Spor Hekimliği Dergisi, 60(1):25-31; 2025
Turkish Journal of Sports Medicine
Turk J Sports Med. DOI: 10.47447/tjsm.0872

Review Article / Derleme

Sepsis-induced skeletal muscle atrophy and mitochondrial dysfunction: The beneficial effects of exercise

Sepsis kaynaklı iskelet kası atrofisi ve mitokondriyal disfonksiyon: Egzersizin yararlı etkileri

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ABSTRACT

Sepsis can lead to a wide range of clinical symptoms due to a dysregulated immune response to infection. It remains a major cause of morbidity and mortality in hospitalized patients, particularly those in intensive care units. The association between sepsis and skeletal muscle atrophy is primarily due to inflammation and immobilization during prolonged sepsis. In addition, the physical inactivity caused by sepsis accelerates skeletal muscle atrophy. Sepsis-induced skeletal muscle atrophy is primarily caused by mitochondrial dysfunction, which is recognized as a major contributing factor. Moreover, oxidative stress is implicated in the etiology of sepsis-induced muscle atrophy by contributing to the functional loss of mitochondria. Numerous studies have demonstrated the positive impact of regular exercise on the overall health of patients with various conditions, including sepsis, by modulating mitochondrial health and quality control pathways. This review will explore the role of mitochondria and the potential benefits of exercise in mitigating sepsis-induced skeletal muscle atrophy.

Keywords: *Sepsis, skeletal muscle atrophy, mitochondria, exercise*

ÖZ

Sepsis, enfeksiyona karşı anormal bağışıklık tepkisi nedeniyle çok çeşitli klinik semptomlara yol açabilir. Hastanede yatan hastalarda, özellikle de yoğun bakım ünitelerindeki (YBÜ) hastalarda morbidite ve mortalitenin önemli bir nedenidir. Sepsis ve iskelet kası atrofisi arasındaki ilişki, esas olarak uzun süreli sepsis sırasında oluşan inflamasyon ve immobilizasyondan kaynaklanmaktadır. Ayrıca, sepsisin neden olduğu fiziksel hareketsizlik iskelet kası atrofisini hızlandırır. Sepsisin neden olduğu iskelet kası atrofisine öncelikle mitokondriyal disfonksiyonun önemli bir katkısı olduğu kabul edilmektedir. Dahası, oksidatif stres, mitokondrinin işlevsel kaybına katkıda bulunarak sepsis kaynaklı kas atrofisinin etiyolojisinde rol oynamaktadır. Çok sayıda çalışma, düzenli egzersizin mitokondriyal fonksiyonu ve kalite kontrol yolaklarını modüle ederek sepsis de dahil olmak üzere çeşitli hastalıklara sahip olan hastaların genel sağlık durumu üzerindeki olumlu etkisini göstermiştir. Bu derleme, sepsis kaynaklı iskelet kası atrofisinde mitokondrinin rolünü ve egzersizin kas atrofisini engellemedeki potansiyel faydalarını araştıracaktır.

Anahtar Sözcükler: *Sepsis, iskelet kas atrofisi, mitokondri, egzersiz*

INTRODUCTION

Accounting for approximately 40% of human body weight and 50% of total protein mass (1), skeletal muscle plays a crucial role in locomotion, posture, metabolic regulation, and thermogenesis (1). Skeletal muscle atrophy, characterized by a reduction in muscle mass and strength, occurs when there is an imbalance between protein synthesis and degradation (2). This condition can develop in adult skeletal muscle under various circumstances, including fasting, denervation, cancer cachexia, heart failure, aging, and sepsis (3).

Mitochondria play a crucial role in regulating the metabolic events of skeletal muscle, functioning as the primary organelle in this process. Mitochondrial dysfunction directly affects the physiological state of skeletal muscle (4). In sepsis, mitochondrial damage or dysfunction led to apoptosis in various tissues and immune cells due to insufficient energy production coupled with increased oxidative stress (5).

