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Evidence-based nutrition for the malnourished, hospitalised patient: one bite at a time

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Summary

Although malnutrition is a highly prevalent condition in the inpatient setting, particularly in older patients with multiple morbidities, the medical community has struggled to find efficient, evidence-based approaches for its prevention and treatment. From an evolutionary perspective, illness-related low appetite may be seen as a protective response with the goal of accelerating recovery from disease by improving autophagy. In line with this, earlier trials in the intensive care setting including severely ill patients have demonstrated unwanted effects of overnutrition on patient outcomes. Uncertainties regarding the best approach to the malnourished inpatient in conjunction with a lack of strong trial data may, in part, explain the low level of attention that hospital medical staff have paid to the issue of malnutrition in the non-critical care inpatient setting. The recent Effect of early nutritional support on Frailty, Functional Outcomes and Recovery of malnourished medical inpatients Trial (EFFORT) study, however, has shown that individualised nutritional support reduces severe complications and improves mortality in medical inpatients, with positive effects on functional outcomes and quality of life. These results from a high quality effectiveness trial in conjunction with other studies, such as the NOURISH trial, should prompt us to improve our management of malnutrition in the in-hospital setting. This procedure should start with a systematic screening for risk of malnutrition of admitted patients, effective assessment of nutritional status in multidisciplinary teams including dieticians, nurses and physicians, and the early start of individualised adequate nutritional support of at-risk patients to reach nutritional goals. Understanding the optimal use of nutritional support in patients with acute illness is complex because timing, route of delivery, and the amount and type of nutrients may all affect patient outcomes. Also, particularly for patients on the medical ward, factors such as the logistics of catering, staffing to provide food and support to the patient (i.e., number of nurses and dieticians per patient), motivation/understanding of the patient to eat in defiance of appetite, the empathic human factor of nutritional care, the quality of meals, the taste of supplements, and unnecessary fasting for diagnostic or therapeutic procedures have a strong influence on nutritional care of patients. Further research and clinical trials are required to better understand, step by step, how we can use clinical nutrition best to maximise recovery of our patient and improve their functional status and their quality of life. Such evidence regarding nutritional therapy may allow us to implement personalised nutrition-driven interventions in the future.

***Keywords**: nutrition, acute illness, inflammation, malnutrition*

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Background

With James Lind conducting the first ever randomised controlled trial in 1747 by comparing of six different treatments for 12 sailors with scurvy, nutritional research really had a promising start [1]. Hippocrates of Kos, one of the most outstanding figures in the history of medicine, also had great hopes for the effect of nutritional interventions to cure disease ("Let food be thy medicine and medicine be thy food"). Much of the current evidence regarding effects of nutritional research, however, stems from observational studies with cross-sectional or cohort-study designs, and there is an important lack of randomised, interventional research, which is needed to establish causal effects rather than just statistical associations [2–4].

The aim of this article is to discuss the difficulties and recent progress in achieving the goal of individualised nutrition that fulfils todays' criteria of "evidence-based" medicine by focusing on some recent trials that have importantly advanced the field.

The concept of evidence-based nutritional support

Evidence-based medicine is an approach to medical practice intended to optimise decision-making by emphasising the use of evidence from well-designed and well-conducted research – typically randomised trials and meta-analyses from such trials. Evidence-based clinical nutrition should use the exact same criteria for classifying evidence by its epistemological strength and requiring that only the strongest types can also yield strong recommendations [4].

As such evidence has been lacking for a long time, current clinical practice guidelines, including the European Society for Clinical Nutrition and Metabolism (ESPEN) [5] and the American Society for Parenteral and Enteral Nutrition (ASPEN) [6], give only weak recommendations to consider initiating nutritional support, defined as provision of oral, enteral or parenteral nutrition, during the hospital stay of medical patients identified as at risk of malnutrition.

