Skeletal muscle wasting after a severe burn is a consequence of cachexia and sarcopenia

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Abstract
Muscle wasting is common and persistent in severely burned patients, worsened by immobilization during treatment. In this review, we posit two major phenotypes of muscle wasting after severe burn, cachexia and sarcopenia, each with distinguishing characteristics to result in muscle atrophy; these characteristics are also likely present in other critically ill populations. An online search was conducted from the PubMed database and other available online resources and we manually extracted published articles in a systematic mini review. We describe the current definitions and characteristics of cachexia and sarcopenia and relate these to muscle wasting after severe burn. We then discuss these putative mechanisms of muscle atrophy in this condition. Severe burn and immobilization have distinctive patterns in mediating muscle wasting and muscle atrophy. In considering these two pathological phenotypes (cachexia and sarcopenia), we propose two independent principal causes and mechanisms of muscle mass loss after burns: (1) inflammation-induced cachexia, leading to proteolysis and protein degradation, and (2) sarcopenia/immobility that signals inhibition of expected increases in protein synthesis in response to protein loss. Because both are present following severe burn, these should be considered independently in devising treatments. Discussing cachexia and sarcopenia as independent mechanisms of severe burn–initiated muscle wasting is explored. Recognition of these associated mechanisms will likely improve outcomes.

KEYWORDS
cachexia, immobilization, muscle atrophy, sarcopenia, thermal injury

INTRODUCTION
Severe burns are a common injury with an occurrence rate of 5/100,000 people per year globally.1 In the United States, 486,000 patients were burned, receiving inpatient treatment in 2015.2 Patients with severe burns on <30% of the total body surface area (TBSA) have a pronounced increase in metabolic rate that persists for years and has significant effects on many organ systems.3

Severe burn is associated with excessive muscle wasting and atrophy.4 Muscle wasting is defined as unintentional weight loss of 5%-10% of muscle mass, and severely burned patients are reported to lose up to 25% of total body mass acutely.5 The proposed reason for the acute muscle catabolic response is to redistribute essential nutrition substrates and support organ activities and wound healing during the acute phase. However, destructive elements are also prominent. Increases in muscle loss are associated with increased death after injury, such that at a 40% loss of lean body mass carries a 90% mortality risk.6

In addition to the injury, clinical interventions to support recovery, such as nutrition support and immobilization to protect skin grafts and...
provide critical care, affect outcomes related to muscle wasting and atrophy. Although intensive efforts are made to provide for physical and occupational rehabilitation as the standard of care, bedrest and immobilization with splints are oftentimes clinically unavoidable and critical for wound healing in patients who are severely burned. Furthermore, patients who are severely burned are often mechanically ventilated and on bedrest for clinical reasons. Previous clinical studies in noninjured populations described that bedrest decreases protein synthesis. In a preclinical model, immobilization via hindlimb unloading significantly exacerbated muscle wasting in burned rats with 40% TBSA scald burns. From this evidence, we propose that cachexia from inflammation associated with severe burns and immobilization during clinical treatment should be considered when investigating treatments to address burn-induced muscle wasting.

Cachexia and sarcopenia are the two major pathologic phenotypes of muscle atrophy. Cachexia is caused by inflammation and is seen principally in cancer and chronic metabolic conditions. Sarcopenia is a metabolic syndrome most often associated with aging and is related to decreased physical activity at any age. In this review, we discuss these two conceptual phenotypes of muscle pathophysiology and the related biologic mechanisms related to the severely injured and critically ill. These two conditions occur in parallel but are independent, and both are likely mediators of muscle wasting in patients who are critically ill. Severe burns and immobilization have distinctive patterns mediating muscle wasting and atrophy, including genetic mechanisms and pathophysiologic alterations. We then explore mechanistic links of cachexia and sarcopenia in burn-induced muscle wasting. Finally, we briefly discuss current treatments and potential directions for future investigation.