Evidence suggests that regular exercise has a beneficial effect on individuals with various medical conditions, including cardiovascular disease, obesity, type 2 diabetes, age-related muscle loss (sarcopenia), and cancer (6). Specifically, endurance exercise has been shown to regulate mitochondrial activity in skeletal muscle through mitochondrial biogenesis, a process linked to increased expression of the peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) protein and resulting in improved mitochondrial mass and function (7).

Received / Geliş: 12.09.2024 · **Accepted / Kabul:** 20.11.2024 · **Published / Yayın Tarihi:** xx.02.2025

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Cite this article as: Kubat GB, Turkel I, Akat F. Sepsis-induced skeletal muscle atrophy and mitochondrial dysfunction: The beneficial effects of exercise. *Turk J Sports Med.* 2025;60(1):28-31; https://doi.org/10.47447/tjsm.0872

Sepsis, a clinical condition characterized by an aberrant host response to infection, can lead to organ failure and negatively impact both the quality and duration of life (8). Sepsis-induced skeletal muscle atrophy is defined by reduction in muscle mass, fiber size, and strength, which ultimately contribute to long-term physical impairment associated with sepsis (9).

This review will focus on elucidating the importance of skeletal muscle and mitochondria, exploring the correlation between sepsis and skeletal muscle atrophy, and examining the benefits of exercise in the context of sepsis-related muscle atrophy.

Importance and characteristics of skeletal muscle

Skeletal muscle tissue represents approximately 40% of body mass in a healthy individual and is characterized as a plastic tissue, enabling it to adapt to physiological and pathophysiological stimulus (10). It is now widely recognized that skeletal muscles are not only components of the musculoskeletal system but also part of the endocrine system, due to their secretion of bioactive molecules known as myokines in response to acute and chronic exercise. These myokines exert their effects in an autocrine, paracrine, and endocrine manner (11). Consequently, changes in skeletal muscle mass and function can contribute to the onset of various pathological states, ranging from physical inactivity to the development of metabolic disorders such as obesity, insulin resistance, and diabetes (12).

Skeletal muscle fibers are classified into four main types: type I, IIa, IId/x, and IIb-based on their predominant myosin heavy chain isoforms. Type I and IIa fibers display high oxidative potential, while type IIx and IIb fibers exhibit glycolytic characteristics (13-15). The soleus and red region of the gastrocnemius are primarily comprised of type I muscle fibers, which have a slower contraction speed (16, 17). In contrast, skeletal muscles such as the extensor digitorum longus (EDL) and tibialis anterior are predominantly composed of type II fibers, also known as fast twitch or fast-contracting fibers (16, 17). These differences lead to distinct physiological and metabolic properties depending on muscle fiber composition. For example, muscle atrophy in antigravity environments predominantly affects the soleus muscle, which is rich in type I fibers. Conversely, conditions such as sepsis, cachexia, diabetes, and aging are associated with atrophy in muscles like the EDL and tibialis anterior, which are rich in type II fibers (18).

Skeletal muscle atrophy

The most prominent morphological feature of skeletal muscle atrophy is a reduction in muscle mass and fiber cross-sectional area (CSA) (19). For example, after approximately 180 days of spaceflight, astronauts exhibited fiber type-specific reductions in the CSA and strength of their soleus and gastrocnemius muscles. This resulted in a shift from a higher to a lower ratio of type I to type II fibers in both the soleus and gastrocnemius muscles (20). A similar atrophy response has been observed in disuse atrophy models. For example, a seven-day tail suspension in C57BL/6 mice resulted in a 24% reduction in soleus muscle mass, while the EDL muscle mass remained unchanged (21). Compared to disuse atrophy, conditions like sarcopenia, cachexia, sepsis, and the use of certain pharmacologic drugs often result in skeletal muscle atrophy with a higher prevalence of type II fibers (22, 23). These findings demonstrate that different stimuli for skeletal muscle atrophy have specific effects on muscle fiber types.

Sepsis-induced skeletal muscle atrophy and its mechanism

Sepsis, defined as a pathological condition characterized by a dysregulated host response to infection, can lead to multiple organ dysfunction, thereby threatening the quality and duration of life (8). Nineteen percent of global deaths are attributable to sepsis, underscoring the necessity for more effective prevention and treatment strategies (24). In conclusion, sepsis represents a significant public health challenge that necessitates improvements in existing treatment modalities and the exploration of new therapeutic approaches (Table 1).

