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Stem Cell Therapy in Athletes with Skeletal Muscle Overuse Injuries

Sarah Gluzman-Chuang (author)[1]

[1]Cambridge Centre for International Research, Cambridge, United Kingdom

Abstract

Overuse injuries account for 50% of the annual 3.5 million injuries sustained by athletes ages 6 to 18 in the United States. Traditional treatments, including the RICE principle, NSAIDs, physical therapy, and surgery, often fail to fully regenerate damaged tissue due to their reliance on the body's natural healing mechanisms. Therefore, mesenchymal stem cell (MSC) therapy has emerged as a promising strategy for enhancing skeletal muscle repair and regeneration. Studies have demonstrated that MSCs derived from bone marrow, adipose tissue, and umbilical cord can improve muscle strength and function by promoting tissue regeneration, modulating immune responses, and reducing inflammation. The use of synthetic scaffolds and 3D bioprinting further enhances the effect of injected MSCs. Despite promising potential, there is a notable lack of preclinical trials specifically focused on MSC therapy for skeletal muscle injuries. Several challenges, including limited preclinical studies, cell viability in culture, standardized cell dosages, and delivery, must be addressed for MSC therapy to be integrated into clinical use. This review highlights the

regenerative potential of MSCs for skeletal muscle overuse injuries and explores emerging strategies that may lead to future clinical applications in sports medicine treatments.

Keywords: biomedical engineering, cell and tissue engineering, regenerative medicine, mesenchymal stem cells, skeletal muscle.

Introduction

In the United States, approximately 30 million children and teenagers participate in organized sports each year, resulting in more than 3.5 million injuries annually (Stanford Medicine Children's Health, n.d.). Additionally, approximately 50% of all sports-related injuries sustained by athletes ages 6 to 18 are related to overuse (Patil, n.d.). Overuse injuries are a broad category of sports injuries that develop from excessive and repeated stress placed on the musculoskeletal system during sports or exercise. While acute injuries occur abruptly due to a specific event, such as fractures, sprains, or muscle tears, overuse injuries develop gradually over time due to microtrauma. Overuse injuries can negatively impact athletic performance and may prevent participation in sports (Franco et al., 2021).

Sports injury treatments vary depending on the severity of the injury. Traditional treatment techniques for minor injuries include resting, icing, compressing, and elevating (RICE) the injured part of the body, as well as over-the-counter anti-inflammatory medications. Severe injuries are treated through immediate immobilization in the form of a cast, splint, or brace in order to support and protect the bones and soft tissue. In some cases, surgery is performed to repair torn connective tissues or to realign bone fractures (Garrick, n.d.). During the recovery process, physical therapy plays a crucial role in rebuilding strength

and mobility through personalized rehabilitation programs. In contrast to these traditional treatment methods that rely on the body's natural healing process, regenerative medicine actively promotes healing and tissue regeneration, providing athletes with a faster and more effective recovery (Thalia, 2025).

Mesenchymal stem cell (MSC) therapy has considerable potential as an alternative approach in regenerative medicine for treating severe overuse injuries. Among the various types of stem cells, MSCs have been the most abundantly used due to their capacity for multipotent differentiation and their ability to be isolated from various tissue sources (Qazi et al., 2019). In the context of sports injuries, MSCs may be used to facilitate the repair and regeneration of damaged skeletal muscle tissue when the natural healing process is insufficient or delayed. Stem cell therapy may become a critical component of regenerative treatment in sports medicine, with the potential to accelerate recovery times and improve athletic performance. This paper reviews the current advances, challenges, and future directions in stem cell therapy for skeletal muscle repair and regeneration.

Skeletal Muscle Regeneration Following Overuse Injuries

Overuse injuries in sports result from the cumulative effect of repetitive strain on the musculoskeletal system without sufficient recovery time. These injuries most commonly impact the lower limbs and affect tissues such as tendons and muscles (Launay, 2015). Two common tendon-related injuries that primarily affect children are Osgood-Schlatter disease and Sever's disease, both of which are forms of apophysitis, or inflammation of the growth plate. Osgood-Schlatter disease affects the patellar tendon, while Sever's disease affects the Achilles tendon. Both injuries are caused by repetitive, high-intensity activities such as

jumping, sprinting, or running (Yun & Fein, 2024). In contrast, muscle strains are caused by practicing excessively high training loads over time. Hamstring strains are a common example, as they are one of the highest reported muscle injuries in sports (Wing & Bishop, 2020).

