Nutritional Consequences of Critical Illness Myopathies

Myopathies in Critical Illness: Characterization and Nutritional Aspects

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ABSTRACT Myopathies related to critical illness have received increasing recognition over the past decade and are common in patients even after a brief period in the intensive care unit. Recent studies have revealed that myopathies in the critically ill may in fact be more prevalent than neuropathies and that morbidity and mortality may be greater. Protein catabolism, an increase in urinary nitrogen loss, and muscle wasting are observed in critical illness myopathy. Muscle biopsies in critically ill patients demonstrate low glutamine levels, low protein/DNA levels, and high concentrations of extracellular water. The increased flux of glutamine in muscle in these patients is thought to be insufficient to meet the body’s requirement for glutamine, and thus in critical illness this amino acid may be classified as “conditionally essential.” Three subtypes of critical illness myopathy have been described that are often grouped together as acute quadriplegic myopathy; thick-filament myopathy, critical illness myopathy, and necrotizing myopathy. These can be differentiated based on clinical features and muscle biopsy. Treatments for critical illness myopathies range from primary prevention, i.e., avoiding myopathy-inducing drugs, to novel nutritional therapies, such as glutamine and glutathione supplementation. One should be particularly vigilant for the development of myopathies in critically ill alcoholic patients, who may have a chronic alcoholic myopathy at baseline. In the past decade, advances have been made in characterizing and identifying patients with myopathies due to critical illness. However, additional studies must be performed in order to develop appropriate therapies for this potentially devastating disorder.

KEY WORDS: • neuromuscular diseases • glutamine • arginine • alcohol abuse • glutathione

In critically ill patients, several key effectors of metabolism lead to the development of myopathies. In these patients, muscle protein depletion is much more rapid and extensive than would be expected merely from inactivity (1). Inflammatory mediators, hormone secretion and action, tissue perfusion, and the level of physical activity are all altered (1). Some of these abnormalities may be beneficially affected by nutritional modulation. For example, upregulation of inflammatory mediators affects the metabolic pathways leading to alterations in skeletal muscle metabolism. TNF-α and IL-1 mediate accelerated gluconeogenesis, protein degradation, and decreases in skeletal muscle protein synthesis. Increases in glucocorticoid, growth hormone, and glucagon levels stimulate gluconeogenesis, protein degradation, and decreases in skeletal muscle protein synthesis. Muscle biopsies in critically ill patients demonstrate low glutamine levels, low protein/DNA levels, and high concentrations of extracellular water. In contrast to this, stressed patients can lose as much as 250 g/d of muscle protein, equivalent to 750 to 1000 g of muscle tissue. In critically ill patients, and decrements in cellular hydration can result in tissue protein catabolism. Increased blood flow to various organ systems including muscle (observed in states such as sepsis) can promote glucose and amino acid utilization. Finally, limited physical activity coupled with inappropriate nutritional support may further contribute to the metabolic alterations seen in critically ill patients.

Characterization and incidence

The hallmark feature of the stress response characterizing critical illness is protein catabolism with an increase in urinary nitrogen loss and muscle wasting. Patients who are starved lose ~75 g/d of muscle protein, equivalent to 200 to 300 g of muscle tissue. In contrast to this, stressed patients can lose as much as 250 g/d of muscle protein, equivalent to 750 to 1000 g of muscle mass/d. As protein is catabolized, amino acids provide the carbon skeletons necessary for gluconeogenesis. Skeletal muscle is the predominant reservoir for these amino acids (3). Moreover, despite standard nutritional support, loss of body protein appears to occur unabated through the early weeks of treatment in the intensive care unit (ICU) (4). Over the past several decades, there has been an evolution in the number of neuromuscular disorders identified in the ICU setting. In the earlier part of the 20th century, patients who