Association of malnutrition and patient outcomes

It is well known from previous studies that protein-energy malnutrition is a strong and independent risk factor associated with mortality, prolonged length of stay in the hospital and higher rates of complications including infections [7, 8]. There is strong evidence showing dramatic muscle loss occurring within the first days of bed rest after hospital admission, particularly in patients with disease-related loss of appetite and thus low food intake [9, 10]. Therefore, it seems obvious that correction of malnutrition by use of nutritional treatment could have a beneficial effect on outcomes [11]. Yet, to the surprise of many, studies conducted in intensive care settings found no benefit in early full-replacement feeding of critically ill patients; in contrast, an increase in complications was observed [12, 13]. These ICU trials led to the current concept of using hypocaloric nutrition with sufficient amounts of protein during the first week in the ICU. The negative effects of nutritional (over-) treatment observed in these trials have been explained mainly by two factors: risk of refeeding syndrome [14, 15] and interference of nutritional intervention with autophagy – a process that is needed for detoxification of cells during stress and acute disease [16]. A benefit of disease-related anorexia during an acute episode of illness may also seems plausible, as anorexia is an integrated part of the acute physiological response to acute illness [17]. Importantly, in chronically ill patients, this physiological response may have gone wrong, thereby negatively influencing recovery and outcomes. Thus, in patients with multiple chronic diseases, who have lost weight and muscle mass over time, use of an adequate nutritional support has potentially a positive role.

Recently, there has been publications of important trials that may help us to better understand the benefits of nutritional support when used in the right patient, at the right time and in the right amount. These trials, which are discussed in more detail below, are important to strengthen the evidence of current clinical nutritional research and to get a step closer to evidenced-based personalised nutrition.

The role of nutrition in the prevention of disease: the PREDIMED trial

In addition to observational research reporting associations of different nutrients and types of food with health outcomes, several large randomised trials have demonstrated an impact of nutritional interventions on mortality and morbidity. Most prominently, the PREDIMED (Prevención con Dieta Mediterránea) trial showed positive effects of a Mediterranean diet supplemented with extra-virgin olive oil or with mixed nuts, as compared with a control diet with advice to reduce dietary fat, on cardiovascular and metabolic disease [18]. In fact, the risk for a major cardiovascular event including myocardial infarction, stroke, or death from cardiovascular causes over the period of 5 years was reduced by about 1% from (from 4.4 to 3.4%) in the intervention group [18]. Importantly, the intervention was not associated with a change in weight, and thus the quality of nutrition, presumably in regards to types of fat, may have made this difference in outcomes. As a limitation to the generalisability of results and the understanding of the specific effect of single nutrition components, the investigators used a bundled approach with several recommendations including consumption of wine, vegetables among others, in the intervention group. In addition, control group patients may have changed their diet, shifting from fat to high sugar foods. Also, the trial was originally published in 2013 and republished in 2018 owing to protocol deviations. Despite all these challenges in the interpretation of the results, the trial has been important for the understanding that specific diets have (strong) preventive effects and influence clinical outcomes and cardiovascular health.

Effect of nutritional support on clinical outcomes in hospitalised patients

Up to 30% and more of patients hospitalised in medical wards are either at increased risk for malnutrition or malnourished [19]. Malnutrition has been associated with adverse outcomes, independently of the underlying disease and other confounders [7, 8], whereas interventional research investigating whether provision of nutritional support has positive effects on outcomes has been scarce. Two meta-analyses focusing on randomised trials in the medical inpatient setting that compared patients receiving nutritional interventions with patients receiving usual care demonstrated that nutritional therapy increases energy and protein intake, as well as body weight, but showed only few significant effects on clinical outcomes [20, 21]. Importantly, both meta-analyses also pointed out the low study quality, with high heterogeneity across trials and risk of bias. Thus, the lack of significant results regarding mortality and morbidity may be due rather to methodological issues and low statistical power, and not lack of effectiveness *per se*.

The above mentioned meta-analysis [20], however, did not include two more recent, large-scale trials investigating the effects of nutritional interventions on outcomes of medical inpatients.