The natural regeneration of skeletal muscle following an injury involves a series of complex biological processes occurring in the affected area. A key component of this initial response is the activation of satellite cells (SCs), which are myogenic stem cells capable of proliferation and self-renewal (Hawke & Garry, 2001). SCs help maintain muscle homeostasis by repairing and regenerating tissue in response to minor damage that accumulates during the development of an overuse injury.

SCs remain in a quiescent state under homeostatic conditions, located between the basal lamina and sarcolemma of myofibers. Upon muscle strain or injury during exercise, SCs become activated through various signaling pathways. Once activated, they proliferate and differentiate into myoblasts, which proliferate further and migrate to the injured site. Next, these myoblasts undergo myogenic differentiation and fuse with the damaged myofibers to repair them and form new myofibers (Chargé & Rudnicki, 2004; Qazi et al., 2019). During this regenerative process, some SCs will self-renew through asymmetric cell division to preserve the quiescent satellite cell pool and regenerate damaged skeletal muscle (Careccia et al., 2024). Ultimately, SCs are essential for effective skeletal muscle regeneration following injury, as shown in Figure 1 (Johnson et al., 2023).

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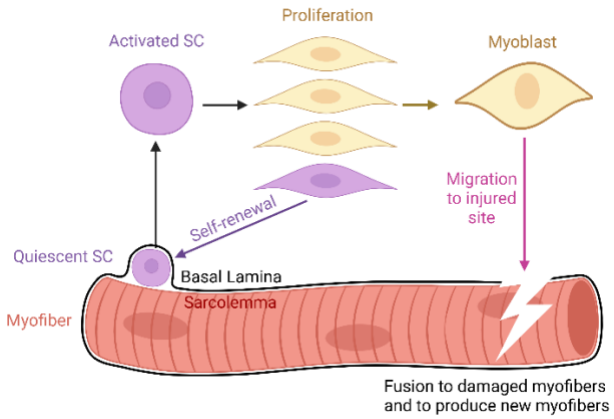
Figure 1

Satellite Cell Differentiation During Skeletal Muscle Regeneration.



Note. This process involves the activation of quiescent SCs in response to muscle strain or injury, which proliferate into myoblasts that subsequently fuse with damaged myofibers to form new myofibers. This figure was created using Biorender by Sarah Gluzman-Chuang.

Clinical Applications for Skeletal Muscle Injuries

The current clinical options for treating skeletal muscle injuries are categorized into conservative treatments and invasive surgical procedures. While these treatments range from basic pain relief to surgical procedures like muscle transposition, they are often limited in their ability to fully regenerate skeletal muscle tissue, prompting research on regenerative medicine treatments.

Conservative Treatment

The RICE principle of rest, ice, compression, and elevation typically begins conservative treatment for minor muscle tears. This principle reduces blood flow to the

injured site, limiting the size of the hematoma and preventing trauma from extending into nearby muscle regions. However, this reduction of blood flow may also delay the healing process (Fernandes et al., 2011). Additionally, while the resting component is helpful in allowing scar tissue strength to develop, long periods of immobility may cause excessive fibrosis and impair muscle function.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used for managing pain and inflammation. NSAIDs can prevent edema caused by the inflammatory process following an injury, decreasing anoxia and further cell death. However, experimental studies have shown conflicting results when NSAIDs are used immediately after injury. NSAIDs should not be given sooner than 48 hours following injury to prevent interfering with the cell chemotaxis necessary for muscle repair and regeneration (Baoge et al., 2012).

Physical therapy is commonly used in the recovery process to maintain skeletal muscle mass by promoting tissue repair and regeneration. It is effective in restoring range of motion, rebuilding strength, improving balance and coordination, and preventing future injuries. However, a limitation of physical therapy is that patients with severe injuries are unable to practice constant exercise (Marygrove College Athletics, n.d.).

Invasive Surgical Procedures

Surgical procedures should be approached with extreme caution, as properly executed conservative treatments often yield good results. Therefore, surgery can only be implemented in specific conditions, including a large intramuscular hematoma, a complete muscle strain or tear, or a partial strain if more than half of the muscle belly is torn (Järvinen et al., 2014).

For severe injuries, such as volumetric muscle loss (VML), surgical treatments mainly include scar tissue debridement and muscle transposition (Liu et al., 2018). The process of scar tissue debridement removes necrotic or infected excess tissue formed during improper injury healing. This procedure stimulates healthy tissue growth, minimizes scarring, and reduces complications of infections. However, it does not regenerate new muscle tissue and relies on the body's natural healing mechanisms (Nunez, n.d.). Autologous muscle transfer is the process where surgeons graft healthy muscles from a donor site unaffected by the injury in order to replace or repair severely injured muscle tissue. Despite their potential benefits, approximately 10% of these reconstructive procedures result in complete graft failure due to complications like infection and necrosis (Liu et al., 2018).