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4 Abbreviations used: CPK, creatine phosphokinase; EMG, electromyography; GH, growth hormone; GLN, glutamine; GSH, glutathione; ICU, intensive care unit; ICUAP, intensive care unit acquired paresis; IGf, insulin-like growth factor; NAC, N-acetylcysteine; NMBA, neuromuscular blocking agent; RMP, resting membrane potential; RR, risk ratio.
were ventilator dependent secondary to the effects of poliomyelitis were commonly identified, whereas in the latter part of that century, newer laboratory techniques allowed clinicians to identify individuals with Guillain-Barré syndrome and such neuromuscular transmission disorders as myasthenia gravis. More recently, with the advent of a multidisciplinary approach to the delivery of critical care, it has been noted that although patient survival appears to be improving overall in the ICU, it is at the expense of the development of neuromuscular disorders in individuals being treated for nonneuromuscular illnesses. A recent prospective multicenter study to determine the incidence, risk factors, and outcomes of intensive care unit-acquired paresis (ICUAP) examined a cohort of patients from both medical and surgical ICUs in France, determining that the incidence of weakness in this group of patients was ~25% (24/95) (5). Electromyographic abnormalities were present in 10 of the 24 paretic individuals, and all muscle biopsies of these patients revealed myopathic changes, ranging from type II fiber atrophy with myosinolysis to muscle fiber necrosis and neurogenic muscle atrophy. Independent predictors of ICUAP were female sex (OR = 4.66; 95% CI = 1.19–1.49), duration of mechanical ventilation (OR = 1.10; 95% CI = 1.00–1.22), and administration of corticosteroids (OR = 14.90; 95% CI = 3.20–69.80).

Earlier investigations focused on the incidence, characterization, and outcomes of myopathies (not merely paresis) in the ICU. Coakley and colleagues (6) performed muscle biopsies in 23 ICU patients with an expected length of stay of >7 d. They determined that a majority of patients had pathology involving the musculature varying from myopathic features with atrophy and regeneration to mild and diffuse atrophy of type I and II fibers. Further, electromyogram (EMG) abnormalities were present in a majority of the patients studied. Lacomis and colleagues (7) at the University of Pittsburgh performed EMGs on 92 patients with weakness; outcomes were available on 83 patients. Myopathy was determined to be present in 43 of the 92 patients (46%). Twenty-seven of these patients had received high doses of intravenous corticosteroids (cumulative doses of 1 g methylprednisolone or its equivalent), and 7 had received large doses of neuromuscular blocking agents (NMBAs). Ultimately 13 of the 43 myopathy patients succumbed to their illnesses (30%), and 6 of the 30 (20%) surviving myopathy patients required >4 mo to become ambulatory. In summary, compared to other neuromuscular diagnoses such as neuropathies, the number of patients affected with myopathies, as well as their morbidity and mortality, was greater.

To better ascertain the changes that occur in muscle in critically ill patients and to develop new treatment options, Gamrin and colleagues (8) examined 20 critically ill patients with heterogeneous diagnoses who had been in the ICU from 3 to 14 d (APACHE II scores ranged from 11 to 31). They concurrently recruited healthy control subjects. Muscle biopsies and blood samples were obtained from all 20 patients. A second biopsy was obtained 3 to 7 d later from 9 patients who were expected to be in the ICU >4 d (9). The initial biopsies were then compared to biopsies from normal healthy control subjects; striking differences were observed. The total amino acid concentration was substantially decreased in the critically ill patients, most strikingly the glutamine concentration (reduced 72% compared to controls). In contrast, the branched-chain amino acid (BCAA) concentration was substantially increased in the patients. The alakali-soluble protein:DNA ratio was substantially decreased in the patients, and concentrations of ATP and creatine phosphokinase were diminished. Extracellular water was increased and intracellular water was decreased in the patient group, compared to controls. Comparison of the 9 repeat biopsies to the first set of patient biopsies (9) showed that glutamine levels did not recover, and BCAA concentrations continued to rise an additional 25%. Further, the alkali-soluble protein:DNA ratio declined an additional 12%. Extra- and intracellular water abnormalities persisted, and the biopsy fat content increased by 130%, compared to the initial sampling.

