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REVIEW

Comprehensive Review of Sepsis-Related Skeletal Muscle Atrophy: Mechanisms, Diagnosis and Therapeutic Strategies

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Abstract: This comprehensive review aims to synthesize current evidence on sepsis-related skeletal muscle atrophy, with a focus on underlying mechanisms, diagnostic approaches, and therapeutic interventions. A systematic literature search was conducted in PubMed, Web of Science, and Cochrane Library up to October 2024, including clinical, translational, and animal studies. We critically analyzed the pathophysiological mechanisms linking sepsis to muscle wasting, including inflammatory signaling, mitochondrial dysfunction, and proteolytic pathways. Epidemiological data indicate a high incidence of muscle atrophy in sepsis patients, particularly among the elderly and those with comorbidities. Diagnostic modalities such as CT, MRI, ultrasound, and emerging biomarkers including urinary titin and myokines are discussed. Treatment strategies encompassing nutritional support, pharmacotherapy (eg, GLP-1RAs, myostatin inhibitors), and rehabilitation are evaluated. Controversies regarding etiology and treatment efficacy are highlighted. Future directions include the exploration of novel biomarkers, genomics-based personalized therapy, and long-term outcome studies. This review provides a structured and critical appraisal of the current state of knowledge, aiming to inform clinical practice and future research.

Keywords: skeletal muscle atrophy, sepsis, inflammatory cytokines, mechanism, nutrition

Introduction

Sepsis represents a formidable challenge in critical care medicine, characterized by a dysregulated host response to infection that leads to life-threatening organ dysfunction. With an estimated incidence of 48.9 million cases and 11 million sepsis-related deaths worldwide in 2017, sepsis remains a leading cause of mortality in hospitalized patients.[1,2] The complex pathophysiology of sepsis involves an intricate interplay of inflammatory cascades, immune dysregulation, coagulopathy, and metabolic disturbances, often culminating in multiple organ dysfunction syndrome (MODS).

Among the various complications of sepsis, skeletal muscle atrophy has emerged as a particularly debilitating condition that significantly impacts patient outcomes. Sepsis-induced skeletal muscle wasting affects up to 60% of critically ill patients and is characterized by rapid loss of muscle mass and strength, contributing to the development of intensive care unit-acquired weakness (ICU-AW).[3,4] This complication not only prolongs mechanical ventilation duration and hospital stay but also leads to long-term functional impairment, reduced quality of life, and increased healthcare costs.

The molecular mechanisms underlying sepsis-related skeletal muscle atrophy are multifaceted, involving the activation of ubiquitin-proteasome system, enhanced autophagy, mitochondrial dysfunction, and impaired protein synthesis. Inflammatory mediators such as TNF-α and IL-6 play pivotal roles in initiating and propagating muscle wasting through various signaling pathways, including NF-κB and JAK/STAT pathways.[5,6] Additionally, metabolic alterations, endocrine disturbances, and microcirculatory impairments further exacerbate the catabolic state in skeletal muscle.

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Despite advances in our understanding of the pathophysiology, several challenges remain in the clinical management of sepsis-related skeletal muscle atrophy. The heterogeneity in patient populations, variations in diagnostic criteria, and lack of standardized therapeutic approaches contribute to inconsistent clinical outcomes. Furthermore, the complex interplay between sepsis pathophysiology and muscle wasting mechanisms necessitates a comprehensive approach to diagnosis and treatment.

This comprehensive review aims to synthesize current evidence on sepsis-related skeletal muscle atrophy, with particular focus on: (1) the pathophysiological mechanisms linking sepsis to muscle wasting; (2) epidemiological characteristics across different patient populations; (3) advances in diagnostic methodologies including imaging techniques and biomarkers; (4) current and emerging therapeutic strategies encompassing nutritional support, pharmacological interventions, and rehabilitation protocols; and (5) future research directions. Through a systematic examination of the literature, this review seeks to provide clinicians and researchers with an updated framework for understanding, diagnosing, and managing this challenging complication of sepsis.

Methods

We conducted a comprehensive narrative review of the literature on sepsis-related skeletal muscle atrophy. The search was performed in PubMed, Web of Science, Scopus, and Cochrane Library from inception to July 2024. Search terms included "sepsis", "skeletal muscle atrophy", "muscle wasting", "critical illness myopathy", "ICU-acquired weakness", combined with "mechanisms", "diagnosis", "treatment", and "biomarkers". We included both human and animal studies to provide a comprehensive perspective. The inclusion criteria were: (1) studies focusing on sepsis or critically ill patients with sepsis and skeletal muscle atrophy; (2) studies investigating mechanisms, epidemiology, diagnosis, or treatment of sepsis-related muscle atrophy; (3) original research, reviews, meta-analyses, and guidelines. Exclusion criteria were: (1) studies not in English; (2) studies not focusing on sepsis or muscle atrophy. The selection process was performed by two independent reviewers, and any discrepancies were resolved by consensus.

Fundamental Theory of Sepsis-Related Skeletal Muscle Atrophy

Pathophysiological Mechanism of Sepsis

Sepsis is defined as a dysregulated host response to infection that results in life-threatening organ dysfunction, posing a significant challenge in critical care medicine.[1,2] The primary features include an aberrant immune response that inflicts extensive damage to host tissues, leading to multiple organ dysfunction syndrome (MODS). The pathophysiology involves inflammatory responses, immune dysregulation, microcirculatory disturbances, and cellular metabolic abnormalities.