Although surgical techniques for skeletal muscle repair and regeneration are highly developed and can provide good results, they are associated with considerable risks and high costs. Research into the rapidly growing field of regenerative medicine is offering new treatment methods for skeletal muscle injuries (Liu et al., 2018). Although there are currently no clinical applications, numerous preclinical trials demonstrate the benefits of regenerative medicine, including biological scaffolds, platelet-rich plasma (PRP) injections, growth factor therapy, and stem cell therapy.

Skeletal Muscle Regeneration with Stem Cell Therapy

Stem Cell Injections

When severe injury causes significant tissue loss, the regenerative capacity of skeletal muscle is exceeded. Consequently, myofibers have a reduced ability to grow, fill, and repair

the injured area. In these scenarios, stem cell therapy may be utilized to promote skeletal muscle growth (Merritt et al., 2010). MSCs are adult stem cells that are isolated from human and animal sources. MSCs can be derived from various tissues, including bone marrow, adipose tissue, and umbilical cord blood, and have the capacity to differentiate into multiple cell types, including skeletal muscle (Ullah et al., 2015). Table 1 summarizes the studies that demonstrate the use of MSCs in treating damaged skeletal muscle tissue.

Table 1

Studies Involving Cell Therapy to Treat Skeletal Muscle Injury.

MSC Source + Scaffold	Animal Model	Targeted Muscle	Key Findings
BM-MSCs	Female rats	Gastrocnemius muscle	Induced muscle regeneration (Boulos et al., 2021)
BM-MSCs	Male rats	Soleus muscle	Significantly improved muscle injury recovery and recovered strength (Matziolis et al., 2006)
AD-MSCs	Female rats	Soleus muscle	Improved muscle strength and fiber regeneration; accelerated muscle repair

			(Peçanha et al., 2012)
BM-MSCs + ECM scaffold	Male rats	Gastrocnemius muscle	Improved muscle function, vascularization, and myofiber formation (Merritt et al., 2010)
BM-MSCs	Female rats	Adductor brevis muscle	Modulated immune responses; improved muscle regeneration; reduced fibrosis (Helal et al., 2016)
Human umbilical cord-derived MSCs + ECM scaffold	Rats	Tibialis anterior muscle	Regulated macrophage polarization by promoting the M2 phenotype and suppressing the M1 phenotype (Qiu et al., 2018)
AD-MSCs + PLGA sphere scaffold	Mice	MSCs cultured in myogenic medium were injected subcutaneously into the neck	Regenerated muscle tissue (Kim et al., 2006)

Human muscle-derived MSCs + 3D bioprinted PEG-fibrinogen hydrogel scaffold	Male mice	Tibialis anterior muscle	Supported differentiation of muscle fiber into aligned muscle bundles; promoted tissue regeneration (Fornetti et al., 2023)

Note. Key findings demonstrate that stem cell therapy, either alone or combined with the use of scaffolds and 3D bioprinting, improves muscle strength, accelerates repair and regeneration, modulates immune responses, and enhances vascularization.

In a study conducted by Boulos et al. (2021), bone marrow-derived MSCs (BM-MSCs) were directly transplanted into injured gastrocnemius muscles in female rats. Because skeletal muscle injury induces an inflammatory reaction that lasts for 14 days, the MSCs were injected during this period. After 14 days, muscle regeneration induced by the MSCs was observed (Boulos et al., 2021). Similarly, Winkler et al. (2019) injected BM-MSCs to study the effects on muscle strength following controlled trauma of the soleus muscle in male rats. The results showed a statistically significant improvement in muscle injury recovery and a higher percentage of recovered strength, measured by tetanic contraction force, three weeks after treatment (Matziolis et al., 2006). In contrast to BM-MSCs, Peçanha et al. (2012) cultured adipose-derived MSCs (AD-MSCs) from male rats and injected them into the soleus muscles of female rats. Similar results were observed, with the treated muscles exhibiting greater muscular strength, as measured by tetanic force, two weeks after injection. Additionally, the muscles displayed an increased number of regenerating myofibers,

demonstrating that muscle repair was accelerated (Peçanha et al., 2012). In another study, Merritt et al. (2010) used BM-MSCs seeded on a decellularized extracellular matrix scaffold for VML of the gastrocnemius muscle in male rats. The MSCs improved muscle function post-repair and increased the formation of blood vessels and myofibers growing within the implant (Merritt et al., 2010). Overall, these studies demonstrate that both BM-MSCs and AD-MSCs significantly improved muscle strength after injury by inducing muscle regeneration.

