⎍ Signa Vitae

REVIEW

Nutritional support in the acute phase of critical illness—how to break the dilemma

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Abstract

Overfeeding caused by the inaccurate estimation of energy might be one of the most important reasons leading to unsatisfactory outcomes of nutritional support, especially for Parental Nutrition (PN). The current method of determining calorie needs by energy expenditure (EE), either measured by indirect calorimetry (IC) or equations, might not accurately represent the actual energy requirements of critically ill patients, especially in the acute phase. Nutrition protocols based on the measurement of time might not be effective. Research on the real-time metabolic status and the actual energy requirements of the patients, as well as more individualized nutrition therapy, is required. Central regulation, especially those involving hypothalamic pathways, is an effective solution for the current dilemma.

Keywords

Nutrition; Critical illness; Energy requirement; Hypothalamic, Central regulation

1. Background

Nutritional support is crucial for critically ill patients. Despite considerable advances in the past decades, the effect of nutritional support is still unsatisfactory. Since studies have provided inconsistent results, nutritional support in critically ill patients has been controversial. The well-known clinical guidelines for the nutritional support of critically ill patients, for example, the Canadian Critical Care Nutrition Guidelines, the ASPEN/SCCM guidelines 2016, and the ESPEN guidelines on EEN 2017, sometimes made contradictory recommendations, which led to some open debates [1–3]. McClave *et al.* [4] reported that only 51.6% and 63.5% of critically ill patients who received enteral nutrition (EN) could reach the calorie target [4, 5]. Malnutrition is one of the most important causes of prolonged hospitalization and poor long-term prognosis in critically ill patients [6–8]. Hence, new approaches are urgently required to accurately determine nutritional support for critically ill patients and improve the effectiveness of nutritional support. In this review, we discussed two major issues, including calorie needs and metabolism in the acute phase. Also, we focused on individualized nutritional therapy, as well as new solutions and what should be considered in the future research of nutritional support during critical illness, especially in the acute phase.

1.1 Does energy expenditure represent actual calorie needs?

Recently, the previous views regarding calorie needs in the acute phase of critical illness were challenged. Most clinical guidelines and trials use energy expenditure (EE) to determine calorie needs in critically ill patients. Many large clinical trials that involved feeding below the actual EE showed similar outcomes compared to the provision of full energy requirements during the first few days in the ICU [9–11]. The EDEN trial compared trophic feeding (15–25% of calorie target) with full enteral feeding for the first six days in participants with acute lung injury, who required mechanical ventilation. The results for the ventilator-free days, 60-day mortality, and infectious complications were similar between the two feeding modes [10]. The PermiT trial compared permissive underfeeding (40% to 60% of calculated caloric requirements) or standard feeding (70% to 100%) for up to 14 days in critical adult patients and showed no difference for the 90-day mortality between the two groups [11]. Permissive underfeeding to approximately 15 kcal/kg with full protein nutrition support might be acceptable in the early stages of critical illness [12]. Recently, observational studies found that feeding 70% of the measured EE was optimum in terms of mortality [13]. As a follow-up to the EPaNIC study, Hermans *et al.* [14] studied the density and thickness of muscle fiber in the low-dose and the high-dose EN groups and found no difference. Additionally, in the ESPEN guidelines for EEN in critically ill patients, 12 RCTs (662 patients) on EEN versus delayed nutritional intake were analyzed. The results suggested no advantage of EEN over delayed nutritional intake in reducing mortality [15]. These results indicated that patients in the acute phase might not require as much energy as we expect.

The calorie needs of critically ill patients may differ from the estimated resting or total EE. The amplitude of EE variations depends on several factors, including the presence of injury or sepsis (type, severity, and metabolic response of the host)

