starving amongst plenty of food. Consequently, realizing the importance of nutrition to the well-being of patients, she suggested methods to remedy this problem. Still, more than one hundred years later, Hill et al. [1] found that 50% of surgical patients and 40% of medical patients were malnourished. In the majority of these patients, this risk increases during hospitalization [2]. As malnutrition in hospitalized patients is underdiagnosed, 70–80% of the malnourished are not identified as such. Therefore, no action is taken to treat their poor nutrition, and the diagnosis of malnutrition is not on their hospital discharge summary [3–5].

Malnutrition is a state of nutrient deficiency, a result of either inadequate nutrient intake or inability to absorb or use ingested nutrients. Professional organizations around the world highlight the frequent underreporting of malnutrition and advocate implementation of a simple and valid screening tool to identify patients at risk [6, 7]. For example, the European Society of Enteral and Parenteral Nutrition advocated nutritional screening because it could improve mental and physical function, reduce the number and severity of complications of disease or its treatment, accelerate recovery, save resources, and shorten hospital stay [7]. In view of the prevalence and deleterious consequences of malnutrition and the existence of an effective treatment, it is pragmatic to apply these recommendations and to introduce routine screening of patients for identification of patients at risk for malnutrition. For that, various screening tools exist, including the Nutritional Risk Screening (NRS-2002), Mini Nutritional Assessment (MNA) and the Malnutrition Universal Screening Tool (MUST) [7]. The different tools differ by the different parameters. Usually there is a tradeoff of complexity on the one hand and validity on the other hand. The NRS 2002 is a two-stage screening tool which takes into account various parameters such as severity of disease, age and could be applied to nonambulant patients. The MUST lacks these parameters but includes only three

variables so it is very easy to perform. With this in mind, we chose the MUST for its validity, reliability, and simplicity even though it does not take into account some of the variables comprising other screening tools.

The objective of this study was to investigate the nutritional status of a cohort of sequential patients in a general surgery ward and to define the correlation between the risk of malnutrition and the hospital course and clinical outcome.

2. Methods

This prospective observational study was conducted in a 37-bed general surgery ward of Rambam Medical Center, a tertiary 970-bed hospital. MUST Assessment was performed as a part of routine work up, upon admission to our department. The study was approved by the local ethical committee. The study group included 100 consecutive patients in the department who were ambulant and could undergo the MUST evaluation on admission.

The MUST includes three variables: unintentional weight loss in the preceding 3 to 6 months, body mass index (BMI), and assessment of how the acute disease might affect the nutritional intake in the subsequent five days. Each is scored on a scale of 0, 1, or 2 and their sum categorizes the malnutrition risk as low (0), medium (1), or high (≥2). The MUST is easy, applicable, and reliable [8–10], and is used routinely to screen patients admitted to our department.

The nursing team received four-hour training in nutrition and nutritional screening. Continuing guidance was provided throughout the study by the nutrition team as part of the clinical service. The MUST was part of the anamnesis taken by the admitting nurse and was integrated into the patient's computed chart that is readily available to the treating physician.

Data collection included, in addition to the MUST score, demographic data and clinical information, hospital course and outcome, namely, age, gender, malignancy, elective or urgent admission, wound infection, the use of total parenteral nutrition or enteral nutrition during hospital stay, need for dialysis, and need for mechanical ventilation. The length of stay (LOS) was calculated, and in-hospital mortality, and at six months and one year of followup were recorded

Data was processed using a statistical software package (SPSS v15). The Student's t-test and the Mann-Whitney test were used for comparison of continuous variables, as appropriate, and the Pearson's chi-square was applied for comparison of frequencies. Charslon comorbidity index was used to compare the group of patients at high risk for malnutrition to the group of patients not found at risk for malnutrition [11].

3. Results

One hundred consecutive patients underwent MUST screening, but 4 were excluded from the study because of subsequent missing data. Fifty four (56.25%) were males, and the median age of the study group was 54 years (18–94 years).

Table 1: Patients characteristics, hospitalization, and outcome.

	High risk group	No risk group	P
Patients	32 (33.33%)	64 (66.67%)	
Median Age (y)	57 (24–94)	54 (19–90)	NS
Gender (male)	17 (53.12%)	35 (54.68%)	NS
Admission- emergency (versus elective)	22 (68.8%)	34 (53.1%)	.3
Malignancy (versus benign)	14 (43.72%)	12 (18.75%)	.02
Surgery performed	19 (59.37%)	38 (59.37%)	.8
LOS (d)*	18.8 ± 11.5	7 ± 5.3	.003
Nutritional therapy	15.6%	7.9%	.3
Mortality			
In hospital	3 (9.4%)	0 (0%)	.017
Cumulative 6 months	6 (18.8%)	1 (1.6%)	.006
Cumulative 12 months	7 (21.9%)	1 (1.6%)	.002

*Mean ± SD.

Thirty-two patients (33%) had a MUST score of 2 or higher, and were therefore categorized as having high-malnutrition risk. Fifty seven patients (∼60%) were categorized in the low-malnutrition risk group with a MUST score of 0, and seven (∼7%) patients had a medium risk for malnutrition, with a score of 1. There was no difference in the age or gender distribution between the high- and the low-malnutrition risk groups. The intermediate risk patients were combined with the low risk group, because no active treatment upon admission is advocated for either group.

Overall, the patients at risk had a longer hospitalization and worse outcome (Table 1). On univariate analysis, the LOS of the malnourished patients was significantly longer than that of patients without malnutrition risk (18.8 ± 11.5 versus 7 ± 5.3 days, resp., $P = .003$). Mortality in the high-risk group was higher overall, in hospital, and after six months and one year of followup. In hospital, three patients from the malnourished group died, while none from those not at risk (10% versus 0%, $P = .03$). One patient died due to sepsis complicating pancreatitis, one patient died of sepsis after traumatic perforation of the rectum, and one patient died of multiorgan failure following mesenteric ischemia. Only one no-risk patient died during the year of followup (in the first six months) compared to four high-risk patients (Table 1). Multivariate analysis could not be done due to the small number of patients overall and deceased. Charlson comorbidity index did not differ significantly between the group of the patients at high risk for malnutrition and the group of patients who was not found to be at risk for malnutrition (maybe because of the small numbers) Table 2.

Overall, more than double, 16% versus 8% ($P = .3$), of the patients in the malnourished group received advanced nutritional therapy (parenteral or enteral). More of the malnourished patients were admitted on an urgent basis directly from the emergency department (68.2% versus 53.2%), but this did not reach statistical significance. No difference was found between rates of dialysis, need for mechanical ventilation, and rate of wound infection.

4. Discussion

Malnutrition has been recognized as a major problem in surgical patients for many years. Hill et al. [1] recognized malnutrition in surgical patients as a leading cause of morbidity and mortality. Frequently unnoticed protein and energy malnutrition can cause anemia, hypoalbuminemia, vitamin deficiencies, and weight loss [1]. Malnutrition is also responsible for impaired immunity [11], and could result in increased complications such as pressure ulcers, delayed wound healing, and increased risk of infections, impaired muscular and respiratory functions as well as increased mortality [8, 12–15].

Nutritive treatment can be enriched by oral diet, or provided through enteral or parenteral route. All these alternatives are efficient in lowering complications and mortality in hospitalized malnourished patients [16, 17]. Enteral nutrition is preferable because there are fewer related complications and it is more cost-effective than parenteral nutrition. When the enteral route is unavailable or fails, parenteral nutrition is indicated; yet, either requires close followup.

Stratton [6] performed a meta-analysis on patients receiving routine care and patients receiving multinutrient oral or tube supplements, and found that those receiving supplements had a significantly lower complication and mortality rates. Supplementation was also associated with reduction in sepsis, wound infection, pneumonia, and decubitus ulcers [6].

Analysis of the risk of mortality and the LOS in a group of patients screened by the MUST found that patients at medium risk (MUST score of 1) had increased mortality, similar to that of high-malnutrition risk patients [18]. However, while our study group includes 96 consecutive patients and provided reliable and unbiased results when applying the MUST as a screening tool, it was not large enough to allow comparison of various subgroups of patients, such as those with malignant or benign diseases, young versus old, and the outcome of patients in the medium risk group. The small number of patients in the intermediate group rises questions on the one hand it could be that the MUST is inadequate as a screening tool for some of the patients; on the other hand this dichotomy could imply that the MUST can differentiate between a high-risk group and the low-risk group very effectively.

One third of the patients in our study were at risk of malnutrition, confirming that malnutrition in hospitalized patients is prevalent. Malnourished patients run a complicated course of hospitalization with worse outcome, longer LOS, and higher mortality rates, and indeed, we found that high-risk patients in our cohort had longer LOS and increased mortality in-hospital and throughout the first year of followup. This data is in line with the data from the European NutritionDay study. This is a cross-sectional study, which takes place every year since 2006. More than 24,000 patients took part in this audit over the years. On the NutritionDay audit, information regarding nutritional status is collected from the treating staff and the patients themselves. In 2010, 8155 patients from a wide range of departments took part in the NutritionDay. Over 40% of the patients lost weight before admission only 50% ate normally on the week before the NutritionDay was held. On NutritionDay itself, only 44% of the patients ate everything that was served for lunch. Data analysis from previous years showed that decreased food intake on NutritionDay or during the previous week was associated with an increased risk of dying, even after adjustment for various patient and disease-related factors. Adjusted hazard ratio for dying when eating about a quarter of the meal on NutritionDay was 2.10 (1.53–2.89) when eating nothing 3.02 (2.11–4.32) [19]. No information regarding food intake was collected in this study. Six-year survival was assessed by Sullivan et al. in a group of 350 patients discharged from the hospital; the variable most strongly associated with mortality was "nutrition risk" [20].

Table 2: Charlson comorbidity index.

		MUST			
		0 + 1		2+	
		64 (n)	%	32 (n)	%
Charlson index score	0	33	51.6	12	37.5
	1	15	23.4	6	18.8
	2	6	9.4	6	18.8
	3	6	9.4	3	9.4
	4+	4	6.3	5	15.6

Mann-Whitney U $P = .08$.

Clinicians need to be able to identify patients who are malnourished or at risk of malnutrition, especially since nutrition treatment protocols are effective, and most of the patients could be treated according to them. A multidisciplinary nutritional support team is beneficial when treating complicated patients [21]. In medical centers where such a team had been established, optimal nutritional care was provided resulting in improved outcome [3, 22]. It is also prudent to identify patients at malnutrition risk, and the MUST is an efficient mean for accomplishing this [23]. We have concluded that screening of patients for malnutrition is mandatory, and the MUST is efficient and simple to apply and interpret. After identification of patients at risk for malnutrition, assessment should be performed. Malnourished patients should be treated by an efficient method. So far, the best-proven treatment modality is artificial nutrition. Enteral nutrition is the preferred route, but the enteral route is unavailable; parenteral nutrition should be given promptly.

The findings of our study reflect the urgent need for awareness of physicians, nursing staff, and dieticians to the problem of malnutrition in surgical departments. Best results are achieved when cooperation of all staff members is enlisted because malnutrition has severe consequences and is easily treated. Future randomized prospective controlled trials are advocated.

5. Conclusion

Malnutrition is prevalent and has association with longer length of stay and higher mortality rates. Identifying patients at risk is easy and feasible. Screening for malnutrition should be performed on a routine basis using a validated tool.

Limitations of the study: this is a small study with a limited number of patients. Further studies preferably prospective randomized studies are warranted so that optimal treatment protocols are set up.

List of Abbreviations

MUST: Malnutrition Universal Screening Tool
BMI: Body Mass Index
LOS: Length of Stay.

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Review Article

Perioperative Nutrition in Abdominal Surgery: Recommendations and Reality

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Introduction. Preoperative malnutrition is a major risk factor for increased postoperative morbidity and mortality. Definition and diagnosis of malnutrition and its treatment is still subject for controversy. Furthermore, practical implementation of nutrition-related guidelines is unknown. *Methods*. A review of the available literature and of current guidelines on perioperative nutrition was conducted. We focused on nutritional screening and perioperative nutrition in patients undergoing digestive surgery, and we assessed translation of recent guidelines in clinical practice. *Results and Conclusions*. Malnutrition is a well-recognized risk factor for poor postoperative outcome. The prevalence of malnutrition depends largely on its definition; about 40% of patients undergoing major surgery fulfil current diagnostic criteria of being at nutritional risk. The *Nutritional Risk Score* is a pragmatic and validated tool to identify patients who should benefit from nutritional support. Adequate nutritional intervention entails reduced (infectious) complications, hospital stay, and costs. Preoperative oral supplementation of a minimum of five days is preferable; depending on the patient and the type of surgery, immune-enhancing formulas are recommended. However, surgeons' compliance with evidence-based guidelines remains poor and efforts are necessary to implement routine nutritional screening and nutritional support.

1. Introduction

The World Health Organization cites malnutrition as the greatest single threat to the world's public health. Indeed, the reported in-hospital prevalence of malnourished patients on admission ranges up to 50% [1–5]. Increasing evidence has been accumulated during recent years that nutritional screening and therapy are important adjuncts in modern surgical care since up to 40% of patients are at nutritional risk preoperatively [6–8]. Malnutrition before gastrointestinal (GI) surgery is caused by decreased oral food intake, preexisting chronic disease, tumour cachexia, impaired absorption due to intestinal obstruction, and previous surgical bowel resection. Moreover, low socioeconomical status, as often seen in elderly and handicapped patients, represents an additional risk factor [7, 9].

Malnourished patients have a significantly higher morbidity and mortality, a longer length of stay (LOS) and increased hospital costs [1, 6, 7, 10, 11]. Perioperative nutrition has been convincingly shown to improve clinical outcome in patients undergoing major GI surgery and to reduce costs [1, 12]. The mechanism of action seems to be not only an improved nutritional status by providing a higher caloric intake, but primarily a reenforced immune response; nutritional formulas containing immune-modulating agents (glutamine, arginine, n-3 fatty acids, and ribonucleic acids) are particularly beneficial modulators of the acute stress response [13, 14]. Various original studies and comprehensive guidelines have been issued recently to define preoperative screening and to standardize perioperative nutrition with regard to mode, timing, duration, and formula [15]. Furthermore, there are only scarce data assessing the

practical implementation of these evidence-based recommendations.

The aim of this study was to assess the current evidence for nutritional screening as well as perioperative nutrition in major abdominal surgery and its implementation in daily clinical practice. Furthermore, a pragmatic algorithm for evidence-based perioperative nutrition is provided.

2. Methods

2.1. Data Sources and Search Strategies. Relevant articles were identified searching Medline (through PubMed) by use of the appropriate MeSH terms for the following search items: malnutrition, nutritional screening, nutritional risk, perioperative (pre-, postoperative) nutrition (oral, enteral, and parenteral), immunonutrition, practical implementation of nutritional screening, and supporting *AND* major GI surgery *AND* clinical outcome (complications, mortality, andhospital stay). Hand-searched electronic links and references of selected articles were cross-checked. The search was limited to studies published between January 1980 and June 2010 as no frequently cited milestone articles on perioperative nutrition have been published before. Only articles published in English were considered eligible [16].

2.2. Study Selection. We privileged systematic reviews and meta-analyses from high-impact peer-reviewed journals and recent evidence-based guidelines. Further, important original studies adding complementary information were included. Selected studies had to treat the clinical impact of either (i) *malnutrition*, or (ii) *nutritional screening* (iii), or *perioperative nutrition*, or (iv) the practical implementation of nutritional screening and support in *digestive surgery*. For each of these areas, two authors independently performed the literature search; studies of interest were identified by screening of title, abstract, or medical subject headings. Final decision on inclusion was made based on the full text articles by the entire research team.

3. Results

The electronic search of the literature identified more than a thousand possible hits. These were carefully screened, and irrelevant studies were excluded by title, abstract, or full text analysis. Covering a large thematic array, many eligible studies fulfilled the inclusion criteria. Therefore, a further selection was necessary based on quality and importance for our aims. Finally, we included 68 publications, of those, 14 reviews/guidelines and 36 randomized controlled trials have been identified as major contributions to the field of perioperative nutrition.

3.1. Definition and Diagnosis of Malnutrition. Since there are no standardized and widely accepted definitions, precise diagnosis of malnutrition remains difficult. This major methodological shortcoming contributes to the heterogeneity of studies and also impairs proper assessment of malnutrition in daily clinical practice. Diagnostic criteria range from simple patient's data, such as amount of food intake, weight loss [18], or body mass index, to biochemical markers (albumin [19], prealbumin [20]) or various physiologic assessments. In order to develop simple, reliable, and reproducible screening tools, these parameter are often combined in scores (i.e., nutritional risk index (NRI) [21]) to grade the severity of malnutrition. Questionnaires such as the subjective global assessment (SGA) [22] are also described. Biometrical analyses, such as the phase angle (PA) [23] which quantifies body lean mass and fat by electrical impedance, are less frequently used (Table 2).

The most valuable tool for nutritional screening for surgical patients is currently the Nutritional Risk Score (NRS) that is officially recommended by the European Society of Parenteral and Enteral Nutrition (ESPEN) [17]. It is based on the amount of malnutrition, as defined by weight loss, food intake, and BMI, as well as on the severity of disease (Table 1). Its predictive value was validated by applying it to a retrospectively 128 RCTs on nutritional support [17] and prospectively in a cohort including 5051 hospitalized patients in 12 European Countries and 26 different surgical centers [8]. The NRS used retrospectively was able to distinguish between trials with a positive effect of perioperative nutritional support versus those with no effect. When applied prospectively, it showed that "at-risk" patients had more complications, higher mortality, and longer lengths of stay than "not-at-risk" patients, and these variables were significantly related to components of NRS-2002, also when adjusted for confounders. The prevalence reported of patients at risk evaluated by NRS varies in literature from 14 to 32.6% [7, 8, 24].

Since the objective in diagnosing malnutrition is to treat it as early as possible in order to improve patient's outcome, screening tools have to be correlated to postoperative outcome. In the comparison of Antoun et al., who evaluated several screening system, only serum albumin <30 g/L showed a significant association to postoperative morbidity after multivariate analysis [19]. Schiesser et al. undertook a comparison between the NRS, NRI, and PA. These methods were well correlated for diagnosis of malnutrition. Moreover, they had a predictive value for postoperative complications. The strongest correlation for the diagnosis of malnutrition was found between NRS and NRI, but only NRS was able to reliably predict postoperative morbidity after multiple regression analysis [23].

3.2. Treatment of Malnutrition. Perioperative malnutrition is considered as a modifiable and treatable cause of postoperative morbidity [25, 26]. While nutritional support has shown to reduce infections, complications, LOS, and costs [27–29], many questions remain concerning patient selection, timing, route of administration, and type of nutritional support remains to be elucidated.

3.2.1. Patient Selection. Patients are considered to be at severe nutritional risk if the NRS is ≥3 or if at least one of the following criteria is fulfilled: weight loss of 10–15% within 6 months, BMI < 18.5 kg/m^2, Subjective Global

Table 1: Nutritional Risk Screening score (NRS 2002) [17]. The total score is obtained by adding the nutritional score to the disease score. Age > 70 years adds 1 to the total score. If age-corrected total is ≥3, the patient presents severe malnutrition, and nutritional support is recommended.

Malnutrition		Mild Score 1	Moderate Score 2	Severe Score 3
Nutritional Status	BMI (kg/m^2)	—	18.5–20.5	<18.5
	Food Intake (%)	50–70	25–50	<25
	Weight loss <5%	3 months	2 months	1 month
Disease severity	Example	Hip fracture, cirrhosis, COPD	Major surgery[a], Stroke	Head injury, bone marrow transplantation, ICU patients (APACHE 20)
Age	(Years)	>70		

[a]Major abdominal surgery includes colorectal, gastric, liver, pancreatic, and esophageal resection for benign and malignant disease by either laparotomy or laparoscopic approach, lasting usually >2 h.

Table 2: Overview on common screening tools for malnutrition and its reported prevalence depending on study and screening tool.

	Antoun et al.					Schiesser et al.		
Malnutrition	Weight loss	BMI (kg/m^2)	SGA	Albumin (g/L)	NRI	NRS (2002)**	PA	NRI
None	**—** (29%)[1]	**18.5–25** (50%)[1]	**A** (66%)[1]	**>35**	**>97.5** (59%)[1]	Score **0**	**>6°** (71%)[2]	**>97.5** (85%)[2]
Mild	**<10%** (39%)[1]	**<18.5** (8%)[1]	**B** (22%)[1]	**<35** (24%)[1]	**84–97.5** (32%)[1]	Score **1** (89%)[2]	**<6°** (28%)[2]	**84–97.5** (13%)[2]
Moderate						Score **2** (8.5%)[2]		
Severe	**≥10%** (20.5%)[1]	**<16** (2%)[1]	**C** (12%)[1]	**<30** (8%)[1]	**<84** (9%)[1]	Score **3** (2.5%)[2]		**<84** (2%)[2]

BMI: body mas index (kg/m^2); SGA: subjective global assessment (weight, food intake, symptoms, and activities); NRI: nutritional risk index (recent weight loss, serum albumin); NRS (2002): nutritional risk screening score (Table 2); PA: phase angle (reactance and resistance from bioimpedance analysis).
[1]Antoun et al. [18] (prevalence %).
[2]Schiesser et al. [23] (prevalence %).
**Nutrition status score only.

Assessment Grade C or Serum albumin <30 g/L [26, 30]. For these patients, major surgery should be postponed until nutritional status has been corrected [26].

Most patients with GI cancer have severe malnutrition preoperatively and their immunological function is suppressed. Moreover, prolonged postoperative fasting and insufficient oral food intake may worsen preexisting malnutrition. Hence, there is an increased risk of postoperative complication, and all patients should therefore benefit from perioperative nutrition prior to major oncological surgery [29].

When the NRS is used, patients, with a score of 3 or more are prone to develop postoperative complications and should benefit from nutritional support [8, 23]. Since age directly influences the NRS [15], elderly patients (>70 years) must be considered as at particular risk [8]. Nutritional profile of these patients is a good prognostic factor and efforts should be made to maintain an optimal nutritional status [31].

It has been shown that even in wellnourished patients, peripoperative nutritional support positively influences postoperative outcome [25]. Enhanced recovery programs have developed for such patients, with a particular focus to minimizing preoperative fasting period and maximizing carbohydrate loading [32].