In another study, Helal et al. (2016) transplanted in vitro cultured BM-MSCs into injured adductor brevis muscles of female rats with VML. The MSCs modified local immune responses by suppressing inflammatory cytokines and activating anti-inflammatory ones, improving muscle regeneration through the restoration of muscle fibers and angiogenesis. Additionally, the MSCs blocked the fibrotic signaling cascade by declining transforming growth factor beta 1 (TGF-β1) and reducing scar tissue (Helal et al., 2016). In addition to BM-MSCs, Abd El Aty et al. (2022) used the plant *Trigonella foenum-graecum* to treat skeletal muscle atrophy in rats. This injection resulted in antioxidant activity, anti-inflammatory properties, and anti-apoptotic effects, contributing to improved muscle recovery (Abd El Aty et al., 2022). Moreover, Qiu et al. (2018) utilized human umbilical cord MSCs and a decellularized extracellular matrix scaffold to promote skeletal muscle tissue regeneration of the tibialis anterior muscle in rats. Both the MSCs and the scaffold collaboratively regulated macrophage polarization by promoting the regenerative M2 phenotype and suppressing the pro-inflammatory M1 phenotype, which played an important role in tissue regeneration (Qiu et al., 2018). These studies demonstrate that MSCs support

skeletal muscle regeneration by modulating the immune system to reduce inflammation, promote tissue repair, and shift immune cell activity to a more regenerative phenotype.

Tissue Engineering Strategies

Tissue engineering combines stem cells, scaffolds, and biologically active molecules to construct functional tissues. Although natural scaffolds, such as decellularized extracellular matrix scaffolds, have shown promising outcomes, there is an increased need for new, synthetic scaffold structures. Stem cell therapy combined with synthetic biomaterials and 3D bioprinting is an emerging strategy in the field of tissue engineering (Howard et al., 2008).

An example of a synthetic scaffold is the combination of AD-MSCs with the biodegradable polymer poly(lactic-co-glycolic acid) (PLGA), used in a study conducted by Kim et al. (2006). The AD-MSCs attached to PLGA spheres and the PLGA spheres alone were cultured for 21 days, then injected into mice. After 30 and 60 days, results showed that the AD-MSCs attached to PLGA spheres were able to regenerate muscle tissue, while the PLGA spheres alone did not. These findings demonstrate that the PLGA spheres are a useful synthetic scaffold in combination with AD-MSCs (Kim et al., 2006). Synthetic scaffolds can also be created using 3D bioprinting, a tissue engineering strategy that develops custom scaffolds tailored for a specific purpose. 3D bioprinting is an excellent tool to produce functional tissues using various synthetic polymers and biomaterials. Various strategies include inkjet, stereolithographic, laser-assisted, and extrusion bioprinting (Sabetkish et al., 2024). In a study conducted by Fornetti et al. (2023), an extrusion-based bioprinting method utilized the hybrid hydrogel PEG-fibrinogen (PF) to create scaffolds for skeletal muscle regeneration. The scaffold supported the differentiation of muscle fibers into aligned bundles

that contracted spontaneously when cultured in vitro. After being transplanted into a VML model in mice, the bioprinted scaffold promoted tissue regeneration of the tibialis anterior muscle (Fornetti et al., 2023).

These studies highlight the potential of stem cell therapy and tissue engineering strategies in repairing and regenerating skeletal muscle. MSCs injected into damaged skeletal muscle tissue improved muscular strength, reduced inflammation, and induced muscle regeneration, while synthetic scaffolds and 3D bioprinting strategies further enhanced tissue regeneration. These strategies are being evaluated in preclinical studies, as there are no widely approved clinical therapies for skeletal muscle regeneration using MSCs.

Preclinical Studies on the Use of Stem Cells for Overuse Injuries

Although stem cell therapy may eventually be used to target muscles specifically affected by sports injuries, current clinical trials primarily focus on other muscle groups. For example, Sarveazad et al. (2017) injected AD-MSCs into patients with defects in the anal sphincter muscle causing fecal incontinence. Their study found that injecting AD-MSCs during repair surgery for fecal incontinence resulted in the replacement of fibrous tissue with muscle tissue, demonstrating the regenerative potential of AD-MSCs in smooth muscles (Sarveazad et al., 2017). In another study, Winkler et al. (2018) injected placenta-derived MSCs into injured gluteus medius muscles in patients undergoing hip arthroplasty. As a result, the stem cell therapy improved strength and volume in the injured skeletal muscle and modulated stress-related immune responses shortly after the surgery (Winkler et al., 2018). Moreover, Carr et al. (2013) injected autologous muscle-derived cells into the urethral sphincter in female patients with stress urinary incontinence who had not improved with

