Commentary

Hyperglycemia and acquired weakness in critically ill patients: potential mechanisms

Leigh Ann Callahan and Gerald S Supinski

Division of Pulmonary, Critical Care and Sleep Medicine, Department of Internal Medicine, University of Kentucky, L543 Kentucky Clinic, 740 South Limestone, Lexington, KY40536, USA

Correspondence: Leigh Ann Callahan, lacall2@email.uky.edu

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Abstract

Critical illness polyneuropathy/critical illness myopathy (CIP/CIM) is a major cause of mortality and long-term morbidity in critically ill patients, but the true incidence and prevalence of these syndromes are not known. Hermans and colleagues show that when intensive insulin therapy is used as part of routine clinical practice in the intensive care unit, the incidence of CIP/CIM as determined by electrophysiologic testing is reduced. Our understanding of the mechanisms responsible for inducing prolonged weakness in intensive care unit patients is limited, and the role of hyperglycemia in modulating these processes is unknown. Intensive insulin therapy currently remains the only effective therapeutic intervention that has been shown to reduce the incidence of CIP/CIM.

In a recent issue of *Critical Care*, Hermans and colleagues showed that intensive insulin therapy (IIT) significantly reduces the incidence of electrophysiologic detection of neuromuscular complications in critically ill patients [1]. These findings are consistent with data obtained from two randomized controlled trials using IIT [2,3], which showed that IIT decreases the incidence of critical illness polyneuropathy/critical illness myopathy (CIP/CIM) diagnosed by electroneuromyography as well as reducing the duration of mechanical ventilation and shortening the length of stay in the intensive care unit (ICU). Improvements in electrophysiology presumably translate into improvements in respiratory muscle strength, decreasing the duration of mechanical ventilation and the length of ICU stay – although none of these studies objectively measured muscle strength.

It is important to note that our understanding of the mechanisms that lead to CIP/CIM is substantially limited. Abundant data suggest that sepsis induces a myopathy characterized by reductions in muscle force-generating capacity (force generation per cross-sectional area), loss of muscle mass and altered bioenergetics, but the mechanisms by which acute hyperglycemia induces prolonged or sustained alterations in the peripheral nervous system and in skeletal muscle are largely unknown.

How does glucose damage tissues? Glucose toxicity has been explained by increased cellular glucose flux and mitochondrially generated oxidative stress. For example, Nishikawa and colleagues showed that excessive mitochondrial superoxide generation is responsible for hyperglycemia-induced damage in endothelial cells [4]. Vincent and colleagues showed recently that 2 hours of high glucose exposure results in severe oxidative stress, mitochondrial disruption, activation of caspase 3 and apoptosis in cultured neurons [5]. Glucose overload and subsequent oxidative stress, therefore, may account for damage to neuronal tissue during acute hyperglycemia. This mechanism cannot account for acute hyperglycemia-induced changes in skeletal muscle, however, because glucose uptake in skeletal muscle is insulin dependent whereas glucose flux in neurons is insulin independent. In fact, if the skeletal muscle glucose uptake was sufficient, hyperglycemia would not occur. As such, it is reasonable to postulate that the mechanisms of hyperglycemia-induced muscle dysfunction are likely to be different from those that mediate hyperglycemia-induced neuronal injury.

What is the evidence that hyperglycemia produces derangements in skeletal muscle that result in weakness? It is critical to understand that overall muscle strength depends on muscle-specific force generation (that is, force generation per muscle mass or force per cross-sectional area) and on total muscle mass. These two parameters represent distinct aspects of muscle function, and the processes that modulate

CIP/CIM = critical illness polyneuropathy/critical illness myopathy; ICU = intensive care unit; IIT = intensive insulin therapy.

force generation and muscle mass are different. In this context, only a few studies have examined the effects of more prolonged hyperglycemia on skeletal muscle contractile function, with some showing reductions in muscle-specific force generation whereas others show no change [6,7]. It is therefore unclear whether hyperglycemia alters muscle force generation. On the other hand, Du and colleagues have shown that hyperglycemia results in skeletal muscle caspase 3 activation, degradation of myofibrillar proteins (specifically actin), and subsequent activation of the ubiquitin–proteasomal degradation pathway, leading to muscle atrophy [8]. Similarly, Russell and colleagues recently demonstrated in cultured myotubes that high glucose induces protein loss via activation of caspase 3, oxidative stress, and decreased protein synthesis [9]. These data indicate that hyperglycemia activates pathways involved in muscle atrophy. In addition, studies evaluating hyperglycemia-induced mitochondrial alterations in skeletal muscle reveal inconsistent data – with some showing normal function, while other studies show decrements in oxidative phosphorylation [10,11]. Moreover, data suggest that mitochondrial ultrastructure, complex activity, and muscle protein content are preserved in patients treated with IIT [12].

These data raise several interesting questions. Does acute hyperglycemia alter neurons and skeletal muscle in such a way as to produce sustained weakness in patients who survive critical illness? Cheung and colleagues show that many acute respiratory distress syndrome survivors have persistent functional impairment with decreased exercise tolerance, muscle weakness and muscle wasting up to 2 years after ICU discharge [13]. Over the past decade, the concept of metabolic memory has described the phenomenon that hyperglycemia produces ongoing sustained damage in target tissues even after blood glucose levels are normalized [14]. Is it possible that acute hyperglycemia induces metabolic memory in neurons and/or in skeletal muscle and produces the prolonged weakness we see in our patients? It is conceivable that hyperglycemia-induced mitochondrial free radical generation, irreversible modification of mitochondrial proteins and mitochondrial DNA damage [14] might induce ongoing injury in neurons and skeletal muscle. Such processes could also inhibit repair. If this is true, perhaps CIP/CIM develops because of an acquired mitochondrial myopathy. While entirely speculative, such possibilities should be entertained.

In summary, substantial evidence supports that IIT reduces the incidence of CIP/CIM. The proposed mechanisms by which insulin therapy protects neurons and skeletal muscle are related to its anabolic effects and anti-inflammatory effects. While IIT remains the only intervention shown to reduce the occurrence of CIP/CIM, many patients develop prolonged weakness even with IIT, indicating that other processes are involved. Future studies to elucidate the mechanisms responsible for CIP/CIM should also address the role of hyperglycemia in these processes. Importantly, if ongoing trials reveal that IIT imparts a prohibitive risk in ICU patients, then this information is crucial.

Competing interests

The authors declare that they have no competing interests.

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