3.2.2. Timing of Nutrition. The role of preoperative nutritional support is to improve undernutrition before surgery, while postoperative nutrition aims at maintaining nutritional status in the catabolic period after surgery. The timing of nutritional support is widely debated. While conventional enteral nutritional support is recommended for 10–14 days prior to major surgery in patients with severe nutritional risk to improve the nutritional state, immunonutrition (IN) is administered for 5–7 days prior to surgery to all cancer patients in order to improve immune function [26].

Although preoperative fasting has long been considered as a dogma, Brady et al. showed that a 2-hour fasting for clear fluids does not increase complications [33]. Nowadays, a preoperative fasting of 2 hours for fluids and 6 hours for solid food is considered as best practice and recommended by the ERAS (Enhanced Recovery After Surgery) group [32].

Postoperatively, normal oral food intake or nutrition through feeding tube should start within the first 24 hours. A recent meta-analysis evaluated early commencement of

postoperative enteral nutrition (within 24 h) versus traditional management in patients undergoing gastrointestinal surgery. It was in favour of early enteral feeding following gastrointestinal surgery to reduce morbidity and mortality rates [34, 35]. The beneficial effect of early oral feeding was also shown by El Nakeeb et al. [36]. There is strong evidence that oral nutritional supplements (200 mL twice daily) given from the day of surgery until normal food intake is achieved are beneficial.

While perioperative nutritional support is recommended, some studies suggest that nutrition limited to the preoperative phase might have the same beneficial effects than combined pre- and postoperative nutrition. As far as IN is concerned, three RCTs have found no difference when comparing pre- and perioperative IN patients [13, 18, 25]. Another study compared IN given perioperatively with control patients receiving IN only postoperatively [37]. A significant decrease in postoperative complications is seen in the perioperative IN group compared to the postoperative IN group.

The optimal duration of nutritional support in the postoperative period remains unclear. While using postoperative oral nutritional supplements for 8 weeks in malnourished patients enhances recovery of nutritional status and quality of life [38], benefits for well-nourished patients are less evident [39]. Concerning postoperative IN, duration of therapy varied from 3 [40] to more than 10 days [18, 25, 41–45], with the most common duration being 7 days [13, 46–51].

3.2.3. Route of Administration. Basically, nutritional support, with or without regular oral diet, can be administered in three ways: orally as oral nutritional supplements (ONSs), enterally through a feeding tube, or parenterally. As stated in the ESPEN 2006 guidelines, the enteral route should always be preferred bar if intestinal obstruction, severe shock or intestinal ischemia is present. Stratton and Elia showed that both oral nutritional supplements (ONSs) and feeding tube nutrition (FTN) were able to reduce postoperative complications in gastrointestinal (GI) surgical patients, when compared to routine care nutrition alone. However they had no influence on mortality [27]. When FTN was compared to parenteral nutrition in cancer patients undergoing surgery, those receiving enteral nutritional support had significantly less infectious complications.

Lassen et al. studied the postoperative outcome of patients undergoing major upper GI surgery. Those allowed to eat at will had less complications and shorter hospital stay than patients fed through a needle-catheter jejunostomy [52].

3.2.4. Type of Supplementation. A whole variety of nutritional supplementation was identified through the electronic database search.

There is strong evidence that clear carbohydrate-rich beverage administration before midnight and 2 to 3 hours before colonic surgery ameliorates pre- and postoperative patient's status, accelerates, recovery and shortens hospital stay [32].

Immunonutrition, which contains a combination of glutamine, arginine, n-3 fatty acids, and RNA, has been evaluated in numerous studies [13, 25, 29, 41, 43, 46, 47, 50, 51, 53, 54]. A recent meta-analysis assessed the impact of IN on postoperative complications, in particular infectious complications, length of hospital, stay and mortality in patients undergoing major GI surgery. Twenty-one RCTs enrolling a total of 2730 patients were included in the meta-analysis. IN significantly reduced overall complications when used preoperatively, perioperative, or postoperatively. Patients receiving IN had less infection. The mean difference in LOS favoured IN (-2.12 (95% CI -2.97, -1.26) days). However, perioperative IN had no influence on mortality (submitted data). In all of the 9 RCTs evaluating preoperative IN, duration of supplementation was within the 5–7 days recommended range [13, 18, 25, 29, 40, 46, 55–57].

When each component of IN was studied separately, disparity was observed in the results.

Jiang et al. compared cancer patients receiving omega 3 supplementation postoperatively for 7 days to patients receiving an isocaloric isonitrogenous diet. They found a lower incidence of infectious complications and a shorter length of stay in the treatment group. However, no significant difference could be demonstrated as far as costs are concerned [58]. A meta-analysis showed a decrease in infection rate, but no advantage in LOS or mortality [59].

While Sun et al. demonstrated that branched chain amino acid enriched total parenteral nutrition reduced postoperative complications in malnourished patients with gastrointestinal cancer undergoing major surgery [60], Gianotti et al. failed to improve the clinical outcome of patients receiving perioperative amino acids [61]. In another RCT, parenteral glutamine supplementation in the preoperative period failed to decrease infection rate, wound complication, days in the intensive care unit, and mortality [62].

3.3. Implementation of Current Guidelines in Clinical Practice. Implementation of nutritional support strategies into daily clinical practice encounters many difficulties and considerable efforts are needed to be successful. It has been shown in several studies that malnutrition is either not recognized or not viewed as clinically significant and that appropriate interventions are not considered necessary [3, 11].

A recent one-day multinational cross-sectional European audit showed that instruments used to identify undernourished patients and those at risk differ widely. Often, national and validated tools are replaced with locally developed ones. Many countries do not implement the recommended screening policy, which leads to underdiagnosis and undertreatment of malnutrition [63].

Our group conducted a survey among Swiss and Austrian public hospitals in order to get information about implementation of the above-mentioned current guidelines. We inquired about nutritional screening and therapy and appraisal of current evidence of perioperative nutritional support.

Conforming to previous data, we observed that implementation of current guidelines was modest at best. Only 20% of the participating centres routinely screened their

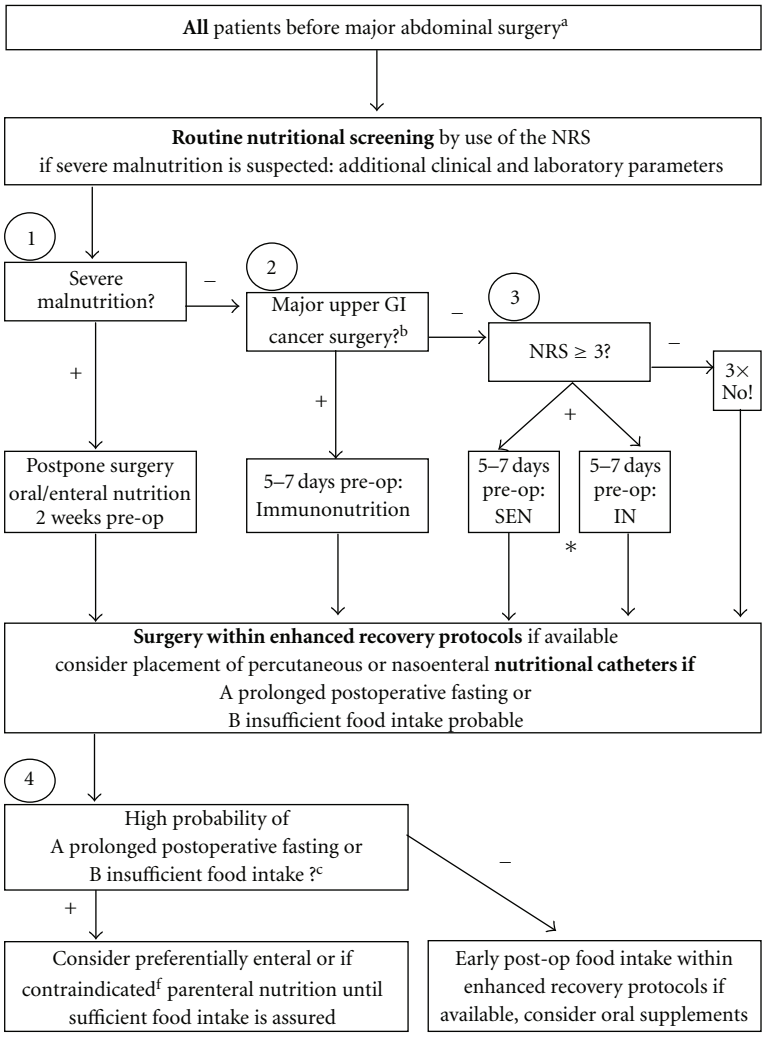

Figure 1: Pragmatic algorithm for preoperative nutritional screening and perioperative nutrition in digestive surgery. The algorithm resumes perioperative care in terms of nutrition in major abdominal surgery. It is largely based on recent systematic reviews and guidelines on perioperative nutrition [26, 27] and enhanced recovery [32]. [a]Major abdominal surgery includes colorectal, gastric, liver, pancreatic, and esophageal resection for benign and malignant disease by either laparotomy or laparoscopic approach, lasting usually >2 h. [b]Major upper GI surgery indicating preoperative IN regardless of nutritional status include oesophageal, gastric and pancreatic resection for cancer [26]. [c]defined as anticipated perioperative starving >7 days and oral intake <60% of recommended for >10 days [26]. NRS: Nutritional Risk Score; pre-OP: pre-operative, IN: immunonutrition, SEN: standard enteral nutrition (usually whole protein formula). *currently evaluated by (http://www.clinicaltrial.gov; trial # NCT005122).

GI surgery patients for nutritional status. Great disparities existed regarding screening methods. Approximately two thirds of centres were using various combinations of clinical and laboratory parameters to assess patients' nutritional status. In our study, the NRS was only used by 14% of centres.

Nutritional treatment was part of perioperative care in about 70% of all centres, and mostly dedicated to cancer patients or patients undergoing major surgery rather than to patients previously screened for their nutritional risk.

Overall, about two thirds of all centres estimated that there is enough scientific evidence in favour of preoperative nutritional support. Reduced complication rates and decreased length of hospital stay were acknowledged as major advantages. Logistic and financial issues were mentioned as reasons against the implementation of nutritional support in daily clinical practice (submitted data).

4. Discussion

The present paper summarizes the current evidence on preoperative nutritional screening and perioperative nutrition in major abdominal surgery. Malnutrition is a common problem in GI surgery patients (40%) and doubtlessly one of the most important risk factors for postoperative complications. The NRS is a validated screening tool that reliably identifies patients at nutritional risk who benefit from a nutritional supplementation. Recent high-quality studies

have delivered convincing evidence that perioperative nutrition is a highly effective treatment that entails reduced complications, hospital stay, and costs. Most impressive results have been obtained by preoperative administration of immunonutrition.

The recent data permitted to issue actual evidence-based guidelines in an attempt to standardize perioperative nutrition in abdominal surgery. We outlined, however, that implementation of these recommendations is not satisfactory.

In a recent survey (unpublished data), most responding surgeons acknowledged clearly the positive impact of perioperative nutrition on postoperative outcome. Nevertheless, cost issues for outpatient nutrition and time restraints are obviously prominent reasons against nutritional care. The formation of specialized multidisciplinary teams failed to improve nutritional care. It can be therefore assumed that the individual surgeon is the most straightforward way to increase adherence to nutritional guidelines!

Based on the current literature and guidelines, we propose a simple and pragmatic algorithm for preoperative nutritional screening and perioperative nutritional therapy (Figure 1). All patients undergoing major surgery should be screened for malnutrition. Depending on the degree of malnutrition and the type of surgery, nutritional support should start within 14–7 days preoperatively. If insufficient postoperative food intake is anticipated, early enteral tube feeding should be started.

In conclusion, malnutrition is a well-known major risk factor for poor postoperative outcome. Preoperative nutritional screening is therefore mandatory to identify patients who need perioperative nutritional support. For most patients, a preoperative oral supplementation by whole protein formulas or immunonutrition is sufficient. The proven benefits for the patients justify the considerable efforts to foster implementation of these current guidelines in clinical practice.

Conflict of Interests

The authors declare that there is no conflict of interests.

Abbreviations

IN: Immunonutrition;
RCT: Randomized controlled trial;
NRS: Nutrirional risk score;
Gl: Gastrointestinal.

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M. Hübner and M. Schäfer initiated and designed the study. Y. Cerantola, F. Grass, A. Cristaudi, and M. Hübner carried out the study, took part in the selection process, performed data analysis, and drafted the paper. M. Schäfer and N. Demartines coordinated the study and helped analyzing the data and drafting the paper. All authors read and approved the final paper. Y. Cerantola and F. Grass share first authorship.

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Review Article

Enteral Nutrition and Acute Pancreatitis: A Review

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Introduction. In patients with acute pancreatitis (AP), nutritional support is required if normal food cannot be tolerated within several days. Enteral nutrition is preferred over parenteral nutrition. We reviewed the literature about enteral nutrition in AP. *Methods*. A MEDLINE search of the English language literature between 1999–2009. *Results*. Nasogastric tube feeding appears to be safe and well tolerated in the majority of patients with severe AP, rendering the concept of pancreatic rest less probable. Enteral nutrition has a beneficial influence on the outcome of AP and should probably be initiated as early as possible (within 48 hours). Supplementation of enteral formulas with glutamine or prebiotics and probiotics cannot routinely be recommended. *Conclusions*. Nutrition therapy in patients with AP emerged from supportive adjunctive therapy to a proactive primary intervention. Large multicentre studies are needed to confirm the safety and effectiveness of nasogastric feeding and to investigate the role of early nutrition support.

1. Introduction

Acute pancreatitis (AP) ranges from a mild and self-limiting disease (80%), which usually resolves spontaneously within days, to a rapidly progressive fulminant illness with significant morbidity and mortality [1, 2]. The two most common etiological factors, representing more than 80% of cases, are gallstones and alcohol abuse [1, 3].

The clinical course of an attack of AP varies from a short period of hospitalization with supportive care to prolonged hospitalization and admittance to an Intensive Care Unit (ICU) because of the development of systemic inflammatory response syndrome (SIRS), multiorgan failure (MOF), and septic complications. Overall, in about 15% to 20% of patients, AP progresses to a severe illness with a prolonged disease course. These severely ill patients may develop organ failure and/or local complications such as pancreatic necrosis. In patients with necrotizing pancreatitis, the mortality is close to 17%, with a mortality of 12% in the case of sterile necrosis and up to 30% in infected necrosis [1].

Usually, the initial treatment of AP consists of a nil per os (NPO) regimen and the administration of analgesics and ample intravenous fluids [1, 2, 4]. The rationale for a period without food intake is the assumption that pancreatic stimulation by enteral feeding may aggravate pancreatic inflammation. The validity of this concept of "pancreatic rest" is heavily debated [5–7]. Moreover, many patients are anorectic and may suffer increasing pain sensations when eating and ileus-related nausea and vomiting. The resumption of oral feeding depends on the improvement of abdominal pain, absence of nausea and vomiting, and return of appetite. Nutritional support is required in those patients who cannot tolerate normal food within several days [1, 4, 8, 9].

To date, there is a substantial scientific proof that enteral feeding is superior to total parenteral nutrition (TPN) [5, 6, 10–15]. The beneficial effects of enteral feeding on mucosal integrity and the prevention of bacterial overgrowth may well explain the superiority of enteral feeding over TPN [16, 17]. Enteral feeding significantly reduces the risk of infections, lowers the need for surgical interventions, and reduces the length of hospital stay [5, 6, 10–12, 15, 18]. Recently, Petrov and coworkers concluded in their meta-analysis that mortality is significantly reduced when patients with a

predicted severe AP are fed enterally [14]. Importantly, this reduction of mortality in patients with a severe AP may also be related to the timing of the start of nutrition, within 48 hours after admission [13]. Whenever enteral nutrition is initiated, issues such as the ideal composition, timing, and route of delivery should be considered, as they may all impact on the outcome of AP. Patients who are unable to tolerate enteral nutrition need to be managed with TPN until such time that they can tolerate enteral feeding [9]. In this review an update is given about several aspects of enteral nutrition in mild and severe AP.

2. Pancreatic Rest and Pancreatic Secretion

Efforts to keep up with the increased energy demands in the case of AP are thwarted by the adage to put the pancreas at rest and the avoidance of pancreatic stimulation via gut luminal nutrition. As mentioned in the introduction, this adage merits reconsideration. The concept of "putting the pancreatic to rest" assumes that pancreatic rest promotes healing, decreases pain, and reduces secretion and leakage of pancreatic juices in pancreas parenchyma and peripancreatic tissue [19]. The concept of pancreatic rest originates from the classic work of Ragins et al. based on a canine model [20]. They demonstrated that jejunal feeding did not stimulate pancreatic secretion as opposed to intragastric or intraduodenal feeding. However, this concept of "putting the pancreas to rest" disregards the persistence of basal pancreatic exocrine secretion. Of the three components of pancreas secretion (protein enzymes, fluid volume, and bicarbonate), protein enzyme output is responsible for autodigestion of the gland and perpetuation of the inflammatory process [19]. Suppression of protein enzyme output alone with continued bicarbonate and fluid volume output may therefore be adequate in putting the pancreas to rest.

2.1. Physiology of Pancreatic Secretion. Basal enzyme secretion is 20% of maximal enzyme secretion and is regulated by cholinergic and cholocystokinin (CCK)-mediated mechanisms. Feeding by mouth increases pancreas secretion by involving three levels of stimulation via three interrelated phases: the cephalic, gastric, and intestinal phase [21, 22]. The cephalic phase is mediated through direct cholinergic stimulation by the vagus nerve on pancreatic acinar cells. The vagus also acts indirectly by stimulating gastrin release from the antrum and vasoactive intestinal peptide (VIP) release from the small intestine. The gastric phase of pancreatic secretion has not been fully elucidated. Gastrin affects pancreatic secretion by two mechanisms: gastric acid secretion, resulting in secretin secretion when a low pH reaches the duodenum and a direct effect of gastrin on acinar cells to produce an enzyme-rich secretion. The intestinal phase accounts for the majority of postprandial exocrine pancreatic secretory output and is orchestrated by multiple mediators: vagus nerve, CCK and VIP, a secretin-like hormone, and cholinergic enteropancreatic reflexes.

Human pancreatic enzyme output reaches maximal rates following a mixed meal of 20 kcal/kg body weight [23, 24]. The duration of the response increases with greater caloric load. The pancreatic response is also influenced by the physical properties of the meal: mixed solid-liquid meals induce a higher response than liquid or homogenized meals with a similar energy content. In both instances, the rate of gastric emptying and thus duodenal delivery of nutrients are the key factors which determine the duration of the pancreatic secretion. Proportion of fat, carbohydrate, and protein contents within a meal also influence the duration and enzyme composition of the pancreatic response in humans.

2.2. Pancreatic Secretion with Total Enteral Nutrition. Recent human studies show that all common forms of EN to some extent stimulate the pancreas and only parenteral nutrition avoids pancreatic stimulation [25, 26]. Considerable evidence exists that the degree to which the pancreas is stimulated by enteral nutrition (EN) is determined by the site in the gastrointestinal tract at which feedings are infused. Feeding infused into the jejunum beyond the ligament of Treitz may bypass the cephalic, gastric, and intestinal phase of stimulation of pancreatic secretion, is less likely to stimulate CCK and secretin, and may stimulate inhibiting polypeptides [27–29]. It has been demonstrated in human studies during jejunal feeding, that pancreatic enzyme output increased significantly over basal levels when it was delivered at the ligament of Treitz, whereas there was no significant increase during more distal jejunal feeding, 60 cm beyond the ligament of Treitz [30]. A more recent study in healthy volunteers showed that EN can be given without stimulating pancreatic trypsin secretion provided that it is delivered into the mid-distal jejunum [31]. Feeding from 20 to 120 cm beyond the ligament of Treitz had no stimulatory effect.

Also the composition of the infused feeds is important. There is considerable evidence to support an added benefit of elemental formulae for putting the pancreas to rest compared to standard formulae with intact protein or blenderized diets [19]. Elemental diets cause less stimulation than standard formulas, because of their low fat content, the presence of free aminoacids instead of intact proteins which bind to free trypsin in the gut, causing trypsin levels to fall, and less acid production from the stomach.

2.3. Outcomes of Pancreatic Rest. Whether pancreatic rest has a role to play in patients with severe AP is still uncertain, as no well-powered randomized, prospective studies have been carried out to address this specific question [6]. Whether pancreatic rest is at all needed is questioned by the results of several studies comparing nasogastric with nasojejunal feeding in severe AP, as nastrogastric feeding appears to be safe and well tolerated [32, 33].

Putting the pancreas to rest is based on the assumption that the inflamed and/or necrotic pancreas is still a secretor of activated enzymes once stimulated. Animal studies have shown that pancreatic exocrine secretion in experimental AP in response to CCK stimulation is suppressed [34]. A small

prospective study showed pancreatic exocrine insufficiency to be common in patients recovering from severe AP; its severity correlated with the extent of pancreatic necrosis [35]. Another study demonstrated that trypsin secretion in AP patients, especially with necrotizing AP, is significantly suppressed compared to healthy individuals. However, despite these low rates of luminal secretion, the rate of appearance of newly synthesized trypsin was unchanged [36]. Thus, a more likely alternative explanation for the absence of exacerbation of the disease during EN is that the pancreas becomes less responsive to EN stimulation during an attack of AP and that the secretory response to EN is suppressed to basal rates [34, 37]. However, there is still some doubt whether the pancreatic secretion is fully suppressed. Overall, the concept of pancreatic rest seems to be less probable.

3. Outcomes of Nutritional Support

Nutritional therapy in the past has been governed by the principle that the gut should be put at rest with avoidance of any stimulation of pancreatic exocrine secretion. These concepts should now be replaced by the principle that pancreatic stimulation should be reduced to basal rates, but that gut integrity should be maintained and that the stress response should be contained to reduce the likelihood of multiorgan failure, nosocomial infections, and mortality [38].

The question remains if nutritional support is beneficial for the outcome of AP. Powell et al. published the only randomized controlled trial comparing EN with no nutritional support and studied the effect of early EN on the markers of inflammatory response in severe AP [39]. Nutrition therapy provided by the enteral route did not have a more favorable impact on patient outcome than standard therapy as no differences were found between the two groups with respect to overall complications, length of hospital stay, or the time to resume an oral diet. Serum markers of inflammation appeared to be lower in the group receiving EN compared with those randomized to standard therapy, but none of the differences was statistically significant. The findings of this study suggest that low-caloric EN does not modify the inflammatory response in severe AP, but limits in the design of the study should be mentioned: only 21% of the caloric requirements were infused in the EN group, the study duration was only 4 days, and small numbers of patients were recruited.

