Nutritional Consequences of Critical Illness Myopathies

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Critical illness myopathy (CIM)4 is a condition of muscle dysfunction that occurs in severely ill patients. Guidelines established by the Centers for Disease Control and Prevention identify the characteristics of CIM, which include low or normal compound muscle action potentials on electromyography; normal sensory nerve action potentials; muscles unexitable from direct stimulation; muscle biopsy that may be abnormal, varying from Type II fiber atrophy to necrosis; a possible contribution from neuromuscular blockers; and steroid administration, sepsis, or prolonged immobility origin. Certainly in hospitalized patients with septic shock, adrenal crisis, or multiple system organ failure a number of these symptoms can be observed, usually with increased frequency consistent with the severity and duration of illness. These symptoms may be exacerbated by pharmacologic management, which may include high-dose corticosteroids and antibacterial and antifungal agents. The question remains, however, as to the underlying cause and the roles of the disease process and the therapy, as well as the distinct roles of additional stressors, which are physiological in nature, e.g., hypokinesia itself. The role of nutrition in the etiology and management of this syndrome remains largely unexplored.

We present these symposium proceedings for the purpose of understanding the relation between CIM and the nutritional implications of this syndrome. The group of participants represents a broad spectrum of interdisciplinary talents in both the basic and the clinical sciences and includes perspectives in nutrition, physiology, metabolism, cell biology, genetics, neurosciences, neuromuscular function, and general medicine. The historic study of muscle function and nutrition is the tale of early applications of modern disciplines of medicine, with later contributions in physiology, biochemistry, and nutrition leading to parallel discoveries. The earliest recorded recognition that muscle was the organ of contractions can be traced to observations of Erasistratus in 300 BC and Rufus of Ephesus in 200 BC, who dissected and identified different muscle groups. Interestingly, it was not until 1873 and 1887 that Ranvier and Grutsner described slow-red and fast-white muscles and delineated the concept of the mixed composition of muscles. The physiology of nerve muscle contraction was described by Butler and colleagues beginning in the early 1960s. Thus, a detailed interdisciplinary understanding of the complex interrelations among muscle anatomy, histology, pathology, neurology, nutrition, and metabolism is a modern-day event. It is in this paradigm of advancing knowledge in an interdisciplinary manner that we offer these symposium proceedings as a further advancement of knowledge in the hopes of proposing mechanisms of action and therapies that might be useful in understanding and ameliorating the underlying causes and sequelae of CIMs.

Although a number of different models are used to study muscle dysfunction, it is not the intent of these proceedings to suggest that immobility hypokinesia or bed rest in healthy individuals is the same as CIM. Neither do we wish to suggest that bed rest and spaceflight present identical paradigms. However, it is the intent of the symposium organizers and supplement editors to assemble a group of articles that together elucidates the similarities among CIM, hypokinesia, bed-rest muscle dysfunction, cortisol administration, physical inactivity, and spaceflight. It is the opinion of the guest editors that the syndromes associated with muscle dysfunction do not necessarily represent distinct identifiable diseases. More so, we propose that CIM, hypokinesia, and spaceflight represent a continuum of conditions with associated stressors that result in varying degrees of muscle dysfunction. We do propose that common sequelae do exist. It is our intent to present these interdisciplinary discussions of each syndrome and to allow each author to link together the common threads inherent in each.

From a scientific perspective, immobilization or hypokinesia on the one side, and myopathy on the other side, is a good example of a physiological two-sided road in which there are “cause–result” interactions. Deconditioning and hypokinesia lead to the atrophy of skeletal muscles. At the same time, alterations in the biochemical (protein kinase C), neuroendocrine (e.g., cortisol, testosterone, growth hormone), and immune (e.g., IL-1) variables may lead to myopathy and force humans to hypokinesia or even immobilization (1–6). Temporary as well as long-term immobility is not an uncommon consequence of a number of illnesses. Likewise, prolonged immobilization may lead to multiple opportunistic infections. CIMs have multiple and often intricate etiologies. They can be observed and studied in the clinic in patients following surgery or organ transplantation (7), in orthopedic patients, burn patients, patients in the later stages of HIV (8–10),...

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4 Abbreviations used: CIM, critical illness myopathy; HPA, hypothalamic-pituitary-adrenal; ICU, intensive care unit.

psychiatric patients (11), and intensive care unit (ICU) patients (7,12–14), and during long-term spaceflight (15–18). For research purposes, the sequelae of these syndromes can be effectively modeled in studies that utilize a bed-rest regime (19–22). It should be taken into consideration, however, that different etiologies of myopathy may be based on the different physiological, cellular, and molecular mechanisms seen in bed rest versus disease states.