Results of the NOURISH trial

First, the NOURISH (Nutrition effect On Unplanned Readmissions and Survival in Hospitalised patients) trial, a multicentre, randomised placebo-controlled trial, evaluated the effect of a high-protein oral nutritional supplement (HP-HMB) containing beta-hydroxy-beta-methylbutyrate (a leucine metabolite) versus a placebo supplement (with low protein and no HMB) in malnourished hospitalised older patients. The trial was industry-sponsored and included 652 older adults who were malnourished (as assessed by the Subjective Global Assessment) and hospitalised for either congestive heart failure, acute myocardial infarction, pneumonia, or chronic obstructive pulmonary disease; it had several exclusion criteria including a previous history of diabetes among others. The trial failed to show a difference in 90-day non-elective readmission rate and incidence

of death, which was the primary composite endpoint, but showed positive effects on secondary endpoints. In fact, there was a significant reduction in 90-day mortality in the intervention group compared with the placebo group (4.8 vs 9.7%), resulting in a number needed to treat (NNT) of 20 [22]. However, it remains unclear whether this beneficial effect is attributed to the specific formula or the difference in proteins, given that control patients received a low protein/energy placebo product.

Results of the EFFORT trial

Second, the Effect of early nutritional support on Frailty, Functional Outcomes and Recovery of malnourished medical inpatients Trial (EFFORT), a pragmatic, investigator-initiated, open-label, non-commercial, multicentre, randomised controlled trial, tested the hypothesis that individualised nutritional support to reach protein and energy goals reduces the risk of adverse clinical outcomes in medical inpatients at nutritional risk [23, 24]. This effectiveness trial was conducted in eight Swiss hospitals and randomised 2028 medical inpatients at nutritional risk, defined by a Nutritional Risk Screening (NRS 2002) score ≥3 points, to receive protocol-guided individualised nutritional support to reach protein and energy goals (intervention group) or standard hospital food (control group). The composite primary endpoint was adverse clinical outcome defined as all-cause mortality, intensive care admission, non-elective hospital readmission, major complications and decline in functional status at 30 days with mortality being the principal secondary endpoint of interest. In the trial, nutritional support was provided according to a previously established nutritional protocol [25], which is in line with the ESPEN guidelines for polymorbid medical inpatients [5]. For each patient, individualised nutritional energy and protein goals were defined upon hospital admission. According to the protocol, energy requirements were predicted using the weight-adjusted Harris-Benedict equation or by indirect calorimetry [26]. Additionally, protein intake was set at 1.2–1.5 g/kg body weight per day, with lower targets for patients with chronic renal failure without renal replacement therapy (0.8 g/kg body weight per day). The protocol also proposed nutritional interventions to reach these goals by the establishment of an individual nutritional plan by a trained registered dietician. The initial focus was on the use of oral nutrition including adjustment of meals according to patient preferences, food fortification (such as enrichment of hospital food by adding protein powder), addition of between-meal snacks and oral nutritional supplements. Escalation of nutritional support to enteral tube feeding (or parenteral feeding) was recommended if at least 75% of energy and protein targets could not be reached through oral feeding (or enteral feeding) within 5 days. Upon hospital discharge, patients received dietary counselling for the continuation of nutritional support and, if indicated, a prescription for oral nutritional supplements in the outpatient setting – although this was not enforced by the protocol.

The EFFORT trial found that nutritional goals could be reached, mostly by use of oral nutrition including oral nutritional supplements, in a majority of intervention group patients, with 79% reaching energy goals and 76% reaching protein goals. In a few patients there was an escalation to either enteral or parenteral feeding. More importantly, in the evaluation of the primary endpoint, the trial reported that by 30 days, 232 of 1015 patients (22.9%) in the intervention group experienced an adverse clinical outcome compared with 272 of 1013 (26.9%) of the control group patient, corresponding to a number needed to treat of 25 to prevent one severe complication. There were also significantly lower rates of death in the intervention group compared with the control group (7.2 vs 9.9%) and notable improvements in functional outcomes and in quality of life measures. Thus, these results provide strong evidence for the concept of systematically screening medical inpatients on hospital admission in terms of nutritional risk, independent of the medical condition, followed by a nutritional assessment and initiation of nutritional support in at-risk patients. The results also contradict the hypothesis that provision of nutritional support during the acute phase of illness would have harmful effects – at least in the non-critically ill setting.