Recent studies have focused on the pathophysiology of sepsis across various tissues and organs, with particular emphasis on its effects on skeletal muscles (9, 25) (Figure 1). Sepsis-related myopathies are characterized by reductions in both skeletal muscle mass and fiber size, impaired muscle function, and a significant decline in physical capacity (26, 27). Eikermann et al. observed no change in arm muscle strength in subjects immobilized for two weeks, whereas patients immobilized due to sepsis exhibited a notable decrease in muscle strength, indicating that the strength reduction is attributable to sepsis itself rather than to bed rest (28). Muscle atrophy in sepsis patients was accompanied by a decline in fiber type CSA, with a reduction of approximately 3-4% per day (29). Furthermore, reductions in skeletal muscle mass led to significant alterations in muscle function (9, 25). Various cell culture and experimental animal models, including cecal ligation and perforation, lipopolysaccharide (LPS) administration, live bacteria injection, pneumonia, and cytokine induction, have been used to investigate sepsis pathophysiology (9). For example, Miyoshi et al. observed a significant decrease in the CSA and muscle mass of the EDL 24 h after a 10 mg/kg dose of LPS, while no change was detected in the soleus (30).

The most important mechanisms underlying skeletal muscle atrophy associated with sepsis are an increased inflammatory response and mitochondrial dysfunction. Specifically, it is proposed that systemic inflammation in sepsis may lead to skeletal muscle atrophy through an increase in cytokine release (31). It is known that levels of certain pro-inflammatory cytokines are elevated, including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-alpha), and IL-1β, which have been shown to induce atrophy of skeletal muscle and myotubes in the context of an enhanced inflammatory response in sepsis (31, 32). An increased cytokine response triggers the activation of several signaling pathways involved in degrading skeletal muscle proteins (32). For example, transgenic overexpression of nuclear factor kappa B (NF-κB), the master regulator of the inflammatory response, has been shown to lead to skeletal muscle atrophy, resulting in increased atrogene levels and a decreased CSA of the EDL muscle in mice (33). These findings are like those observed in muscle atrophy induced by cachexia (33). Similarly, it has been documented that inhibition of NF-κB can prevent protein degradation and myotube atrophy in C2C12 myotubes (32). Transgenic mice with skeletal muscle-specific NF-κB inhibition exhibit augmented skeletal muscle strength and endurance, along with enhanced resistance to denervation-induced skeletal muscle atrophy (34).

