Loss of appetite in acutely ill medical inpatients: physiological response or therapeutic target?

An area of current uncertainty

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Summary

Loss of appetite and ensuing weight loss is a key feature of severe illnesses. Protein-energy malnutrition (PEM) contributes significantly to the adverse outcome of these conditions. Pharmacological interventions to target appetite stimulation have little efficacy but considerable side effects. Therefore nutritional therapy appears to be the logical step to combat inadequate nutrition. However, clinical trial data demonstrating benefits are sparse and there is no current established standard algorithm for use of nutritional support in malnourished, acutely ill medical inpatients. Recent high-quality evidence from critical care demonstrating harmful effects when parenteral nutritional support is used indiscriminately has led to speculation that loss of appetite in the acute phase of illness is indeed an adaptive, protective response that improves cell recycling (autophagy) and detoxification. Outside critical care, there is an important gap in high quality clinical trial data shedding further light on these important issues. The selection, timing, and doses of nutrition should be evaluated as carefully as with any other therapeutic intervention, with the aim of maximising efficacy and minimising adverse effects and costs. In light of the current controversy, a reappraisal of how nutritional support should be used in acutely ill medical inpatients outside critical care is urgently required. The aim of this review is to discuss current pathophysiological concepts of PEM and to review the current evidence for the efficacy of nutritional support regarding patient outcomes when used in acutely ill medical patient population outside critical care.

Key words: nutrition; acute illness; malnutrition; inflammation

Introduction

Although nutritional support using either oral nutritional supplements (ONS) or enteral feeding is one of the most common interventions in medicine, there is no current standard algorithm for the use in unselected, polymorbid, acutely ill medical inpatients at risk of protein-energy malnutrition (PEM). In the light of recent high-quality evidence from critical care demonstrating contrasting results, either late beneficial effects [1], lack of benefit [2] or harmful effects [3, 4] when clinical nutrition is used indiscriminately and/or too aggressively, a reappraisal of how nutritional therapy should be used in medical inpatients is now required.

Several considerations support the current approach of systematically screening inpatients for PEM risk and of starting nutritional therapy in at-risk patients. Epidemiological studies from various countries and healthcare settings have shown strong associations between PEM and patient outcomes. For example, an observational cohort study of nutrition practices in 167 intensive care units (ICUs) across 37 countries including 2,772 mechanically ventilated patients found that an increase of 1,000 calories per day was associated with a significant reduction in mortality (odds ratio for 60-day mortality 0.76; 95% confidence interval

Figure 1

Association of PEM measured with the NRS 2002 and 30 days mortality in a 6-month observational cohort study performed in the Medical University Clinic at the Kantonsspital Aarau, Switzerland [7]. In red, 30-day mortality is shown. In black, the number of patients in different NRS risk classes are displayed. NRS = nutritional risk screening; PEM = protein-energy malnutrition
Nutritional risk screening

Nutrition screening aims at identifying patients with nutritional deficits who benefit from further detailed nutritional status assessment and nutritional therapy interventions [11]. The European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines state that the purpose of nutrition screening is to predict the probability of a better or worse outcome due to nutrition factors and whether nutritional treatment is likely to influence this. Optimally, patients admitted to acute-care hospitals should be screened for risk of PEM within 24 hours. There are several screening tools validated for this purpose in the acute-care setting [12]. Many institutions trigger automatic support when certain screening criteria are met for in-depth assessment of patients.

