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Opinion paper

Combining nutrition and exercise to optimize survival and recovery from critical illness: Conceptual and methodological issues

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SUMMARY

Survivors of critical illness commonly experience neuromuscular abnormalities, including muscle weakness known as ICU-acquired weakness (ICU-AW). ICU-AW is associated with delayed weaning from mechanical ventilation, extended ICU and hospital stays, more healthcare-related hospital costs, a higher risk of death, and impaired physical functioning and quality of life in the months after ICU admission. These observations speak to the importance of developing new strategies to aid in the physical recovery of acute respiratory failure patients.

We posit that to maintain optimal muscle mass, strength and physical function, the combination of nutrition and exercise may have the greatest impact on physical recovery of survivors of critical illness. Randomized trials testing this and related hypotheses are needed. We discussed key methodological issues and proposed a common evaluation framework to stimulate work in this area and standardize our approach to outcome assessments across future studies.

1. Introduction

Critically ill patients receiving mechanical ventilation are at high risk of developing ICU-acquired complications. Survivors of critical illness commonly experience neuromuscular abnormalities, including muscle weakness known as ICU-acquired weakness (ICU-AW) [1]. The incidence of neuromuscular abnormalities ranges from 25% to 100% of critically ill patients depending on definitions used and populations studied [1]. Patients who develop sepsis, multi-organ failure, or prolonged mechanical ventilation or immobility are at particular risk for developing neuromuscular abnormalities [1–3]. ICU-AW is associated with delayed weaning from mechanical ventilation, extended ICU and hospital stays, more healthcare-related hospital costs, a higher risk of death, and impaired physical functioning and quality of life in the months after ICU admission [1,2,4]. These observations speak to the importance of developing new strategies to aid in the physical recovery of acute respiratory failure patients.

Conceptually, nutrition and exercise may be potential strategies to prevent or attenuate ICU-acquired weakness and associated physical impairments; however, further evidence is needed [5]. The objective of this paper is to discuss the concept of early implementation, during critical illness, of a combined nutrition and exercise intervention to improve survival and recovery from critical illness. Herein, we provide rationale for a combined intervention

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and some conceptual and methodological issues to consider for research evaluating this hypothesis.

2. Concepts in support of a combined intervention

2.1. Nutritional intervention

Prior large-scale observational studies of critically ill patients suggest that optimal amounts and timely provision of nutritional intake is associated with reduced infectious complications, duration of mechanical ventilation, and mortality [6–8], along with perceptions of faster physical recovery [9]. Further examination of the data suggests that optimizing daily protein intake, rather than total daily caloric intake, may more positively affect ICU patient outcomes [10,11]. Large, randomized controlled trials (RCT) evaluating the potential benefit of enhanced protein intake on clinically important endpoints are lacking. However, small trials demonstrate that greater protein intake is associated with improved weaning from mechanical ventilation [12] while larger trials show non-significant improvements in long-term physical functional performance (6 min walk test at 12 months) [13] and a significant improvement in 60-day quality of life [14]. In contrast, some observational studies have suggested that greater versus lesser protein intake is associated with greater muscle wasting [15] and lower likelihood of an early discharge from ICU [16]. However, these observational studies have methodological flaws that limit the validity of their findings [8,17].

Overall, controversy exists regarding optimal protein and amino acid doses in critically ill patients. Some advocate that doses as high as 2.5 g/kg/day are effective and safe [18]. A recent prospectively defined subgroup analysis of a large RCT infusing amino acids up to 2.0 g/kg/day demonstrated a significant survival advantage (6% absolute risk reduction in mortality) in a subgroup of patients with no renal impairment at baseline (unpublished data). Controlled prospective randomized trials could help resolve this controversy and confirm this subgroup effect.

2.2. Exercise interventions

With increasing recognition of ICU-AW and related physical impairments, there has been an increasing interest in early ICU-based exercise/rehabilitation strategies. These interventions have shown reductions in durations of mechanical ventilation and ICU stay as well as improved physical function [19]. However, existing studies have not reported nutrition intake or have grossly underfed their patients [20–23]. Hence, there may be an opportunity to simultaneously optimize the ICU delivery of nutrition and early ICU rehabilitation.