These results have several implications (8,9). First, despite the heterogeneity of the patients, interpatient results were reasonably consistent, with the most consistent being low levels of glutamine, low alkali-soluble protein:DNA ratio, and high concentration of extracellular water. The concentration of muscle glutamine appeared to be a good qualitative marker of the presence of a protein catabolic state in muscle. The continued decline observed in the alkali-soluble protein:DNA ratio appeared to indicate augmented degradation of muscle proteins, in addition to decreased synthesis of these proteins, and appeared to be associated with the time course of the illness. The authors felt that this probably reflected a mismatch between protein synthesis and degradation. In addition, an inverse relation existed between glutamine and ATP levels, perhaps implying ineffective tricarboxylic acid cycling within the mitochondria of muscles. That is, energy production was not occurring from the utilization of glutamine/glutamate, resulting in the accumulation of glutamate. The observation that glutamine levels decreased early in the course of illness, and then did not decline further over time, potentially indicated a regulatory mechanism operable at full throttle from the beginning of illness. The increased concentrations of BCAs may have indicated continuous proteolysis to provide amino acids for other tissues and provided a good candidate to monitor for the efficacy of nutritional intervention. The presence of an increased amount of fat in the muscle biopsies over time perhaps indicated storage of supplied nutrients, or rather implied overfeeding of the patients. Also, the loss of whole-body intracellular water reinforced the concept of progressive cellular dehydration as affecting the regulation of protein metabolism.

Glutamine (GLN) is involved in more metabolic processes than any other amino acid, with the majority of free GLN synthesized and stored in skeletal muscle, where levels are >30-fold higher than in blood. This amino acid both stimulates protein synthesis and inhibits protein breakdown. Despite the obvious need for this amino acid during critical illness, glutamine is not present in conventional parenteral nutrition solutions and is available only in modest amounts in most commercial enteral nutrient products (Ziegler, T., Emory University School of Medicine (2003); personal communication). To assess the metabolism of this amino acid in critically ill patients, Jackson and colleagues (10) administered radiolabeled glutamine intravenously to 7 critically ill patients and 12 control subjects. They demonstrated an increase in the metabolic clearance rate of glutamine, but a lower plasma glutamine concentration. These findings were believed to be secondary to a change in the glutamine transport process in critically ill patients, such that glutamine was supplied more often from protein breakdown and less often from de novo synthesis. This suggests that the increased flux of glutamine from the muscle is insufficient to meet the increased demand for glutamine and that in fact glutamine may be “conditionally essential” in critically ill patients. Recently, the role of the ubiquitin-proteosome pathway, which may be key in protein degradation, has been elucidated (11). Most cellular proteins are degraded by a multienzymatic process requiring ATP. Proteins degraded by this process are first marked for break-
down by covalent linkage to the small protein cofactor, ubiquitin. Medical conditions such as sepsis, burns, and trauma activate the ubiquitin-proteosome pathway. IL-1 and TNF activate this ATP-dependent proteolysis. When ubiquitin mRNA was measured in the muscles of animals and humans with the serious medical conditions mentioned, it was present in higher concentrations.

The loss of amino acids and muscle does not explain the whole phenomenon of critical illness myopathy (12). Although the loss of muscle mass is certainly a culprit, disturbances in electrolytes and calcium gradients of the muscle result in loss of muscle contractility through their effects on the resting membrane potential (RMP). This in turn may lead to the loss of amino acids and thereby muscle mass. Protein balance within the muscle can only be normalized after the recovery of the RMP; otherwise, transporters of amino acids appear to work abnormally. Increases in intracellular calcium will activate proteases and phospholipases that may contribute to muscular atrophy and cell death. Various pathways contribute to abnormal muscular contractility; thus, an abnormal RMP includes neuropathies that can occur concurrently with myopathies in critical illness, leading to decreased amplitude of the nerve’s action potential, with resulting decrements in contractility. Reductions in calcium-pump activity of the muscle’s sarcoplasmic reticulum lead to higher cytosolic calcium and slowing of muscle relaxation. Motor endplates responsible for the transmission of contractile signals to the muscle may function abnormally in patients treated with NMBAs. And finally, the loss of the sodium/potassium gradient of the muscle fiber membrane leads to decreased membrane potential and excitability.