Still, the results of EFFORT should not be used to support full-replacement nutritional therapy in medical inpatients. Harmful effects of “overfeeding” have been demonstrated in previous studies [12, 17]. The nutritional algorithm used in the EFFORT trial was thus not very aggressive and recommended escalation of nutritional support to enteral and parenteral nutrition if patients met only <75% of nutritional goals. Thus, EFFORT rather proved that the concept of using individualised nutritional support with an aim of reaching at least 75% of nutritional goals has better clinical outcomes compared with not providing nutritional therapy on top of hospital food. The implementation of the nutritional protocol was based on a pathophysiological rationale and results of observational as well as smaller randomised trials. Unlike the NOURISH trial, which investigated the effect of a specific nutritional formula [22], within EFFORT a variety of nutritional support strategies were used by trained dieticians to reach nutritional goals. Thus, EFFORT does not provide evidence regarding single nutritional components or types of foods, but rather proves that the multifaceted strategy of providing nutritional therapy to reach protein and energy goals during the acute phase of illness is beneficial for patients.

Outlook and conclusions

Understanding the optimal use of nutritional therapy is highly complex because timing, route of delivery, and the amount and type of nutrients may all have important considerations and potentially affect patients' outcomes. Whereas in the NOURISH trial one specific product was tested, namely a high-protein oral nutritional supplement (HP-HMB), the EFFORT trial asked the basic question of whether nutritional therapy based on different nutritional components during the hospital stay improves clinical outcomes of medical patients at nutritional risk compared with standard hospital food. Both trials provide important information to strengthen the evidence regarding the use of nutritional therapy during the acute phase of illness, but both trials also suggest important questions to be addressed by future clinical trials.

Despite strong associations between malnutrition and adverse outcomes, there has for long been a lack in interventional research proving causal inferences. The NOURISH

and the EFFORT trials have now provided evidence that nutrition improves patients outcomes beyond just weight and food intake. From the results of these trials, we now know that individualised nutritional support in medical inpatients at nutritional risk is effective in lowering the risk of adverse outcomes and mortality at 30 days. These findings thus strongly support the concept of systematic screening of medical inpatients, followed by a nutritional assessment and initiation of individualised nutritional support in at-risk patients. It is now important to look closer at clinical nutrition per se and ask whether certain proteins, in regard to quality or quantity, have better or worse effects. The selection, timing, dose and feasibility of nutritional treatment should be evaluated as carefully as those of any other therapeutic intervention, with the aim of maximising efficacy and minimising side effects as well as costs.

The term "personalised medicine" relates to the observation that not all patients show the same response to medical therapies. For example, some patients may derive a marked benefit from nutritional therapy, whereas other patients may have no benefit or may even suffer harm from that intervention. Whether or not a patient benefits from nutritional therapy may relate to illness-specific factors (e.g., comorbidities, acute vs chronic course) or patient-specific factors (e.g., age, gender, comorbid illnesses). Additionally, there may be specific genetic traits that will help in identifying patients who may or may not benefit from nutritional therapy. The metabolomic approach, among others, allows measurement of a plenitude of different markers and signatures, and correlation of these with specific patient phenotypes [27–30]. This should allow us to find specific markers and combinations of markers (termed "signatures") that would enable us to predict response to nutritional treatment and thus, in the future, provide more personalised nutritional clinical treatment of patients. Also, it will be important to understand the effects of nutritional interventions on the microbiome, which might play a key role in answering this question.

Instead of pragmatically using nutritional interventions based on a few rigorous randomised trials, we should go back to where James Lind started in 1747 and perform the large and well-conducted trials needed to truly understand the potential of nutritional therapy to positively influence recovery from disease in the medical inpatient population.

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