In the inflammatory response, innate immune cells recognize pathogens via pattern recognition receptors (PRRs), leading to activation and secretion of inflammatory cytokines including TNF-α and IL-6.[3,4] These cytokines stimulate additional immune cells, culminating in systemic inflammatory response syndrome. Excessive inflammation increases vascular permeability, causes tissue edema, and activates coagulation, forming microthrombi that impede blood circulation and exacerbate tissue hypoxia.[7]

Sepsis disrupts immune regulation, with initial excessive inflammation often followed by immune suppression due to lymphocyte apoptosis, immune cell exhaustion, and heightened regulatory T-cell activity.[8] Microcirculatory dysfunction involves endothelial cell damage, promoting leukocyte and platelet adhesion, microthrombus formation, and impaired oxygen delivery.[9]

Cellular metabolic disorders feature mitochondrial dysfunction due to hypoxia, oxidative stress, and inflammatory mediators, leading to impaired oxidative phosphorylation and diminished ATP production.[10] Persistent stress initiates apoptotic pathways, while dysregulated autophagy may contribute to cell damage.

The progression to MODS in sepsis exacerbates skeletal muscle atrophy through organ-specific mechanisms. Hepatic dysfunction impairs synthesis of insulin-like growth factor-1 (IGF-1) and albumin,[11] while reduced ammonia detoxification leads to hyperammonemia that activates muscle proteolysis. Renal impairment promotes muscle wasting through uremic toxin accumulation and metabolic acidosis. Cardiac dysfunction reduces peripheral perfusion, limiting nutrient delivery, while pulmonary dysfunction increases respiratory muscle workload, creating an energy deficit.

The Molecular Biological Basis of Skeletal Muscle Atrophy

Muscle atrophy represents a multifaceted pathological condition characterized by a marked reduction in muscle mass and strength resulting from the interplay of various factors. This process is associated with alterations in an extensive array of gene expression and signal transduction pathways. Central to this process is the ubiquitin–proteasome system (UPS), which constitutes a primary pathway for intracellular protein degradation, facilitating the precise tagging and breakdown of specific proteins.[12,13] In the context of muscle atrophy, there is notable upregulation of the expression of muscle-specific E3 ubiquitin ligases, such as Atrogin-1 and MuRF-1.[14] These ubiquitin ligases function as molecular "tags," identifying and binding to muscle proteins, thereby earmarking them for degradation.[15–17] The proteasome subsequently recognizes and degrades these tagged muscle proteins, culminating in a decrease in muscle mass. For example, in models of glucocorticoid-induced muscle atrophy, there is a significant increase in the expression levels of Atrogin-1 and MuRF-1.[18–21] Glucocorticoids, which are stress hormones, are secreted in substantial quantities under certain pathological or physiological conditions, such as prolonged stress or illness.

Inflammatory signalling pathways are integral to the process of skeletal muscle atrophy.[22–24] Inflammatory mediators, such as tumour necrosis factor (TNF)-α and IL-6, are known to activate associated signalling pathways, thereby facilitating the progression of muscle atrophy. Notably, IL-6 functions not only as an inflammatory marker but also as a crucial signalling molecule. It operates through multiple signalling pathways, among which the JAK2/STAT3 pathway is particularly significant in inducing muscle atrophy.[25–27] Upon binding to its receptor, IL-6 activates the JAK2 kinase, leading to the phosphorylation of the STAT3 transcription factor.[28,29] Phosphorylated STAT3 subsequently dimerizes and translocates to the nucleus, where it serves as a transcriptional activator by binding to promoter regions of genes implicated in muscle atrophy, thereby inducing their expression. The proteins encoded by these genes are involved in the degradation of muscle proteins or the inhibition of muscle protein synthesis, ultimately promoting protein degradation and resulting in reduced muscle mass and strength.

The IGF-1 signaling pathway plays a pivotal role in regulating skeletal muscle mass by promoting protein synthesis and inhibiting proteolysis. IGF-1 activates the PI3K/Akt/mTOR pathway,[30,31] which stimulates mRNA translation initiation and protein synthesis through downstream effectors including S6K1 and 4E-BP1. Concurrently, Akt phosphorylates and inhibits FoxO transcription factors, preventing their nuclear translocation and subsequent activation of atrophy-related genes such as Atrogin-1 and MuRF-1.[32] In sepsis, circulating IGF-1 levels are significantly reduced due to hepatic dysfunction and growth hormone resistance. Furthermore, sepsis-induced inflammation impairs IGF-1 signaling through multiple mechanisms,[33] including increased expression of IGF-binding proteins and activation of negative regulators such as PTEN. The restoration of IGF-1 signaling represents a promising therapeutic approach for counteracting sepsis-related muscle atrophy, though clinical translation requires careful consideration of potential side effects related to its growth-promoting properties.

Moreover, oxidative stress and mitochondrial dysfunction are critical contributors to the pathogenesis of skeletal muscle atrophy.[34] Under normal physiological circumstances, mitochondria function as the cell's energy powerhouses, generating adenosine triphosphate (ATP) through respiration to support various cellular activities. However, in pathological states, such as chronic diseases and ageing, there is an overproduction of reactive oxygen species (ROS). Cellular antioxidant defence mechanisms are often insufficient to eliminate these excessive ROS promptly, resulting in oxidative stress.[35] This overabundance of ROS can inflict direct damage on mitochondria, thereby disrupting their dynamic equilibrium and impairing their autophagic processes.[36] Mitochondrial autophagy, also known as mitophagy, is a crucial cellular self-preservation mechanism that ensures mitochondrial integrity by facilitating the degradation of dysfunctional mitochondria. The inhibition of mitochondrial autophagy leads to the accumulation of impaired mitochondria within the cell, exacerbating the production of ROS and perpetuating a deleterious cycle. The resulting surplus of ROS not only compromises mitochondrial structure and function but also impairs the normal operations of other organelles, culminating in cellular metabolic disturbances. These disturbances are associated with increased degradation of muscle proteins, a reduction in muscle mass, and the onset of skeletal muscle atrophy. Empirical studies have demonstrated that the administration of antioxidants can effectively reduce oxidative stress and ameliorate the symptoms

associated with skeletal muscle atrophy. This evidence underscores the pivotal role of oxidative stress in the pathogenesis and progression of muscle atrophy and offers a theoretical foundation for the development of novel therapeutic strategies.