[16], the time course of the disease or the time spent in ICU [17, 18], the current care and treatment provided [19], the nutritional status or the fat-free mass [20], the complications and factors related to the original disease, *etc.* [21, 22]. This variability contributes to the difficulty in estimating the energy needs for the nutritional support of these patients. The 2016 ASPEN/SCCM guidelines recommended that indirect calorimetry (IC) should be used to determine energy requirements when available and when there are no variables that affect measurement accuracy. Additionally, a published predictive equation or a simplistic weight-based equation (25–30 kcal/kg/d) should be used in the absence of IC [23]. Predictive equations could be one of the causes of underfeeding or overfeeding some critically ill patients [24]. However, we argue that the EE method to determine calorie requirements has many limitations and could be the main factor leading to overfeeding. Metabolism includes catabolism and anabolism. The energy expenditure measured by IC mainly represents catabolism [25]. Anabolism is the process of biosynthesis, *i.e.*, it represents the amount of energy the host needs to synthesize proteins, carbohydrates, lipids, *etc.* [26]. Hence, anabolism should also be considered while determining calorie requirements. Additionally, the classic viewpoint considers that caloric needs equal energy expenditure (EE). Thus, the "appropriate" caloric intake is defined as the amount of energy required for the basal metabolism of the body [27]. The caloric needs generally imply the difference between the EE and the level of endogenous calories produced, while caloric debt is the difference between the EE and the caloric intake [28]. Hence, the caloric demands cannot be deducted from the determination of EE alone, as the production of endogenous calories is not quantified. Therefore, during the first few days after the onset of critical illness, the risk of overfeeding is probably higher because the endogenous non-inhibitable production of calories (mainly endogenous glucose production) matches 50–75% of the EE [29]. In the late or chronic phase, when endogenous caloric production is low and might be negligible, assessing the EE can help to determine the maximum caloric intake [28].

Higher EE (measured by IC) indicates higher catabolism, accompanied by lower anabolism. In this case, exogenous nutrients cannot be used, leading to redundant metabolic burdens to the host. According to Casaer and Rabinowitz, feeding in the early phase of critical illness might not be necessary as the patient is highly stressed; improper nutritional therapy could activate autophagy and cause adverse outcomes [30, 31]. Therefore, if calorie intake is determined based on the EE and the energy catabolism is ignored, it may lead to excessive intake of nutrients, which might cause additional metabolic problems in critical patients, especially in the acute phase. Thus, critical patients should be provided lesser nutrients than the EE in the acute phase. In the first 2–3 days, trophic nutrition should be provided. If this mode of feeding is tolerated after 48–72 h, the energy intake can be gradually increased to >80% of the target energy in the late or recovery phase. IC would be suitable for measuring energy intake. Bedside 13C/12C breath carbon ratio mass spectroscopy might be promising in the future [32, 33].

1.2 EN *vs*. PN, which is better?

EN was shown to be better than PN in several studies. The advantages of EN include maintaining the integrity of the intestinal mucosal barrier, immunoregulation, modulation of stress, promoting gastrointestinal motility, *etc.* [34, 35]. On the other hand, the adverse events associated with PN include a higher nosocomial infection rate [36]. Thus, in critically ill patients who require nutrition support therapy, EN is preferred to PN.

However, different opinions have emerged in recent years. In the CALORIES trial, within 36 h of admission to ICU, initiation of early EN or early PN did not affect 30-day mortality [37]. Participants in the EPN trial received either early PN or standard nutrition therapy, with no significant differences observed either in 60-day mortality or the length of ICU stay. However, coagulation biomarkers and the duration of ventilation showed better results in the EPN group [38]. As mentioned in the ESPEN guidelines on EEN, data from seven RCTs with 2686 patients were analyzed in a meta-analysis. The results showed that EEN had similar mortality compared to early PN [15]. A more recent meta-analysis also could not determine whether EN is better (or worse) than PN at 90 days and 180 days, as well as, on ventilator-free days and during adverse events [39]. An updated systemic and meta-analysis including 18 RCTs with 3347 patients showed no difference in the total mortality between the groups receiving EN or PN, although EN, compared to PN, showed significantly lower infectious complications [40]. These results challenged the idea that EN is preferred to PN for critical patients. Most studies showing advantages of EN over PN have used different equations to calculate full energy needs, but these equations have been shown to lead to overfeeding [41]. Studies comparing early PN in both children and adults have shown negative results with early supplemental PN (SPN). These studies aimed to meet full equation-based energy targets during the first two days in critical patients [30, 42]. In the most recent trial where EN and PN were provided at a similar rate, the hypothesis of PN being the only reason for mortality and infection was not confirmed in the CALORIES trial [37]. The patients who received PN were more likely to reach the calorie target than those who received EN. In the EDEN trial, patients in the full feeding group only met 70% of the energy targets, while in the CALORIES trial, more patients in the early PN group reached the calorie target than those in the EN group [10, 37]. Thus, overfeeding in the early stage (more likely achieved by PN as compared to EN), and not the use of PN, accounts for the negative results [43]. EN has more advantages than PN in the case of small dose/nourishing dose. While addressing full energy requirements (most of the time, excessive), the advantages of EN over PN are weakened or even abolished. Regarding the nutrition substrates and the calories provided, there might be no difference between PN and EN.

