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The Metabolic Phenotype of Skeletal Muscle During Early Critical Illness



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The Muscle UK Critical Care program was set up 10 years ago and focused on the association between muscle and skeletal muscle wasting to weakness to clinical outcome. There are a total of five pivotal trials, including Bernhard Jonghe et al.¹ and Herridge M.² that looked at skeletal muscle weakness and its impact on patients. In the Herridge study, all patients reported poor function and attributed this to loss of muscle bulk, proximal weakness, and fatigue.

According to the National Institute of Clinical Excellence, the lack of detailed understanding of the pathophysiology of muscle wasting must be addressed. Data from early mobilisation trials do not show enhanced functional capacity and improved health-related quality of life in critical illness survivors.

There is a huge array of studies which have shown the impact of critical illness on skeletal muscle - both the diaphragm and peripheral skeletal muscle. It occurs rapidly and early. It can be exceptionally pronounced. Diaphragm dysfunction is twice as frequent as peripheral muscle weakness and diaphragm and limb weakness are predictors of clinical outcome. The severity of the illness determines the degree of muscle wasting and the chronic health that the patient actually enters the ICU determines their trajectory of recovery.

A comprehensive study³ was conducted to characterise skeletal muscle wasting and to define the pathogenic roles of altered protein synthesis and breakdown. It was observed in these studies that muscle wasting was significantly greater in the sickest patients.

Critically ill patients are wasting away. If we look at studies done with biopsies at day 1 and day 7, the critical care patient is the same in terms of muscle protein synthesis. However, muscle protein breakdown is high and remains high throughout that first week of critical illness.

A study was conducted by Puthuchery et al.⁴ which investigated if adenosine triphosphate (ATP) bioavailability and lipid metabolism are drivers of early and rapidly acute skeletal muscle wasting that

occurs during critical illness. As demonstrated in the study, the ATP in the control group reduced from day one to day 7. In other words, energy declined. There was also a decline in phosphocreatine from day one to day 7. Creatine remained the same from day one to day 7.

Glucose is also a central component. Fat is utilised through beta-oxidation, and it's really key. If we don't utilise glucose, we would need another energy substrate. In critically ill patients, what we see over the first week is a reduction in mitochondrial biogenesis as patients do not produce the same number of mitochondria. This results in a reduction in mitochondrial DNA copy number as well as a reduction in mitochondrial beta-oxidation enzyme numbers. Mitochondrial beta-oxidation falls in the first week, and there's a reduction in lipid metabolism, and not surprisingly there's a rise in intramuscular phosphate lipids. Therefore, we're increasing the amount of lipid that's actually in the muscle.

Decreased ATP, decreased creatine, and decreased phosphocreatine availability are directly and closely related to acute skeletal muscle wasting. The activation of the hypoxic inflammatory signals is closely related and directly related to the impairment of the anabolic signaling pathway/ Injured muscular ATP is skeletal muscle matter unrelated to the quantity of lipids that are being delivered. There is a relationship between loss in muscle mass in early critical illness and skeletal muscle bioenergetic status, inflammatory, hypoxic and protein homeostatic signalling (Figure 1). Skeletal muscle wasting in critical care is associated with impaired lipid oxidation and reduced ATP bioavailability, driven by intramuscular inflammation and altered hypoxic signalling, which may account for the inconsistent outcome observed in the nutrition and exercise clinical trials.

□ **Figure 1.** Skeletal Muscle Wasting

Key take-home messages from this discussion are as follows:

- Decreased ATP, creatine, and phosphocreatine availability are closely and directly related to acute skeletal muscle wasting.
- Activation of hypoxic and inflammatory signaling are closely and directly related to impairment of anabolic signaling pathways.
- Changes in intramuscular ATP content and skeletal muscle mass are unrelated to the quantity of lipids delivered.

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