Associations Between Sepsis and Skeletal Muscle Atrophy

The interaction between sepsis and skeletal muscle atrophy is both intricate and multifaceted and involves numerous underlying mechanisms. Inflammation serves as a pivotal link between these two conditions. During sepsis, excessive activation of the immune system results in the release of a substantial quantity of inflammatory cytokines, notably TNF-α and IL-6, which are central to this process. These cytokines circulate through the bloodstream and directly contribute to the degradation of skeletal muscle proteins. TNF-α is known to activate various signalling pathways, including the nuclear NF-κB pathway.[37] Upon activation, NF-κB translocates from the cytoplasm to the nucleus, where it regulates the expression of genes associated with muscle atrophy, thereby facilitating muscle protein hydrolysis.[38] Similarly, IL-6 functions by activating specific transcription factors via the JAK/STAT signalling pathway, which promotes the transcription and translation of genes involved in muscle protein degradation, ultimately accelerating muscle protein breakdown and contributing to muscle atrophy. Research indicates that IL-6 knockout mice, developed through gene knockout technology, demonstrate a marked reduction in skeletal muscle atrophy in sepsis models.[39] These findings suggest that IL-6 is pivotal in the mechanism of sepsis-induced skeletal muscle atrophy, offering valuable insights into the intricate relationship between sepsis and skeletal muscle degradation.

Mitochondrial dysfunction is a pivotal factor in sepsis-induced skeletal muscle atrophy. Sepsis can induce damage to skeletal muscle mitochondria, leading to aberrant mitochondrial calcium uptake. This phenomenon is specifically marked by a reduction in the ratio of mitochondrial calcium uptake 1 (MICU1) to mitochondrial calcium uniporter (MCU) proteins. Under physiological conditions, MICU1 and MCU collaboratively regulate mitochondrial calcium uptake and release, thereby maintaining calcium homeostasis within the mitochondria. An imbalance in their protein ratio results in dysregulated mitochondrial calcium uptake. The ensuing disruption of calcium homeostasis adversely affects multiple aspects of mitochondrial function, culminating in impaired muscle contraction. Given the essential role of calcium ions in the muscle contraction process, disorders in mitochondrial calcium uptake disrupt the muscle excitation–contraction coupling mechanism, thereby inhibiting normal muscle contraction.[40] Furthermore, mitochondrial dysfunction can induce muscle fibre atrophy. Sepsis may impact skeletal muscle by activating the autophagy pathway.[41] Under normal physiological conditions, autophagy is a crucial mechanism for maintaining cellular homeostasis and is responsible for the clearance of damaged proteins and organelles within the cell.[10] However, during sepsis, the autophagy pathway becomes excessively activated. This heightened autophagic activity resembles an uncontrolled "cleaning operation," which not only removes damaged components but also may lead to the excessive degradation of normal muscle proteins. Such dysregulated autophagy disrupts protein equilibrium within the cell, causing the degradation rate of muscle proteins to significantly surpass the synthesis rate, ultimately resulting in muscle atrophy.[42]

The aetiology of sepsis-related skeletal muscle atrophy remains incompletely understood and is a subject of ongoing debate. While the involvement of inflammatory responses and immune dysregulation is widely acknowledged, the precise initiating factors and critical mechanisms necessitate further comprehensive investigation. Some scholars posit that excessive inflammatory responses during sepsis are the primary drivers of skeletal muscle atrophy, as a substantial release of inflammatory cytokines directly harms muscle cells and facilitates protein degradation.[39,43] Conversely, other studies have indicated that mitochondrial dysfunction may serve as the initiating factor, with mitochondrial damage precipitating aberrant energy metabolism, thereby triggering a cascade of intracellular signalling alterations that ultimately culminate in muscle atrophy.[44] Moreover, the involvement of autophagy in sepsis-induced skeletal muscle atrophy remains a subject of debate. Certain studies suggest that during sepsis, overactivation of autophagy results in excessive degradation of muscle proteins, thereby worsening muscle atrophy. Conversely, moderate autophagy may serve as a protective mechanism, facilitating the clearance of damaged organelles and proteins and maintaining cellular homeostasis. It is further hypothesized that aberrant autophagy might be a consequence of other factors rather than a direct causative agent.[10,42] The key mechanisms through which sepsis leads to skeletal muscle atrophy, highlighting their interconnected nature, are summarized in Table 1.