As already mentioned, the pancreas is in a state of unresponsiveness during an attack of AP and the secretion of pancreatic juice and trypsin is reduced during AP [34, 37]. Eckerwall et al. investigated the role of immediate oral feeding versus fasting in 60 patients with AP [40]. All patients received initial aggressive fluid resuscitation to maintain intravascular circulatory volume, microcirculation, and renal function, thereby minimizing the extent of ischemia and reperfusion injury. Compared to the fasting patients, the orally fed group had a significantly shorter period of intravenous fluids, less days of fasting, and a 2-day earlier introduction of solid foods, with no differences in blood chemistry, gastrointestinal symptoms, complications, and interventions. The orally fed group had a significant 2-day shorter length of hospital stay without differences in recurrent attacks of pancreatitis in a follow-up of 3 months.

4. Modifications of Enteral Nutrition

4.1. Standard Composition: Elemental, Semielemental, or Polymeric Formulas. Few studies to date compare the results of feeding elemental, semielemental, and polymeric diets to patients with AP [7, 15]. Elemental formula are completely predigested and consist of aminoacids, simple sugars, and enough fat to prevent essential fatty acid deficiency. Semielemental formulas required less digestion than polymeric foods and contain peptides of varying chain length, simple sugars, glucose polymers, or starch and fat primarily as medium chain triglycerides. Polymeric feeds contain non-hydrolyzed proteins, complex carbohydrates, and long chain triglycerides. Based on the assumption that elemental and semielemental formulas cause less pancreatic stimulation than standard formulas, most EN studies have used an elemental or a semielemental formula. It would seem that the location of the enteral tube is just as important as the type of enteral formulas in stimulating pancreatic secretion. Few data exist on the use of standard enteral formula in such patients. Both Windsor et al. and Pupelis et al. have shown that polymeric formula can be safely fed through jejunal tubes in AP patients [17, 41]. In a longitudinal study by Makola et al., 126 patients received standard formula via a jejunal tube which was inserted through a percutaneous endoscopic gastrostomy (PEG-J) [42]. The standard enteral formula resulted in both a significant decrease of the median CT severity index and increase of serum albumin compared from baseline to the time of tube removal. Few studies have defined the benefits of semielemental versus polymeric formulas in severe AP. In 1989, Cravo et al. found a similar tolerance in 102 patients with AP given semielemental versus polymeric formulas [43]. Tiengou et al. compared in a randomized trial semielemental and polymeric formulas in 30 AP patients [44]. Both formulas were well tolerated and well absorbed, but the semielemental group had less weight loss and a shorter length of hospital stay compared with the polymeric group. Recently, Petrov et al. conclude from their adjusted meta-analysis that the use of polymeric, compared with (semi)elemental formulation, does not lead to a significantly higher risk of feeding intolerance, infectious complications, or death in AP patients [45]. It should be remembered that (semi)elemental feeds are sevenfold as expensive as polymeric feeds. In summary, the evidence base to just use (semi) elemental formulas becomes less clear.

4.2. Use of Supplements in Enteral Nutrition. Although the use of glutamine supplementation, immunonutrition and prebiotics, and/or probiotics is conceptually sound and attractive, their use is not supported by large-scale studies [15, 46, 47].

Two studies evaluated the use of immune-enhancing formulas, containing glutamine, arginine and fibers or

glutamine, arginine, ω-3 fatty acids, vitamins, and micronutrients [48, 49]. Hallay et al. compared the effect of a glutamine-rich with a nonglutamine-rich enteral formula on immunologic parameters in 16 patients with AP [48]. The recovery of immunological parameters was better and the time of disease recovery was shorter in the glutamine-treated group. Pearce et al. supplemented in a randomised controlled trial arginine, glutamine, ω-3 fatty acids, and antioxidants in 31 patients with severe AP [49]. Surprisingly, an increase in CRP was found in the study group compared with the control group. No significant difference in the length of hospital stay was observed. Although a lower incidence of pneumonia and MOF, and shorter length of ICU- and hospital stay was observed in the immunonutrition group, none of these differences reached statistical significance.

Lasztity et al. randomly administered ω-3 fatty acids enterally to 28 patients with moderately severe AP [50]. Supplementation significantly lowered the length of hospital stay and the duration of nutritional therapy, without a significant decrease in overall complication rate.

Karakan et al. performed the only study to look at a possible role of prebiotics in the attenuation of the severity of AP [51]. They found a significant reduction in hospital stay and duration of the acute phase response in patients receiving prebiotics compared with controls. The study comprised only 30 patients and needs confirmation in larger series.

Probiotics might prevent infectious complications by reducing small-bowel bacterial overgrowth, restoring gastrointestinal barrier function, and modulating the immune system [52–54]. Oláh et al. demonstrated that *Lactobacillus plantarum* (probiotic) in conjunction with oat fiber (prebiotic) was successful in reducing septic complications (4.5%) versus control (30%) in patients with AP, suggesting that the probiotic therapy enhances the effect of EN in reducing infectious morbidity, however, without a difference in length of hospital stay [55]. Oláh et al. also studied four different prebiotics and probiotics, contained in Synbiotic 2000, and found a decrease in inflammatory response and multiorgan failure in the presence of severe AP [56]. Besselink et al. performed the only large-scale multicenter randomized trial in which 298 patients with a predicted severe AP were randomly assigned to receive a multispecies (Lactobacilli and Bifidobacterium) probiotic preparation or placebo administered enterally [57]. There was no difference in the rate of infectious complications; however, in the probiotic group, the incidence of MOF and the mortality (16% versus 6%) was significantly higher [58]. Nine patients in the probiotics group developed bowel ischaemia, but none in the placebo group. The pathophysiological mechanism that explains why bowel ischaemia developed in patients having had probiotics is unclear, but based on these unexpected study results the use of probiotic prophylaxis in patients with predicted severe AP is highly discouraged. Petrov et al. conclude in their systematic review that supplementation of EN with immunonutrition or probiotics does not significantly improve clinically outcomes and their use is not recommended [45]. Fibre-enriched formulation may be safely administered, but an adequately powered RCT is warranted.

In conclusion, specific supplements added to EN such as arginine, glutamine, ω-3 polyunsaturated fatty acids, and prebiotics may be associated with a positive impact on outcome, but studies are too few and underpowered to make strong treatment recommendations [15, 47]. Probiotics should not be administered routinely in patients with predicted severe AP.

5. Timing of Enteral Support

The precise timing for initiating enteral support has not been specifically addressed in the pancreatitis population but has been studied to a large extent in the critically ill population.

The delivery of EN to critically ill patients early upon admission to the ICU alters physiology in a way that down regulates systemic immunity, reduces overall oxidative stress, and improves patient outcome [59]. Early EN started prior to 48 hours from admission in critically ill patients is associated with a significant 24% reduction in infectious complications and a 32% reduction in mortality compared with delayed feedings started after that point time [59, 60].

Marik and Zaloga found in their meta-analysis that "early" EN (within 36 hours) versus delayed EN (after 36 hours) delayed infectious complications and reduced the length of hospital stay in head injury, trauma, burns, postoperative and medical ICU patients [61]. However, caution must be exercised when making inferences about patients with pancreatitis based on information that is gathered from the critically ill.

Recently, Petrov et al. conducted a systematic review of randomized controlled trials on the effect of EN versus TPN in patients with mild and severe AP with regard to the timing of nutrition support [13]. EN started within 48 hours of admission resulted in a significant reduction in multiorgan failure, pancreatic infectious complications, and mortality. These significant differences between EN versus TPN faded away when nutrition support started after 48 hours of admission. So EN started within 48 hours of admission may be beneficial and a randomized controlled trial, which has been started, may give a more definite answer.

6. Route of Enteral Nutrition Support and Tolerance of Enteral Feeding

Per oral ingestion of nutrients is often hampered by abdominal pain with food aversion, nausea, vomiting, gastric atony, and paralytic ileus or by partial duodenal obstruction from pancreatic gland enlargement [19]. The application of early EN may be limited by the severity of the pancreatitis attack and the occurrence of ileus.

Traditionally, AP management involved fasting the patient until resolution of symptoms. Recent work has suggested that EN via a jejunal tube is safe and may increase antioxidant activity and reduce the acute phase response and the magnitude of the inflammatory response [17].

Most of the feeding tubes are placed as nasojejunal tubes using an endoscopic or a radiologic procedure. Alternatively,

especially if the expected period of feeding is 4–6 weeks or more, laparoscopic or radiologic jejunal feeding tubes can be placed. Tolerance is defined by the provision of adequate feeding without ill effects. Tolerance is primary determined by the balance between feeding into the gastrointestinal tract which can be in a state of partial ileus and providing enteral nutrients while causing only minimal stimulation of pancreatic exocrine secretion. Therefore, patients with nasointestinal tubes placed at or below the ligament of Treitz should be monitored very closely for evidence of tube migration as well as evidence of intolerance such as high residual volume, nausea and vomiting, diarrhea, or aspiration of feeding formula. A wide range of tolerance to EN exists irrespective of known influences such as mode (continuous or bolus) and level of infusion within the gastrointestinal tract (gastric versus postpyloric). In patients operated on for complications of AP, continuous infusion appeared to be safer and reduced the stimulation of the pancreas better than bolus infusion [62]. However, insufficient data do not allow a determination of whether continuous or bolus infusion is superior.

After a feasibility study, Eatock et al. performed a randomized controlled study of early nasogastric versus nasojejunal feeding in severe AP [63, 64]. They discovered a surprising tolerance to nasogastric feeding and recommended that nasogastric feeding should be considered a therapeutic option because of its simplicity, obviating the need for endoscopic, radiologic procedures. Eatock's study, however, had several limitations, one of them being the failure to fluoroscopically confirm that the nasojejunal tubes were appropriately positioned in the jejunum. There is no indication whether the nasojejunal tubes were placed distal enough (at least 60 cm from the ligament of Treitz) to avoid gastric and pancreatic stimulation. The failure to find a difference may have been related to continued gastric and duodenal stimulation occurring in both groups of patients. Similar findings from randomized studies were reported by Kumar et al. (nasogastric versus nasojejunal) and Eckerwall et al. (nasogastric versus TPN) [65, 66].

Jiang et al. included the 3 RCTs, involving 131 patients, in a meta-analysis [32]. The primary outcome of effectiveness was overall mortality, secondary outcomes of effectiveness were hospital stay, complications and their management. Outcome measure of safety was the occurrence of pain on refeeding and adverse events related to nasogastric EN. The comparator intervention was early EN through a nasogastric tube, the control intervention was one of the conventional pancreatic-rest nutritional support routes of total parenteral or intrajejunal feeding. The meta-analysis showed no significant differences in mortality rate between nasogastric and conventional routes (nasojejunal and parenteral feeding). Also, other outcomes were not different such as length of hospital stay, infectious complications, multiorgan failure, rate of admissions to the ICU, or conversion to surgery. Also, the recurrence of pain on refeeding and adverse events associated with nutrition were similar.

Petrov et al. performed an extended systematic review which included the 3 RCTs included in the Jiang meta-analysis and the study of Eatock [33]. They also concluded that nasogastric feeding appeared to be safe and well tolerated in the majority (79%) of patients. The aggregated data from the two RCTs comparing nasogastric to nasojejunal feeding showed no statistically significant difference in mortality and tolerance. Both meta-analyses conclude that a well-powered randomized trial on nasogastric versus nasojejunal feeding is indicated to provide a more firm and conclusive evidence to recommend nasogastric feeding as routine clinical practice in patient with acute pancreatitis.

7. Timing and Nutrient Composition of Oral Support

Data about when to resume oral feeding in patients with acute pancreatitis or the optimal nutrient composition are scare [40, 67, 68]. The usual criteria to initiate oral feeding are (1) absence of abdominal pain, (2) absence of nausea and vomiting, and return of appetite, and (3) absence of complications. It is possible that the recurrence of pain during the reintroduction of the oral diet is related to ingestion of larger volumes rather than to ongoing or renewed intrapancreatic release of enzymes [64]. Usually, patients are refed small amounts of food frequently during the day and the total number of daily calories is gradually increased over a three- to six-day period [69]. Therefore, feeding is often begun using a clear liquid, a diet for the first 24 hours. If tolerated the diet is advanced to soft low-fat diet over the next 24 hour and then to a low fat solid diet. No clinical trials evaluating these routines are available. A low-fat diet is advised when oral intake is resumed in patients recovering from AP. This is based on the observation that intraduodenal lipids increase volume, bicarbonate, trypsin, and amylase output in volunteers [70]. Besides the presumed stimulation of pancreas exocrine secretion by fat, there might be another reason to postpone fat intake. Pancreatic lipase is less stable than other pancreatic enzymes against acid denaturation and destruction by pepsin and pancreatic proteases, in particularly by chymotrypsin present in chime. This may render lipid digestion more vulnerable in pathologic conditions [71, 72]. Trypsin is not inactivated by acid but only by pepsin.

Tolerance to advancement to oral diets was evaluated in 274 patients at the point at which abdominal pain had resolved and ileus had subsided [73]. Sixty patients (21.9%) experienced pain relapse and 47 of these 60 subjects pain relapsed within 48 hours of commencement of oral feeding. No pain relapse or pain occurred in those patients randomized to jejunal tube feedings, started a median of 7 days after the onset of symptoms [74]. However, in 4 of the 15 patients (27%) randomized to oral bolus feedings after a median of 5 days after the onset of symptoms, pain on refeeding was associated with longer duration of initial pain and a higher severity index on CT. Lévy et al. came to the same conclusion in a large number of 116 patients [69]. According to the Ranson score ≥ 3, 35% had a severe AP, and according to the Balthazar CT score >D, this was the case in 42% of patients. Twenty-one per cent of patients

had a relapse of pain. The risk of pain relapse increased if serum lipase was greater than three times normal the day before the start of feeding, and was higher in patients who had a longer duration of pain (11 days versus 6 days) and in patients who had a worse CT score (Balthazar score greater than D). The exacerbation of symptoms resulted in doubling of the length of stay in hospital (from 18 to 33 days). Chebli et al. found a similar number of days of abdominal pain before oral refeeding in those that did and did not relapse [75]. Pain relapse was predicted by peripancreatic fluid collection, serum CRP on the 4th day, and serum lipase on the day of oral feeding.

Jacobson et al. hypothesized that patients recovering from mild AP would be discharged from the hospital sooner if they resumed oral nutrition with a low-fat solid diet compared with a clear liquid diet [67]. Patients with mild pancreatitis were randomized to a clear liquid diet or low-fat solid diet when they were ready to resume oral nutrition. Patients were monitored daily for recurrence of pain, need to stop feeding, post-refeeding length of hospital stay (primary endpoint), and for 28 days post-refeeding to capture readmission rates. 1335 patients were assessed for eligibility and 66 allocated to a clear liquid diet (588 kcal, 2 g fat) and 55 to a low fat solid diet (1200 kcal, 35 g fat). Because of the large number of excluded patients, a bias by selection may have occurred. The number of patients requiring cessation of feeding because of pain or nausea was similar (6% and 11%, resp.), the median length of stay after refeeding was similar, and there was no difference in the 28-day readmission rates. Patients on the low fat diet consumed significantly more calories and grams of fat during their first meal and on study day 1 (301 kcal and 2 g fat versus 622 kcal and 13 g fat, $P < .001$). Initiating oral nutrition after mild pancreatitis with a low fat solid diet appeared to be safe and provided more calories than a clear liquid diet, but did not result in a shorter length of hospitalization. The abdominal pain score on the day of refeeding was associated with a failure of oral intake with those experiencing more pain having a higher likelihood of being made nil per mouth. Unfortunately, the authors failed to resolve the important question of what the optimal diet should be in patients recovering from mild pancreatitis. Sathiaraj et al. performed a randomized trial to determine the length of hospital stay and tolerance to oral refeeding in patients with mild AP and acute on chronic pancreatitis when started on a soft diet ($n = 52$, 1040 kcal and 20 g fat) as compared to a clear liquid diet ($n = 49$, 458 kcal and 11 g fat) [68]. The length of hospital stay (post-refeeding and total) decreased significantly on a soft diet. They observed no significant difference in the need for cessation of feeding because of pain or nausea. Patients on the soft diet consumed significantly more calories and grams of fat during their first meal and on study day 1 (921 kcal and 15 g fat versus 370 kcal and 8 g fat, $P < .001$). They concluded that oral refeeding with a soft diet was safe and resulted in a shorter length of hospital stay. However, in both nonblinded studies, a definition of when to discharge patients was not given. Hospital discharge was decided by the medical team without input from study team.

8. Guidelines of Enteral Nutrition in Acute Pancreatitis

Recently, several general practice guidelines for AP have been published [1, 4, 8, 76–78]. These comment on nutritional management in mild and severe AP. The European Society of Parenteral and Enteral Nutrition (ESPEN) published a revised and comprehensive guideline on EN in AP in 2006 [8]. The several guidelines cover mostly the same recommendations. To date some of the recommendations require updating according to the best available evidence as discussed above. Generally, for mild AP it is recommend to initiate EN if patients cannot consume normal food after 5–7 days. For severe AP nutritional support is indicated when it becomes evident that the patient will not be able to tolerate oral intake for a prolonged period of time, for example, for at least 7 days. This assessment can usually be made within the first 3-4 days of admission. EN should be supplemented by parenteral nutrition if needed. Also, in severe pancreatitis with complications such as pancreatic fistulas, ascites, and pseudocysts, tube feeding can be given uneventfully. If gastric feeding is not tolerated, the jejunal route should be tried and continuous feeding in stead of bolus feeding should be used. In gastric outlet obstruction, feeding beyond the obstruction with the tube tip distal to the obstruction should be tried. If this is impossible, parenteral nutrition should be given. In case of surgery for complications of AP, an intraoperative jejunostomy for postoperative feeding is feasible.

Peptid-based semielemental formulas can be used safely and standard formulae can be tried if they are tolerated.

9. Summary of Recent Developments

Most patients with AP have mild disease and do not need additional nutritional support during admission. According to the guidelines, nutritional support is indicated if patients cannot consume normal food after 5–7 days or when it becomes evident that the patient will not be able to tolerate oral intake for a prolonged period of time (7 days or more). When artificial nutrition is indicated, EN is preferred over TPN, because it reduces complications and mortality in AP when compared with TPN. TPN should only be used in patients unable to tolerate EN. It is likely that EN has a beneficial influence on the disease course and should be initiated as early as possible (within 48 hours of admission). With some caution it can be stated that nasogastric tube feeding in severe AP is possible, making the concept of pancreatic rest less probable. However, larger multicentre studies are needed to confirm the safety and effectiveness of nasogastric feeding when compared to nasojejunal feeding and to investigate the role of early (within 48 hours) versus late nutrition support. Randomized controlled trails have been started and will hopefully give a more definite answer. The clinical evidence for the use of just (semi) elemental formulas is weak. Supplementation of enteral formulas with glutamine and prebiotics and the use of immune enhancing formulas cannot routinely be recommended. Probiotics should not be administered routinely in patients with predicted severe AP.

To date, some of the recommendations as stated in the latest guidelines require updating according to the best available evidence.

Abbreviations

AP: Acute pancreatitis
NPO: Nil per os
EN: Enteral nutrition
TPN: Total parenteral nutrition
SIRS: Systemic inflammatory response syndrome
MOF: Multiorgan failure
ICU: Intensive care unit
RCT: Randomized controlled trial
CCK: Cholecystokin
VIP: Vasoactive intestinal peptide.

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Competing Interest

The author declared that there is no competing interest.

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Review Article

Hyperglycemia in Hospitalized Patients Receiving Parental Nutrition Is Associated with Increased Morbidity and Mortality: A Review

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Parenteral Nutrition (PN) is a valuable life saving intervention which can improve the nutritional status of hospitalized malnourished patients. PN is associated with complications including the development of hyperglycemia. This paper aims to provide a descriptive systematic review regarding the effects of PN-induced hyperglycemia in hospitalized patients, either in the intensive care unit or ward, while formulating and complementing existing guidelines on the administration of PN and glucose monitoring in hospitalized patients. Medline and Pubmed were searched for relevant articles describing complications arising from the development of hyperglycemia in patients receiving PN; four relevant studies were identified in the search. These articles had different glycemic targets and patient populations, and their protocols varied with regards to glycemic control. However, there was consistency regarding the association between hyperglycemia and mortality in patients receiving PN. These studies highlight the need for guidelines regarding monitoring and initiation of therapy in hyperglycemic patients. Unfortunately, all the currently available studies are retrospective in design; a large, prospective, randomized controlled trial regarding glycemic control in patients receiving PN is required for the development of standardized protocols.

1. Introduction

Parenteral nutrition (PN) is a form of intravenous nutritional support, originally developed at the University of Pennsylvania School of Medicine in 1968 to support malnourished surgical patients [1]. Shortly thereafter, PN was shown to be valuable in providing life-saving nutrition for both complex medical and surgical patients with a nonfunctioning GI tract. It has been well established that PN has a beneficial effect in improving the nutritional status of hospitalized malnourished patients [2] and is predominately used in those patients who are unable to receive nutrition either orally or enterally largely due to intestinal failure. Despite the life saving benefits attributed to PN, it is known to be associated with a number of short- and long-term complications including liver disease, catheter-related sepsis, septic shock, fluid and electrolyte abnormalities, and hyperglycemia. Arguably, the interest in blood glucose control and subsequent consequences of hyperglycemia among hospitalized patients receiving PN is rapidly increasing, mirroring the interest in the general inpatient population. The mechanism of harm from hyperglycemia on various organ systems has not been well defined but it is known that hyperglycemia alters the activity of phagocytes, interfering with neutrophil and monocyte functions [3]. Hyperglycemia also increases inflammatory cytokines, oxidative stress and promotes apoptosis [4–7]. Cell and tissue injury caused by hyperglycemia through oxidative stress adversely affects the immune, cardiovascular and nervous system as well as hemostasis, inflammation, and endothelial cell function [8].