**Acute myopathy of intensive care**

Three main subtypes of myopathy are grouped together as either acute quadriplegic myopathy or acute myopathy of intensive care (13). The 3 subtypes include thick-filament myopathy, critical illness myopathy, and acute necrotizing myopathy of intensive care. In differentiating among the various types of myopathy, it is important to remember that striated (skeletal) muscle tissue consists of both fast-twitch (type I) and slow-twitch (type II) muscle fibers. Further, each sarcomere is composed of both thin actin filaments and thick myosin filaments. Fast-twitch muscle fibers have a less active oxidative metabolism and thus are less susceptible to hypoxia. They are overall less resistant to fatigue. These fibers predominate in muscle groups where much rapid movement occurs, such as the legs. On the other hand, slow-twitch muscle fibers have a more active oxidative metabolism and are more susceptible to hypoxia. They are, however, more resistant to fatigue and predominate in those muscle groups involved in the maintenance of posture, such as the muscles of the back. Knowledge of the clinical aspects of each subtype of myopathy may aid the clinician in tailoring nutritional and other therapies toward individual patients with myopathies.

Thick-filament myopathy is seen in ICU patients who may have been treated with corticosteroids or NMBAs, and in some patients with the sepsis syndrome (14). The etiology underlying this disorder is not known precisely but is believed to involve steroids or mediators of sepsis, stimulating muscle proteolysis that then is amplified by muscle inactivity. Pathologically, one may see a selective loss of myosin filaments that is either focal or diffuse, with a loss of myosin ATPase staining. Neurogenic changes are typically absent. Patients may progress to diffuse myonecrosis. Clinically, one might expect the patient to have difficulty with ventilator weaning or to have a history of steroid and/or paralytic use. On physical examination, patients will exhibit a severe areflexic flaccid paralysis, ophthalmoplegia, and occasionally an elevated creatine phosphokinase (CPK) level. Unfortunately, there is no good correlation of this disorder with steroid or paralytic doses, and CPK levels are typically not useful in monitoring the course of the disease. Case reports seem to indicate that the neuromuscular blocking agent vecuronium is particularly nefarious in its association with this disorder.

Critical illness myopathy is a more insidious subtype of the acute myopathies of critical care (15). Patients who are at risk for this disorder include those with a severe catabolic critical illness, particularly those who have had a protracted course in the ICU. Possible etiologies for this disorder include the direct and indirect influences of the cytokine network on skeletal muscle protein metabolism, with involvement of glucocorticoids, IL-1, and TNF. Also, upregulation of the ubiquitin-proteosome pathway has been implicated. The pathology described for this disorder is not highly specific but includes variations in the size of the muscle fibers with fiber atrophy, some angulation of fibers, fatty degeneration of muscle fibers, and fibrosis. No inflammatory response is typically seen in the muscle, and CPK levels are normal. This type of myopathy should be suspected in patients who fail to wean from the ventilator, particularly in those patients who have been affected by severe sepsis or other catabolic diseases. It should also be suspected in those individuals who exhibit muscle wasting with biochemical signs of malnourishment despite adequate energy intake. Mild abnormalities on EMG examination make this disorder difficult to diagnose, and muscle biopsy may be required. Critical illness myopathy may frequently accompany chronic inflammatory polyneuropathy, thus adding to the confusion of this diagnosis. It must be remembered that this subtype of myopathy is not necessarily associated with the prior use of steroids or NMBAs.

Necrotizing myopathy is probably the most straightforward subtype of acute myopathy of intensive care to diagnose (16). Pathologically, one would expect to see prominent myonecrosis along with vacuolization and the phagocytosis of muscle fibers. CPK levels are frequently elevated. The underlying cause of this type of myopathy is thought to be certain “priming” factors that render the muscle sensitive to several noxious “triggering” factors. This type of myopathy may progress to frank rhabdomyolysis.