2.3. Studies in support of combined administration of early nutrition and early exercise

In various non-critically ill populations and in various conditions with muscle atrophy, combining protein and exercise interventions have the largest treatment effects compared with either nutrition or exercise alone. For instance, in older people, exercise along with protein supplementation may promote greater rates of protein synthesis [24,25] and greater improvements in strength compared with exercise alone or nutritional supplements [26–28]. Other studies in patients with obesity [29], HIV/AIDs [30], chronic obstructive pulmonary disease [31] and healthy volunteers undergoing 60 days of bed rest [32,33] suggest that the nutritional intervention, alone, has minimal effect on muscle, but that the combination of exercise and nutritional intervention yields the greatest improvement in muscle mass and strength. In a recent meta-analysis, protein supplementation, when combined with resistance-type exercise training, enhanced gains in strength and muscle mass in both young and elderly non-critically ill adults compared with groups that did not supplement with protein [34]. Accordingly, recent international guidelines recommend 1.0–1.2 g of protein/kg/day protein intake and daily exercise in older adults (resistance training and aerobic exercise) [35].

Although the generalizability of these findings to critically ill patients is unclear, there is biologic plausibility that applying this combined approach may optimize the reduction of muscle atrophy and physical impairments. Patients in the ICU have substantial muscle wasting, which may be related to several postulated factors among which are inflammation, insulin resistance and disuse atrophy [1,36].

2.3.1. Inflammation has a catabolic effect on muscle

Regardless of health status and age, inflammation is associated with muscle atrophy. Pro-inflammatory cytokines, including tumor necrosis factor (TNF)-α and interleukin (IL)-6, are particularly catabolic and are elevated not only in critically ill patients, but also with prolonged bed rest [37–39]. Interestingly, short-term bed rest (7 days) in older adults was associated with increases in some pro-inflammatory cytokines in muscle despite the absence of change in systemic pro-inflammatory cytokines [40]. Thus, immobility may also contribute to pro-inflammatory processes, which may further exacerbate muscle atrophy when combined with critical illness in an older population.

2.3.2. Insulin resistance has negative implications on muscle mass

Insulin normally prevents muscle protein breakdown [41]. Insulin resistance is a condition in which muscle is resistant to the action of insulin, resulting in reduced insulin-stimulated glucose transport [42] and amino acid delivery into muscle [43]. In an insulin resistant state, there is increased muscle protein catabolism. In ICU patients [44], insulin resistance is generally present and associated with deleterious outcomes [45,46]. Animal models have documented the development of insulin signaling defects in muscle, leading to insulin resistance within muscle [47,48]. In humans, muscle is insulin resistant and can respond to intensive insulin therapy [49]. However, in other clinical populations, insulin sensitivity also can be modified with physical activity [50] and by increased availability of specific amino acids, such as leucine [51].

2.3.3. Disuse atrophy as a result of immobility will modify muscle protein kinetics and strength

With bed rest, associated muscle breakdown is related to functional losses and reduced protein synthesis [52]. Studies in healthy populations using diverse immobilization protocols have all demonstrated accelerated muscle loss within the first 10 days of immobilization [51–53]. With immobility [48] and prolonged bed rest [49,50], as is commonly experienced during critical illness [2,54], muscle develops anabolic resistance, where decreased uptake of amino acids reduces the ability to promote anabolism [55]. Muscle loss is further exacerbated when compounded by hypercortisolemia, which can occur endogenously from the stress response or from common exogenous administration to critically ill patients [56,57].

2.4. Exercise stimulates a net positive muscle protein balance

Exercise will not only enhance anti-inflammatory processes and improve muscle insulin sensitivity, but it may reduce insulin requirements. Secondary analysis of an RCT evaluating early versus late physical rehabilitation in ICU patients demonstrated reduced insulin dose for the same measure of glycemic control and reduced

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