Recent groups have described an increase in medical complications and mortality occurring in both critically ill and noncritically ill hyperglycemic inpatients receiving PN [9–12]. The prevalence of hyperglycemia occurring in

patients receiving PN is quite variable and ranges between 10–88% [9, 13, 14]. It has been well established that in-hospital hyperglycemia occurring in patients without any attributable risk factor is associated with higher mortality rates. [15–17]. Three recent studies of hospitalized patients including both critically ill and noncritically ill, identified PN-associated hyperglycemia as a risk factor for development of infection, cardiac, and renal dysfunction and increased mortality [9–11]. A fourth study of hospitalized, noncritically ill patients receiving PN found hyperglycemia to be a risk factor for increased mortality alone [12]. Therefore, the purpose of this manuscript is to provide a descriptive systematic review examining the medical complications of parenteral nutrition-associated hyperglycemia, and its association with mortality in critically ill and noncritically ill patients. It will also review glucose monitoring and therapy regimens and its effect in hospitalized inpatients.

2. Methods

A systematic review was carried out by two reviewers to search for articles relevant to this topic using Medline and PubMed applying the following search terms alone and in combination: hyperglycemia, total parental nutrition, and hospitalized patients. There were no language or time frame limits. Inclusion criteria were articles that examined hospitalized patients, critically or noncritically ill, receiving parenteral nutrition and the effects of hyperglycemia on this population compared with those who did not develop hyperglycemia. Articles were excluded if they did not specifically look at this population. However, clinical studies, reviews, consensus statements, and meta-analysis relevant to the identification and management of hospitalized hyperglycemic patients receiving PN were selected and included. Articles found were assessed for eligibility and compared between the two reviewers. The references and citations were also reviewed to identify other relevant articles. Data extracted included patient demographics, mean glucose level, study definition of hyperglycemia, method of glucose monitoring, duration of PN, outcomes/complications associated with the development of hyperglycemia while receiving PN (i.e., mortality, acute renal failure, any complication, any infection, etc.) as well as their odds ratios and 95% confidence intervals. Authors were contacted via email if the papers lacked data that pertained to this study. The studies were heterogeneous in their methods, therefore the data could not be combined statistically, but general trends were assessed.

3. Results

The search resulted in 38 possible articles, which were further narrowed down to four articles that met our eligibility criteria. There was a kappa agreement of 100% between the two reviewers on the inclusion of these articles. These four retrospective studies [9–12] explored the relationship between hyperglycemia and health outcomes and are described in Table 1. Demographics were underreported in these studies and hence they could not be combined for this review.

Cheung et al. [9] were the first group to look at adverse outcomes associated with PN-induced hyperglycemia. They conducted a retrospective analysis reviewing 109 hospitalized patients in the ward or the intensive care unit, who received PN during the year 2002 in the Westmead Hospital, Sydney, Australia. Mean blood glucose levels were calculated from daily serum glucose readings taken for the duration that patients were receiving PN. Hyperglycemic patients, defined as having blood glucose greater than 10 mmol/L, would undergo blood glucose testing q4 hours by finger prick and PN calories would be reduced. If the blood glucose level remained greater than 10 mmol/L, the protocol called for commencement of an insulin infusion for the duration of PN therapy irrespective of whether the patient was critically ill or not. Outcome measures included development of any infection (culture proven), septicemia (blood culture proven), cardiac complication (myocardial infarction, cardiac arrhythmia, and cardiac arrest), acute renal failure, or death (during admission). The mean duration of PN was 12.1 ± 20.4 days and the mean daily blood glucose during PN was 8.0 ± 1.5 mmol/L.

Lin et al [10] conducted a similar study in a group of patients, also with mixed indications, in the Taipei Veterans General Hospital, Taipei, Taiwan during the year 2004. A retrospective cohort study including 457 hospitalized patients was undertaken to determine associations between hyperglycemia and adverse outcomes in patients receiving PN. All euglycemic subjects had serum glucose measurements twice a week. In this study, patients were defined as having hyperglycemia if a single blood glucose measurement was greater than 6.3 mmol/L. Hyperglycemic patients underwent capillary glucose testing q6 hours by finger prick. The number of blood glucose values per patient ranged from 1 to 207; the mean blood glucose level was calculated using these capillary glucose readings. Treatment of hyperglycemia was not outlined in the methods. Outcome measures included parameters described by Cheung et al. [9]. Additionally, documented bacteremia, fungemia, and respiratory failure defined as the requirements for mechanical ventilation while receiving PN were included as additional clinical outcomes. The mean duration of PN was 17.8 ± 17.7 days and the mean daily blood glucose was 8.6 ± 3.2 mmol/L.

Pasquel et al. [11] conducted a retrospective study of 276 hospitalized patients, in the ward and the intensive care unit at the Grady Memorial Hospital, Atlanta, Georgia, United States during the year 2006. Blood glucose levels on admission, pre-PN, within 24 hours of initiation of PN, and during days 2–10 of PN were included in the analysis. Hyperglycemia was defined as a blood glucose level above 6.7 mmol/L. The monitoring and treatment of these patients was not outlined in the methodology. Outcome measures included mortality, development of any infections, length of stay (LOS), and renal failure. The mean duration of PN was 15 ± 24 days. The mean daily blood glucose on admission was 7.7 ± 4.7 mmol/L. The mean blood glucose prior to initiation of PN was 6.8 ± 1.8 mmol/L and increased to a mean blood glucose of 8.1 ± 2.4 mmol/L within 24 hours and remained

Table 1: Characteristics of the studies examining hyperglycemia in patients receiving PN.

Study	Cheung (2005)	Lin (2007)	Sarkisian (2009)	Pasquel (2009)
Study Design	Retrospective	Retrospective	Retrospective	Retrospective
#of Patients	109	457	100	276
Patient Population	Mixed	Mixed	Mixed	Noncritically Ill only
Mean Age ± SD	51.9 ± 18.7	66.4 ± 16.3	61.9 ± 17	51 ± 18
Glucose Monitoring	Daily and capillary glucose testing q4 hours for duration of PN	Twice weekly and capillary glucose testing q6 hours for duration of PN	Variable, including first 9 days on PN	On admission, pre PN and daily for PN day 1–10
Mean Glucose	Blood Draw	Finger Prick	Blood Draw & Finger Prick	Blood Draw
Blood glucose cut points examined (mmol/L)	<6.9	<6.3	<10	<6.7
	6.9−7.8	6.3−7.6	≥10.0	6.7−8.3
	7.9−9.1	7.6−10		8.4−10
	>9.1	>10.0		>10.0

elevated at 7.8 ± 2.2 mmol/L for the remainder of the days analyzed.

Sarkisian et al. [12] conducted a retrospective study of 100 hospitalized patients in the Foothills Medical Centre, Calgary, Canada. This cohort excluded critically ill individuals unlike the preceding three studies outlined [9–11]. Mean blood glucose values were calculated for each patient based on the total number of readings during their first 9 days receiving PN including serum and finger prick readings. Hyperglycemia was defined as mean blood glucose levels above 10mmol/L. Outcomes measured included development of any infection, acute coronary event, acute renal failure, LOS, ventilator use, ICU admission, and death. Additionally, this group reviewed the median frequency of glucose monitoring in both euglycemic and hyperglycemic patients and the association of the frequency of monitoring with mortality.

3.1. Mortality. All four studies showed significantly increased mortality in patients with mean blood sugars greater than 10 mmol/L while receiving PN after adjusting for age, gender, and previous diabetes status, when compared to a lower blood glucose group (Table 2). Pasquel et al. [11] were the only group to examine blood glucose levels at differing time periods in relation to PN initiation. They grouped the patients into three groups; pre-PN initiation, within 24 hours of PN initiation, and during days 2–10 of PN. In comparison to living patients, deceased patients in their cohort had a significantly higher blood glucose pre-PN (7.2 ± 2.1 mmol/L versus 6.7 ± 1.8 mmol/L), within 24 hours of PN initiation (9.0 ± 3.1 mmol/L versus 7.7 ± 2.1 mmol/L) and during days 2-10 of PN (8.9 ± 2.9 mmol/L versus 7.9 ± 1.9 mmol/L). Their study indicates that blood glucose values prior to and within 24 hours of initiation of PN are better predictors of hospital mortality and complications than the mean blood glucose during the entire duration of PN. Pasquel et al. found that mortality was independently predicted by pre-PN blood glucose values between 8.4-10mmol/L (OR 3.41, 95% CI 1.3–8.7, $P < .01$) and greater than 10mmol/L (OR 2.2, 95% CI 0.9–5.2, $P = .077$), as well as by blood glucose within 24 hours of PN greater than 10 mmol/L (OR 2.8 95% CI 1.2–6.8, $P = .020$) versus patients without hyperglycemia.

3.2. Complications. Not all the groups agreed on the association between hyperglycemia and complications (Table 2). Sarkisian et al. [12] did not find an association between hyperglycemia and acute coronary events, renal failure, infection, hospital length of stay, ventilator use, or admission to a critical care unit. This may be in part due to the less critically ill population studied in comparison to the other three studies which included both critically ill and noncritically ill patients. Cheung et al. [9] found that for every 1 mmol/L increase in blood glucose above 6.9 mmol/L, the risk of any complication increased by a factor of 1.58. Patients with a mean blood glucose greater than 9.1 mmol/L had the highest relative risk for complications (OR of 4.3, 95% CI 1.4–13.1 $P = .01$) using blood glucose of less than 6.9 mmol/L as the reference. Lin et al. [10] found a similar association. For every 0.56 mmol/L increase in blood glucose above 6.3 mmol/L the risk of any complication increased by a factor of 1.14. The highest relative risk of complications was in the group of patients with mean blood glucose greater than 10 mmol/L (OR of 5.5, 95% CI 2.5–12.4 $P < .001$) using blood glucose of less than 6.3 mmol/L as the reference category. Pasquel et al. [11] noted that patients with higher blood glucose levels during TPN had a longer hospital ($P = .011$) and ICU length of stay ($P = .008$). They also found an association between the risk of pneumonia (OR=3.6, 95% CI 1.6–8.4) and acute renal failure (OR=2.2, 95% CI 1.0–4.8) in patients with blood glucose greater than 10 mmol/L during the first 24 hours of TPN compared with patients having a mean blood glucose less than 6.7 mmol/L.

3.3. Monitoring. Blood glucose monitoring methods and frequency was reported in each of the studies' methods, but not all examined the effect on outcomes. Unfortunately, it was not reported if monitoring was considerably different between the critically ill and noncritically ill

Table 2: Risk of mortality and complications due to hyperglycemia in patients receiving PN.

Study	Cheung (2005)	Lin (2007)	Sarkisian (2009)	Pasquel (2009)
Hyperglycemia(mmol/L)	>9.1*	>10**	≥10***	>10****
Mortality OR(95%CI)	10.90(2.0 − 60.5)^{X}	5.0(2.4 − 10.6)^{X}	7.22(1.08 − 48.3)^{X}	2.80(1.20 − 6.80)^{X}
Any Infection OR(95%CI)	3.9(1.2 − 12.0)^{X}	3.1(1.5 − 6.5)^{X}	0.9(0.3−2.5)	NA
Cardiac OR(95%CI)	6.2(0.7−57.8)	1.6(0.3-7.2)	1.3(0.1−12.5)	NA
Acute Renal Failure OR(95%CI)	10.9(1.2 − 98.1)^{X}	3.0(1.2 − 7.7)^{X}	1.9(0.4−8.6)	2.2(1.0−4.8)
Septicemia OR(95%CI)	2.5(0.7−9.3)	NA	NA	NA
Any Complication OR(95%CI)	4.3(1.4 − 13.1)^{X}	5.5(2.5 − 12.4)^{X}	NA	NA

All study results are adjusted for age and sex.
^{X} Significant at $P < .05$.
*ORs are expressed using blood glucose ≤6.9 mmol/L as a reference category.
**ORs are expressed using blood glucose <6.3 mmol/L as a reference category.
***ORs are expressed using blood glucose <10 mmol/L as a reference category.
****ORs are expressed using blood glucose ≤6.7 mmol/L as a reference category as measured within 24 hours of PN initiation.

patients included in these studies. Of these four studies, only Sarkisian et al. [12] examined the frequency of blood glucose monitoring and outcomes related to this. Patients with hyperglycemia had their blood glucose monitored more frequently in both the first 48 hours (median 4 times, IQR: 2–7, $P = .003$) and in the first week (median 6 times, IQR: 3–18, $P \leq .001$) compared to euglycemic patients. There was no association between frequency of glucose monitoring and mortality in the first 48 hours of PN or in the subsequent week of PN. The other studies reported varying schedules to monitor hyperglycemia and did not statistically analyze complications or mortality associated with monitoring frequency.

4. Discussion

In our descriptive systematic review of the four available retrospective studies examining hyperglycemia in hospitalized patients receiving PN, one consistent finding was observed; mortality was increased significantly if blood sugars were above 10 mmol/L. Unfortunately, of the published studies examining hyperglycemia in PN patients, glycemic targets differed, patient populations were not identical, protocols for monitoring blood sugars varied, and there was a lack of information regarding hyperglycemic and euglycemic control. These heterogeneous methods likely account for the variations in results regarding complications and morbidity associated with hyperglycemia. Three of these studies included both critically ill and noncritically ill patients and assessed outcomes in a homogeneous manner, not accounting for potential confounding factors in their analysis such as the indication for PN. This limitation in study design demonstrates the need for the establishment of large, controlled trials regarding glycemic control in more homogenous patients receiving PN, either critically ill or noncritically ill, for the development of standardized protocols regarding monitoring and glucose therapy in PN patients.

All four studies failed to monitor blood glucose to the level suggested by The American Society of Parenteral and Enteral Nutrition (A.S.P.E.N) [18]. To our knowledge, this expert organization in nutrition support practices has the only published set of established guidelines regarding glucose monitoring in patients receiving PN. They suggest glucose monitoring q6 hours upon initiation of PN and at least three times daily within days 3–9 until the blood glucose has reached less than 11mmol/L. These guidelines do not give further recommendations regarding closer monitoring for critically ill patients. Based on the findings from Cheung, Lin, Pasquel, and Sarkisian [9–12], the level of 11mmol/L recommended by A.S.P.E.N as an indicator of acceptable blood sugars may need to be further reduced.

Several studies with heterogeneous designs and outcome measures have examined the relationship between tight glycemic control and outcomes in critically ill patients. Griesdale and colleagues report results from a meta-analysis of 26 studies involving over 13,500 patients [19]. The original landmark study conducted by Van den Berge et al. [20] compared intensive insulin therapy versus conventional treatment among surgical intensive care patients, predominantly PN fed. Fasting blood glucose targets were 4.4–6.1 mmol/L and 10-11.1 mmol/L in the intensive and conventional arms, respectively. They demonstrated a 34% decrease in mortality with intensive insulin therapy. However, subsequent studies in slightly different populations have failed to show such benefit. The Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation (NICE-SUGAR) is currently the largest randomized controlled study comparing intensive versus conventional glucose control among both surgical and medical intensive care patients who were predominantly enterally fed. The NICE-SUGAR study defined intensive glucose control with a target blood glucose range of 4.5–6.0 mmol/L and conventional control as a target of 10.0 mmol/L or less. The authors found that intensive glucose control increased the absolute risk of death at 90 days by 2.6% compared with conventional glucose control. This represents a number needed to harm of 38. There was also a 6-fold increase in the rate of occurrence of hypoglycemia with use of intensive therapy in all ICU patients [21]. Since the publication of these studies and the recent meta-analysis, the American College of Endocrinology (ACE) and the American Diabetes

Association (ADA) have generated a consensus statement which adopts less stringent blood glucose targets between 7.8–10.0 mmol/L for critically ill patients to prevent hypoglycemia, while controlling for hyperglycemia [22, 23]. They also recommend intravenous insulin infusions for critically ill patients and subcutaneous basal-bolus, prandial and correctional dosing for all noncritically ill patients [24, 25]. Based on the aggregated results from the 4 studies examining outcomes in PN patients and the guidelines from the ACE and the ADA described above, we could conclude that the mean blood glucose in patients receiving PN, whether they are critically ill or noncritically ill, should be less than 10 mmol/L and potentially the appropriate target range would lie between 6.3 to 9.1 mmol/L.

Only Cheung et al. clearly outlined treatment of hyperglycemia in their patients. Their protocol called for an insulin infusion for all patients irrespective of their inpatient location if during PN treatment blood sugars were persistently above 10 mmol/L. Treatment of hyperglycemia with insulin infusion was associated with an increased rate of complications (OR 2.7, 95% CI 1.3–5.6, $P = 0.01$), although not statistically significant for death. There were no documented cases of hypoglycemia in patients receiving insulin infusions. Incidentally, the mean blood glucose levels for these patients were significantly higher than patients who did not require insulin therapy, suggesting that insulin infusions were inadequately administered. This was the only study in our review to examine treatment of hyperglycemia, and the evidence is inconclusive regarding harm or benefit of the use of insulin infusions in patients receiving PN, furthering the need for more evidence regarding treatment of hyperglycemia in PN patients.

Currently, as recommended by ACE/ADA, insulin is the most appropriate agent for management of hyperglycemia [25]. There are many methods by which insulin can be administered to patients receiving PN, including subcutaneous administration, insulin infusion, addition of insulin to the PN bag, or a combination of these methods. No head to head comparisons of these methods are available at this time to comment on the best available technique. Previously, there was a controversy surrounding the amount of insulin available when mixed with PN solutions. However, Dunham et al. [26] published a very well-designed study showing the recovery of regular insulin from all-in-one PN mixtures in ethylene vinyl acetate bags to be up to 95%. Surprisingly, there have been very few studies describing glucose control in PN patients with hyperglycemia treated with insulin provided in the PN mixture. There is some discordant opinion among PN experts regarding insulin delivery via this method, and therefore no consistent comment can be provided regarding the safety and effect of this method of intervention.

Glucose management strategies in the critically ill PN recipient should involve frequent glucose monitoring and implementation of IV insulin infusion. The 2009 ACE/ADA recommends IV insulin infusions for all critically ill patients. The target blood glucose is recommended to be kept between 7.8 to 10 mmol/L. Administration of insulin infusions to PN patients with hyperglycemia in the noncritically-ill setting would be a significant burden on the system, given the extra monitoring required and nursing care involved. In the ICU setting, one-on-one nursing allows the adoption of a tighter glycemic control/insulin protocols; however, this is not practical for ward patients.

Glucose management strategies in the noncritically ill PN recipient typically involve subcutaneous insulin in a variety of breakdowns. The ACE/ADA recommends basal/bolus/correction subcutaneous insulin regiments tailored to the individual patient with adequate adjustments as the patient condition changes, Targeting random blood glucose levels of less than 10 mmol/L, and once the patient is eating premeal blood glucose targets of less than 7.8 mmol/L. A multidisciplinary approach may be necessary for successful implementation of effective glycemic management in the hospital setting. Individualized plans taking into account the patient profile, nursing support, and monitoring capabilities are likely the most prudent way to proceed until further studies are done regarding optimal therapy regimens. Most noncritically ill patients can be managed effectively using subcutaneous route of delivery. However, sliding scale regimens, defined as administration of a preestablished amount of rapid acting insulin in response to hyperglycemia, are ineffective [23, 27]. This method does not emulate the natural circadian rhythm; it is more reactive than proactive and does not include basal insulin. The ACE/ADA discourages use of these sliding scales due to wide fluctuations in glucose levels documented in several observational studies. A prospective randomized in 130 hospitalized noncritically ill patients with type 2 diabetes showed that basal-bolus insulin regiment (using a daily long-acting insulin analog with preprandial rapid-acting insulin analog) was superior to a standard sliding scale protocol. The target blood glucose of less than 7.8 mmol/L was achieved in 66% of patients in the basal-bolus group versus only 38% of patient in the sliding scale group [28].

Management of hyperglycemia and insulin dosing in patients receiving parenteral nutrition should be done on an individual basis, regardless of indication. Insulin dosing requirements may change rapidly as the patient's underlying illness evolves. It is recommended that insulin requirements be reassessed after any changes in nutritional status, and certainly with changes in the nutrition support prescription and with changes in oral intake. Close glucose monitoring with frequent insulin dose adjustments is a critical part of effective glycemic management, and a generalized cookbook approach may not be suitable for patients on PN. The A.S.P.E.N guidelines recommend q6 hour capillary blood sugars. All four studies had less than optimal glucose monitoring in their hyperglycemic patients and only one looked at outcomes associated with monitoring. Sarkisian et al. [12] did not show an increased mortality associated with frequency of glucose monitoring. However, this was a retrospective study including only 100 patients in a noncritically ill setting

We can only infer a trend towards increased mortality and morbidity in hyperglycemic PN patients from these studies because they were limited in their design; all were retrospective and differed in glycemic targets. Their patient

populations were not identical and their protocols for monitoring blood sugars varied. It is difficult to conclude from these studies that hyperglycemia alone led to the observed complications and increased mortality, as preexisting comorbid conditions and indications for PN were not accounted for. Additionally, as we could not separate the critically ill from the noncritically ill in these studies, the increased mortality seen in patients with poorly controlled glucose may have been a result of preexisting conditions and a sicker population. Our review has inherent limitations since our search yielded only four papers which varied in their design not allowing us to statistically combine the results or draw sound conclusions.

5. Conclusion

Hyperglycemia is associated with poor outcomes in patients receiving PN; this applies to patients with and without diabetes and both critically ill and noncritically ill. There is a significant increase in mortality when blood sugars are above 10 mmol/L. There is a suggestion of increased complication rates in this patient population but further studies need to be done to confirm these findings. These studies suggest that the most acceptable level of blood glucose should range between 6.3–9.1 mmol/L. Conclusions regarding the most appropriate method for management of hyperglycemia could not be drawn from this cohort due to lack of information regarding therapy. Given the lack of standardized protocols regarding monitoring and therapy in this population, a large prospective, randomized controlled trial in patients receiving PN with hyperglycemia is necessary to determine optimal monitoring, optimal delivery of insulin, and whether the control of blood glucose can improve outcomes in this patient population.

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Review Article

Refeeding Syndrome: A Literature Review

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Refeeding syndrome (RFS) describes the biochemical changes, clinical manifestations, and complications that can occur as a consequence of feeding a malnourished catabolic individual. RFS has been recognised in the literature for over fifty years and can result in serious harm and death. Crude estimates of incidence, morbidity, and mortality are available for specific populations. RFS can occur in any individual but more commonly occurs in at-risk populations. Increased awareness amongst healthcare professionals is likely to reduce morbidity and mortality. This review examines the physiology of RFS and describes the clinical manifestations. A management strategy is described. The importance of a multidisciplinary approach is emphasized.