Various nutrition screening tools are used in hospitals, but many of them have not been well validated for the acute-care setting. Thus, it is unclear if they appropriately identify patients who need further nutrition assessment and potentially nutritional therapy. The most widely used tools are the Nutritional Risk Screening (NRS) 2002, the Malnutrition Universal Screening Tool (MUST), the subjective global assessment of nutritional status (SGA) and the Mini Nutritional Assessment® (MNA) (reviewed in [12]). These screening instruments differ in the variables included and patient populations to be targeted, and either assess patients for the presence of malnutrition (SGA, MNA) or for being at risk for malnutrition (MUST, NRS). Among them, the NRS 2002 is recommended by ESPEN as the preferred screening tool for hospitalised patients. The NRS 2002 was developed by Kondrup and colleagues based on a retrospective analysis of controlled trials [13]. Their premise was that the indications for nutritional support should depend on two factors: (i) the severity of impaired nutritional status and (ii) the increase in nutrition requirements resulting from disease (stress metabolism). For this reason, the NRS 2002 includes both a measure of current potential undernutrition and a measure of disease severity. In addition, older age is considered a risk factor, with an additional point added for age ≥70 years. A score of ≥3 is generally accepted cut-off, which indicates the need to start nutritional therapy.

The NRS 2002 tool performed well in a validation study including 128 controlled nutrition support trials and was capable in identifying patients who would or would not benefit from nutritional intervention [13]. In fact, the likelihood ratio for a positive effect at cut-offs of 3.0 and 4.0 points were 1.7 and 5.0. As an important limitation to the medical inpatient setting, most of the included trials were surgical trials and none of them included the typical acutely ill medical inpatient population outside the ICU. In addition, a subsequent prospective, controlled trial with 212 hospitalized patients did not show significant effects of nutritional therapy in regard to mortality, hospital length-of-stay or quality of life [14]. Thus, there is remaining uncertainty about the potential of the NRS 2002 to identify patients who will benefit from nutritional therapy in the medical inpatient setting.
Pathophysiology of PEM due to acute and chronic illness

Acute and chronic illness is associated with loss of appetite and poor nutritional intake, frequently associated with a proinflammatory state, and loss of lean and adipose tissue. Cachexia is the result of various metabolic pathways and mechanisms [10, 15]. Weight loss associated with acute and chronic illness may result directly from caloric deprivation due to loss of appetite, as well as from dehydration and sarcopenia. Also, hormonal imbalance with an increase in glucocorticoid hormones and a decrease in testosterone and other sexual steroids may further enhance catabolism and aggravate PEM (fig. 2). Nonetheless, although numerous acute medical diseases are associated with cachexia, the underlying pathophysiological mechanisms remain ill defined.

Recent investigations point to the central role of cytokines in the pathogenesis of cachexia. This relationship between acute disease and cachexia may well be bidirectional, with illness affecting nutritional status, and dietary factors influencing the inflammatory response and the course of illness. Cytokines are released in the body as part of the systemic inflammatory response associated with acute illnesses and have been implicated in the aetiology of anorexia, weight loss, cognitive dysfunction, anaemia, and frailty mediated by different mechanisms. Cytokines, such as interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α), influence brain circuits that control food intake, delayed gastric emptying and skeletal muscle catabolism [16, 17]. Cytokines not only activate nuclear transcription factor kB (NF-kB) resulting in decreased muscle protein synthesis, but also reduce MyoD protein, a transcription factor that modulates signalling pathways involved in muscle development (fig. 2) [18, 19]. TNF-α and interferon-γ act synergistically to inhibit the activation of messenger ribonucleic acid (RNA) for myosin heavy chain synthesis and thereby stimulate the proteolysis of myosin heavy chains [19]. Cytokines also activate the ubiquitin-mediated proteolytic system, which plays a key role in disease-related hypercatabolism [20]. Ubiquinated proteins and subsequent muscle proteolysis provide amino acids that are consumed in hepatic synthesis of acute-phase proteins such as C-reactive protein. Additionally, cytokines are able to modulate the response of the hypothalamic-pituitary-adrenal axis at each level and stimulate the release of various stress hormones including cortisol and catecholamines, which in turn lead to an increase in resting metabolic rate [21, 22]. Other hormones that may be important for the development of cachexia are incretin hormones such as glucagon-like peptide-1 (GLP-1) released directly from gut tissues. Recent evidence found a cross-talk of inflammatory cytokines (mainly IL-6 and IL-1β) and GLP-1 and its analogues that resulted in reduced food intake and thus eventually weight loss [23]. Although this effect is beneficial in obese diabetic patients, it may negatively affect malnourished acutely ill medical patients. Synergistically, these various activated pathways during acute illness result in negative energy balance and weight loss – ultimately resulting in cachexia and PEM.