conservative treatments. The muscle precursor cells then integrated into existing muscle tissue, assisting in the repair and strengthening of the sphincter muscle (Carr et al., 2013). In contrast to the direct muscle repair by autologous muscle-derived cells, another study demonstrated that MSCs promote skeletal muscle repair indirectly. Wang et al. (2018) injected BM-MSCs into the anterior tibialis muscle of patients with critical limb ischemia. Although it was initially believed that the stem cells would engraft, differentiate, and directly replace the damaged tissue, the study found that less than 0.1% of the injected cells engrafted in the tissue. Instead, the results suggested that MSCs promote tissue repair indirectly through cellular crosstalk. This communication between MSCs and the patient's damaged cells involves MSCs secreting bioactive proteins, triggering genes in the surrounding tissue that regulate immune responses, and transferring exosomes to damaged cells (Wang et al., 2018).

Currently, there are no clinical trials involving the direct injection of MSCs into skeletal muscles, which are the most commonly affected by overuse injuries. Specifically, the rotator cuff muscles, including the supraspinatus, infraspinatus, teres minor, and subscapularis, and the elbow flexor and extensor muscles. However, given the promising results demonstrated in studies targeting other muscle groups, stem cell therapy holds potential for future application in sports medicine.

Challenges and Future Directions

Due to several limitations, MSCs are not currently used clinically for the repair and regeneration of skeletal muscle tissue. Overcoming these challenges is essential for future research on the use of stem cells in sports-related overuse injuries. As previously noted, preclinical studies exploring the use of MSCs for skeletal muscle regeneration have been

primarily conducted in small rodent models. These studies are limited to a small number of muscle groups, typically the hindlimb and external sphincter muscles, which have a large variability in fiber type composition, size, and cell populations. This variability makes it difficult to standardize cell dosage and predict outcomes (Qazi et al., 2019). Moreover, to reach an adequate amount, MSCs often require extensive expansion in culture before application. However, prolonged culture can cause replicative senescence, or deterioration, of the MSCs (Dias et al., 2023). Additionally, the window for effective cell delivery is limited to approximately seven days post-injury, adding to the challenge of preparing MSCs before application (Winkler et al., 2012). Another complication arises from the intramuscular injection of MSCs into damaged tissue. Although it is the most common method, injecting stem cells may cause mechanical damage to the cells due to shear forces, substantial cell loss resulting from a lack of anchorage, immune-mediated rejection, or cytokine-induced cell death (Qazi et al., 2019). Furthermore, aging can affect the functionality of stem cells. The proliferative activity of MSCs significantly decreases during the aging process, limiting their differentiation potential. This reduces the pool of stem cell donors for effective stem cell therapy, as older donors are excluded (Nurkovic et al., 2016).

Although many challenges remain, ongoing research in regenerative medicine continues to explore strategies to improve stem cell therapy and support its integration into clinical applications. For example, the heterogeneity of MSCs can limit the development of standard protocols for clinical use. Therefore, researchers have been exploring the derivation of MSCs from induced pluripotent stem cells (iPSCs). This has the potential to generate a high yield of patient-specific MSCs, which can be derived from a single iPSC clone, thereby reducing heterogeneity (Dias et al., 2023). Another developing strategy is the genetic

modification of MSCs to produce specific, desired biological functions. Numerous preclinical studies have successfully engineered MSCs to express therapeutic peptides and proteins in animal models. CRISPR/Cas9 technology can also be utilized to genetically modify MSCs with higher efficiency and specificity (Zhou et al., 2021). Moreover, although encapsulating MSCs in biomaterials has been shown to improve the retention and survival of MSCs in vitro, further studies are needed to explore the effects of biomaterials on skeletal muscle regeneration in vivo. In the context of sports injuries, MSCs can be beneficial for overuse injuries that result in chronic muscle strain and microtrauma, which commonly occur due to repetitive motions.

Conclusion

Skeletal muscle overuse injuries are a prevalent issue in athletes, yet traditional treatments are often limited in their ability to regenerate skeletal muscle tissue fully. As a result, stem cell therapy combined with the use of scaffolds and 3D bioprinting has emerged as a promising alternative treatment. Although there are currently no clinical applications of MSC therapy for skeletal muscle damage, preclinical studies demonstrate that MSCs promote muscle repair, modulate immune responses, and improve muscle strength and function after repair. Overall, stem cell therapy and regenerative medicine are promising treatment strategies for overuse injuries, with the potential to regenerate damaged skeletal muscle tissue, shorten recovery time, and allow athletes to return to their sport more quickly.

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