1. Introduction

RFS is well recognised. It occurs after the reintroduction of feeding after a period of starvation or fasting [1]. RFS describes a series of metabolic and biochemical changes that occur as a consequence of reintroduction of feeding after a period of starvation or fasting. This unfavorable metabolic response causes nonimmune-mediated harm to the body and can be mild, moderate, or severe. Although, the physiology and pathophysiology are well known, the circumstances under which RFS occurs, the clinical manifestations, and the management of these patients are less clear [2, 3].

1.1. Methods. A PubMed search for the terms "refeeding syndrome" AND "hypophosphataemia" generated two hundred and seven separate articles. There were no randomized controlled trials identified.

1.2. Physiology. With food in abundance, carbohydrates provide for most of our energy requirements. Glucose, the principal product of carbohydrate digestion, is actively cotransported along with sodium at the intestinal brush border against a concentration gradient. Glucose enters the portal circulation by facilitated diffusion and blood sugar levels rise. This stimulates the release of the peptide hormone insulin from pancreatic islet cells. Insulin secretion has several effects. It promotes glucose uptake and storage (glycogenesis), inhibits the breakdown of fats (lipolysis), and increases cellular uptake of potassium. When glycogen storage capacity is exceeded, lipogenesis occurs with nonoxidised glucose being converted to fat and stored as triglycerides in adipose tissue. Together, the consequence is for blood glucose levels to fall with a concomitant reduction in insulin secretion [4].

With starvation, levels of glucose begin to fall within 24 to 72 hours. This results in the release of the peptide hormone glucagon and a reduction in insulin secretion [10]. Glucose levels are maintained by glycogenolysis but glycogen stores rarely last more than 72 hours [11]. Glucose homeostasis is essential because certain tissues, such as brain, erythrocytes, and cells of the renal medulla are obligate glucose users [12]. These demands for glucose are met by the process of gluconeogenesis by which noncarbohydrate sources are metabolized to glucose. The most important of these is the muscle protein alanine. In addition, fatty acid oxidation in liver hepatocytes generates ketone bodies. These are converted to acetyl-coenzyme-A generating energy via the Kreb's cycle. Further energy production from lactate and pyruvate (the products of glycolysis) and amino acids occurs via the Cori cycle [4]. In summary, metabolic adaptation occurs to ensure survival on fat fuel economy [13]. There is a resultant loss of body fat and protein and an accompanying depletion of potassium, phosphate, and magnesium [14, 15].

Table 1: Clinical manifestations of electrolyte abnormalities associated with refeeding syndrome [1, 5–9].

	Clinical Manifestation
Phosphate (PO_4^{2-})	Hypophosphataemia (normal range 0.8–1.45 mmol/l) presents as Cardiovascular: heart failure, arrhythmia, hypotension, cardiomyopathy shock, death Renal: acute tubular necrosis, metabolic acidosis Skeleton: rhabdomyolysis, weakness, myalgia, diaphragm weakness Neurology: delirium, coma, seizures, tetany Endocrine: hyperglycemia, insulin resistance, osteomalacia Haematology: haemolysis, thrombocytopenia, leukocyte dysfunction
Potassium (K^+)	Hypokalemia (normal range 3.5–5.1 mmol/l) presents as Cardiovascular: hypotension, ventricular arrhythmias, cardiac arrest, bradycardia or tachycardia Respiratory: hypoventilation, respiratory distress, respiratory failure Skeleton: weakness, fatigue, muscle twitching Gastrointestinal: diarrhoea, nausea, vomiting, anorexia, paralytic ileus, constipation Metabolic: metabolic alkalosis
Magnesium (Mg^{2+})	Hypomagnesaemia (normal range 0.77–1.33 mmol/l) presents as Cardiovascular: paroxysmal atrial or ventricular arrhythmias, repolarisation alternans Respiratory: hypoventilation, respiratory distress, respiratory failure Neuromuscular: weakness, fatigue, muscle cramps (Trousseau and Chvostek) weakness, ataxia, vertigo, paresthesia, hallucinations, depression, convulsions Gastrointestinal: abdominal pain, diarrhoea, vomiting, loss of appetite, and constipation Other: anaemia, hypocalcemia NB: many cases of hypomagnesaemia do not manifest clinically till very late
Sodium (Na^+)	Hyponatremia (normal range 136–145 mmol/l) ensues during RFS due to hyperglycaemia and presents as: Cardiovascular: heart failure and arrhythmia Respiratory: respiratory failure, pulmonary oedema. Renal: renal failure Skeleton: muscle cramps, fatigue, fluid retention and swelling (oedema)
Vitamins	Deficiency of thiamine (especially in alcoholism) presents as Neurology: Wernicke-Korsakoff syndrome, Karsakoff's psychosis, Cardiovascular: congestive heart failure and lactic acidosis, beriberi, disease Skeleton: muscle weakness

Homeostatic mechanisms maintain serum concentrations of these ions at the expense of intracellular stores. Serum levels may remain normal despite a marked reduction in total body levels.

The reintroduction of nutrition to a starved or fasted individual results in a rapid decline in both gluconeogeneis and anaerobic metabolisms [13]. This is mediated by the rapid increase in serum insulin that occurs on refeeding [10]. Insulin stimulates the movement of extracellular potassium, phosphate, and magnesium to the intracellular compartment. Depleted intracellular stores and a large concentration gradient ensure a rapid fall in the extracellular concentration of these ions [16, 17]. Osmotic neutrality must be maintained resulting in the retention of sodium and water [18]. Reactivation of carbohydrate-dependent metabolic pathways increases demand for thiamine, a cofactor required for cellular enzymatic reactions [19, 20]. The deficiencies of phosphate, magnesium, potassium, and thiamine occur to varying degrees and have different effects in different patients [5]. Some, such as chronic alcohol abusers or those with long-term starvation, are more vulnerable to the metabolic consequences of mineral or elemental deficiencies [21–28]. This explains why RFS is not defined by a clear set of signs and symptoms but is considered an arbitrary term referring to a wide spectrum of biochemical abnormalities and clinical consequences [5] (Table 2).

1.3. What Is Refeeding Syndrome? First reports of the syndrome appeared in the 1950s after observations of malnourished prisoners of war who developed cardiac and neurological symptoms soon after the recommencement of feeding [31, 32]. There is no internationally agreed definition of RFS [6]. In 2001 Crook et al. referred to a syndrome of severe electrolyte and fluid shifts associated with metabolic abnormalities in malnourished patients undergoing refeeding, whether orally, enterally, or parenterally [1].

Table 2: Malnourished patients at risk of RFS [5, 6, 8, 29].

Anorexia nervosa	Chronic alcoholism
Radiation therapy	Major stressors without food for >7 days
Oncology patients	Postoperative patients
Severe malnutrition (Marasmus/Kwashiorkor)	Institutionalized patients
Pathological weight loss	Hunger strikes
Stroke (Neurological problems)	Malabsorption diseases
Inflammatory bowel diseases	Post bariatric surgery
Chronic pancreatitis	Elderly, poor social circumstance
Acquired Immunodeficiency Syndrome	Diabetes Mellitus

Table 3: Monitoring patients at risk of developing RFS [5, 6, 8, 30].

Clinical monitoring	Biochemical monitoring
Early identification of high risk patients	Monitor biochemistry and electrolyte levels
Monitor blood pressure and pulse rate	Monitor blood glucose levels
Monitor feeding rate	ECG monitoring in severe cases
Meticulously document fluid intake and output	Account other sources of energy
Monitor change in body weight	(dextrose, propofol, medications)
Monitor for neurologic signs and symptoms	
Patient education	

As there is no strict definition, it is not surprising that the incidence of RFS is unclear. Robust epidemiological studies are lacking in part due to the absence of accepted diagnostic criteria or internationally agreed guidelines for detecting RFS [5]. Most published data from prospective and retrospective case series do not reflect overall incidence.

Hypophosphataemia is the adopted surrogate marker for diagnosing RFS though low serum phosphate is not pathognomonic [33]. Estimates of hypophosphataemia in those at risk of RFS are high [2, 7, 34]. In a prospective study of sixty-two patients in the intensive care unit refed after being starved for 48 hours, twenty-one patients (34%) experienced refeeding hypophosphataemia. There was an association with low prealbumin concentration [7]. In a separate study of one hundred and six patients with histologically confirmed cancer, the incidence was 25% [34]. Hypophosphataemia is uncommon in the hospitalized patient population, occurring in 2% of all requests received for serum phosphate determination in one institution over an eighteen-month period [33]. There are limitations to relying on low serum phosphate and levels may be normal in patients with multiorgan failure or in the presence of impaired renal function.

An alternative to the lack of reliable RFS incidence data is to examine the prevalence of those at risk of RFS. A consensus exists in the literature that prevention is preferable to treating established RFS. Therefore, estimating the prevalence of those at risk might assist in understanding the potential scale of RFS. The predominant risk factor for RFS is malnutrition. The report of the British Association of Parenteral and Enteral Nutrition (BAPEN, 2008) estimated in the UK that there were more than three million people who are either malnourished or at risk of malnutrition whilst the British Dietetic Association estimated a 20% to 60% risk of malnutrition in patients being admitted to hospital. In 2005 Hise et al. estimated that 30% to 50% of hospitalized patients are malnourished [35]. Morley in 2002 estimated the prevalence of malnutrition is 1% to 15% in patients attending outpatient, 25% to 60% in the institutionalized patients, and it is 35% to 65% in hospitalized patients [36]. A hospital-based study screened 32,837 patients finding nearly one fifth were severely undernourished or at risk for undernutrition and that the risk was directly related to age [37]. Malnutrition is a problem in many different disease groups, including cancer (5–80%), neurology (4–66%), elderly (0–85%), surgical/critical illness (0–100%), respiratory disease (5–60%), gastrointestinal and liver disease (3–100%), HIV/AIDS (8–98%), and renal disease (10–72%) [30] (Table 2). These data underscore the significant possibility for RFS and highlight the link between comorbidity, nutritional status, and RFS.

2. Clinical Manifestations

Symptoms of RFS are variable, unpredictable, may occur without warning, and may occur late. Symptoms occur because changes in serum electrolytes affect the cell membrane potential impairing function in nerve, cardiac, and skeletal muscle cells. The variable clinical picture in RFS reflects the type and severity of biochemical abnormality present. With mild derangements in these electrolytes, there may be no symptoms. More often, the spectrum of presentation ranges from simple nausea, vomiting, and lethargy to respiratory insufficiency, cardiac failure, hypotension, arrhythmias, delirium, coma, and death. Clinical deterioration may occur rapidly if the cause is not established and appropriate measures not instituted. Low serum albumin concentration may be an important predictor for hypophosphataemia [7] although albumin is not a nutritional marker. The biochemical abnormalities and associated symptoms seen in RFS are summarized (Table 1).

3. Management

The principles of management are to correct biochemical abnormalities and fluid imbalances returning levels to normal where possible. The optimum timing for correcting abnormalities in established RFS has been the source of controversy. The view that correction of electrolyte abnormalities must occur before commencement of feeding [1] has been revised and recent National Institute of Health and Clinical Excellence in the United Kingdom guidelines

Table 4: Refeeding regime for patients at risk of RFS [5, 29].

Day	Calorie intake (All feeding routes)	Supplements
Day 1	10 kcal/kg/day For extreme cases (BMI < 14 kg/m^2 or no food >15 days) 5 kcal/kg/day Carbohydrate: 50–60% Fat: 30–40% Protein: 15–20%	Prophylactic supplement PO_4^{2-}: 0.5–0.8 mmol/kg/day K^+: 1–3 mmol/kg/day Mg^{2+}: 0.3-0.4 mmmol/kg/day Na^+: <1 mmol/kg/day (restricted) IV fluids-Restricted, maintain "zero" balance IV Thiamine + vitamin B complex 30 minutes prior to feeding
Day 2–4	Increase by 5 kcal/kg/day If low or no tolerance stop or keep minimal feeding regime	Check all biochemistry and correct any abnormality Thiamine + vitamin B complex orally or IV till day 3 Monitoring as required (Table 3)
Day 5–7	20–30 kcal/kg/day	Check electrolytes, renal and liver functions and minerals Fluid: maintain zero balance Consider iron supplement from day 7
Day 8–10	30 kcal/kg/day or increase to full requirement	Monitor as required (Table 3)

If RFS is suspected based on clinical and biochemical assessment or the patient develops intolerance to artificial nutritional support, the energetic intake should be reduced or stopped.
Feeding rate should be increased to meet full requirements for fluid, electrolytes, vitamins, and minerals if the patient is clinically and biochemically stable.

[29] indicate that feeding and correction of biochemical abnormalities can occur in tandem without deleterious effects to the patient [5, 8]. No published randomised trial data is available to support either view.

Prevention is the key to successful management [38]. Three factors appear fundamental: early identification of at risk individuals, monitoring during refeeding (Table 3), and an appropriate feeding regimen. Anticipating the risk of developing RFS prevents complications before they develop. This is aided by taking a detailed history, through clinical examination and by identifying high-risk patients with early involvement of the nutrition support team [39, 40]. Patients should be screened for risk of developing RFS on admission to hospital or when being assessed in the community. Those identified as being either malnourished or at high risk of not being able to meet their nutritional requirements should be appropriately referred for a formal nutritional assessment. Qualified dieticians or specialist nutrition nurses are required to perform nutritional assessments leading to the formulation of individualized strategies for the patient [16]. Effective communication within and between teams is a pre-requisite to achieve best care. The successful management of patients requires a multidisciplinary approach including nutritionists, nurses, and doctors meeting regularly to discuss changing nutritional needs of patients [39, 41–43].

4. Feeding Regimen in RFS

There are numerous published regimens for feeding patients at risk of RFS. None are evidence based. Irrespective of which particular feeding regimen is employed, the common denominator must be to follow the principles of permissive underfeeding. We recommend a regime (Table 4) based on current guidelines, published literature, and expert opinion [5, 29, 44, 45].

5. Summary

All clinicians caring for vulnerable groups who might require nutritional support should recognize the risk of RFS. The lack of randomized controlled trials in this area of medicine means that management is based on anecdotal data rather than evidence. This emphasizes the importance of minimizing risks of RFS by cautious reintroduction of feeding. We recommend that all patients receiving artificial nutritional support are entered into a database that can be regularly audited and evaluated to ensure best practice and adherence to current guidelines.

It is important to emphasize that RFS does not represent a singular condition or syndrome rather it describes an illness spectrum that occurs under particular circumstances within high-risk populations. Improved understanding of energetic requirements in healthy and sick patients will help improve understanding and allow for developing novel strategies to minimize risk of RFS to patients.

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Clinical Study

Propofol-Based Sedation Does Not Increase Rate of Complication during Percutaneous Endoscopic Gastrostomy Procedure

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Objectives. To evaluate and compare the complication rate of sedation with or without propofol regimen for percutaneous endoscopic gastrostomy (PEG) in a hospital in Thailand. *Subjects and Methods*. A total of 198 patients underwent PEG procedures by using intravenous sedation (IVS) from Siriraj Hospital, Thailand from August 2006 to January 2009. The primary outcome variable was the overall complication rate. The secondary outcome variables were sedation and procedure related complications, and mortality rate. *Results*. After matching ASA physical status and indications of procedure, there were 92 PEG procedures in propofol based sedation group (A) and 20 PEG procedures in non-propofol based sedation group (B). All sedation was given by residents or anesthetic nurses directly supervised by staff anesthesiologist in the endoscopy room. There were no significant differences in patients' characteristics, sedation time, indication, complications, anesthetic personnel and mortality rate between the two groups. All complications were easily treated, with no adverse sequelae. Mean dose of fentanyl and midazolam in group A was significantly lower than in group B. *Conclusion*. Propofol-based sedation does not increase rate of complication during PEG procedure. Additionally, IVS of PEG procedure is relatively safe and effective when performed by physicians in training. Serious complications are none.

1. Introduction

Percutaneous endoscopic gastrostomy (PEG) has become the procedure of choice for enteral feedings in patients with a functioning gastrointestinal tract who need long-term enteral feeding, when oral access is impossible [1, 2]. PEG has replaced the surgical gastrostomy procedure because of its lower cost and shorter recovery time. Many patients requiring PEG are older, frail, and malnourished and have a significant comorbidity. PEG insertion is an invasive procedure requiring both endoscopy and sedation. It usually carries a risk of high mortality rates in the early postinsertion period, with 30-day mortality rates varying between 4% and 26% [3]. Furthermore, there is a substantial risk of morbidity, especially from sedation and/or anesthesia [4].

Anesthesia consultation before the procedure is needed. Fluid and electrolyte disorders should be corrected and any infection treated. Antibiotic prophylaxis is recommended due to the infection risks. Ideally, PEG should be performed in an operating room. In practice, however, most procedures are performed in the endoscopy room, with special precautions. The type of anesthesia used is decided according to the patient's medical condition and the anesthesiologist's preference. Intravenous sedation (IVS) can be used, but to assure better patient comfort during this complicated procedure, short-term deep sedation is preferred.

We conducted a retrospective study to discover whether there is a difference in the incidence of complication rate between patients who received PEG procedure with or without propofol-based sedation and to evaluate the safety of IVS when sedated by anesthetic personnel from the World Gastroenterology Organization (WGO) Endoscopy Training Center in Thailand.

2. Materials and Method

2.1. Patients. A total of 279 consecutive patients from Siriraj Hospital, Bangkok, Thailand who underwent PEG

procedures from August 2006 to January 2009 were eligible for the study. Of these, 198 patients underwent PEG procedures by using intravenous sedation (IVS). Inclusion criteria were age ≥18 and PEG procedures performed using IVS technique. Exclusion criteria were patients younger than 18 years, procedures performed in the intensive care units, procedures performed without sedation, or procedures performed under monitored anesthesia care and general anesthesia.

2.2. Study Design. This study is a retrospective descriptive study. All patients were classified into two groups according to the type of IVS technique. In group A, PEG was done by using propofol-based IVS technique. In group B, PEG was performed with non-propofol-based IVS technique. The primary outcome variable of the study was the overall complication rate during and immediately after procedure. The secondary outcome variables were sedation- and procedure related complications during and immediately after procedure and mortality rate.

2.3. Assessment of Complication Rate. After PEG procedure, all patients were observed in the recovery room at least two hours before discharged to ward. Additionally, all patients were admitted in the ward to rule out post-PEG complications at least one day after the procedure. We did not call each patient at the thirtieth day after the procedure. Overall complication rate in both groups was recorded. Additionally, sedation- and procedure related complication and mortality rate in the two groups were also assessed.

2.4. Sedation-Related Complications. All Sedation-related complications were recorded. Sedation-related complications were defined as follows: hypertension or hypotension (increase or decrease in blood pressure by 20% from baseline and above or below normal for age); tachycardia or bradycardia (increase or decrease in heart rate by 20% from baseline and above or below normal for age); any cardiac arrhythmias; hypoxia (oxygen desaturation, $SpO_2 < 90\%$); airway obstruction.

2.5. Procedure Related Complications. Procedure related complications during and early post procedure such as bleeding, laceration or puncture of visceral organs, and PEG-site infection were recorded. We did not assess the late complications.

2.6. Statistical Analysis. Results were expressed as mean ± SD or percentage (%), when appropriate. Comparisons between group A and B weredone by using Chi-square tests (for categorical variables), Chi-square tests for trend (for ordinal variables), and two-sample independent t-test (for continuous variables). The statistical software package SPSS for Window Version 11 (SPSS Inc., Chicago, IL) was used to analyze the data. All statistical comparisons were made at the two-sided 5% level of significance.

3. Results

Two hundred and seventy-nine PEG procedures were performed during the study period. Of these, 81 patients who underwent PEG procedure by using general anesthesia and monitored anesthesia care techniques were excluded. A total of 198 PEG procedures were performed by using IVS. Of these, 178 patients were classified in propofol-based sedation group and 20 patients were in non-propofol-based sedation group. After matching ASA physical status and the indications of procedure, there were 92 PEG procedures in group A and 20 PEG procedures in group B.

Table 1 showed the characteristics of patients, duration of sedation, and indications of procedure. There were no statistically significant differences in age, gender, weight, ASA physical status, sedation time, and indication of the procedure between the two groups.

Cardiovascular monitoring, including blood pressure measurements, electrocardiogram, heart rate, and oxygen saturation, was performed. No premedications were used before the procedure. All patients were oxygenated with 100% O_2 via nasal canular and sedated by well-trained anesthetic personnel directly supervised by a staff anesthesiologist in the endoscopy room. Anesthetic personnel included residents in anesthesiology and anesthetic nurses who were well trained in the use of IVS technique and airway management. All sedated patients were sedated in either moderate (conscious) or deep sedation level, according to guideline of the American Society of Anesthesiologists [5]. Subsequently, all cases were concluded with the satisfactory completion of the procedure.

Table 2 demonstrated overall complication rate, sedation and procedure related complication, anesthetic personnel, and mortality rate. Overall, 23 patients (25.0%) in group A and 4 patients (20.0%) in group B experienced adverse events. In group A, the respiratory adverse events occurred in 5.4% of patients and comprised 21.7% of all adverse events, and all of these were under the care of an anesthesiologist. Interestingly, there were no respiratory adverse events in group B. Cardiovascular adverse events arose in 18.5% and 20.0% of patients in group A and B, respectively. They mainly consisted of hypotension (16.3% in group A and 10.0% in group B). One patient in group B developed hypertension and tachycardia but none in group A. No procedures were aborted as a result of insufficient sedation or complications of sedation. In addition, only one patient in group A developed bleeding after the procedure. In both groups, IVS was mainly employed by the residents, and mortality rate was none. However, there were no significant differences in overall complication rate, sedation and procedure related complication, anesthetic personnel, and mortality rate between the two groups.

Table 3 showed the sedative agents used in both groups. Of these, fentanyl and midazolam were frequently used in both groups. Mean dose of fentanyl and midazolam in group A was significantly lower than in group B ($P = .012$ and $<.001$, resp.). However, there was not statistical difference in the mean dose of ketamine between the two groups ($P = .333$).

Table 1: Characteristics of patients, duration of sedation, and indications of procedure (mean, SD and percentage).