Cachexia

Cachexia is a wasting syndrome characterized by severe body weight, muscle and fat loss, fatigue, and anorexia. Approximately 50% of cancer patients suffer from cachexia and is common in other chronic disease processes such as cardiac cachexia, chronic renal failure, and chronic pulmonary obstructive disease. Currently, the definition of cachexia was extended as a complex metabolic syndrome associated with underlying illness and was characterized by loss of muscle with or without reduction of fat mass.

The ubiquitin-proteolytic pathway is the most important molecular pathway driving cachexia. Cytokine activity plays a central role in its pathogenesis, as inflammatory cytokines are upregulated by reactive oxygen species activated via nuclear transcription factor NF-κB. Other pathways such as mitochondrial dysfunction with autophagy, endoplasmic reticulum stress, and insulin resistance also contribute to cachexia.

Sarcopenia/muscle disuse

Sarcopenia was originally described as the degenerative loss of skeletal muscle mass and strength with aging, and the definition was further extended to immobility in other chronic disease states. The European Working Group on Sarcopenia in Older People (EWGSOP) recently described sarcopenia as a muscle disease with low muscle strength, low muscle quantity and quality, and/or low physical performance. We can add that such a condition is not limited to older adults, as it is found in many other conditions such as paralysis and bedrest/immobilization.

The most prominent mechanism of sarcopenia is anabolic resistance. Insensitivity to insulin signaling through mTOR/Akt to PGC-1α leads to a reduction in overall muscle protein synthesis. In addition, four major proteolytic pathways drive protein degradation, including the ubiquitin-proteasome system, calpain, caspase pathways, and autophagy-lysosomal pathways. A consequential significant reduction in muscle precursor satellite cells is associated with diminished anabolic signals and/or inflammatory responses. A form of chronic inflammation is observed in patients with sarcopenia associated with elevated TNF-α and IL-6. Oxidative stress disrupts redox balance and is independently associated with inflammatory mediators contributing to sarcopenia.

MECHANISMS REGULATING MUSCLE WASTING AFTER BURNS

Systemic stress response

Muscle wasting occurs under systemic stress following severe burns. Endocrine disturbances following severe burns are well known. Stress hormones such as catecholamines and glucocorticoids are markedly elevated immediately after injury and may be prolonged for years depending on severity of the injury. These catabolic stress hormones dominate the induction of muscle proteolysis and muscle wasting. Meanwhile, anabolic hormones such as insulin-like growth factor (IGF-1) and growth hormone remain depressed.

Once the innate inflammatory response is activated, profound cytokine surges occur. In vitro studies provide evidence of increased cytokine expression with muscle wasting through either TNF-inhibited myogenesis or IL-6–stimulated mitochondrial fragmentation. Merritt et al explored elevations in the specific inflammatory cytokines TNF and IL-6 in patients with severe burns, and found increased protein ubiquitination through metabolic signals via calpain-2. Nerve damage associated with cachexia has also been described. Basic research reports revealed that nerve-related impairment after severe burns contributes to muscle wasting and atrophy through either damaged motor neurons or abnormal neuromuscular junctions.

Hypercatabolism persists with elevated resting energy expenditure for up to 2 years following a severe burn. Muscle protein synthesis remained elevated up to a year in pediatric patients; however, the protein breakdown catabolic response dominated, leading to a net negative protein balance. Meanwhile, energy homeostasis of lipid, carbohydrate, and other micronutrients are disrupted and thus also contribute to muscle wasting after a burn.
FIGURE 1 The mechanisms of muscle wasting after a burn. Severe burns are often accompanied with immobility, which have massive systemic responses, including the effects on the endocrine, immune, metabolism, neural system. Skeletal muscles respond at the levels of transcription genes, subcellular organelle, and cell turnover. The complex network of signal regulation finally leads to muscle mass reduction and function impairment.

Muscle cell turnover and intracellular mechanisms

Muscle cell turnover accelerates in response to severe burn, recapitulating increased protein turnover in skeletal muscle. The principal proponent of cell death after burn is by apoptosis. Fry et al. demonstrated increased muscle satellite cell death in pediatric patients who were burned, and Merritt et al further confirmed that burn serum reduced differentiated myotube fusion signals and myogenin expression, indicating impaired myogenic differentiation following burn injury.