Table 1 Key Mechanisms Linking Sepsis to Skeletal Muscle Atrophy

Mechanism Category	Key Pathways/Processes	Major Mediators/ Components	Functional Impact on Skeletal Muscle
Inflammatory Signaling	• NF-κB pathway • JAK/STAT pathway • p38 MAPK pathway	TNF-α, IL-6, IL-1β	• Promotes proteolysis via ubiquitin-proteasome system (UPS) activation • Inhibits protein synthesis • Induces muscle cell apoptosis
Proteolytic System Activation	• Ubiquitin-Proteasome System (UPS) • Autophagy-Lysosomal Pathway • Calpain system	Atrogin-1, MuRF-1, LC3, Beclin-1, Calpains	• Accelerates degradation of contractile proteins and organelles • Leads to loss of muscle mass and function
Mitochondrial Dysfunction	• Oxidative phosphorylation impairment • Mitochondrial dynamics (Fission/ Fusion) • Mitophagy • Calcium homeostasis dysregulation	ROS, MICU1/MCU ratio, PGC-1α, Damaged mitochondria	• Reduces ATP production, impairing energy-dependent processes • Increases oxidative stress, damaging cellular components • Disrupts excitation-contraction coupling
Anabolic Suppression	• IGF-1/PI3K/Akt/mTOR pathway	IGF-1, Akt, mTOR, FoxO transcription factors	• Decreases muscle protein synthesis • Fails to suppress proteolytic pathways (eg, by inactivating FoxO)
Multi-Organ Dysfunction (MODS) Interaction	• Hepatic dysfunction • Renal dysfunction • Cardiac dysfunction	Reduced IGF-1 synthesis, Uremic toxins, Reduced peripheral perfusion	• Exacerbates catabolic state and impairs anabolic signaling • Limits nutrient/oxygen delivery to muscle • Accumulation of toxins promotes proteolysis
Neuroendocrine & Metabolic Dysregulation	• Glucocorticoid signaling • Insulin resistance • Growth hormone resistance	Cortisol, Glucagon, Catecholamines	• Creates a hypercatabolic state • Promotes gluconeogenesis using amino acids from muscle breakdown

Epidemiology of Sepsis-Related Skeletal Muscle Atrophy

Incidence of Skeletal Muscle Atrophy in Patients with Sepsis

In the population of sepsis patients, skeletal muscle atrophy is a common complication that significantly adversely affects patient outcomes.[45,46] This condition has garnered considerable attention from researchers, yet there is notable variation in the reported incidence of skeletal muscle atrophy within the literature.[47–49] For example, Fan[48] et al reported a median incidence of septic myopathy of 43%, with an interquartile range of 25–75%. This variation may arise from several factors, including differences in study subject selection, variations in diagnostic methodologies, and disease severity. With respect to study subject selection, discrepancies in characteristics such as age, sex, and underlying health conditions exist among the patient cohorts examined in different studies. These factors may independently influence the occurrence of skeletal muscle atrophy. For example, elderly sepsis patients may be more susceptible to skeletal muscle atrophy due to diminished physical function and poorer nutritional status, whereas the incidence in younger patients may be comparatively lower. Variations in diagnostic methodologies can result in data discrepancies. Certain studies predominantly utilize clinical symptoms and signs to diagnose skeletal muscle atrophy, whereas others employ more sophisticated imaging techniques or biochemical markers. The use of differing diagnostic criteria can substantially influence study outcomes. Furthermore, disease severity is a critical factor affecting incidence rates. Patients with severe sepsis often experience rapid disease progression and are in a state of heightened physiological stress, rendering them more vulnerable to skeletal muscle atrophy.[4] In a study by Ma[50] et al, the dynamic changes in the diaphragm and limb skeletal muscles of sepsis patients were examined, revealing that the incidence rates of skeletal muscle atrophy on the 4th and 7th days in the ICU were 54.3% and 62.1%, respectively. Recent multicenter studies have reported incidence rates ranging from 50% to 70% in sepsis survivors, with higher rates observed in patients with MODS or prolonged ICU stays.[47,51,52] For instance, a prospective cohort study by Puthucheary[53] et al demonstrated that 60% of septic patients developed significant muscle wasting within the first week of ICU admission. Additionally, the impact of deconditioning in critically ill patients must be considered, as immobilization and systemic inflammation

synergistically accelerate muscle loss. These findings underscore the high prevalence of skeletal muscle atrophy among sepsis patients. These findings have significant implications for clinical practice, emphasizing the need for health care professionals to vigilantly monitor skeletal muscle atrophy in sepsis patients to facilitate timely intervention and enhance patient outcomes.

In animal studies investigating the relationship between sepsis and skeletal muscle atrophy, researchers have utilized the caecal ligation and puncture (CLP) technique to establish a sepsis model.[54] This model effectively replicates the pathophysiological processes of human sepsis, thereby serving as a robust tool for research. In experiments where sepsis was induced in mice via CLP, researchers noted significant skeletal muscle atrophy.[42] Notably, there was a reduction in muscle mass in the tibialis anterior and gastrocnemius muscles, which serves as a critical indicator of skeletal muscle atrophy. Furthermore, a decrease in the cross-sectional area of muscle fibres was observed. The size of the muscle fibre cross-sectional area is a direct reflection of the muscle's development and functional status, with a reduction indicating a decrease in both muscle volume and strength. The observed atrophic characteristics corroborate the conclusion that sepsis is associated with skeletal muscle atrophy. These experimental findings offer significant insights into the mechanisms underlying sepsis-induced skeletal muscle atrophy. Using animal models, we can conduct an in-depth investigation into the cellular and molecular mechanisms involved in sepsis-related skeletal muscle atrophy, thereby establishing a foundation for the development of novel therapeutic strategies.