	Group A (N = 92)	Group B (N = 20)	P- value
Age (yr) (mean, SD)	70.3 (8.5)	75.2 (10.7)	.376
Gender (%): Male	43 (46.7)	9 (45.0)	.888
Female	49 (53.3)	11 (55.0)	
Weight (kg) (mean, SD)	49.6 (4.8)	48.1 (6.4)	.107
ASA physical status (%): I-II	26 (28.3)	5 (25.0)	.768
: III-IV	66 (71.7)	15 (75.0)	
Duration of sedation (min) (mean, SD)	25.3 (5.5)	27.3 (7.0)	.121
Indication			.980
Cerebro-vascular accident	29 (31.5)	7 (35.0)	
Dementia	22 (23.9)	5 (25.0)	
Oral, larynx and esophageal malignancy	16 (17.4)	3 (15.0)	
Prolonged nasogastric tube insertion	8 (8.7)	1 (5.0)	
Others	17 (18.5)	4 (20.0)	

Group A: propofol-based; Group B: non- propofol based.

Table 2: Overall complication rate, sedation and procedure related complication, anesthetic personnel, and mortality rate (n, %).

	Group A (N = 92)	Group B (N = 20)	P-value
Overall complication rate	23 (25.0)	4 (20.0)	.636
Sedation-related complication			
Respiratory system	5 (5.4)	0	.286
Hypoxia	2 (2.2)	0	.506
Upper airway obstruction	3 (3.3)	0	.413
Cardiovascular system	17 (18.5)	4 (20.0)	.874
Hypotension	15 (16.3)	2 (10.0)	.476
Hypertension	0	1 (5.0)	.031*
Bradycardia	2 (2.2)	0	.506
Tachycardia	0	1 (5.0)	.031*
Procedure related complication			
Bleeding	1 (1.1)	0	.640
Anesthetic personnel			.986
Residents	55 (59.8)	12 (60.0)	
Anesthetic nurses	37 (40.2)	8 (40.0)	
Mortality rate	0	0	1.000

Group A: propofol-based; Group B: non-propofol based.
*Considered statistically significant.

Hemodynamic parameters including systolic and diastolic blood pressure, heart rate, and oxygen saturation were demonstrated in Table 4. There were not significant differences between the groups in hemodynamic parameters at baseline, insertion of endoscope, and at 15, 25, and 30 minutes after scope insertion. However, mean systolic blood pressure at 5 and 10 minutes after scope insertion, as well as mean diastolic blood pressure at 5 and 20 minutes, after scope insertion in the propofol-based group was significantly lower than in the non-propofol-based group. In addition, mean heart rate at 20 minutes after scope insertion in the non-propofol-based group was significantly higher than in the propofol-based group. Oxygen saturation in both groups was over 99% through out the study period.

4. Discussion

PEG has rapidly replaced surgical gastrostomy as the procedure of choice in virtual patients requiring long-term enteral nutrition. Increasing numbers of patients are being referred for PEG placement. PEG can be inserted in the operating room, endoscopy suite, or at the bedside using IVS. The overall success rate for PEG placement is rather consistent at 95% to 98% in all studies, regardless of technique [6–8]. Procedure-related complications are infrequent (1.5% to

Table 3: Sedative agents used in both groups.

	Group A (N = 92)	Group B (N = 20)	P-value
Propofol (mg/kg)			
N (%)	92 (100.0)	0	
Mean (SD)	0.90 (0.20)		
Fentanyl (mcg/kg)			
N (%)	81 (88.0)	20 (100.0)	
Mean (SD)	0.65 (0.19)	0.83 (0.23)	.018*
Midazolam (mg/kg)			
N (%)	74 (80.4)	18 (90.0)	
Mean (SD)	0.02 (0.01)	0.03 (0.01)	< .001*
Ketamine (mg/kg)			
N (%)	6 (6.5)	2 (10.0)	
Mean (SD)	0.54 (0.11)	0.79 (0.13)	.333

Group A: propofol-based; Group B: non- propofol-based.
*Considered statistically significant.

Table 4: Hemodynamic parameters: systolic and diastolic blood pressure (mmHg), heart rate (beat/minute) and oxygen saturation (SpO_2, %) (mean, SD).

	Group A (N = 92)	Group B (N = 20)	P-value
Baseline			
SBP, DBP	137.3 (18.9), 76.6 (14.1)	139.1 (19.3), 84.6 (11.4)	.099, .585
HR, SpO_2	73.1 (11.3), 99.3 (1.0)	79.3 (11.0), 99.8 (0.5)	.502, .267
At insertion			
SBP, DBP	119.3 (18.9), 67.7 (12.8)	124.2 (21.6), 78.5 (15.7)	.075, .436
HR, SpO_2	70.3 (10.4), 99.8 (0.7)	76.2 (10.9), 100.0 (0.0)	.068, .618
5 minutes after insertion			
SBP, DBP	113.1 (13.5), 68.1 (12.6)	122.5 (26.3), 76.3 (16.6)	.039*, .026*
HR, SpO_2	69.5 (11.1), 99.9 (0.6)	71.1 (16.9), 99.9 (0.2)	.226, .887
10 minutes after insertion			
SBP, DBP	107.9 (10.4), 67.7 (11.7)	121.4 (27.2), 75.1 (17.9)	.035*, .476
HR, SpO_2	69.2 (11.7), 99.9 (0.6)	75.3 (9.8), 99.9 (0.2)	.281, .902
15 minutes after insertion			
SBP, DBP	109.9 (10.2), 68.5 (10.4)	119.9 (22.4), 74.6 (13.1)	.107, .306
HR, SpO_2	70.7 (11.4), 99.9 (0.6)	74.1 (10.7), 100.0 (0.0)	.473, .699
20 minutes after insertion			
SBP, DBP	110.7 (11.7), 66.5 (11.9)	125.7 (20.2), 78.3 (10.7)	.091, .024*
HR, SpO_2	70.2 (11.5), 99.9 (0.6)	73.7 (10.0), 100.0 (0.0)	.031*, .817
25 minutes after insertion			
SBP, DBP	110.1 (10.6), 70.1 (11.3)	125.2 (18.4), 79.0 (13.4)	.097, .297
HR, SpO_2	70.7 (12.7), 99.8 (0.9)	76.5 (7.6), 100.0 (0.0)	.352, .751
30 minutes after insertion			
SBP, DBP	111.9 (10.2), 72.3 (9.4)	117.5 (13.3), 78.3 (7.1)	.516, .220
HR, SpO_2	69.8 (14.0), 99.9 (0.3)	72.3 (5.4), 99.8 (0.5)	.394, .531

Group A: propofol-based; Group B: non-propofol based.
SBP: systolic blood pressure; DBP: Diastolic blood pressure; HR: heart rate; SpO_2: oxygen saturation.
*Considered statistically significant.

4.0%) [9, 10]. However, cardiovascular complications related to sedation/analgesia are the most frequent complications of diagnostic endoscopy and PEG procedure [11–13].

Our study showed that the rate of complication during PEG procedure with or without propofol-based sedation was comparable to our previous reports [12, 13]. In addition, the propofol-based sedation does not increase the complication rate in comparison to the non-propofol-based sedation ($P = .636$). However, the complication rate in this present study is markedly higher than the published study [11]. One possible explanation of this finding is that the number of PEGs underwent IVS technique has remarkably increased over the last few years. The depth of sedation in our report was moderate to deep level. Additionally, this study collected only PEG procedures by using IVS technique. In that published study [11], upper and lower gastrointestinal endoscopy procedures done with conscious (moderate) sedation technique were included the sedation-related complication rate was 0.54%. However, the previous series did not mention about the frequently used propofol-based sedation technique. The result of our study also demonstrated that the complication rate would be correlated to the depth of sedation directly. Moreover, the results of other studies [14–17] also confirmed that patients could withstand PEG procedure without sedation, and the rate of complication was fairly low in this technique.

PEG procedure is a minimally invasive one, with low procedure-related major complications and mortality rates [10, 18–20]. It is an essential procedure among GI abnormality treatments, even in our institution, where we observe an increase in number of these procedures every year. Therefore, it is mandatory to standardize a safe, easy, well-tolerated anesthesiological procedure, which is feasible in the GI endoscopy unit. In our previous experiences, we have noted that topical anesthesia alone is not sufficient for pain-free procedures. In contrast, general anesthesia, which may be of benefit for the patient and endoscopist comforts, may be difficult to administer, especially in comorbidity patients. In addition, the lack of experience in anesthesia care among endoscopy personnel might increase the risk of complications.

Propofol, combined with short-acting benzodiazepine, with or without fentanyl, has already been used in several GI endoscopic procedures. The present study shows that sedation with or without propofol is safe and well tolerated by the patient. Furthermore, it is well accepted by endoscopists. No patients enrolled in the study needed to be resuscitated during PEG procedure. All patients could be discharged to the ward within 30 minutes from the end of this procedure, and this discharge time was not correlated with age, ASA physical status, and total sedative doses.

Patients were breathing spontaneously; however, oxygen saturation was always over 99%, and age, ASA physical status, and the combination of sedative agents did not negatively influence this parameter. Sedation is performed to ensure the patient's safety, to minimize physical discomfort or pain, to provide analgesia and procedural amnesia, to control behavior during the procedure and to return the patient to pretreatment level of consciousness. The amount of sedation required depends on the patient's physical status and age. Propofol is widely employed for anesthesia outside the OR because it is easy to use, has a good safety and efficacy profile due to its quick onset of action, rapid metabolism, and significantly shorter recovery time, and has some antiemetic effects [21–23]. Low-dose of midazolam as well as ketamine, combined with low dose fentanyl and/or propofol, did not prolong recovery time. Additionally, ketamine in the company of these agents did not produce emergence reactions or hallucinations.

The present study used only standard monitoring, including an assessment of blood pressure, pulse rate, respiratory rate and pulse oximetry, as well as electrocardiogram. We detected a relatively high overall rate of adverse events in both groups. This rate is higher than that commonly reported, and there may be several explanations. We used these criteria in defining adverse events: hypo/hypertension and brady/tachycardia measured as the changes of blood pressure and heart rate of more than 20% of baseline values. Hypoxia was defined as oxygen saturation <90%. Hypercapnia ($ETCO_2 > 50$ mmHg) could not be detected directly in this study. Moreover, if only serious adverse events are included, the adverse event rate is 2.2% in the propofol-based group and none in the non-propofol-based group. Interestingly, we found that all respiratory-related adverse events occurred in the propofol-based group.

In a previous study [24], 151 high risk patients underwent PEGs (126), and direct jejunostomies (PEJs, 25) were sedated by the use of anesthesiologist-administered propofol. Minor complications occurred in 25 patients (16.6%): 13 patients (8.6%) fevers, 12 patients (7.9%) systolic blood pressure drops of >25%, and 1 patient (0.6%) oxygen desaturation <90%. Major complications occurred in 4 patients (2.6%): 3 patients (2%) aspiration pneumonias and one patient death (0.6%). We believe that the appropriate selection of patients for sedation is very important for everyday practice and will most likely reduce the rate of adverse events. Finally, the use of pulse oximetry to monitor hypoxemia is important, especially in cases when supplemental oxygen is administered.

Data from our previous study [25] showed that satisfaction of both patient and endoscopist about sedated patients was higher than in nonsedated patients. The use of sedation was the major determinant of patient satisfaction and willingness to repeat. Among all of these benefits, it is advantageous to identify the particular factors that might encourage patients to undergo PEG procedure with sedation. Moreover, the present study showed that PEG procedures can be performed safely and effectively with a lower complication rate under propofol-based sedation. Additionally, our recent report [12] also shows that the PEG procedure done with sedation by well-trained anesthetic personnel is as safe and effective as that done with general anesthesia. In our hospital, IVS technique was extensively used for PEG procedures. However, this is not widespread in the district community hospitals.

Limitations of this study exist. First, there is the wide range in age of the patients in our study. Drug requirements and adverse events can be related to patient's age. Second,

inaccurate and incomplete documentation of certain measures, as occured with many chart reviews, also occurred in this study. Third, the limitation of monitoring, such as of end-tidal carbon dioxide, could result in a lower rate of adverse events. Overall, despite these limitations, we are, however, confident that these findings are generalizable to the practice of PEG procedure using any type of sedation. Finally, because the serious complications in our series were low, further studies in larger prospective groups of patients are therefore needed.

In conclusion, we report the performance of the clinical efficacy of sedation with or without propofol regimen utilizing anesthesiologist or anesthetic personnel with appropriate basic monitoring for PEG procedure in a unit outside OR from a tertiary-care teaching hospital in Thailand. The findings of the present study show that propofol-based sedation does not increase rate of complication during PEG procedure. IVS of PEG procedure is relatively safe and effective when performed by physicians in training. Serious complications are none. We hope that our practice will help modeling the development of IVS for PEG procedure in the community hospitals in Thailand.

Disclosures

The authors declare that they have no competing interests.

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Review Article

The Use of Green Coffee Extract as a Weight Loss Supplement: A Systematic Review and Meta-Analysis of Randomised Clinical Trials

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The purpose of this paper is to assess the efficacy of green coffee extract (GCE) as a weight loss supplement, using data from human clinical trials. Electronic and nonelectronic searches were conducted to identify relevant articles, with no restrictions in time or language. Two independent reviewers extracted the data and assessed the methodological quality of included studies. Five eligible trials were identified, and three of these were included. All studies were associated with a high risk of bias. The meta-analytic result reveals a significant difference in body weight in GCE compared with placebo (mean difference: −2.47 kg; 95%CI: −4.23, −0.72). The magnitude of the effect is moderate, and there is significant heterogeneity amongst the studies. It is concluded that the results from these trials are promising, but the studies are all of poor methodological quality. More rigorous trials are needed to assess the usefulness of GCE as a weight loss tool.

1. Introduction

Overweight and obesity have become a serious health concern [1]. Different weight management strategies are presently utilised, and a variety of weight loss supplements sold as "slimming aids" are readily available. However, the efficacy of some of these food supplements remains uncertain. One such supplement is the green coffee extract (GCE).

GCE is present in green or raw coffee [2]. It is also present in roasted coffee, but much of the GCE is destroyed during the roasting process. Some GCE constituents, such as chlorogenic acid (CGA) can also be found in a variety of fruits and vegetables [3]. The daily intake of CGA in persons drinking coffee varies from 0.5 to 1 g [4]. The traditional method of extraction of GCE from green coffee bean, *Coffea canephora robusta*, involves the use of alcohol as a solvent [5]. Extracted GCE is marketed as a weight loss supplement under a variety of brand names as a weight loss supplement such as "Coffee Slender", and "Svetol".

Evidence is accumulating from animal studies regarding the use of GCE as a weight loss supplement [6, 7]. In human subjects, coffee intake has been reported to be inversely associated with weight gain [8]. Consumption of coffee has also been shown to produce changes in several glycaemic markers in older adults [9]. Similarly, other research has indicated that the consumption of caffeinated coffee can lead to some reductions in long-term weight gain, an effect which is likely to be due to the known thermogenic effects of caffeine intake as well as effects of GCE and other pharmacologically active substances present in coffee [10]. GCE has also been postulated to modify hormone secretion and glucose tolerance in humans [11]. This effect is accomplished by facilitating the absorption of glucose from the distal, rather than the proximal part of the gastrointestinal tract.

The objective of this paper is to analyse the results of human clinical trials assessing the efficacy of GCE as a weight-reducing agent.

2. Methods

Electronic searches of the literature were conducted for the following databases: MEDLINE, EMBASE, CINAHL, AMED, and *The Cochrane Library*. Each database was searched from inception up until April, 2010. Search terms used included coffee, green coffee, green coffee extract, roasted coffee, decaffeinated coffee, chlorogenic acid, caffeoylquinic acid, antiobesity agent, appetite suppressant, abdominal fat, BMI, body mass index, body fat, body weight, overweight, over weight, corpulen*, obes*, weight loss, weight decrease, weight watch, weight cycle, weight control, weight gain, weight maintenance, weight reduction, weight change, dietary supplement, food supplement, nutraceutical, nutri*supplement, over-the-counter OR OTC, nonprescription drugs, randomised controlled trial, clinical trial, and placebo. We also searched other internet databases for relevant conference proceedings, as well as our own files. Hand searches of the bibliography of retrieved full texts were also conducted.

Only randomised, double-blind, and placebo-controlled studies were included in this paper. To be considered for inclusion, studies had to test the efficacy of GCE for weight reduction in obese or overweight humans. Included studies also had to report body weight and/or body mass index (BMI) as an outcome. No age, time, or language restrictions were imposed for inclusion of studies. Studies which involved the use of GCE as part of a combination treatment or not involving obese or overweight subjects were excluded from this paper.

Two independent reviewers assessed the eligibility of studies to be included in the paper. Data were extracted systematically by two independent reviewers according to the patient characteristics, interventions, and results. The methodological quality of all included studies was assessed by the use of a quality assessment checklist adapted from the consolidated standard of reporting trials (CONSORT) guidelines [12, 13]. Disagreements were resolved through discussion with the third author.

Data are presented as means with standard deviations. Mean changes in body weight were used as common endpoints to assess the differences between GCE and placebo groups. Using the standard meta-analysis software [14], we calculated mean differences (MD) and 95% confidence intervals (CI). The I^2 statistic was used to assess for statistical heterogeneity amongst studies.

3. Results

Our searches produced 2160 "hits". 328 articles were excluded because they were duplicate citations, while 767 articles were excluded because of wrong titles and abstracts. Another 598 articles were excluded because they did not investigate a food supplements, and 454 articles excluded due to no report on clinical outcome. A further 13 articles were excluded due to unsuitable study design. Thus, 5 potentially relevant articles were identified (Figure 1). One trial was excluded because it involved only normal weight individuals, and did not measure weight as an outcome [15]. Another trial was excluded because it was not randomised [16]. In effect, 3 randomised clinical trials (RCTs) including a total of 142 participants met our inclusion criteria, and were included in this systematic paper [5, 17, 18]. Their key details are summarized in Tables 1 and 2.

A forest plot (random-effect model) for the three trials is shown in figure 2. The meta-analysis reveals a statistically significant difference in body weight between GCE and placebo (MD: -2.47 kg; 95% CI: $-4.23, -0.72$). The I^2 statistic of 97% suggests that there is considerable heterogeneity amongst the studies. A further plot of two trials which involved CGA-enriched GCE revealed a statistically nonsignificant difference in body weight between GCE and placebo (MD: -1.92 kg; 95% CI: -5.40, 1.56). Heterogeneity was also considerable in this analysis (I^2 statistic of 99%). One of the studies reported a statistically significant decrease in the percentage of body fat in the GCE group compared with baseline, but no significant difference in the placebo group [5]. There was no mention of intergroup differences regarding the percentage of body fat. None of the trials reported any adverse events associated with the use of GCE.

4. Discussion

The main purpose of this systematic paper was to assess the efficacy of GCE as a weight loss supplement. The overall meta-analysis revealed a significant difference in change in body weight between GCE and placebo. The magnitude of this significance is moderate, and the clinical relevance is therefore not certain. There is also considerable heterogeneity amongst the three trials.

In animals, GCE has been reported to influence postprandrial glucose concentration and blood lipid concentration [5]. This is thought to be via reduction in the absorption of glucose in the intestine; a mechanism achieved by promoting dispersal of the Na^+ electrochemical gradient. This dispersal leads to an influx of glucose into the enterocytes [19]. GCE is also thought to inhibit the enzymatic activity of hepatic glucose-6-phosphatase, which is involved in the homeostasis of glucose [20]. Reports from animal studies have suggested that GCE mediates its antiobesity effect possibly by suppressing the accumulation of hepatic triglycerides [6]. Some authors have also posited that the antiobesity effect of GCE may be mediated via alteration of plasma adipokine level and body fat distribution and downregulating fatty acid and cholesterol biosynthesis, whereas upregulating fatty acid oxidation and peroxisome proliferator-activated receptor alpha (PPARα) expression in the liver [7].

Diets rich in polyphenols may help to prevent various kinds of diseases associated with oxidative stress, including coronary heart disease and some forms of cancer [21, 22]. GCE has been reported to have antioxidant activity, demonstrated by its ability to scavenge free radicals *in vitro*, and to increase the antioxidant capacity of plasma *in vivo* [16, 23]. There is also evidence that certain dietary phenols, including GCE, may modify intestinal glucose uptake in a

Table 1: Methodological characteristics of included studies.

Author Year Country	Main outcome (s)	Main diagnoses of study participants	Study design	Gender M/F	Randomisation appropriate?	Allocation concealed?	Groups similar at baseline?	Similar follow-up of groups?	Outcome assessor blinded?	Care provider blinded?	Patients blinded?	Attrition bias?	ITT analysis?
*Ayton Research 2009 United Kingdom	Body weight, waist, bust and hip circumference	Healthy overweight subjects	Parallel	Unclear	?	?	+	+	?	?	?	?	?
Thom 2007 Norway	Body weight, body mass index	Slight to moderately overweight subjects	Parallel	12/18	?	?	+	+	?	?	?	–	–
Dellalibera 1998 France	Body weight, body mass index	Overweight volunteers	Parallel	Unclear	?	?	+	+	?	?	?	–	–

Abbreviation: ITT (intention-to-treat); M/F: Males/Females.
Symbols: *: Unpublished study, +: Yes, –: No, ?: Unclear.

Table 2: Main results of included RCTs[1].

Author Year	GCE specification	No. of participants randomised	Age in yrs; Sex: M/F	Body weight at baseline	Dosage of GCE	Treatment duration	Main results; reported as means with standard deviations	Adverse events	Control for lifestyle factors
Ayton Res. 2009 (unpublished)	CGA enriched green coffee	62	Not reported	76.65 ± 7.25 kg (GCE) 77.44 ± 12.93 kg (PLA)	180 mg daily	4 weeks	Weight loss was 1.35 ± 0.81 kg and 0.12 ± 0.27 kg for GCE and PLA respectively	Not reported	Normal lifestyle
Thom 2007	CGA enriched green coffee	30	Not reported 12/18	85.2 ± 4.5 kg (GCE) 84.3 ± 4.3 kg (PLA)	200 mg daily	12 weeks	Mean weight loss was 5.4 ± 0.6 kg (GCE) and 1.7 ± 0.9 kg (PLA). Mean fat loss was 3.6 ± 0.3% (GCE) and 0.7 ± 0.4% (PLA)	No adverse events	Regular diet, normal level of exercise
Dellalibera 2007	Green coffee extract	50	Range: 19–75	Not reported	200 mg daily	12 weeks	[2] Mean weight loss was 4.97 ± 0.32 kg and 2.45 ± 0.37 kg for GCE and PLA, respectively	Not reported	Not reported

Abbreviation: PLA: placebo
[1] Unless otherwise specified, values are reported as means with standard deviations.
[2] Values reported as means with standard errors.