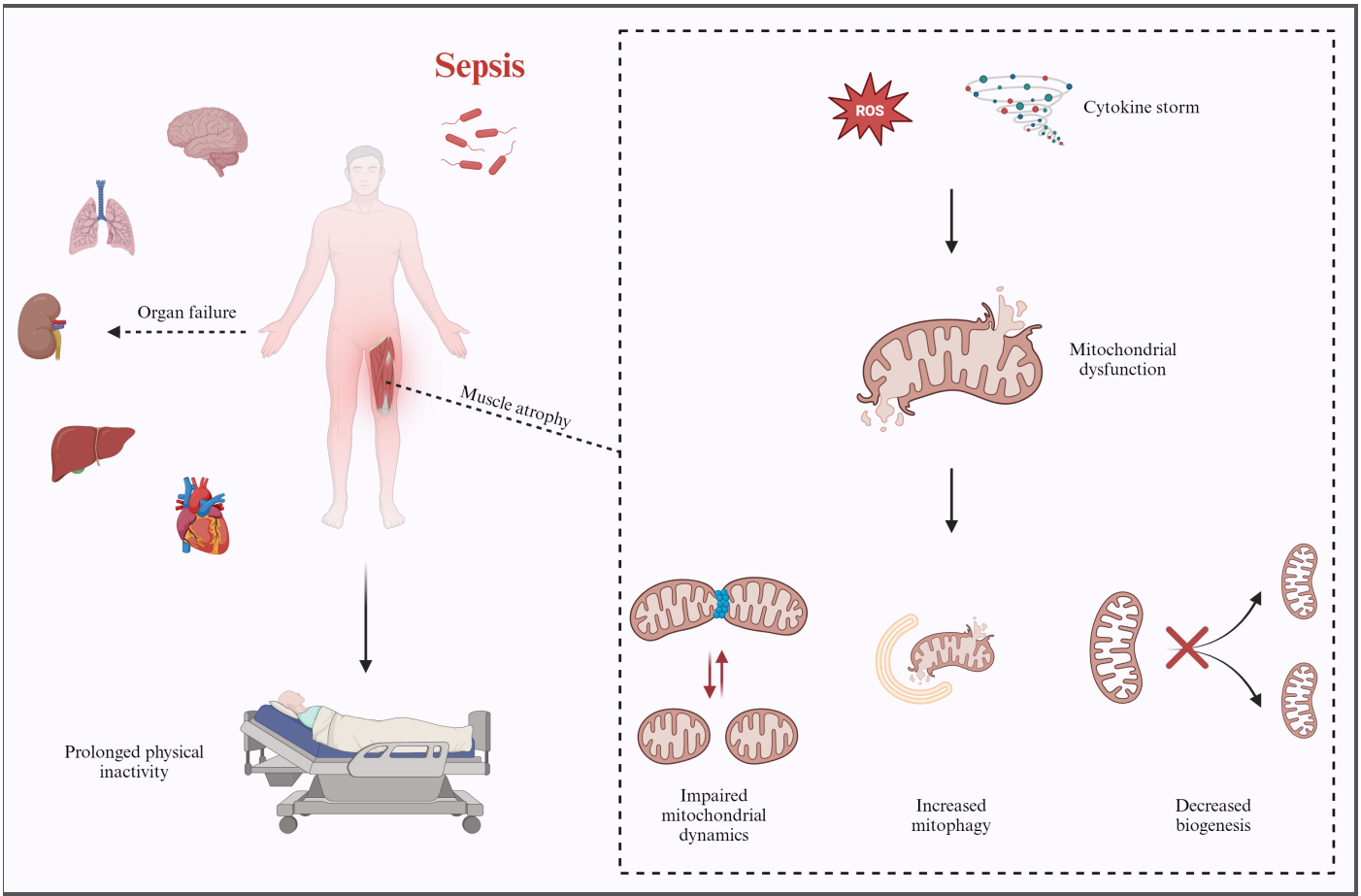

Figure 1. Sepsis-induced skeletal muscle atrophy and mitochondrial damage. Sepsis is associated with a range of systemic complications, including organ failure affecting the brain, lungs, kidneys, liver, and heart, as well as skeletal muscle. Prolonged physical inactivity in septic patients serves to exacerbate these effects. At the cellular level, sepsis-induced oxidative stress (ROS) and a cytokine storm contribute to mitochondrial dysfunction. Impaired mitochondrial dynamics result in dysregulated fission and fusion, leading to increased mitophagy and a subsequent inability to maintain functional mitochondria. This imbalance contributes to cellular energy deficits, which serve to further drive the pathophysiology of sepsis. Figure was created with BioRender.com

Mitochondrial dysfunction represents another mechanism responsible for sepsis-induced muscle atrophy. Given the role of mitochondria in cellular energy production, it is evident that maintaining a healthy mitochondrial population is crucial for the optimal functioning of skeletal muscles (35).

Skeletal muscle atrophy may result from various underlying pathologies, including chronic diseases, cachexia, the natural process of aging, and extended periods of bed rest (6).

Although the mechanisms underlying the loss of skeletal muscle mass are complex and multifaceted, mitochondrial dysfunction is postulated to be a significant contributor to the development of skeletal muscle atrophy (6). In the skeletal muscles of patients suffering from sepsis, there is a reduction in the production of adenosine triphosphate (ATP), accompanied by a decrease in the number and content of mitochondria (36, 37).