A group of hormone-like proteins, termed myokines, are constitutively expressed in muscle tissue and participate in local and distant organ responses with both beneficial and detrimental effects. IL-6 has a binary effect in both supporting muscle growth and inhibiting skeletal myogenesis during muscle wasting.

Mitochondria are key intracellular organelles regulating cachexia in patients who are burned. Studies of mitochondrial genetics and function show mitochondrial destruction following a severe burn including autophagy or mitophagy relevant to inflammation. Deletion of the muscle-specific autophagy gene Atg7 results in severe muscle atrophy with abnormal mitochondrial accumulation.

The systemic response to injury was described at the transcriptional level by the Glue Grant group, suggesting that 80% of gene pathways in circulating cells are significantly influenced by burns or blunt trauma. Padfield et al. summarized four functional gene categories disturbed in response to direct burn injury. These four categories include the inflammatory response, protein synthesis and degradation, mitochondrial-related energy metabolism, and muscle development (Figure 1).

Cachexia, sarcopenia, and muscle atrophy after burn

Based on the similar phenotypic responses, we speculate that burn-induced muscle mass loss has characteristics of both cachexia and sarcopenia. The main crux of cachexia is inflammatory cytokine activation of the ubiquitin-proteolytic pathway leading to muscle catabolism; this results in muscle wasting. During recovery, the condition is confounded by comorbidities such as inhalation injury and sepsis as well as clinical treatments such as immobilization/disuse. Among these factors is the unavoidable consequence of bed rest in severe burns, resulting in sarcopenia in addition to cachexia. The mechanisms of sarcopenia are impairment of signals that stimulate muscle growth and relative inhibition of protein synthesis, which worsens protein breakdown associated with cachexia.

Burn-induced muscle wasting is most likely initiated in the acute stage by cachexia and extends through convalescence as is seen in other chronic diseases. Cachexia is then inflammation-induced protein degradation and increased cell death in muscle associated with the indigenous response to injury. Massive increases in inflammatory cytokines, in response to burn, have been reported leading to cachexia.
Muscle wasting occurs through the stress hormone independent atrogens atrogin-1 and MuRF-1, and expression of polyUb, as does muscle atrophy associated with mitochondrial dysfunction in response to severe burn. Abnormal mitochondria are also observed in those with cachexia due to cancer with decreased oxidative capacity in mitochondria.

Cachectic symptoms such as weight/fat loss, anemia, and anorexia are observed in burn patients as well. In addition, significantly decreased fat body mass was found at day 14 in burned rats and anorexia was reported in patients who were burned long ago. Dysfunctional neurotransmitters are also noted; acetylcholine receptors were upregulated and associated with hyperkalemia after a severe burn, which persists with infection and immobilization.

Beginning with the acute phase after a burn injury, cachexia associated with hypercatabolism is combined with sarcopenia associated with immobilization/disuse. Ferrando et al. showed that prolonged bed rest decreases protein synthesis by 50% in human participants. Preclinical data showed that the additive effect of both conditions, burn and disuse, resulted in vastly more substantial muscle mass loss and function impairment. So, it is not only cachexia associated with injury and inflammation, but the effects of immobilization in clinical treatment that must be considered. Differing from cachexia alone, the principal component of burn-related muscle wasting is relative inhibition of protein synthesis with bed rest rather than increased protein degradation (Figure 2).

Cachexia and sarcopenia are both associated with inactivity, and the complex interactions of the associated molecular mechanisms likely overlap. Mitochondrial damage is probably related to increased oxidative stress both from the injury and immobility, and thus mitochondria are likely a significant contributor regulating the skeletomuscular pathophysiological response. Recent studies and reviews provide some insights into this notion, though molecular mechanisms have not been distinguished in detail.