Loss of appetite may develop during hospital stays either as a consequence of an underlying medical condition (e.g., pneumonia) or medical treatments (e.g., pain medication, chemotherapy), or may pre-exist as a primary condition owing to depression, social isolation and advanced age. This distinction maybe important as it impacts the effects of nutritional interventions. As loss of appetite secondary to acute disease may be seen as an evolutionary process, there is an ongoing debate about possible biological explanations why the human body adapts in such a manner during acute disease. Interestingly, there are some preclinical and clinical studies suggesting that starvation may indeed improve cell recycling by induction of autophagy, a survival mechanism serving to recycle intracellular nutrients such as toxic protein aggregates and damaged organelles [24]. In a recent animal study, early parenteral nutrition – particularly proteins and lipids – suppressed the ubiquitin-proteasome pathway [25]. This contributes to the preservation of muscle mass, but also leads to autophagy deficiency in liver and skeletal muscle. Thus the maintenance of muscle mass might come at the price of accumulation of toxic protein aggregates that ultimately compromises cell function. A similar observation was also made in critically ill patients [26] and was recently shown to contribute to mitochondrial dysfunction, organ failure and adverse outcome in a rabbit model of critical illness [27]. Based on these observations, it is tempting to speculate that starvation during the early phase of acute illness may indeed have some beneficial effects and improves the cell recycling system. At which time point these beneficial effects may become harmful as a result of progressive catabolism and PEM remains unclear today.

Clinical trials

Different randomised controlled trials (RCTs) have investigated the effects of nutritional support using ONS and/or enteral feeding on patient outcomes in the medical inpatient setting. These trials have looked at different types of outcomes including clinical outcome (physician focus), quality of life and recovery duration (patient focus), and costs (healthcare system focus). Table 1 shows a summary of the most recent RCTs focusing on different patient populations. The two trials conducted in Switzerland [28, 29] included an individual nutritional therapy intervention aiming to improve energy and protein intake. According to individual patient’s preferences and needs, hospital standard food combined with dietician counselling and interventions: fortification measures and beverages, snacks, protein powder, maltodextrin and/or ONS. The control group in both trials received either energy-dense ONS without dietetic counselling [29] or standard nutritional care including ONS or nutritional therapy on request if considered necessary by the independent treating physician [28]. As a result, protein intake [28] or energy and protein intake [29] was increased in the intervention group compared with the control group during study period. This provides strong evidence that individualised nutritional counselling and support improves energy intake in malnourished medical inpatients. Owing to the small sample size, it remains unclear from these trials whether or not an increase in en-
energy and protein intake results in improved patient outcome. Importantly, quality of life measured with either the Function Assessment Anorexia-Cancer Therapy (FAACT) tool and visual analogue scale (VAS) [29] or the SF36 questionnaire [28] was improved in the intervention group in both trials. As a limitation, improvement in quality of life may also be attributable to the intervention per se, i.e., the higher attention provided to patients during the study period.

The RCT conducted by Starke et al. [28] with a sample size of 134 patients (67 intervention group, 67 control group) found a lower rate of in-hospital complications, use of antibiotics and readmissions associated with the intervention. However, the trial failed to demonstrate a benefit in regard to mortality or hospital length-of-stay (LOS). Again, the sample size was small and the trial thus underpowered to find such effects.

Table 1: Overview of most recent randomised controlled trials evaluating nutritional therapy in medical inpatients. Trials using parenteral nutrition are excluded.