There are clear links among neurological function, endocrine response, and nutritional implications of muscle dysfunction. Neuroendocrine and immune mediators, as well as malnutrition, may exacerbate a negative nitrogen balance due to loss of muscle protein. It has been shown that TNF-α substantially contributes to muscle necrosis (23). There was strong expression of mRNA for IL-1β, granulocyte-macrophage colony-stimulating factor, and transforming growth factor-β1 and -β2 in the muscle tissue of subjects with inflammatory myopathy. In addition, an enhanced expression of IL-1α mRNA was observed in the mononuclear inflammatory cells (24,25). Low levels of growth hormone and diminished growth factors may also contribute to the myopathy of skeletal muscles (26–28).

Burnham et al. (29) provide an extensive overview of myopathies in ICUs. The authors discuss the changes that take place in CIMs, including the increases in glucocorticoid production, growth hormone production, and circulating glucose levels. They argue convincingly that upregulation of these systems stimulates gluconeogenesis at the expense of lean body tissues, predominately skeletal muscle tissue. The authors also present a wide range of current approaches in the treatment of CIM.

Friedrich et al. (30) discuss the roles of sepsis, steroids, and impaired neuromuscular transmission; how they act synergistically in patients to stimulate muscle proteolysis; and the subtypes of critical illness myopathy seen as a result. They suggest that changes seen in sodium channel properties may reflect a compensatory mechanism in CIM patients.

Lee (31) explores the molecular mechanism of skeletal muscle apoptosis in response to steroid-induced myopathy. The study includes Western blot analysis of the proteins involved in signal transduction in rat skeletal muscle. The author shows that steroid-induced myopathy is associated with activation of apoptosis-triggering mechanisms.

Prolonged muscle disuse leads to increased gluconeogenesis and decreased fatty acid oxidation. The atrophied muscle relies heavily on glucose for energy. Stein and Wade (32) study the reductive remodeling of skeletal muscle with disuse. This includes the upregulation of glycolytic enzymes in such tissue after spaceflight and the response of the liver.

Finally, Paddon-Jones et al. (33) discuss the potential benefits of amino acid supplementation for reversing such myopathy in volunteers subjected to a 28-d flat bed-rest regime and in vivo injection of cortisol. They show that despite the catabolic effects of elevated cortisol concentrations, amino acid supplementation stimulated net muscle protein synthesis in the subjects.

Other laboratories have illustrated that many metabolic changes observed in the muscle disuse of spaceflight resemble the changes seen during prolonged bed rest. Such changes include fluid shifts, perturbation of circadian rhythms, loss of RBC mass, immune system alterations, loss of bone and muscle, and regulation of energy balance (34–39). The acute response to entry into microgravity includes large hormonal-based changes, such as the induction of the hypothalamic-pituitary-adrenal (HPA) axis (40–43).

The consequences of CIM resemble in some manner the sequelae observed in the response to spaceflight, which include increased protein catabolism, increased muscle wasting, and increased nitrogen loss. The stress response of critical illness, such as activation of the HPA axis, can lead to increased production of glucocorticoid release from the adrenal cortex. Hypercortisolemia, in turn, causes proteolysis primarily in fast-twitch Type II white muscle fibers. The combination of muscle inactivity and hypercortisolemia is particularly detrimental to critically ill patients, leading to myopathy at higher levels than that seen from inactivity alone. Protein loss is systemic and muscle atrophy is localized to unweighted or disused muscles. The atrophied fibers are structurally weaker and susceptible to contraction-induced tearing. As mentioned above, the combination of muscle disuse and hypercortisolemia is extremely detrimental.

Myopathy is very common in critically ill patients and usually leads to extended stays in the ICU, thus prolonging rehabilitation. In addition, alterations in neuroendocrine (HPA response) and immune (e.g., cytokines) variables may substantially interfere with treatment. Any studies that address the physiological, biochemical, and molecular mechanisms of myopathy in critically ill patients are urgently needed for clinical application as well as for extension of our knowledge in areas such as stress physiology. There are a number of sequelae of CIM, hypokinesia, bed rest, cortisol administration, and spaceflight that are similar. The following articles describe these similarities in detail.

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LITERATURE CITED