Epidemiological Characteristics of Sepsis-Related Skeletal Muscle Atrophy in Different Populations

Among diverse populations, the epidemiological characteristics associated with sepsis-induced skeletal muscle atrophy demonstrate significant heterogeneity.[55] A study by Yu[49] et al revealed that among a cohort of patients who experienced sepsis-related skeletal muscle atrophy, 71.4% were male, and 62.0% were over the age of 60. From an age-related perspective, the elderly population experiences a decline in physiological functions and a progressive reduction in organ functionality due to the deterioration of physiological processes, which is accompanied by a weakening of the immune system.[56] Compared with younger individuals, the onset of sepsis significantly impairs the elderly population's ability to manage inflammatory responses and infection-induced shock. The reduced regenerative capacity of myocytes and the slowdown in protein synthesis contribute to an increased incidence of skeletal muscle atrophy in this population.[57] Moreover, elderly individuals exhibit a diminished capacity for recovery following skeletal muscle atrophy, largely attributable to reduced nutrient absorption efficiency and hormonal imbalances that negatively affect muscle repair and growth processes.[58,59] In particular, during inflammatory conditions, the levels of proinflammatory cytokines remain persistently elevated in older adults, thereby disrupting muscle synthesis signalling pathways and subsequently inhibiting muscle repair and growth.

From a gender perspective, research conducted by Borges[55] et al suggested that males may have a greater predisposition to sepsis-related skeletal muscle atrophy, although the mechanisms underlying this disparity remain unclear. Current hypotheses propose that the levels of hormones, particularly androgens such as testosterone, may play a role in influencing muscle metabolism under certain conditions. A decrease in testosterone levels could lead to reduced protein synthesis, thereby affecting muscle growth and repair. Additionally, lifestyle factors may contribute to this difference, as males and females often differ in their living habits and occupational roles, which may result in varied responses to sepsis. With respect to disease types, sepsis patients with preexisting chronic conditions are at increased risk of developing skeletal muscle atrophy. For example, in diabetic patients, a hyperglycaemic environment adversely impacts muscle metabolism and increases susceptibility to skeletal muscle atrophy during sepsis.[60,61]

Beyond age and gender, other demographic and clinical factors significantly influence the risk of sepsis-related muscle atrophy. Comorbidities such as diabetes, chronic kidney disease, and heart failure are associated with accelerated muscle loss due to pre-existing metabolic and inflammatory dysregulation.[62,63] Ethnic disparities have been observed, with some studies suggesting higher susceptibility in certain racial groups, though data remain limited. Socioeconomic status and geographic location also impact access to early rehabilitation and nutritional support, further modulating atrophy risk. Future studies should stratify by these variables to better understand population-specific vulnerabilities.

Risk Factors for Sepsis-Related Skeletal Muscle Atrophy

Several factors contribute to the increased risk of sepsis-induced skeletal muscle atrophy, with the inflammatory response playing a critical role. During sepsis, the body initiates an exaggerated inflammatory response, leading to the release of numerous inflammatory mediators.[64] These mediators have direct harmful effects on skeletal muscle cells, accelerating the degradation of muscle proteins. Notably, there is a marked increase in the levels of inflammatory cytokines, such as TNF-α and IL-6, which compromise the structural and functional integrity of muscle tissue. As these cytokines proliferate within the body, the environment for skeletal muscle cell survival becomes compromised, impairing their ability to maintain normal physiological functions and ultimately resulting in muscle atrophy. The muscle damage mediated by this inflammatory response is a complex and persistent process, with the severity of muscle atrophy increasing in parallel with the escalation of inflammation. Moreover, nutritional status and muscular disuse are critical risk factors in this context. Malnutrition leads to a significant deficiency of essential nutrients necessary for muscle synthesis, thereby hindering muscle growth and repair processes and increasing susceptibility to skeletal muscle atrophy.[65,66] Patients with sepsis often experience inadequate nutritional intake due to inflammatory stress and anorexia. As a result, the body's nutritional reserves become severely depleted and cannot be replenished promptly, further exacerbating muscle atrophy. In addition, the impact of muscular disuse due to prolonged immobilization is significant. Research indicates that extended bed rest is associated with more pronounced skeletal muscle atrophy in sepsis patients.[67] The cessation of physical activity results in a reduction in muscle fibre diameter and volume, ultimately leading to skeletal muscle atrophy.

Analysis of Heterogeneity in Clinical Research Results

In the domain of clinical research concerning sepsis-related skeletal muscle atrophy, the findings exhibit considerable heterogeneity. This variability is attributable primarily to differences in patient inclusion criteria, treatment protocols, and observational indicators across various studies, which complicates the direct comparison of research results. For example, in investigations evaluating the efficacy of specific interventions for sepsis-related skeletal muscle atrophy, some studies emphasize muscle mass as the principal observational parameter, whereas others prioritize muscle function or patient quality of life. This divergence in focus has led to disparate research outcomes.[68]

Moreover, variables such as race, age, and preexisting medical conditions of the study participants can significantly impact research outcomes. Diverse racial groups may exhibit varied responses to treatments, and physiological responses, as well as muscle recovery capabilities in sepsis, may differ between older and younger populations.[57] These factors contribute to the variability observed in clinical research findings, thereby complicating the development of a standardized treatment protocol. As a result, there is a pressing need for large-scale, multicentre, and standardized studies to determine the most effective treatment strategies.[68]

Diagnostic Techniques for Sepsis-Related Skeletal Muscle Atrophy

Imaging Diagnostic Methods for Skeletal Muscle Atrophy

In the diagnostic evaluation of sepsis-associated skeletal muscle atrophy, imaging modalities are of paramount importance.[69] Magnetic resonance imaging (MRI) technology offers comprehensive insights into muscle soft tissues, enabling the detection of pathological alterations such as muscle fatty infiltration and oedema. This capability facilitates the early identification of subtle skeletal muscle lesions.[70,71] In the context of diagnosing and differentiating specific muscle diseases, MRI can elucidate distinct patterns of muscle damage.[72]