The development of mitochondrial dysfunction in the acute phase of sepsis leads to a reduction in skeletal muscle mass and a decline in muscle function in the later stages of the disease (38). This phenomenon can be attributed to the enhanced production of reactive oxygen species (ROS) by mitochondria with diminished functionality (38). Animal studies with mitochondria-targeted antioxidant agents have shown that these agents can prevent sepsis-induced atrophy in the diaphragm and skeletal muscle, improve mitochondrial function, reduce oxidative stress, and inhibit the caspase-calpain and proteasomal systems, which are molecular mechanisms contributing to muscle atrophy (39, 40). The administration of LPS has been found to reduce mitochondrial respiratory capacity in both mouse C2C12 myotubes and human primary skeletal muscle cells (41, 42). Recovery of impaired mitochondrial function has been observed in cells treated with N-acetyl cysteine, a well-known antioxidant (41). In addition, administration of SS-31, a mitochondria-targeted antioxidant peptide, prior to LPS treatment in C2C12 myotubes prevented LPS-induced reductions in myotube diameter (43).

Table 1. The Summary of Sepsis-Induced Skeletal Muscle Changes

Study/Reference	Experimental Model	Muscle Type	% Change in CSA	Mitochondrial Dysfunction Indicators	Additional Observations
Eikermann et al. (28)	Sepsis patients vs. immobilization	Arm muscles	No change	N/A	Atrophy linked to sepsis, not bed rest
Miyoshi et al. (30)	LPS	EDL	↓ Significant	↓ ATP production ↑ ROS levels	Soleus unaffected; early sepsis impacts fast-twitch fibers
Li et al. (31)	TNF-α-induced muscle wasting	C2C12 myotubes	N/A	N/A	NF-κB inhibition prevented protein loss
Cai et al. (33)	Transgenic mice (NF-κB activation)	EDL	↓ Significant	↑ Atrogene expression	Inhibition of the IKKβ/NF-κB/MuRF1 pathway reversed muscle atrophy. ;
Frisard et al. (41)	LPS	Gastrocnemius	N/A	↓ ETC capacity	Recovery observed with N-acetyl cysteine and catalase
Eggelsbuch et al. (43)	LPS	C2C12 myotubes	↓ Significant	↓ Mitochondrial efficiency ↓Mitochondrial size	IL–1β exposure does not affect mitochondrial morphology or function

LPS: Lipopolysaccharide, TNF-α : Tumor necrosis factor-alpha, EDL: Extensor digitorum longus, ATP: Adenosine triphosphate, ROS: Reactive oxygen species, ETC: Electron transport chain, NF-κB: Nuclear Factor kappa B, IKKβ: Kappa B kinaz beta, MuRF1: Muscle RING-finger protein-1, IL-1β: Interleukin-1β, N/A: Not available

While many factors contribute to skeletal muscle wasting, muscle loss in patients with prolonged bed rest and sepsis presents a significant challenge in managing severe infections. Despite a 53% reduction in sepsis mortality between 1990 and 2017 due to medical advances (24), approximately one-third of sepsis survivors experience permanent physical disability 6 months after leaving hospital (44). One of the major causes of long-term physical impairment is the loss of skeletal muscle mass that occurs during the acute phase of sepsis. In fact, sepsis is associated with a 10-20% loss of skeletal muscle mass within one week, which correlates with functional decline and increased mortality (45). Skeletal muscle atrophy is a significant complication of sepsis, affecting 40-70% of patients (5). Sepsis-induced muscle atrophy is linked to increased morbidity and mortality, with systemic inflammation identified as a primary underlying factor (46). It occurs in 40% of critically ill patients in the intensive care unit (ICU) and is associated with prolonged mechanical ventilation, extended hospital stays, increased mortality, and long-term functional impairment (47). Loss of muscle mass, particularly in the context of sepsis, is a rapid and pronounced phenomenon that occurs within the first ten days of an ICU (48). Moreover, many patients who survive critical illness experience a reduced quality of life after leaving hospital, largely due to impaired physical functioning (49).