Current interventions and future direction

Current treatment for severe burns is directed to ameliorate catabolism and muscle wasting as early as possible. Treatment includes aggressive wound closure, appropriate critical care, and nutrition management; however, these are still challenged. These are mostly directed at ameliorating cachexia but do not address sarcopenia directly. Mobilization and exercise training are the first choices to counteract muscle wasting with sarcopenia, though this is not often implemented during initial treatment of injury because of clinical concerns. Improvements in sarcopenia have been shown after both aerobic and resistance exercise, so either will likely suffice. Exercise alleviates oxidative stress and improves protein synthesis, which may occur through improved mitochondrial respiration function with increased complex I and II substrates. We advocate for exercise training to be aggressively implemented as part of standard treatment following a severe burn; if aggressive therapy is limited by the patient’s clinical condition, alternative treatments such as whole-body vibration or electric acupuncture might be considered.

Therapeutic pharmaceutical agents such as insulin, oxandrolone, and other anabolic agents improve muscle mass and function in burn patients. Giving insulin prevents cell death, decreases proteolysis, and positively affects muscle protein synthesis via the protein kinase B (Akt) pathway. Regarding sarcopenia, considerations are directed more towards increases in muscle regrowth. Oxandrolone treatment has been studied with induction of net protein synthesis and is in common use both in burns and in older adults. A recent genetic study showed that only Forkhead Box O1 (FOXO1) increased in cachexia/sarcopenic conditions, and therapeutic development of FOXO1 inhibition may have a role in preventing muscle wasting following severe burn.

In cachectic states such as severe burn, nutrition support is of benefit to prevent nutrition complications associated with underfeeding that could compound muscle wasting and atrophy due to cachexia and sarcopenia. In patients who are burned, nutrition evaluation by dietitians and medical providers is the standard of care. Providing nutrition substrate and micronutrients such as vitamins and minerals is vital, and aggressive replacement is also the standard of care. Metabolic changes after severe burn are dynamic and in response, nutrition components and volumes should be titrated to maintain sufficient support. Of course, injury severity and populations such as older adults, people who are obese, and people with severe medical pre-existing conditions should also be considered. This review explored theoretical mechanisms that influence the dynamic changes in metabolism affecting nutrition provision following severe burn, and future studies are warranted to understand and
define the dynamics of nutrition support, which are likely to change across time as conditions change.

Systemic stem cell injections have been tested in older adults who would be considered sarcopenic59 and might be considered in those who are severely injured. A recent summary of wasting disorders described the updated preclinical and clinical therapies for cachexia and sarcopenia. Specific treatments were proposed, targeting genes such as Fn14 and MuRF1 and mitochondrial dynamics.70 Though these were developed for cachexia and sarcopenia specifically, similar approaches might be beneficial in patients who are severely burned.

CONCLUSION

Muscle wasting and atrophy following severe burn is the result of muscle protein degradation in excess of protein synthesis. A principal component is activation of the ubiquitin/proteasome pathway with severe inflammation, leading to increased cell death and cachexia; however, these are not alone in defining the cause—considerations for effects of sarcopenia from disuse must also be taken into account. Furthermore, nutrition therapies alone are insufficient in alleviating muscle wasting in this condition. Strategies for treatment might be focused on the muscle wasting from burn-induced cachexia in the acute phase, whereas the effects of sarcopenia might take precedence in the rehabilitation phase.

Severe burns are an excellent model to study for both cachexia and sarcopenia, which can likely be generalized to other medical conditions. Cachexia and sarcopenia investigated in connection to burn research will likely clarify mechanisms leading the muscle wasting in patients who are severely injured and/or critically ill, and aid in developing therapeutic strategies. Consideration of both mechanisms of muscle loss is particularly critical in the elder population with poorer prognosis after severe burn injury and may be of benefit in the study of other chronic disease-related muscle atrophy.

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CONFLICT OF INTEREST
None declared.

AUTHOR CONTRIBUTIONS
Juquan Song, Charles E. Wade, and Steven E. Wolf equally contributed to the conception and design of the research; Juquan Song and Audra Clark contributed to the acquisition and analysis of the literature search and analysis; Juquan Song and Charles E. Wade contributed to the interpretation; and Juquan Song, Steven E. Wolf, and Charles E. Wade drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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