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Population and No.</th>
<th>Treatment of the nutritional intervention group</th>
<th>Treatment of the control group</th>
<th>Endpoints</th>
<th>Limitations</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rüfenacht U, 2010 [29]</td>
<td>Adult patients admitted to a general medical ward, NRS ≥3 n = 53</td>
<td>ONS 400 ml daily, 600 kcal, 24 g protein and individual nutritional counselling</td>
<td>Only ONS 400 ml daily, 600 kcal, 24 g protein</td>
<td>Energy and protein intake, LOS, QoL (functional assessment anorexia-cancer therapy [FAACT] and VAS)</td>
<td>QoL difference only at one timepoint, confounding by intensive nutritional care possible</td>
<td>Significant increase in energy and protein intake as well as QoL.</td>
</tr>
<tr>
<td>Starke J, 2011 [51]</td>
<td>Adult patients admitted to a general medical ward, NRS ≥3 n = 132</td>
<td>Individual nutritional care, including detailed nutritional assessment, individual food supply, fortification of meals, in-between snacks and ONS</td>
<td>Standard nutritional care</td>
<td>Daily energy and protein intake, weight, complications, antibiotic therapy of infectious complications, LOS, QoL, hospital readmission, mortality, compliance with supplement consumption, Levels of 25-OH-vitamin D3, ascorbic acid and glutathione</td>
<td>No functional outcome assessed</td>
<td>Intervention beneficial for nutritional status QoL, fewer complications and rehospitalisations.</td>
</tr>
<tr>
<td>Potter JM, 2001 [49]</td>
<td>Patients admitted to a “general medical ward for the elderly” (&gt;60 y) any kind of nutritional status n = 381</td>
<td>Protein energy sip feed supplement containing 1.5 kcal/ml energy intended to provide 22.5 g protein and 540 kcal/d. Three times daily 120 ml</td>
<td>Normal ward diet and snacks, dietary intervention available to all patients in the study</td>
<td>Weight, arm muscle circumference, triceps skinfold thickness, BMI, 20-point Barthel ADL, survival, discharge destination, LOS, energy intake</td>
<td>Lower mortality, better functional outcome in severely malnourished patients after intervention</td>
<td></td>
</tr>
<tr>
<td>Gariballa S, 2006 [52]</td>
<td>Patients over age 65 y, medical or surgical (not GI surgery) diagnosis, any kind of nutritional status n = 445</td>
<td>400 ml ONS in addition to standard hospital diet</td>
<td>Placebo with minimal calorie content (60 kcal)</td>
<td>Barthel score, nonelective readmissions, LOS, discharge destination, morbidity and mortality</td>
<td>Nonsignificant results in primary endpoints</td>
<td>No significant effect of intervention</td>
</tr>
<tr>
<td>Hickson M, 2004 [53]</td>
<td>Patients ≥65 years of age, admitted to a “medicine for the elderly ward”, any kind of nutritional status n = 592</td>
<td>Encouragement of patients, offering of snacks and drinks</td>
<td>Standard hospital diet alone</td>
<td>LOS, Barthel, weight, MAC, TSF, albumin, abbreviated mental test, intake, infection rate measured by antibiotic use, fluid intake, in hospital mortality.</td>
<td>Intervention conducted by nondieticians (healthcare assistants)</td>
<td>Employing extra healthcare assistants in preventing weight loss is not effective</td>
</tr>
<tr>
<td>Johansen N, 2004 (12)</td>
<td>Adult patients admitted for medical disease or surgical diagnosis or interventions, nutritionally at risk n = 212</td>
<td>Nutritional team for motivation, estimation of requirements, advice and assurance of adequate nutrition</td>
<td>Usual care</td>
<td>LOS-NDI (nutritional discharge index) SF-36 QoL, intake of energy and protein, use of antibiotics</td>
<td>Inclusion of surgical and medical patients</td>
<td>No differences in rate of complications and LOS</td>
</tr>
</tbody>
</table>

ADL = activities of daily living; BMI = body mass index; d = day(s); GI = gastrointestinal; h = hour(s); LOS = length of stay; m = month(s); NRS = nutritional risk screening; ONS = oral nutritional supplement; QoL = quality of life; VAS = visual analogue scale
tient outcomes, ONS was associated with important improvements in long-term institutionalised malnourished geriatric patients and in perioperative patients in some trials [31, 32]. But also in this setting, not all trials found such effects and the benefit of ONS remains somewhat unclear [33]. A major shortcoming in the above mentioned trials was low protocol adherence and thus nutritional targets were not met. Whether this was the main reason for the lack of significant results remains debated. Outside critical care, trials using enteral and/or parenteral nutrition to reach nutritional targets and that could shed a light on this important issue are lacking.