The acute myopathies of critical illness have proven problematic to study systematically (17). It is difficult to differentiate these myopathies from rhabdomyolysis due to drugs or sepsis, and critical illness-related myopathy may in fact be part of the spectrum of rhabdomyolysis. In addition, it is difficult to separate critical illness polyneuropathy from myopathy, because patients may have EMG features characteristic of either diagnosis (e.g., low-amplitude compound motor action potentials). Unfortunately, muscle biopsy alone does not always provide a conclusive diagnosis. Examining the existing data with regard to nutritional support in critical illness and trying to extrapolate useful information translating into treatments or prophylaxis for myopathies is also problematic. Study groups are often small and heterogeneous, with definitions of malnutrition varying across studies. Patients are often examined over short treatment periods with uncertain adherence to protocol, and clinically relevant outcome variables are often overlooked. In addition, responses to nutritional therapy are certainly affected by the course and type of the disease process, with nutritional therapy only one part of the overall therapy of patients with these complex disorders.
Treatments for critical illness myopathies range from the obvious to the novel. It is hoped that clinicians can minimize the use of steroids and NMBAs, particularly vecuronium, which has been implicated in myopathy after a single dose. Also, the utilization of these agents in combination may pose a greater threat to a patient in terms of developing myopathy than either agent alone. Earlier therapeutic intervention in physical therapy may prove to be of benefit, to obviate the disuse atrophy that undoubtedly potentiates this disorder. Lack of physical activity, in fact, may amplify the catabolic effects of cortisol on muscle protein degradation (18).

Nutritional and supplemental therapies include protein and amino acid supplementation, antioxidant therapy, and hormonal therapy. Studies examining nutritional supplementation are difficult to extrapolate to the treatment of myopathies, in that they typically focus on enhancement of the immune system or other global outcomes and not the correction of end-organ problems, such as myopathies.

Novak and colleagues (19) conducted a meta-analysis in 2002 to examine the relation of glutamine supplementation to hospital length of stay, complication rates, and mortality in both patients undergoing surgery and those with critical illness. They focused on 14 randomized trials. Using aggregated results, glutamine supplementation and mortality were associated with a risk ratio (RR) of 0.78 (95% CI = 0.58–1.04). For glutamine supplementation and complications from infection, the RR was 0.81 (95% CI = 0.64–1.00). In addition, glutamine supplementation was associated with a shorter hospital length of stay (−2.6 d; 95% CI = −4.5 to 0.7). A priori defined subgroup analysis indicated that the greatest treatment benefit was associated with parenteral, high-dose glutamine supplementation, and hospital length of stay was affected most favorably in surgical patients instead of critically ill patients. Although this meta-analysis did not explore the effects of glutamine supplementation directly, one could infer that patients with a shorter length of stay might have a lower incidence of ICU-acquired myopathies. Supplemental glutamine in total parenteral nutrition was associated with a survival benefit in ICU patients that apparently was sustained over a 6-mo trial period (20).

Garcia de Lorenzo and colleagues (21) examined 69 patients with sepsis, divided into 3 groups that received 3 different types of isocaloric total parenteral nutrition, each type varying in the quality and quantity of amino acids. The short half-life of plasma proteins increased in those patients treated with high loads of BCAAs. In addition, there was a relation among plasma concentrations of leucine, isoleucine, valine, arginine, and BCAAs as part of a nutritional support regimen. The primary outcome (and major finding) of this study was the lower mortality observed in patients treated with high BCAA loads (i.e., ≈0.5 g·kg⁻¹·d⁻¹). Other investigators (3) studying BCAA-rich total parenteral nutrition found these solutions capable of correcting the plasma amino acid imbalance that exists in sepsis. As mentioned previously, plasma BCAA measurement may be used to quantify the efficacy of nutritional replacement in critically ill patients (9). It must be recognized, however, that the major role for BCAA metabolism is to provide nitrogen for the formation of glutamine that can then be utilized by cells of the immune system and used to repair damaged muscle.

Arginine is another conditionally indispensable amino acid for maintaining body protein homeostasis and nutrition after burn injury or sepsis; nonetheless, outcomes in various types of catabolic critical illness have been variable (22). In postsur-
anabolic actions has been reported. More alarmingly, various untoward side effects were associated with these therapies, including hyperglycemia and increased splanchnic oxygen consumption (30–36). A recent randomized controlled trial demonstrated substantially increased rates of mortality and multiple organ failure with high-dose recombinant GH administered during the acute post-ICU admission phase (37). These investigations imply that blocking skeletal muscle catabolism during the acute phase of critical illness may not be desirable, and future studies will be needed to determine the exact role for this type of therapy, if one exists, in the prevention or treatment of myopathy.