Sepsis-induced mitochondrial damage and related mechanisms

Sepsis-induced mitochondrial damage or dysfunction results in apoptosis in various tissues and immune cells due to inadequate energy production combined with elevated oxidative stress levels (50) (Figure 1). Experimental models of sepsis have demonstrated mitochondrial morphological abnormalities, including condensed matrix, mitochondrial swelling, cristae anomalies, internal vesicles, and disruption of mitochondrial membranes, which are associated with mitochondrial dysfunction (51). Furthermore, disruptions in the electron transport chain (ETC) have also been observed in septic conditions. Inflammatory mediators such as nitric oxide , carbon monoxide, ROS, and reactive nitrogen species, which are increased

during sepsis, directly disrupt various components of the mitochondrial ETC complex and mitochondrial respiration (52). The ATP content in skeletal muscles decreases in patients from severe sepsis, while higher ATP levels are observed in survivors (36). ROS accumulated in the mitochondrial matrix have been shown to suppress ETC complex activities, with ETC complexes I and IV being particularly sensitive to ROS-induced damage (50). It is evident that in cases of sepsis, there is a decline in the ETC's capacity to produce ATP coupled with an overproduction of ROS (53).

Mitochondrial dysfunction in sepsis results in the activation of mitochondrial fission and the inactivation of mitochondrial fusion. Mitochondrial fission leads to the activation of Bcl-2 associated X protein (Bax), increased permeabilization of the outer membrane, remodeling of the cristae, excessive ROS production, and decreased ATP production, all of which collectively contribute to cell death and organ failure (54). The processes of mitochondrial fission and the expression of dynamin-related protein 1 (DRP1) are observed to increase in skeletal muscle under sepsis conditions (55). In the initial phases of sepsis, the elimination of damaged mitochondria (mitophagy) and the enhancement of mitochondrial biogenesis can, at least temporarily, prevent organ damage. However, in the later stages, the cessation of mitochondrial biogenesis adversely affects prognosis (56). Inata et al. demonstrated that the activation and nuclear translocation of AMP-activated protein kinase and PGC-1α are time-dependent processes following sepsis. Furthermore, they established that these changes lead to mitochondrial dysfunction in aged mice (57).

Autophagy plays a pivotal role in the pathogenesis of organ dysfunction associated with sepsis and undergoes continuous changes during the progression of the disease (56). In the later stages of sepsis, autophagy becomes inadequate and maladaptive, accompanied by enhanced signaling of the mammalian target of rapamycin (mTOR). This ineffective elimination of toxic substances and damaged organelles leads to the accumulation of mitochondrial damage-associated molecular patterns ; (58). In sepsis, the extrinsic apoptotic pathway is activated via TNF receptor-associated death domain receptors. Activation of these death receptors results in the activation of caspase-8, which then cleaves and activates other caspases, thereby triggering cell death (59).

Exercise and skeletal muscle atrophy

The beneficial effects of regular exercise on the health of patients with various pathological conditions are well-documented, including benefits for cardiovascular diseases, obesity, type 2 diabetes, sarcopenia, and certain types of cancer (11). According to the current World Health Organization (WHO) guidelines, adults should engage in at least 150 minutes of moderate-intensity or 75 minutes of high-intensity aerobic physical activity, or an equivalent combination, distributed throughout the week (60). Despite the known benefits of exercise, skeletal muscles are central to the molecular adaptations that occur in response to exercise (11).

Endurance exercise enhances the body's capacity to transport and utilize oxygen for energy production by stimulating mitochondrial biogenesis and angiogenesis (61). Conversely, resistance exercise (4 to 12 repetitions and 8 to 12 weeks) induces skeletal muscle hypertrophy, characterized by increased muscle strength and CSA (62). These exercise-mediated adaptations result from changes at the organelle level and alterations in cell signaling pathways that regulate protein synthesis and degradation (10, 63).