1.3 EN provides more than nutrition and protection

As mentioned above, patients receiving parenteral nutrition are more likely to meet the energy demand than enteral nutrition. However, a large number of experiments have shown that en-

teral nutrition is better and indispensable. Many international guidelines and expert opinions suggest that the enteral route is the first choice in critically ill patients without EN contraindications [44–47]. Thus, enteral nutrition may not only provide nutrition and protection to the intestinal mucosa but also stimulate the production of gastrointestinal hormones through food to provide feedback to the central nervous system, such as the hypothalamic melanocortin system [48, 49]. The central nervous system (CNS) receives peripheral correlational signals, which are capable of regulating personal energy balance through metabolic, neural, and endocrine signals. Ingested nutrients are in contact with multiple parts of the gastrointestinal tract, potentially altering peptides and nerve signals [50]. The intestine releases several peptides during feeding that affect the hypothalamic pathways engaged in the modulation of satiety and metabolism. Within the hypothalamus, there are complicated relationships among nuclei, of which, the arcuate nucleus is one of the most vital hypothalamic centers for regulating food intake. The neuropeptides in the hypothalamus involved in the regulation of food intake also play a pivotal role in the regulation of glucose metabolism and energy expenditure. Additionally, gastrointestinal hormones also impact glucose metabolism and energy expenditure [51–53].

1.4 Managing metabolic disorders in the acute phase of critical illness

Recent evidence suggests that accounting for endogenous energy production and metabolic changes in early critically ill patients is essential for making nutritional decisions [54, 55]. In the acute phase of critical illness, exogenous nutrients provided by either EN or PN might have little or no effect on metabolic alterations, especially on anabolism, leading to anabolism resistance [26]. Anabolism resistance is the result of several metabolic changes associated with an increase in protein breakdown, glucose and lipid metabolic disorders, a decrease in liver synthetic functions, *etc*. [56]. Besides suffering from anabolism resistance, critically ill patients also suffer from hypercatabolism in the acute phase. Anabolism resistance and hypercatabolism reduce the effectiveness of nutritional support [57]. Thus, interventions to correct metabolic disorders might be an effective management strategy for the problem associated with nutritional support in critical illness.

Metabolic disorders, including excessive catabolism and anabolic resistance, are a systemic pathological response rather than a local change, which prompts people to believe that central regulation must play an important role in its pathogenesis. Among all the metabolic disorders, high protein catabolism and muscle wasting are considered to be the most important factors related to morbidity and mortality [57]. In the last few years, we focused on studying the mechanism of hypercatabolism, especially muscle wasting, in critically ill patients and determining some possible solutions. Our previous studies suggested that central regulation, especially involving the hypothalamic arcuate nucleus (ARC), might play an important role in septic muscle wasting in animal models [58]. ARC is composed of two populations of neurons, POMC and AgRP neurons [59]. POMC expresses anorexigenic peptides, POMC and CART, resulting in negative energy

balance, while AgRP expresses ingestive peptides, NPY, and AgRP, resulting in positive energy balance [60]. First, we showed that the expression of certain hypothalamic neuropeptides (*e.g.*, POMC, CART, and AgRP) were closely associated with muscle wasting (measured by 3-Methylhistidine and tyrosine, mRNA expression of MuRF and MAFbx genes) in septic animal models [61]. Additionally, we found that the iKKβ/NF-κB inflammation pathway and the AMPK autophagy pathway might be involved in the central regulation of septic metabolic disorders [57, 62, 63]. Then, we showed that the administration of dexmedetomidine and hypothermia could alleviate muscle wasting by regulating the expression of certain hypothalamic neuropeptides in septic animal models [64, 65]. Although these results are based on animal models, these effects could also be relevant in critically ill patients. Our results and hypothesis support the rationale that future studies on hypercatabolism in critical illness should investigate central regulation, which might provide some new strategies to improve the effect of nutritional support on critically ill patients.