Current evidence from RCT data is inconsistent regarding the effectiveness of different nutritional strategies in the acutely ill inpatient setting. However, all the above-mentioned trials were relatively small, highly heterogeneous in design, patient populations and type of intervention, and lacked statistical power to demonstrate safety and, altogether, produced inconclusive results. Blinding of therapy was not performed since this is not feasible when nutritional interventions are used. This could also have resulted in an investigator bias. Unsurprisingly, two previous aggregate data meta-analyses confirm the important lack of high-quality evidence to endorse or refute nutritional support [33, 34]. Both meta-analyses, however, were based on aggregate data only and did not specifically examine the effect of early nutritional therapy in medical inpatients. Rather, one meta-analysis focused on such therapy in critical-care/perioperative patients [34], and the other only considered general protein and energy supplementation in the elderly [33]. Moreover, having been published in 2007 and 2009, respectively, neither meta-analysis captures the most recent work.

Guideline recommendations of European and American professional societies

Considerable efforts have been made to standardise nutritional treatment on an inpatient and outpatient basis. National and international consensus committees developed and published guidelines focusing each on distinct medical conditions and different indications [35–46]. The most important guidelines are from the American Society for Parenteral and Enteral Nutrition (ASPEN) and ESPEN. Most of the recommendations, however, are based on small trials in selected patient populations, and recommendations for general medical inpatients do not exist currently. Due to the lack of high quality clinical data, most guidelines give only weak recommendations and no unequivocal instructions on patient selection, the time-points when to start and stop, route, amount and duration of nutritional support. As a result and despite widespread acceptance, implementation of nutritional guidelines is still insufficient [47]. Also, the substantial differences between national and international guidelines may further slow down the widespread implementation of guidelines. In the case of renal failure, for instance, the ASPEN guidelines [37] recommend adapting energy and protein targets based on the requirements measured by indirect calorimetry and nitrogen balance. In contrast, ESPEN guidelines [38] specify general targets for micro- and macronutrients for each stage of acute and chronic renal failure. However, neither guideline gives specific recommendations about the time-point, route of delivery and amount of nutritional therapy (energy) in this situation. Importantly, malnutrition may exist before hospital admission, and develop and/or aggravate during the hospital stay, which should also influence the medical strategy for treatment of the patients in question [48, 49]. In addition, to our knowledge few published data included analysis of the barriers to the practical implementation of nutritional guidelines [50]. However, it can be assumed these would include unawareness and insufficient knowledge, ethical considerations and patient resistance among others.

Conclusions and outlook

Although the use of nutritional therapy involving dietary counselling, ONS or enteral nutrition is one of the most common interventions in medical inpatients, there is no current scientific clear evidence of its efficacy, and standard algorithms for its use in acutely ill medical inpatients at risk of PEM are generally lacking. In light of recent high-quality evidence from parenteral nutrition in critical care, a reappraisal of how nutritional support should be implemented in acutely ill medical patients is now required. The selection, timing, dose and feasibility of nutritional treatment should be evaluated as carefully as with any other therapeutics interventions, with the aim of maximising efficacy and minimising side effects and costs.

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References


Figure 1

Association of PEM measured with the NRS 2002 and 30 days mortality in a 6-month observational cohort study performed in the Medical University Clinic at the Kantonsspital Aarau, Switzerland. In red, 30-day mortality is shown. In black, the number of patients in different NRS risk classes are displayed.

NRS = nutritional risk screening; PEM = protein-energy malnutrition
Figure 2

The complex interaction of acute illness and cachexia is mediated by various mechanisms (adapted from [10]).

CRP = C-reactive protein; GLP-1 = glucagon-like peptide-1; IL = interleukin; TNF-α = tumour necrosis factor-α