Finally, tightly controlling glucose levels with i.v. insulin infusions may hold some promise in the treatment and prevention of critical illness myopathies. Skeletal muscle wasting associated with critical illness prolongs the need for mechanical ventilation. Van den Berghe and colleagues (38) performed a prospective, randomized, controlled study examining surgical patients admitted to the surgical intensive care unit who required mechanical ventilation. Patients were randomly assigned to receive intensive insulin therapy [maintenance of blood glucose level at 80–110 mg/dL (0.80–0.11 g/L)] or conventional treatment [infusion of insulin only if the blood glucose level exceeded 215 mg/dL (2.15 g/L)] at 12 mo, intensive insulin therapy reduced mortality from 8% in the conventional treatment group to 4.6% (P < 0.04). The benefit was most pronounced in those individuals who remained in the ICU > 5 d (20% vs. 10.6%, P = 0.005). Secondary outcomes that were examined included duration of ventilatory support, bloodstream infections, and EMG evidence of critical illness polyneuropathy. Substantially more patients in the conventional treatment group required >14 d of ventilatory support (11.9% vs. 7.5%, P = 0.003), perhaps implying a greater prevalence of neuromuscular disorders. To support this hypothesis, EMG evidence of critical illness polyneuropathy was demonstrated in 52% of the conventional treatment group patients, compared to 29% of the intensive treatment group (P < 0.001). As mentioned previously, polyneuropathies of critical illness often occur concurrently with myopathies, and the two are sometimes indistinguishable. From the data available it is not clear, but undoubtedly some of the individuals in this cohort of patients suffered from myopathies as well.

Special consideration of the alcoholic critically ill patient

The presence of a concomitant diagnosis of alcohol abuse may prove helpful in tailoring nutritional therapy for patients with myopathies of critical illness. Alcoholic myopathies occur in both acute and chronic forms, along a continuum. The acute form occurs in conjunction with muscle necrosis and is typified by rhabdomyolysis. The chronic form usually occurs in conjunction with the gradual progression of proximal muscle weakness and atrophy. Chronic alcoholic myopathy, initially described by Ekblom et al. (39) in 1964, is usually painless and frequently overlooked until it has been present for many years (40), although it appears to be quite common. In a series by Estruch et al. (41), ~47% of patients were diagnosed with this form upon entering an alcohol treatment program, an incidence confirmed by Duane and Peters (42) in 48% of patients admitted to a center for problems relating to alcohol abuse. Nutritional status appeared to play a limited role in myopathy in these patients, although reduced levels of some nutritionally derived antioxidants have been reported in alcoholic patients with myopathies. Thus, reactive oxygen species generated by alcohol abuse may play a role in mediating damage and could be targeted for nutritional therapy. Pathologically, chronic alcoholic myopathy is characterized by selective atrophy of type II skeletal muscle fibers. Plasma CPK levels are typically not elevated. Whole-body muscle mass may be decreased by as much as a third. The pathogenesis of this disorder can be explained by the direct toxic effects of alcohol or its metabolite, because skeletal muscle cannot metabolize alcohol. Interestingly, many similarities exist between chronic alcoholic myopathy and critical illness myopathy. For example, both types exhibit defects in the skeletal-muscle calcium-pump activity and calcium responses in the sarcoplasmic reticulum (in vitro). Both myopathies exhibit altered resting transmembrane potential of the muscle, and both have reduced amounts of contractile proteins. Both types of patients have disturbed whole-body nitrogen homeostasis and alterations in intermediary metabolism, with reductions in skeletal muscle protein synthesis. One could hypothesize that patients with chronic alcohol abuse may be predisposed toward the development of more severe, clinically deleterious critical illness myopathy in the right clinical situation, such as sepsis, and would benefit from earlier nutritional interventions.

CONCLUSION

Myopathies in critically ill patients are becoming more widely acknowledged as contributing to the long-term morbidity and mortality associated with ICU care. Over the past decade, great improvements have been made toward identifying and characterizing patients with critical illness myopathies. As further advances are made in understanding the pathophysiology of this disorder, more inroads toward treatment and prevention of this oftentimes devastating sequela of critical illness will undoubtedly be made. From the available data, nutritional and supplemental therapies will likely prove to be useful adjuncts in the management of myopathies. Nevertheless, better designed studies with more clearly defined patient populations and endpoints will surely be needed in the interim.

LITERATURE CITED