Computed tomography (CT) technology provides precise visualization of the morphology, structure, and density characteristics of skeletal muscles.[73] Through quantitative analysis of the skeletal muscle area at specific anatomical landmarks, such as the third lumbar vertebra, muscle mass can be effectively assessed. Empirical evidence suggests that the skeletal muscle index, as determined by CT, is significantly correlated with patient muscle strength and clinical outcomes. For example, within oncological patient cohorts, a reduced skeletal muscle index frequently is correlated with a less favourable prognosis.[74]

Conversely, ultrasound examination, characterized by its convenience, noninvasiveness, and high reproducibility, allows for real-time assessment of muscle morphology, thickness, and echo characteristics, thereby providing an evaluation of muscle atrophy.[75] Studies utilizing ultrasound technology to measure muscle thickness in patients with sepsis have demonstrated

a significant correlation with muscle strength, suggesting that ultrasound examination is an effective tool for monitoring muscle status.[76]

The Application of Blood Biomarkers in Sepsis-Related Skeletal Muscle Atrophy

Blood biomarkers have significantly advanced research in the diagnosis and monitoring of sepsis-related skeletal muscle atrophy.[77] Specific serum protein markers, such as creatine kinase (CK), are indicative of muscle damage and atrophy, as CK is released into the bloodstream during muscle injury; however, its elevated levels have relatively low specificity.[78,79] Conversely, various subtypes of muscle-specific troponin I (sTnI), particularly the fast skeletal muscle subtype (fsTnI), demonstrate greater specificity for assessing skeletal muscle damage under certain conditions. Notably, increases in fsTnI levels can serve as valuable monitoring indicators for statin-induced skeletal muscle damage.[80]

Furthermore, specific cytokines and inflammatory markers have been linked to sepsis-induced skeletal muscle atrophy[81–83] Inflammatory mediators, including IL-6 and TNF-α, play dual roles in both the inflammatory response associated with sepsis and the pathogenesis of skeletal muscle atrophy. Urinary titin fragments have been identified as potential biomarkers for the early detection of skeletal muscle proteolysis and atrophy.[84] In several disease models that result in skeletal muscle atrophy, elevated urinary titin levels are observed at an early stage, preceding conventional indicators.[85]

Emerging research has identified myokines and muscle-specific metabolites as promising biomarkers for sepsis-related skeletal muscle atrophy.[86] Myostatin,[87,88] a transforming growth factor-β family member, is significantly elevated in sepsis and correlates with muscle wasting severity through its inhibition of satellite cell activation and muscle regeneration. Conversely, irisin,[89] an exercise-induced myokine, demonstrates protective effects by promoting mitochondrial biogenesis and reducing inflammation, with decreased levels observed in septic patients. Metabolomic analyses have revealed alterations in muscle-specific metabolites including carnosine, which exhibits antioxidant and pH-buffering capacities, and 3-methylhistidine, a specific marker of myofibrillar protein degradation. The ratio of 3-methylhistidine to creatinine in urine provides a non-invasive measure of ongoing muscle proteolysis.[90] These novel biomarkers offer potential for early detection and monitoring of muscle atrophy, though their clinical utility requires validation in large prospective studies.

Functional Assessment Tools for Sepsis-Related Skeletal Muscle Atrophy

The functional evaluation of skeletal muscle atrophy associated with sepsis is essential for comprehending the pathophysiology of the disease and developing effective treatment strategies. Handgrip strength assessment, a traditional and accessible technique, serves as an indirect measure of upper limb muscle strength by quantifying handgrip force. This measure is strongly associated with the patient's capacity to perform activities of daily living.[91,92] Empirical research indicates that individuals with sepsis typically exhibit a marked reduction in handgrip strength, with the extent of this decline correlating with both the degree of muscle atrophy and the severity of the disease.[48]

Handgrip strength has demonstrated good test-retest reliability (ICC > 0.85) in critically ill populations and correlates strongly with overall muscle function and clinical outcomes.[93] The repeated sit-to-stand test shows moderate to high validity in assessing lower limb muscle endurance, though its applicability in acutely ill sepsis patients requires further validation.[94] It is important to note that these tools were primarily developed for general muscle function assessment and have not been specifically validated for sepsis-related atrophy, highlighting a gap in the current literature.

The evaluation of muscle function encompasses the assessment of both muscle endurance and explosive power.[95] For example, the repeated sit-to-stand test serves as a measure of lower limb muscle endurance, with the outcomes being significantly correlated with the patient's mobility and prognosis. Furthermore, sophisticated techniques such as magnetic resonance spectroscopy (MRS) facilitate the detection of muscle metabolites and the assessment of muscle energy metabolism status, thereby contributing to a more comprehensive understanding of the functional alterations in skeletal muscles under septic conditions.[96,97]

Treatment Strategies for Sepsis-Related Skeletal Muscle Atrophy

The Role of Nutritional Support in Sepsis-Related Skeletal Muscle Atrophy

Nutritional support is pivotal in the management of sepsis-related skeletal muscle atrophy, with adequate protein intake serving as the cornerstone for preserving muscle mass by supplying essential substrates for muscle synthesis.[98,99] According

to the Chinese guidelines for medical nutrition therapy in adult sepsis patients,[99] which integrate findings from multiple prior studies, early protein intake of 0.6–1.2 $g \cdot kg^{-1} \cdot d^{-1}$ within the first 72 hours is recommended (weak recommendation, low-certainty evidence). This approach is suggested to enhance the nutritional status of sepsis patients and improve clinical outcomes. A previous large-scale randomized controlled trial (RCT) involving 3036 participants reported that early protein restriction (0.2–0.4 $g \cdot kg^{-1} \cdot d^{-1}$), compared with standard protein intake (1.0–1.3 $g \cdot kg^{-1} \cdot d^{-1}$), did not lead to statistically significant differences in mortality rates; however, it was advantageous for clinical improvement and the reduction of complications such as skeletal muscle atrophy.[100] Conversely, meta-analyses conducted by van[101] et al revealed that protein intake >1.2 $g \cdot kg^{-1} \cdot d^{-1}$ was correlated with decreased mortality and mitigated muscle atrophy, whereas excessive protein intake (≥2.2 $g \cdot kg^{-1} \cdot d^{-1}$) did not confer additional benefits. These findings collectively underscore the critical role of nutritional support while also indicating that excessive supplementation may have detrimental effects.