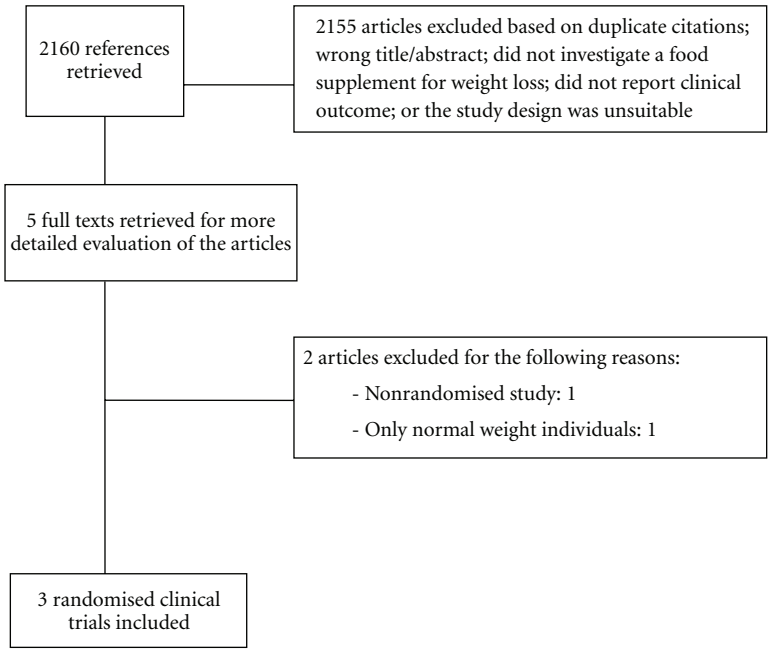

Figure 1: Flow chart for inclusion of randomised clinical trials.

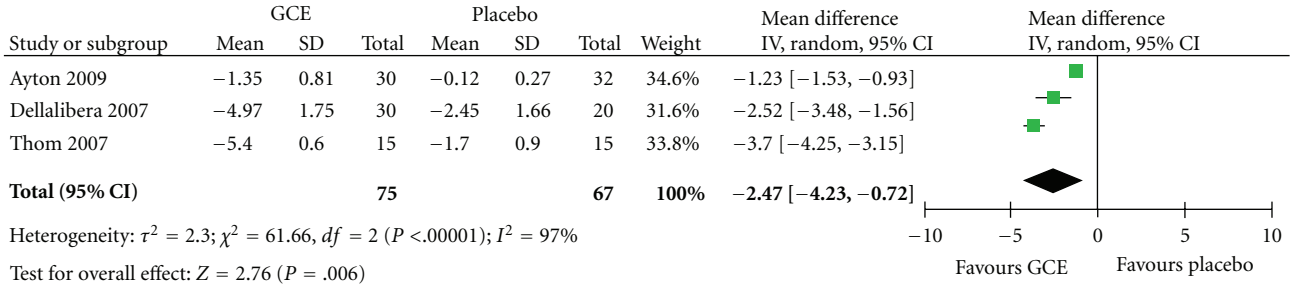

Figure 2: Forest plot showing the effect of GCE on body weight.

number of ways [8, 24]. This activity might provide a basis for explaining its effects on body weight. The purported slimming effect of GCE would have a protective effect against diabetes mellitus, via changes in gastrointestinal hormone secretion [10]. A few questions, however, arise from the RCTs which involve the use of GCE as a weight loss aid.

All the RCTs involving the use of GCE which have been conducted so far have very small sample sizes, with the largest number of participants being 62 in one trial [17]. These small sample sizes increase the possibility of spurious or false positive results. Two of the RCTs were unclear about drop-outs of participants from the trial; neither did they report on intention-to-treat analysis [17, 18]. All of the trials so far identified have been of very short duration. This makes it difficult to assess the efficacy and safety of GCE as a weight reduction agent on the medium to long-term. Although none of the RCTs identified reported any adverse events, this does not indicate that GCE intake is "risk-free". Two participants in a study report dropped out due to adverse events associated with the intake of GCE [16]. These included headache and urinary tract infection. Thus, the safety of this weight loss aid is not established.

The effective dosage of GCE for use as a weight loss supplement is also not established. The dosages of GCE reported in most of the human trials identified were estimated, as the GCE was a component of coffee. While 2 of the RCTs identified enriched their GCE with CGA [5, 17], the third trial did not report that the GCE used was fortified with CGA [18]. This warrants further investigation.

The RCTs identified from our searches were not also clear on blinding issues. None of the RCTs reported on how randomisation was carried out, and none provided information regarding blinding of outcome assessors. This casts doubt on the internal validity of these trials. Future trials involving the use of GCE as a weight loss supplement should be conducted in line with the CONSORT guidelines. This will ensure the validity and applicability of study results. Two authors in one study were affiliated to a company which markets Svetol [18] but did not specify whether or not they had any conflicts of interest.

This systematic review has several limitations. Though our search strategy involved both electronic and nonelectronic studies, we may not have identified all the available trials involving the use of GCE as a weight loss supplement. Furthermore, the methodological quality of the studies identified from our searches is poor, and all are of short duration. These factors prevent us from drawing firm conclusions about the effects of GCE on body weight.

5. Conclusion

The evidence from RCTs seems to indicate that the intake of GCE can promote weight loss. However, several caveats exist. The size of the effect is small, and the clinical relevance of this effect is uncertain. More rigorous trials with longer duration are needed to assess the efficacy and safety of GCE as a weight loss supplement.

Conflict of Interests

I. Onakpoya is funded by a grant from GlaxoSmithKline. The funder had no role in the preparation of the paper. R. Terry and E. Ernst declare no potential conflict of interests.

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Review Article

Why and How Meet n-3 PUFA Dietary Recommendations?

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Obesity and the metabolic syndrome are systemic inflammatory diseases reaching epidemic proportions. Contemporary changes in human nutrition occurred characterized by increased consumption of fat and of vegetable oils rich in n-6 polyunsaturated fatty acids (PUFAs) together with decrease in n-3 PUFA-rich foods, resulting in an n-6/n-3 ratio of 10–20/1 in Western diet for a ratio around 1/1 in the diet of our ancestors. The literature provides compelling evidence for the health benefit of n-3 PUFA consumption on inflammation and metabolic syndrome prevention and treatment. Such evidence led to the establishment of comprehensive recommendations. However, we show here that, both in collective catering proposed to children and in hospital diet, it is not straightforward to meet such recommendations. Willingness of governments to institute changes, with accountable decisions on catering, nutritional education, and food processing, is required to face our neglected responsibility in promoting balanced diet and consumption of foods rich in essential nutrients in the general population.

1. Introduction

The metabolic syndrome (MetS) is defined as a cluster of symptoms such as visceral obesity, insulin resistance, elevated blood pressure, and dyslipidemia, associated with increased risk of type 2 diabetes, cardiovascular disease [1], nonalcoholic fatty liver diseases (NAFLD) [2], and some types of cancers [3]. This pathological condition is currently reaching epidemic proportions (Figure 1) and may soon represent the first health issue worldwide in terms of costs and mortality, even in developing countries. Although multifactorial processes participating are yet to be unraveled, there is a general agreement that the rising prevalence of MetS is largely due to the increasing incidence of adiposity [4]. Obesity, and in particular abdominal obesity or visceral fat, as well as the MetS has been identified as low-grade and systemic inflammatory conditions [5, 6], with an imbalance between pro- and anti-inflammatory molecules and elevated serum markers of inflammation [7]. Increased macrophage infiltration in adipose tissue and possibly liver [8, 9], as well as recruitment of lymphocytes [10] is recognized causes of inflammation and insulin resistance in this context.

During the past 15 years, research efforts have focused on the primary factors responsible for the MetS and its increasing prevalence worldwide. Contemporary to the rise in MetS prevalence, important changes in human nutrition and dietary habits were observed (Figures 1 and 2) in parallel with the adoption of a more sedentary life style, owing to industrialization and drastic changes in strategies for communication, crystallized under the emblematic so-called "occidental way of life". Consequently, this has resulted in a disruption of the balance between energy intake and consumption/expenditure, as well as relative excess/deficiency in some metabolically relevant nutrients. Such modifications are thought to be part of the MetS epidemic.

In particular, a steady increase in dietary refined sugar and fructose, that parallels the rise in obesity and diabetes, is observed since the 70s due to the increased consumption of soda, soft drinks, and manufactured candy and pastry [11] and use of enriched (high) fructose corn syrup as sweetening agent (Figure 1) [11, 12, 14]. Concomitantly, the rate of fatty acid (FA) consumption has increased. Indeed, in today's diet, FA represents 28%–42% of total energy consumed by European populations [15], affording 128 g/d in developed

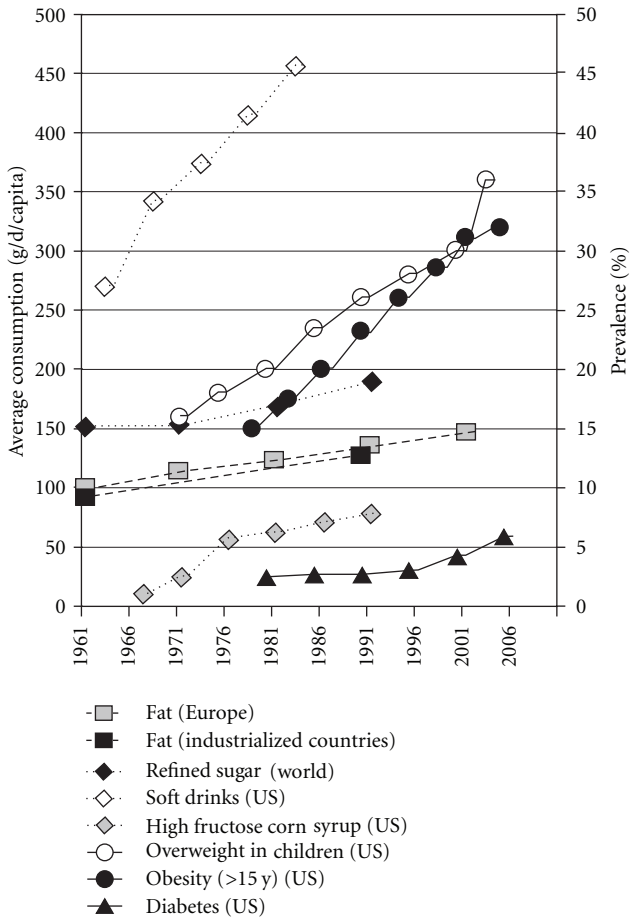

Figure 1: Evolution of Occidental dietary content in specific macronutrients and prevalence of obesity and diabetes in United States. Compiled from [11–13]; FAO, AGROSTAT.PC, 1993; Centers for Disease Control and Prevention, National Center for Health Statistics, Division of Health Interview Statistics, data from the National Health Interview Survey; French National Epidemiological Study on Overweight and Obesity: ObEpi-Roche 2009.

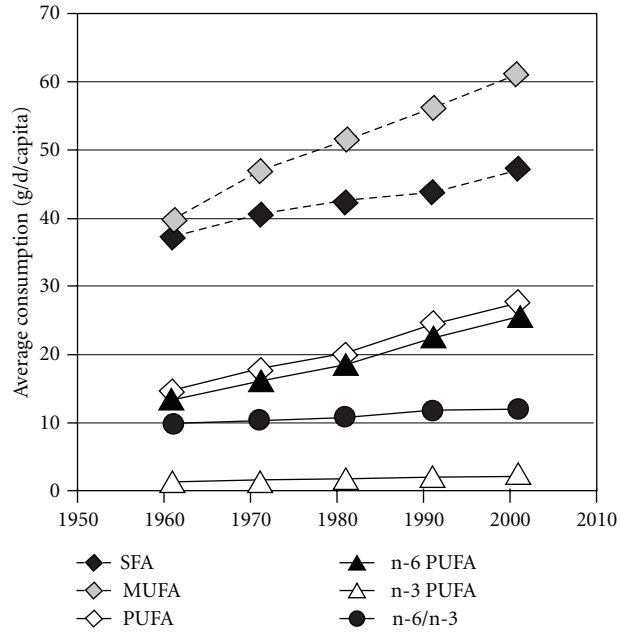

Figure 2: Evolution of fatty acids consumption in European Union. Adapted from [13].

countries in 1990, while in 1961 it was estimated to 93 g/d [16]. In ancestral nutrition, FA consumption was approximated around 20%–30% of energy intake [17, 18]. Also, qualitative changes in the type of FA taken in have occurred over the past 50 years, as depicted in Figure 2 for European populations [13]. These changes are characterized by increased consumption of saturated fat (especially from meat), vegetable oils rich in linoleic acid (LA, n-6 PUFA) on the one hand, and an overall decrease in n-3 PUFA intakes relative to n-6 PUFA on the other hand [19]. This was mainly attributable to insufficient consumption of fatty fish [20], reduced nuts, seeds, and whole-grain cereals in alimentation [21] and a progressive preferential use of safflower oil, poor in n-3 PUFA. Importantly, marine fish and especially fatty ones are the most important source of n-3 PUFA in the Occident. Aside from marine alga and newly engineered oils and supplements [20, 22], marine fish represent the only natural edible source of long-chain (LC) n-3 PUFA eicosapentaenoic and docosahexaenoic acids (EPA and DHA), the most biologically active n-3 PUFA [23]. In Occidentalized countries, fish consumption is very variable and globally low [24, 25]. Intensive farming could also be an additional factor contributing to insufficient n-3 PUFA consumption as n-3 PUFA content in some species of farmed fish, as rainbow trout [26], bream [27], salmon coho, or catfish [28], are reduced compared to their wild counterparts. As a result, n-6 PUFA consumption has become progressively much higher than that of n-3 PUFA [29], so that Western diets have a n-6/n-3 ratio ranging from 10/1 to 20/1 for a ratio of 1/1 in the diet of our ancestors [17, 30].

2. Metabolic Consequences of Altered Fatty Acid Nutritional Intakes

A body of epidemiological evidence highlights that high consumption of saturated FAs and trans-FAs may have adverse effects on lipid and glucose homeostasis and evolution towards the MetS [31]. The mechanisms involved are (i) the accumulation of toxic diacylglycerol and ceramides, (ii) the activation of nuclear factor-κB, protein kinase C, and mitogen-activated protein kinases which induce the expression of inflammatory genes in adipose tissue and immune cells, (iii) the decrease of peroxisome proliferator-activated receptor (PPAR) α and adiponectin levels and consequent decreased oxidation of FA and glucose, and (iv) recruitment of immune cells in adipose tissue and muscle [32].

The recent literature provides convincing evidence of the detrimental role of low dietary n-3 PUFA for the MetS and the cardiovascular risk. It has been shown that n-3 PUFA in muscle membrane phospholipids are inversely related to

insulin resistance, whereas the amount of LA (n-6 PUFA) incorporation into membrane phospholipids is positively related to insulin resistance. The links between n-3 PUFA and MetS is confirmed in many studies conducted independently around the world. For example, in The Multiple Risk Factor Intervention Trial involving 6,250 middle-aged American men determined to be at high risk of coronary heart diseases, evaluation using four annual dietary recall interviews showed that low n-3 PUFA consumption was associated with increased mortality. On the contrary, no significant association with mortality was detected for LA (n-6), which was the predominant dietary PUFA [33]. A study by Delavar et al. involving 984 random sampled Iranian women (30–50 y) suggests that a diet that lacks n-3 PUFA and vitamins-rich foodstuffs such as fish, vegetables, and nuts, increases the likelihood of having MetS [34]. Similarly, in France, low consumption of fish, and thus of n-3 PUFA, is associated with a higher probability of MetS, as assessed on 912 men (45–64 y) [21].

Distinct beneficial effects of fish (LC n-3 PUFA) consumption have been reported on insulin sensitivity, type 2 diabetes mellitus (T2DM), lipid profile, and risk for death from coronary heart diseases in healthy individuals [35–38] or of α-linolenic acid (ALA) intake on reduced risk of myocardial infarction [39]. Total n-3 PUFA supplies were also associated with higher levels of anti-inflammatory markers (soluble IL-6r, IL-10, TGFβ) in healthy adults [40]. Together, all those observations support that dietary n-3 PUFA may specifically influence the development of insulin resistance and progression of the MetS, and associated cardiovascular risk.

3. Metabolism of n-3 PUFA

FAs, whether saturated, mono- (MUFA) or polyunsaturated, are oxidized in the mitochondria and represent the most energetic substrates of the diet. They are incorporated into phospholipids as the major components of cellular membranes or packaged into triglycerides for storage and export. The essential PUFA of the n-3 series (EPA and DHA, found in fish oil and ALA, precursor of EPA and DHA, found in nut, soy, and rapeseed oils) and of the n-6 series (arachidonic acid -AA- and LA found in sunflower and nut oils) are precursors for different signaling molecules. Initial steps in their metabolism are desaturations catalyzed by rate-limiting Δ6 and Δ5 desaturases (Figure 3). In humans, Δ5 and Δ6 desaturase activities, and thereby the conversion rate of ALA to EPA/DHA, are low and can further be modulated by genetic and epigenetic factors and dietary co-factors, including magnesium, zinc, and vitamin B6 [44, 45]. Therefore, exogenous sources of EPA/DHA are important as they generate the most potent n-3 PUFA-derived protective mediators [23].

Site-specific oxygenation by cyclooxygenases (COX) and lipoxygenases (LOX) produces different signaling molecules among which are eicosanoids, comprising prostaglandins (PGs), thromboxanes, and leukotrienes (LTs) (see Figure 3) [41–43]. While n-6 PUFA are substrates for synthesis of proinflammatory eicosanoids (series 2 prostanoids and series 4 LT), n-3 PUFA metabolism rather yields less or anti-inflammatory eicosanoids amongst them series 3 prostanoids and series 5 LT [46]. Some of these LC metabolites (EPA, DHA, PGI3, PGE1, and PGI2) may serve as endogenous inhibitors of the angiotensin converting enzyme and HMG-CoA reductase and as nitric oxide enhancers to produce antihypertensive, anti-inflammatory, and antiatherosclerotic effects by acting on vascular cells, leukocytes, and platelets [47] and function as signaling molecules via activation of peroxisome proliferator-activated receptor (PPAR) transcription factors regulating lipid metabolism [48]. There is also increasing evidence that n-3 PUFA directly protect against cellular aging and age-related diseases [49], possibly through reduction of telomeres shortening in leukocytes from patients with coronary heart disease [50]. Recently, classes of autacoids as the E- and D-series resolvins, protectins, and maresin 1 derived from LC n-3 PUFA as well as lipoxins derived from LC n-6 PUFA have been identified as specialized mediators that stimulate host defense and dampen inflammation, prevent platelet aggregation, lower blood pressure, have antiarrhythmic action, reduce LDL cholesterol, activate telomerase, and have cytoprotective properties [36, 43, 46]. Whereas some of the effects of PUFA are undoubtedly mediated by eicosanoids, the PUFA-mediated suppression of lipogenic and glycolytic genes is independent of eicosanoid synthesis and appears to involve a nuclear mechanism directly modified by PUFA [51]. Thus, n-3 PUFA mediate anti-inflammatory, anti-steatosis, and vascular protective effects through several mechanisms, including modifications in cell membrane composition and function, gene expression modulation, or distinct eicosanoids production.

Importantly, genetic polymorphisms in Δ5 and Δ6 desaturase-encoding genes (FADS1 and FADS2) are associated with variation in n-6 and n-3 PUFA content in serum phospholipid fractions and tissues [52]. Also, polymorphisms altering activity of FADS1/2 [52], LOX5 [53], and COX2 [54] genes products have been related to increased deleterious effects of n-6 PUFA, which were blunted by increasing n-3 PUFA consumption. Acquired modifications in enzymatic machinery metabolizing PUFA have been described in association with obesity, insulin resistance, and cancer [48, 54]. High-energy diet, SFA, and transfats during perinatal period have been shown to repress the expression of Δ5 and Δ6 desaturases in both maternal and fetal tissues and influence PUFA metabolism in adulthood, representing an additional mechanism for decreased tissue and membrane LC n-3 PUFA [55]. Interestingly, relevant to the characterized consequences of diet for epigenetics [56], Devlin et al. reported hypermethylation of FADS 2 gene promoter associated to decreased Δ6 desaturase activity and DHA levels in the liver in a nutritional model of hyperhomocysteinemia [45].