1.5 Individualized nutritional support strategy: the future direction

Recent guidelines recommend the use of supplemental PN after 7–10 days for patients at low or high risk of nutrition which cannot meet >60% of their energy and protein requirements by the enteral route alone. Starting supplemental PN in some critically ill patients on EN before these 7–10 days does not improve outcomes and may be detrimental to the patient [23]. Making nutritional decisions based on the "one size fits all" approach for critically ill patients using time as the only determinant is no longer considered appropriate. First, due to the differences in body mass, complexity, rapid changes during illness, and different stress response levels, each critically ill patient could have different metabolic requirements over time [66, 67]. Thus, recommending the initiation of PN or EN based solely on time since admission, while disregarding the current metabolic status, may not be accurate. Second, for most critical illnesses, the acute phase lasts for about 7–10 days [26]. Then, metabolic disorders might start to recover gradually, with a decrease in catabolism and an increase in anabolism [45]. This may explain why most existing clinical trials making protocols based on the number of days showed positive results. However, a duration of 7–10 days does not cover the acute phase for all critically ill patients. Thus, initiating nutritional interventions only based on time should be abandoned.

Generally, there are two major problems in nutritional support for critical patients in the acute phase. The first problem involves correcting metabolic disorders, including hypercatabolism and anabolism resistance. The second problem involves searching for sensitive anabolism biomarkers to determine energy requirements for critically ill patients. The current method to determine calorie requirements by EE, either measured by IC or through equations, mainly represents catabolism rather than anabolism. Most of the critical patients suffer from high catabolism and low anabolism in the acute phase. Thus, the calorie requirements determined by EE do

not represent the actual energy requirements of the patients.

Instead, a shift of focus on the metabolic status and actual energy requirement of each patient is more likely to improve the nutritional support strategies in critically ill patients. Individualized nutritional therapy requires assessment of the real-time metabolic status and the actual energy requirements. This can help to make better decisions on nutritional support in critically ill patients. Ideally, accurate monitoring of metabolic responses should direct nutritional therapy, including decisions regarding the time to start feeding and the proper calorie target [43]. Unfortunately, such monitoring techniques are currently unavailable. A primary factor restricting optimal management is the inability to measure the dynamics of the glucose, protein, and lipid turnover at the bedside of an individual patient [34]. Having such monitoring tools would enable precise nutritional and metabolic therapy to reverse hypercatabolism and anabolism resistance.

2. Conclusions

Overfeeding caused by the inaccurate estimation of energy might be one of the most important reasons for unsatisfactory outcomes of nutritional support, especially for PN. The current method of determining calorie requirements by EE, either measured by IC or through equations, might not accurately represent the actual energy requirements of critically ill patients, especially in the acute phase. It is not recommended to make nutrition protocols based on the measurement of time. Focus on the real-time metabolic status and actual energy requirements of the patients, as well as more individualized nutrition therapy, should be considered in future studies. Central regulation, especially involving the hypothalamic pathways, might be one of the most effective solutions for the current problem.

ABBREVIATIONS

ICU, Intensive Care Unit; EN, Enteral Nutrition; PN, Parental Nutrition; ASPEN, American Society of Parenteral and Enteral Nutrition; SCCM, Society of Critical Care Medicine; ESPEN, European Society of Clinical Nutrition and Metabolism; RCT, Randomised controlled trial; EDEN, Early *vs.* Delayed Enteral Feeding to Treat People with Acute Lung Injury or Acute Respiratory Distress Syndrome; EPaNIC, Early Parenteral Nutrition Completing Enteral Nutrition in Adult Critically Ill Patients; EE, Energy Expenditure; IC, Indirect Calorimetry.

AUTHOR CONTRIBUTIONS

JD, MC and YX equally contributed to the original draft writing and investigation; WY contributed to the conceptualization and reviewing of the review. All authors critically revised the manuscript, agreed to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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