Endurance exercise has been shown to regulate mitochondrial activity in skeletal muscle through mitochondrial biogenesis, a process linked to increased expression of the PGC-1α protein and resulting in improved mitochondrial mass and function (2). Endurance exercise (~ 50-70% of VO_2max, 30 min, 12 weeks) improves mitochondrial function by increasing mitochondrial size, number, maximal oxygen consumption, and enzyme production (64). PGC-1α, which increases mitochondrial content, plays a pivotal role in regulating mitochondrial biogenesis (65). Endurance exercise (a speed of 15 m/min, 60 min, 12 weeks) stimulates the expression of PGC-1α in skeletal muscle (66) and directly stimulates mitochondrial protein synthesis (67). The expression of PGC-1α is elevated by endurance exercise (~ 60% of VO_2max, 40 min, 6 weeks) through activation of the energy metabolism signaling pathway, particularly in vastus lateralis muscle (68). Additionally, resistance exercise (8 to 10 repetitions) facilitates skeletal muscle protein synthesis by activating the mTOR pathway (69). Overexpression of PGC-1α in transgenic animals inhibits Forkhead box-O transcription factors (70). Endurance exercise (30-45 min, 3-5 day/week) stimulates muscle protein synthesis for up to two to four days following the last exercise session (71).

Exercise and mitochondria in sepsis-induced skeletal muscle atrophy

Sepsis-induced skeletal muscle atrophy is defined by a decrease in muscle mass, fiber size, and strength, leading to prolonged physical disability (9). During exercise, an antioxidant system is activated to maintain redox balance, as exercise simultaneously increases ROS generation and oxygen uptake (72). This increase in oxygen consumption and enhanced antioxidant defenses during endurance exercise

(~ 75% of VO_2max, 40 min, 12 weeks) may help scavenge ROS in sepsis (72-74).

Bagby et al. demonstrated that endurance exercising (5-10 min, 4 days) rats to near exhaustion before an intravenous LPS challenge significantly reduced the systemic TNF response typically observed in response to LPS (75). Starkie et al. reported that cycling exercise (~ 75% of VO_2max, 3 hours min, 1 week) can mitigate the elevation of TNFα caused by endotoxemia while simultaneously increasing plasma levels of the anti-inflammatory cytokines (76). Their findings suggest that physical activity may play a role in reducing inflammatory processes (76). Endurance exercise (15-60 min, 4 weeks) also lessens the effects of sepsis on the body, including tachycardia, nitrite/nitrate levels, muscle glycogen depletion, reductions in blood cells, and elevations in pro-inflammatory cytokines and biochemical variables (77).

Numerous studies have demonstrated the anti-inflammatory benefits of exercise on bodily tissues (78). Reduced levels of TNF-α and p38 mitogen activated protein family of kinases activity were observed in peritoneal macrophages isolated from endurance exercised (60 min, 8 weeks) mice exposed to LPS (79). The preservation of muscle fiber CSA during the initial stages of septic shock may be attributed to limiting excessive autophagy activation, a strategy that not only prevents muscle inflammation but is also well-tolerated (27). Enhancing exercise participation among older patients is hypothesized to prevent the onset of sarcopenia and improve outcomes for elderly patients with sepsis (80).

CONCLUSION

Skeletal muscle atrophy resulting from sepsis significantly impacts patients' overall health, exacerbating the extended duration of hospitalization and inflammation-related deterioration. A key factor in this process is the impairment of mitochondrial function, which is essential for cellular energy production. Addressing mitochondrial dysfunction may therefore offer therapeutic potential to mitigate sepsis-induced muscle wasting, improve patient outcomes, and shorten recovery time following hospitalization. Regular exercise has been shown to prevent muscle atrophy by enhancing mitochondrial function, promoting mitochondrial biogenesis, and improving oxidative capacity. Therefore, combining exercise into the rehabilitation of critically ill patients may play a pivotal role in reducing sepsis-induced skeletal muscle atrophy and improving physical function, making it an important complement to other therapeutic strategies.

Conflict of Interest / Çıkar Çatışması

The authors declared no conflicts of interest with respect to authorship and/or publication of the article.

Financial Disclosure / Finansal Destek

The authors received no financial support for the research and/or publication of this article.

Author Contributions / Yazar Katkıları

Concept: GBK, IT, FA Design: GBK, IT, FA Supervision: GBK,FA Data Collection and/or Processing: GBK, IT Analysis and Interpretation: GBK, IT, FA Literature Review: GBK, IT, FA Writing Manuscript: GBK, IT, FA Critical Reviews: GBK, IT, FA. All authors contributed to the final version of the manuscript and discussed the results and contributed to the final manuscript.

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