This clearly underlies that, beside nutrition, genetic factors, concurrent pathological conditions, and epigenetic modifications also play an important role in the regulation of LC-PUFA metabolism and may thus influence the development of inflammatory and metabolic diseases. It also

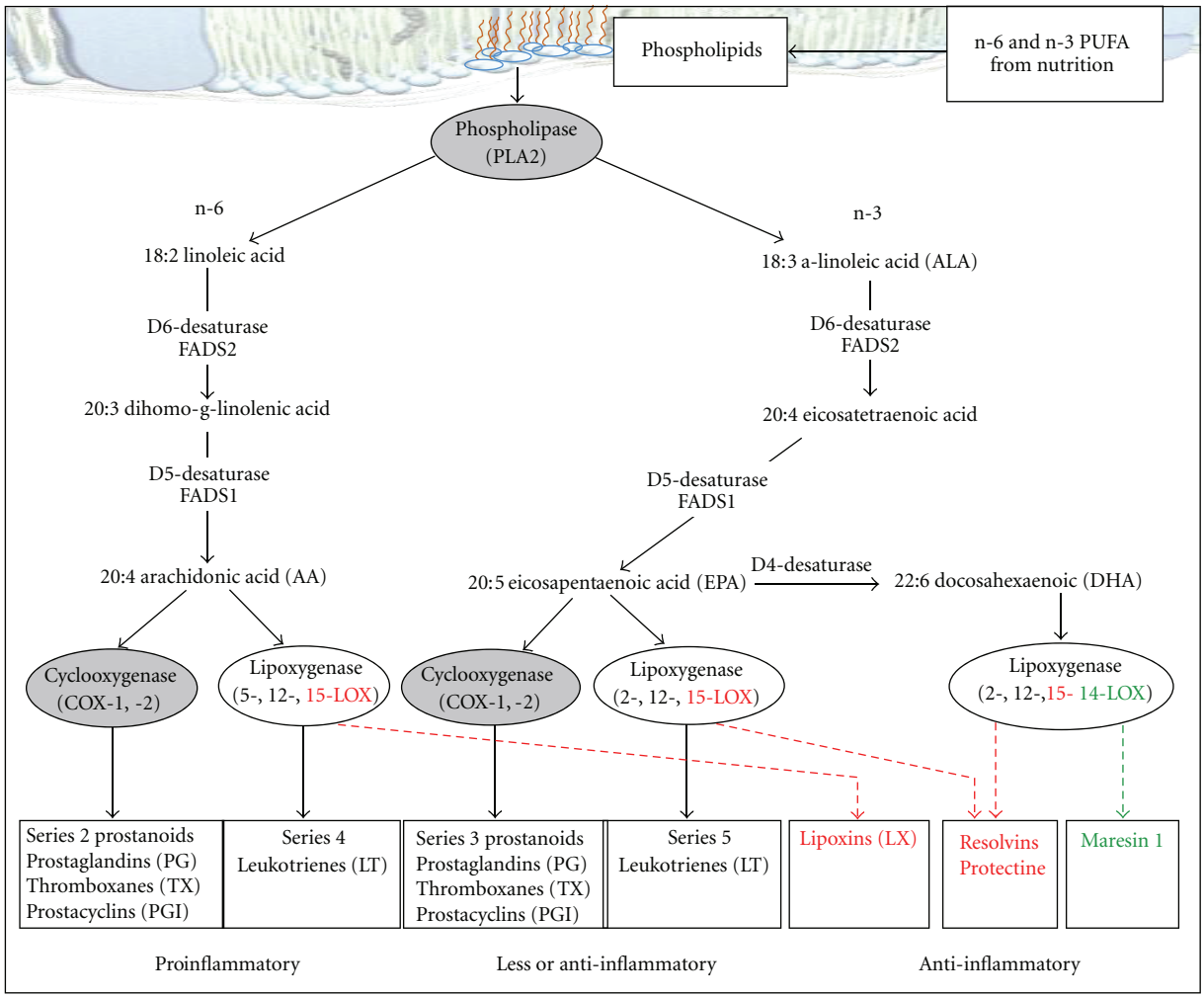

Figure 3: Metabolism of polyunsaturated fatty acids and their signaling molecules. Adapted from [41–43]. The 3D plasma layer image was modified from the one provided by Mélanie Villeneuve, La cellule animale, CCDMD, 2008 (http://www.ccdmd.qc.ca/ri/cellule/index.php?nh=18).

suggests interindividual variations for requirements in n-3 PUFA.

4. n-3 PUFA and Benefits in the Metabolic Syndrome

Next to epidemiological evidence, literature provides a profusion of data reporting that increased n-3 PUFA consumption in intervention studies may alleviate metabolic and cardiovascular risk. Thus, consistent with the inverse correlation found between fish and fish oil consumption and biomarkers of inflammation (TNFα, IL6, CRP) in many populations (healthy adults -[40, 57]; patients with insulin resistance [58]; coronary heart disease [59]; or the MetS [44, 60]), dietary enrichment in n-3 ALA and in EPA/DHA reduced low grade inflammation in at-risk populations [61–64].

Despite a relatively low accumulation in adipocytes [41], LC n-3 PUFA elicit beneficial effects on adipose tissue in obesity, as indicated by (i) reduced body fat mass and stimulated lipid oxidation [65], (ii) improvement of body weight and satiety regulation [66], (iii) amelioration of cytokines profile, including leptin and adiponectin [66], and (iv) reduction of inflammation [44, 60]. Additionally, n-3 PUFA have been shown to reduce adipose tissue macrophage infiltration associated with obesity in animal models [67], but this requires confirmation in humans.

Human trials confirmed that LC n-3 PUFA from either fish or fish oil supplements as well as ALA enrichment significantly reduce blood triglyceride levels in patients with MetS in a dose-dependent manner [35, 68], an effect that appears to be mediated through inhibition of hormone-sensitive lipase and VLDL secretion, and increase in apo B liver degradation [35].

A body of evidence demonstrates that n-3 PUFA are involved in the control of glucose homeostasis and insulin sensitivity [69]. In murine models of obesity and insulin resistance, incorporation of LC n-3 PUFA into cell membrane phospholipids increases membrane fluidity

and expression, affinity, and number of insulin receptors [58] as well as GLUT-4 protein level in adipocytes [70], thereby improving insulin sensitivity. In overweight patients, n-3 PUFA reduce transition from glucose intolerance to T2DM [29], and fish and fish oil consumption during energy reduction elicit an additional positive effects on insulin resistance [71]. However, a majority of n-3 PUFA administration trials did not prove efficient in reducing insulin resistance in T2DM [29].

Diet interventions with increased n-3 PUFA clearly demonstrated therapeutically, reliability in lowering mortality in subjects with cardiovascular diseases or the MetS [31, 72], an effect primarily related to increased DHA intakes [73]. This justifies the recommendation for daily consumption of 1 g/d of LC n-3 PUFA as part of secondary prevention strategy post ischemic heart event [74].

NAFLD, now recognized as the hepatic complication of the MetS, might trigger development of T2DM. Low dietary n-3 PUFA content induces hepatic desaturase activity [75]. In addition, enzymes involved in eicosanoid synthesis are located at the periphery of lipid droplets [76]. It is therefore plausible that in the context of diet- or obesity-induced fatty liver associated with excessive n-6/n-3 ratio, hepatic eicosanoid production is tilted towards proinflammatory components and participates to proinflammatory and insulin resistant status aggravating the MetS. Animal diet-induced obesity experiments clearly show that EPA and DHA supplementation reduces severity of NAFLD, if not preventing it [23], suggesting that increasing n-3 PUFA intake and fish consumption might prevent the occurrence of NAFLD in humans [2]. Properly conducted clinical trials are awaited to confirm this.

As important, emerging evidence indicates that incidence and tumour growth of some cancers associated with the MetS can be attenuated by n-3 PUFA [3]. Independently of the total amount of n-3 PUFA, the n-6/n-3 ratio seems to be determinant as a ratio of 2.5/1 reduced rectal cell proliferation in patients with colorectal cancer, whereas a ratio of 4/1 with the same amount of n-3 PUFA had no effect [77].

5. Recommendations for n-3 PUFA Consumption

From the above, it is obvious that there is a need for recommendations for n-3 PUFA nutritional supplies both for the prevention of MetS and associated disorders in the general population and for secondary prevention or treatment. Establishing such guidelines represents a complex issue for three main reasons. First, there is a large interindividual variability in n-3 PUFA metabolism based on genetic determinants, gender and age, further magnified by concurrent associated diseases or epigenetic modifications. Therefore, ideal requirement for physiological effect needs to be tailored for a specific individual [52–54, 78]. Secondly, dietary composition, for example, high dietary SFA or high n-6 PUFA, interferes with the biological effects of n-3 PUFA [31, 77]. The consequences of excessive n-6 PUFA remain controversial: n-6 PUFA have intrinsic cardiovascular protective effects [79], justifying the latest FAO/WHO recommendations on maintaining high n-6 PUFA intakes if n-3 PUFA ones are fulfilled [80]. However, n-6 PUFA compete with n-3 PUFA for processing to eicosanoids, thereby limiting production of antiinflammatory n-3 PUFA derived mediators [46]. Moreover, there are convincing evidence that a low n-6/n-3 PUFA ratio is determinant for the prevention of pathologies associated to the MetS, as colorectal cancer [77] and NAFLD [81–83]. Thus, we propose that n-3 PUFA recommendations must be part of a more global dietary counseling and should be associated with maximum reduction in SFA and limitation of n-6 PUFA intakes to their recommended levels (from 5% to 10% energy intake in Europe and USA [79], resp.). The n-6/n-3 PUFA ratio is a good indicator of this balance. Thirdly, there are concerns about availability of certain foodstuffs (such as wild fish) and food contaminants, as seafood, rich in LC n-3 PUFA, is also a dietary source of heavy metals (methylmercury), polychlorinated biphenyls, dioxins, and other organic pollutants [84].

Deduced from ancestral nutrition, in an ideal balanced diet, fat should represent no more than 20%–30% of total energy intake amongst which 5-6 g/d of n-3 PUFA with a great proportion of EPA+DHA and the n-6-to-n-3 ratio should average 1 [17, 30]. To keep in with a developmental approach and with the epigenetic consequences of the diet [56], a ratio of n-6/n-3 around 1 in breast milk should serve as a bench mark to determine the appropriate dietary requirements during pregnancy, lactation, and infant feeding [85].

Previously, health organizations and government agencies in most western countries recommended daily consumption of 0.6 to 1 g n-3 PUFA from which 100–200 mg of LC n-3 PUFA (EPA+DHA). However, in intervention studies reporting a beneficial health effect, the consumption of fish oils or their derivatives resulted in LC n-3 PUFA daily intakes well above those "recommended" 200 mg/day and ranged from 0.5 to 9 g/d. Indeed, in a meta-analysis, a 37% reduction in the relative risk of coronary heart disease in the general population was seen with a daily intake of EPA/DHA of 566 mg. Therefore, this justifies readjustments of nutritional guidelines to an upper level. Governments (France, Belgium, UK, The Netherlands, New Zeeland, and Australia) and health organizations (FAO/WHO, American Dietetic Association, American Heart Association) now recommend dietary intakes for total n-3 PUFA of 1.4 to 2.5 g/d, with EPA and DHA ranging from 140 to 600 mg/d depending on the authority issuing guidelines, FOA/WHO making a relatively low recommendation of 250 mg/d, the average being around 500 mg/d [80, 86, 87]. This represents minimum of 2 servings of fish per week (30–40 g/d), including one of oily fish (salmon, tuna, mackerel, and sardine). In the light of the literature and interindividual variability in PUFA metabolism and requirement, probably the minimal EPA+DHA supplies for healthy adults should reach 0.5–1 g/d (2–4 servings per week of fish, half of oily fish); that is, minimal consumption proved to reduce MetS [86], with a total intake of n-3 PUFA of 5-6 g/d as found

in ancestral nutrition to which our metabolism is best fit [18, 51]. Such levels are met in the traditional Japanese diet as it contains 80–100 g fish and shellfish/d/capita [88].

6. Are These Recommendations Followed?

To address this question, we calculated FA composition in meals proposed by nutritionist coordinated collective caterings to which health is of concern: first, in lunches supplied by the township of Lille (France) to healthy pupils (4–6 and 6–9 y) and adults and second, in meals proposed to patients hospitalized in St. Luc University Hospital (Brussels, Belgium).

Total content in FA and specific contents in SFA, MUFA, PUFA, n-6, n-3, and LC n-3 PUFA were calculated in menus over 6 representative weeks for the township collective catering of Lille and in 4 weeks winter menus and 4 weeks summer menus, proposed in rotation along the year by the university hospital. Three types of menus were analyzed: normal, for diabetic patients, and low fat. We used (i) the official table of composition in saturated, mono- and polyunsaturated FA of foodstuffs provided by the French Agency for Food Safety [89], (ii) the table of composition in n-6 and n-3 PUFA of fish, meat, oils, and dairy provided either by the project "Nutritional Composition of Aquatic Products" [27] or by the French Institute for Nutrition [90], and (iii) the EPA and DHA contents of specific foodstuffs provided by the USDA National Nutrient Database for Standard Reference [28]. The ANC guidelines [91] were taken as reference for daily recommended intakes (DRI) and calculated lunch daily recommended intakes (LDRI) as 35%–40% of DRI, with a range representing minimum supplies for girls and maximum ones for boys.

Results are presented in Table 1. In collective lunches proposed by the township of Lille whether to children or adults, the mean contents in FA and SFA were relatively high, estimated at 117%–141% and 116%–149% of LDRI, respectively, and MUFA supplies were relatively insufficient (59%–91%). However, supplies in both total and n-6 PUFA exceeded LDRI by 200%–300%. This is related to systematic replacement of processed fats with safflower oil (rich in n-6) as the main dressing and cooking oil. Strikingly, n-3 PUFA contents were low, representing only 68%–91% of LDRI, although there were 8 servings of fish over the 6 weeks menus, 4 servings were white fish (1.2% fat), 2 canned tuna (4.1% fat), and 2 salmon (11.8% fat), but one of which as small portion served as baked pasta dish. As a result, n-6/n-3 ratio was dramatically elevated (18,6–24,1/1).

In the meals proposed at St. Luc University Hospital, total FA were relatively low (66%–74% of DRI and 48% of DRI in low fat menus), SFA were in the recommended range or below, but MUFA were dramatically low (38% of DRI and 27% for low fat). Recommended amounts of total and n-6 PUFA were supplied in classical and low-fat diets, but they were outleveled in the diabetic regimen, owing to the addition of 2 safflower-based dressings per day for lunch and evening salads. Regarding n-3 PUFA, the content in total n-3 PUFA was between 1.8 and 1.9 g/d and that of LC n-3 PUFA (EPA+DHA) of 460 mg/day. Those are close to or within the recommendations [91]. Thus, n-6/n-3 ratio varied from 5/1 to 8/1 (the ideal being 1/1, the recommendation 4/1, and currently in the global population 20/1). It is of note that the quasiadequate amounts of n-3 PUFA and LC n-3 PUFA are supplied owing to the presence of 2 portion/d (breakfast, diner) of an n-3 PUFA-enriched margarine containing 16% n-3 PUFA and 0.5% EPA+DHA. This represents 1.2 g/d n-3 PUFA and 0.2 g/d EPA+DHA, without which n-3 PUFA supplies would be insufficient with an n-6/n-3 ratio higher than 15.

Thus, consistent with other reports [17, 29, 30, 77], despite increasing awareness and nutritionist-assisted food catering, reaching adequate or recommended n-3 PUFA supplies in collective nutrition still needs effective and applicable solutions. For reflection, in in-hospital catering, replacement of white fish by fatty fish in one serving has been discussed in order to try to overtake minimum DRI for n-3 PUFA and reduce n-6/n-3 ratio (particularly in menus for diabetic subjects). In school catering, increasing the use of rapeseeds oil (59% MUFA, 20% n-6, and 9% n-3) in replacement of safflower oil (20% MUFA, 64% n-6 and 0.2% n-3) for 50% of the dressings was considered. Forecast calculations show that this would greatly participate in reducing excessive n-6, PUFA intake (−2 g/d) and increase both MUFA (+1,6 g/d) and n-3 PUFA (+0,4 g/d) intakes, resulting in a half reduction of n-6/n-3 ratio (9,5 versus 20). This appears as a simple measure, easily implemented, while very effective. As exemplified in results from hospital menus, the incorporation of enriched manufactured products such as n-3 PUFA-enriched margarine is an alternative to compensate for insufficient supply of natural products.

7. How Could We Modify Our Diet to Improve n-3 Intakes?

Fish and oils rich in ALA (flaxseed, canola, soybean, walnut) represent the main sources of n-3 PUFA. As conversion rate from ALA to EPA/DHA is low in humans, a minimum part of the recommended nutritional supplies in n-3 PUFA should be provided as marine LC PUFA (500 mg/d). The first effective measure for increasing n-3 PUFA intakes should consist in actively promoting fish consumption, to reach 35–40 g fish/d. Ideally, wild fish should be given the preference as some species have a higher n-3 PUFA content and/or a lower n-6/n-3 ratio than farmed ones, which usually contain more n-6 PUFA [26–28, 92] partially owing to alimentation. Given the declining stocks of marine fish and high pollution in some fishing areas, this is most likely not a sustainable and globally applicable solution.

An additional measure is to use ALA rich oils, as envisaged in school catering. For example, replacement of dressing oils rich in n-6 PUFA (mainly safflower oil) by oils rich in n-3 PUFA (flaxseeds, walnuts, wheat germ, rapeseeds, and soybean) provides a substantial additional n-3 PUFA supply (15 g walnuts oil = 1.5 g ALA = 2 dressings) while decreasing n-6 intake. However, such modifications require nutritional education and education to different tastes

Table 1: Daily fatty acids supplies in municipal and hospital catering.

		FA			
		Total g (% LDRI)	SFA g (% LDRI)	MUFA g (% LDRI)	PUFA g (% LDRI)
Lille municipal catering	Children 4–6 y	28,3 (141%)	8,5 (139%)	8,4 (91%)	10,3 (381%)
	LDRI min-max	*16,5–23,8*	[a]*5,5–6,8*	*6,6–11,9*	*1,3–4,1*
	Children 6–10 y	30,0 (117%)	9,1 (116%)	9,0 (76%)	10,7 (310%)
	LDRI min-max	*20,9–30,2*	[a]*7,0–8,6*	*8,4–15,1*	*1,7–5,2*
	Adults	32,6 (117%)	10,0 (149%)	9,9 (59%)	11,3 (265%)
	LDRI min-max	*23,1–32,4*	[a]*5,6–7,8*	*14,0–19,6*	*3,5–5,0*
St. Luc Hospital, Brussels	Classic	48,28 (66%)	18,38 (104%)	16,79 (38%)	13,10 (116%) [b]11,90 (105%)
	Diabetic	54,15 (74%)	20,16 (114%)	17,52 (39%)	16,47 (146%) [b]15,27 (135%)
	Low-fat	35,36 (48%)	12,64 (71%)	12,07 (27%)	10,64 (95%) [b]9,44 (84%)
	DRI women-men	*66–81*	[a]*16,0–19,5*	*40,0–49,0*	*10,0–12,5*
		PUFA			
		n-6 PUFA g (% DRI)	n-3 PUFA g (% DRI)	EPA+DHA g (% DRI)	n-6/n-3 ratio (% DRI)
Lille municipal catering	Children 4–6 y	9,9 (441%)	0,4 (91%)	0,16	24,1 (482%)
	LDRI min-max	*1,1–3,4*	*0,2–0,7*		*5,00*
	Children 6–10 y	10,2 (359%)	0,5 (82%)	0,22	20,8 (415%)
	LDRI min-max	*1,4–4,3*	*0,3–0,9*		*5,00*
	Adults	10,8 (316%)	0,6 (68%)	0,27 (130%)	18,6 (466%)
	LDRI min-max	*2,8–4,0*	*0,7–1,0*	*0,20*	*4,00*
St. Luc Hospital, Brussels	Classic	11,24 (125%)	1,92 (85%) [b]0,72 (32%)	0,46 (93%) [b]0,26 (53%)	5,86 (147%) [b]15,61 (390%)
	Diabetic	14,66 (163%)	1,85 (82%) [b]0,65 (29%)	0,46 (92%) [b]0,26 (52%)	7,91 (198%) [b]22,55 (563%)
	Low-fat	8,90 (99%)	1,79 (80%) [b]0,59 (26%)	0,46 (93%) [b]0,26 (53%)	4,96 (124%) [b]15,08 (377%)
	DRI women-men	*8,0–10,0*	*2,0–2,5*	*0,50*	*4,00*

LDRI: lunch daily recommended intakes [91]; numbers in brackets correspond to the % of average DRI/LDRI; [a]For SFA, values represent the range of 35% of the maximum intakes for women and 40% of the maximum intakes for men; [b]Values without enriched margarine.

(oils rich in n-3 PUFA have pronounced tastes), probably easier to integrate onto the developing palette of taste during infancy. As edible wild plants provide higher amounts of ALA and antioxidants than intensively cultivated plants [39], encouraging agricultural methods that are more respectful of developmental cycles and natural nutritional contents of plants would help increase n-3 PUFA consumption.

Consideration has also to be brought to the cooking methods as n-3 PUFA are highly sensitive to oxidation by oxygen, light, and heat, leading to production of deleterious free radicals. Indeed, cooking fish might reduce by up to 50% its content in n-3 PUFA [93]. Thus consumption of freshly harvested raw (or cooked at low heat) fish and raw n-3 PUFA-rich oils should be promoted.

Food enrichment is emerging as perhaps the best long-term solution to the chronically low intake of n-3 PUFA that plagues western cultures [87]. First, n-3 PUFA-rich oils should more systematically replace n-6 PUFA-rich oils in industrial preparations. Second, efforts are being made to produce a variety of food products, most notably eggs, yogurt, milk, and spreads, enriched with n-3 PUFA-rich food [94]. Alternatively, n-3 PUFA synthesis might be induced by genetic manipulation. This has been done in plants by transgene-driven expression of Δ6 desaturase. In derived oil, LC n-3 PUFA concentration amounts those found in native marine organisms [95]. At the experimental level, this application has been extended to mice. Indeed, the team of Kang realized a stable transfection of FADS3 from *C. Elegans*, an enzyme missing in mammals which catalyses conversion of n-6 to n-3 PUFA [96]. This resulted in spontaneous enrichment of their lipids with n-3 PUFA. Such experiment might pave the way to genetic manipulation of cattle and poultry to produce n-3 PUFA-rich raw material. Innumerable ethical, ecological, economical, and cultural issues need to be addressed prior to generalization of such experimental trials.

8. Concluding Remarks

The literature provides compelling evidence for the health benefit of n-3 PUFA consumption not only on the MetS, cardiovascular risks, and associated comorbidities but also on other conditions such as neuroinflammatory and neurodegenerative diseases. This evidence must be taken into consideration, and efforts have to be made to promote increased n-3 PUFA consumption together with lowering intakes of high glycemic food, fructose, and fat, in particular SFA and n-6 PUFA when clearly excessive, and increasing ingestion of fruits, vegetables, whole grains, and nuts. Despite this awareness, what is still needed is an educational program for professionals and for the public [17] as well as manifestation of the willingness of governments to institute changes, notably through achieving accountable decisions on catering (as undertaken here) as well as modifications of food processing and industrial food ingredients legislations, all towards promoted use and preservation of n-3 PUFA rich food. Increasing experimental evidence supporting the pivotal roles of nutrition in the regulation of homeostasis highlight our neglected responsibility in promoting balanced diet and consumption of food rich in essential nutrients in the general population.

Abbreviations

ALA:	Alpha-linolenic acid
COX:	Cylooxygenase
DHA:	Docosahexaenoic acid
DRI:	Dietary recommended intake
EPA:	Eicosapentaenoic acid
FA:	Fatty acids
FAD:	Fatty acid desaturase
LC PUFA:	Long-chain polyunsaturated fatty acids
LDRI:	Lunch dietary recommended intake
LOX:	Lipoxygenase
LT:	Leukotriene
MetS:	Metabolic syndrome
MUFA:	Monounsaturated fatty acids
NAFLD:	Nonalcoholic fatty liver disease
PG:	Prostaglandin
PUFA:	Polyunsaturated fatty acids
T2DM:	Type 2 diabetes mellitus.

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