Furthermore, certain nutrients, including vitamin D and ω-3 polyunsaturated fatty acids, have shown potential health benefits. Vitamin D plays a crucial role not only in the regulation of calcium and phosphorus metabolism but also in muscle function, where it promotes muscle protein synthesis and enhances muscle strength.[102] Research conducted by Prokopidis[103] et al revealed a correlation between vitamin D deficiency and diminished muscle function, as well as an elevated risk of sarcopenia. A longitudinal study by Yoo et al further supported the notion that vitamin D deficiency may act as an independent risk factor for sarcopenia.[104] Additionally, several RCTs have demonstrated that vitamin D supplementation can lead to improvements in muscle strength and physical function indicators.[105,106] ω-3 polyunsaturated fatty acids exhibit anti-inflammatory properties, which can attenuate the inflammatory response induced by sepsis, thereby providing indirect protection to skeletal muscle.[107]

Recent Advances in Pharmacotherapy

Research on pharmacotherapy for sepsis-related skeletal muscle atrophy has garnered significant attention in recent years.[108] Certain pharmacological agents, including GLP-1 receptor agonists (GLP-1RAs), exert their effects by modulating inflammatory responses; these agents not only lower glucose levels but also possess anti-inflammatory and antioxidant properties. Preclinical studies have demonstrated that GLP-1RAs can mitigate organ dysfunction and skeletal muscle atrophy associated with sepsis.[109,110]

Furthermore, there is an active pursuit of drug development aimed at enhancing muscle growth and metabolism. For example, myostatin inhibitors counteract the negative regulatory effects of myostatin on muscle growth, thereby facilitating muscle hypertrophy.[111,112] In animal models, the myostatin inhibitor YK11 has been shown to reduce muscle atrophy in septic mice, decrease the levels of inflammatory cytokines, and improve survival rates.[113] Additionally, antioxidants such as edaravone have been found to alleviate mitochondrial oxidative stress, enhance muscle function, and exhibit potential therapeutic benefits in relevant disease models.[114]

Impacts of Rehabilitation Training on Sepsis-Related Skeletal Muscle Atrophy

Rehabilitation training plays a pivotal role in mitigating the skeletal muscle atrophy associated with sepsis.[115,116] Engaging in early physical activity and exercise training facilitates improved muscle blood circulation, enhances the delivery of oxygen and nutrients to muscle tissues, and stimulates muscle protein synthesis, thereby decreasing the incidence of muscle atrophy. For patients in the ICU, the early initiation of rehabilitation interventions, including bed limb exercises and sitting-up training, has demonstrated significant efficacy in enhancing muscle strength and motor function, ultimately contributing to a reduction in both the duration of mechanical ventilation and the length of hospitalization.[65]

Research indicates that different modalities of exercise training exhibit significant variations in their physiological effects. Aerobic exercise is known to enhance cardiopulmonary function, augment individual endurance, and improve muscle metabolic conditions, whereas resistance training focuses primarily on increasing muscle strength and hypertrophy. A comprehensive rehabilitation program that integrates both aerobic and resistance training has been shown to produce more pronounced improvements in skeletal muscle atrophy and functional recovery in patients with sepsis. For example, Cunha[117] et al reported notable improvements in lower limb muscle atrophy in rats with heart failure following a regimen of aerobic training. Similarly, Cai[118] et al demonstrated that both aerobic and resistance exercise significantly mitigated skeletal muscle atrophy and enhanced muscle strength in rats with heart failure compared with baseline measurements.

Natural Products in Sepsis-Related Skeletal Muscle Atrophy

Natural products have gained increasing attention as potential therapeutic agents for sepsis-related skeletal muscle atrophy due to their multi-target mechanisms and favorable safety profiles.[119] Curcumin,[120] the active compound in turmeric, demonstrates potent anti-inflammatory effects by inhibiting NF-κB activation and reducing pro-inflammatory cytokine production, while also ameliorating mitochondrial dysfunction through enhancement of oxidative phosphorylation and reduction of reactive oxygen species. Resveratrol,[121] a polyphenol found in grapes and berries, activates SIRT1 and AMPK pathways, promoting mitochondrial biogenesis and autophagy regulation. Epigallocatechin-3-gallate (EGCG) from green tea exhibits antioxidant properties and modulates protein synthesis and degradation pathways.[122] Ginsenosides from Panax ginseng have shown promise in enhancing muscle regeneration through regulation of IGF-1 signaling and satellite cell activity.[123] While preclinical studies demonstrate efficacy of these natural compounds in attenuating muscle atrophy, clinical evidence remains limited. Future research should focus on standardized extraction methods, bioavailability optimization, and well-designed clinical trials to establish dosing regimens and validate therapeutic benefits in septic patients.

Controversy Over the Efficacy and Safety of Treatment Strategies

At present, there is significant discourse regarding the effectiveness and safety of treatment strategies for sepsis-related skeletal muscle atrophy. Nutritional support is broadly acknowledged as an essential therapeutic intervention;[98] however, the specific choice of nutritional formula and the ideal timing for supplementation necessitate further elucidation. Certain studies suggest that early and intensive nutritional supplementation may enhance patient outcomes, whereas other research indicates that excessive nutrient intake could impose a metabolic burden, potentially increasing the risk of complications such as hyperglycaemia and hyperlipidaemia.[124]

Although certain drugs have shown promising therapeutic effects in preclinical animal studies, their efficacy and safety in clinical settings necessitate further validation. For example, some novel drugs may exhibit adverse effects that limit their broader application. Additionally, the efficacy and safety profiles of various drug combinations remain insufficiently investigated, highlighting the pressing need to identify optimal drug combinations and treatment regimens in current clinical practice.[109]

Future Research Directions in Sepsis-Related Skeletal Muscle Atrophy

Exploration of Novel Biomarkers

Investigating novel biomarkers is essential for the early diagnosis and monitoring of treatment of sepsis-induced skeletal muscle atrophy. Contemporary research has focused predominantly on protein levels, metabolites, and gene expression. Within the domain of proteomics, the utilization of proteomic techniques facilitates a comprehensive analysis of alterations in protein expression in skeletal muscle during sepsis, thereby enabling the identification of potential biomarkers. For example, several studies have reported that specific proteins exhibit characteristic changes in expression during sepsis-induced skeletal muscle atrophy and may serve as biomarkers for diagnosing or monitoring disease progression.[114]

Metabolomics technology is capable of detecting dynamic alterations in metabolites within the body, thereby offering potential insights for the identification of novel biomarkers. In the context of sepsis, notable modifications in muscle metabolism occur, with changes in specific metabolites potentially linked to skeletal muscle atrophy. Furthermore, investigations into the regulatory mechanisms of gene expression, including the modulatory effects of microRNAs (miRNAs) and long noncoding RNAs (lncRNAs) on genes associated with muscle atrophy, are anticipated to reveal new biomarkers and therapeutic targets.[125,126]

Genomics-Based Personalized Therapy

Genomics-based personalized therapy is increasingly recognized as a pivotal area for future development. By conducting comprehensive analyses of the genomes of patients with sepsis, it is possible to elucidate their drug response patterns and disease susceptibility, thereby enabling the formulation of more precise personalized treatment plans. In the realm of cancer therapy, for example, identifying specific genetic mutations in patients allows for the selection of targeted drugs,

which can significantly increase treatment outcomes. Similarly, when sepsis-related skeletal muscle atrophy is addressed, an examination of gene polymorphisms associated with muscle metabolism and inflammatory responses can predict patients' responsiveness to nutritional support and pharmacotherapy, thus providing a scientific foundation for individualized treatment strategies.[127]

Moreover, the employment of gene-editing technologies, such as CRISPR-Cas9, facilitates the precise targeting of specific genetic defects for therapeutic purposes. While the application of this technology in the treatment of sepsis-related skeletal muscle atrophy remains in the early stages of research, its substantial potential suggests that it may lead to revolutionary advancements in this field.[128]

Long-Term Prognostic Research on Sepsis-Related Skeletal Muscle Atrophy

Currently, there is a notable deficiency in long-term prognostic research concerning sepsis-related skeletal muscle atrophy, highlighting the urgent need for further investigations in this area. Longitudinal studies are crucial for elucidating the recovery trajectory of patients' muscle function, quality of life, and incidence of long-term complications. For example, assessment of the persistence of skeletal muscle atrophy in patients postsepsis recovery, along with its enduring impact on physical activity and daily living, can provide a scientific basis for formulating comprehensive long-term rehabilitation strategies.[129]

Furthermore, examination of the factors that impact long-term prognosis, including age, preexisting conditions, and treatment regimens, can aid in optimizing therapeutic strategies and improving patients' long-term outcomes. The development of extensive databases and the integration of multicentre, longitudinal clinical data for detailed analysis can lead to a more comprehensive understanding of the long-term prognosis of sepsis-related skeletal muscle atrophy, thereby offering more robust support for clinical practice.[129]

Conclusion

This comprehensive review synthesizes current understanding of sepsis-related skeletal muscle atrophy, highlighting the multifactorial nature of its pathophysiology involving inflammatory signaling, proteolytic systems, mitochondrial dysfunction, and multi-organ interactions. The epidemiological evidence demonstrates significant variability in incidence rates influenced by age, gender, comorbidities, and disease severity. Advances in diagnostic methodologies, including sophisticated imaging techniques and novel biomarkers, have improved early detection and monitoring capabilities. Current therapeutic strategies encompass optimized nutritional support, targeted pharmacological interventions, and structured rehabilitation programs, though substantial controversies persist regarding optimal approaches.

The clinical implications of these findings emphasize the importance of early recognition and multidisciplinary management of sepsis-related muscle atrophy. Healthcare providers should implement regular muscle mass and function assessments in septic patients, particularly those with MODS or prolonged ICU stays. Nutritional interventions should be individualized based on metabolic status and organ function, while rehabilitation programs should be initiated as early as clinically feasible.

Future research directions should prioritize several key areas: First, the validation of novel biomarkers in large multicenter cohorts to establish standardized diagnostic criteria. Second, the development of targeted therapies based on individual genetic and metabolic profiles. Third, long-term prospective studies to characterize the natural history of muscle recovery and identify predictors of poor functional outcomes. Finally, exploration of combination therapies addressing multiple pathological pathways simultaneously may yield synergistic benefits. Collaborative efforts between basic scientists, clinicians, and rehabilitation specialists are essential to translate these research advances into improved patient outcomes.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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