Review

Stefano Palermi, Rossana Gnasso, Immacolata Belviso, Irene Iommazzo, Marco Vecchiato, Andrea Marchini, Alessandro Corsini, Filippo Vittadini, Andrea Demeco, Mariarosaria De Luca, Domiziano Tarantino, Veronica Romano, Annamaria Sacco and Felice Sirico*

Stem cell therapy in sports medicine: current applications, challenges and future perspectives

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Abstract: Stem cells have demonstrated significant potential for tissue repair and regeneration, making them a promising therapeutic avenue in sports medicine. This review aims to provide a comprehensive overview of the current state of research on the application of stem cells in sports medicine. We will discuss the types of stem cells used, their mechanisms of action, and the clinical outcomes of stem cell therapy in different sports-related injuries. Furthermore, we will delve into the challenges and ethical considerations associated with stem cell therapy, as well as future directions and potential applications of stem cells in sports medicine.

Keywords: sports medicine; stem cells; regeneration medicine; sports injury

Introduction

Sports injuries are a common occurrence among athletes across all levels and ages, often leading to prolonged recovery times, decreased athletic performance, and reduced quality of life [1, 2]. A recent retrospective study of approximately 8,000 Olympic athletes revealed that the knee and shoulder joints are most prone to severe injuries [3]. Traditional treatments for sports injuries, such as physical therapy, physiotherapy, and surgery, have been successful in many cases. However, they are not always effective and can lead to long-term complications, such as early onset osteoarthritis, and contribute to substantial public health expenses [4]. As a result, researchers have been exploring alternative approaches to treating sports injuries, including stem cell therapy [5, 6].

Stem cell therapy is a promising field that offers the potential for tissue regeneration and repair [7, 8]. It has been used to treat a wide range of medical conditions, including heart disease, diabetes, and spinal cord injury [9–12]. In sports medicine, stem cell therapy has emerged as a promising alternative to traditional treatments, offering the potential for more rapid and complete healing of injured tissues and a return to full athletic function [5]. Stem cells are undifferentiated cells that can differentiate into various types of cells in the body, making them an attractive option for repairing damaged tissues [13, 14].

In sports medicine, stem cell therapy has been used to treat a variety of injuries. Injuries sustained during sports activities often involve damage to tissues such as ligaments, tendons, cartilage, muscles, and bones. Stem cell therapy offers the potential to address these injuries by promoting tissue repair and regeneration, accelerating healing, and restoring function (Figure 1). Clinical trials have shown promising results [15, 16].

Several types of stem cells have been explored for their therapeutic potential in sports medicine, each with unique properties and considerations for clinical use. Stem cells can be classified by potency and sources [17]. Potency refers to a stem cell's differentiating capabilities into various types of cells: totipotent-all; pluripotent-most; toti- or multipotent – closely related cell family; oligopotent – few; and unipotent – cellular production of self/same type. The

***Corresponding author: Felice Sirico**, Public Health Department, University of Naples Federico II, 80131 Naples, Italy, E-mail: sirico.felice@gmail.com.
Stefano Palermi, Rossana Gnasso, Immacolata Belviso, Irene Iommazzo, Domiziano Tarantino, Veronica Romano and Annamaria Sacco, Public Health Department, University of Naples Federico II, Naples, Italy
Marco Vecchiato, Sports and Exercise Medicine Division, Department of Medicine, University of Padova, Padova, Italy
Andrea Marchini, J Medical, Torino, Italy
Alessandro Corsini, Genoa CFC, Genoa, Italy
Filippo Vittadini, Venezia FC, Venice, Italy
Andrea Demeco, Department of Medicine and Surgery, University of Parma, Parma, Italy
Mariarosaria De Luca, Department of Translational Medical Sciences, Federico II University of Naples, Naples, Italy

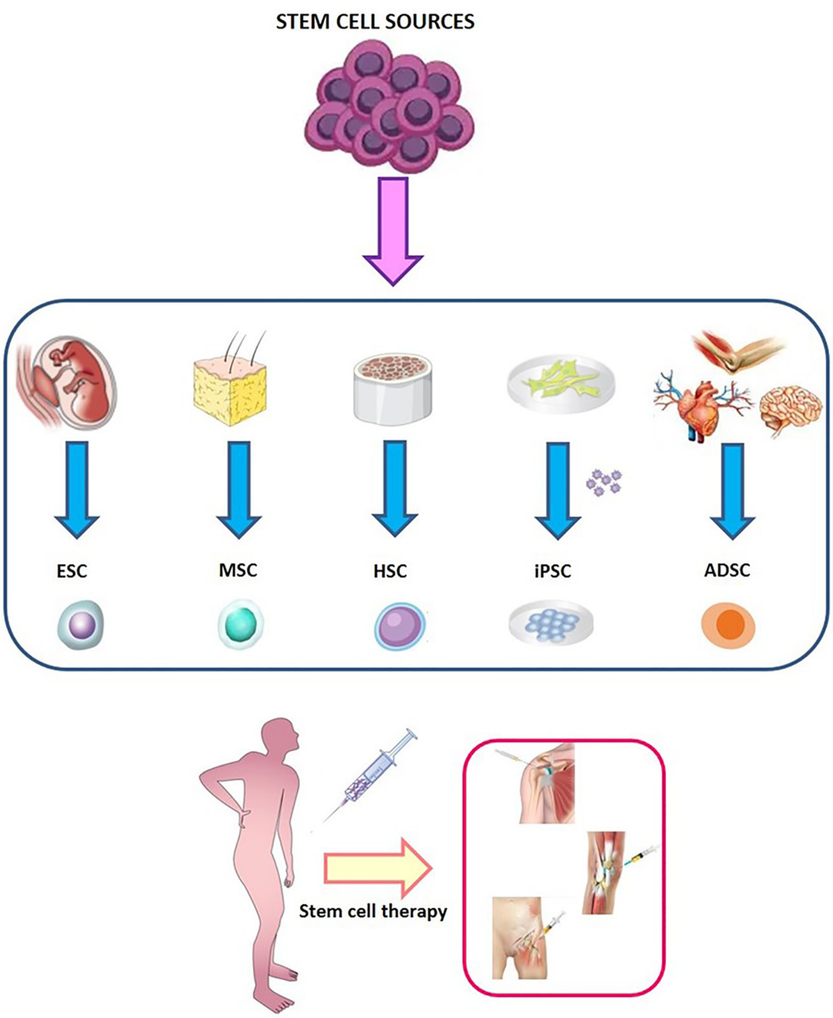

Figure 1: The figure illustrates the potential applications of stem cells in sports medicine, including the treatment of ligament injuries, tendonitis, cartilage defects, muscle injuries, bone fractures, and neurological injuries. Stem cells have the potential to accelerate healing, reduce inflammation and pain, improve tissue regeneration, and enhance functional outcomes for athletes.

source classification system describes donor site(s) from where they originate (before or after birth) [17]:

- Embryonic stem cells (ESCs) are derived from embryos and can differentiate into any type of cell in the body. However, the use of ESCs is controversial due to ethical concerns regarding the destruction of embryos [18, 19].
- Induced pluripotent stem cells (iPSCs) are generated by reprogramming adult cells, such as skin cells, into an embryonic-like state. iPSCs can differentiate into any type of cell in the body and have the potential to be used in regenerative medicine without the ethical concerns associated with ESCs [20, 21].
- Mesenchymal stem cells (MSCs) are found in various tissues, such as bone marrow, adipose tissue, and umbilical cord tissue. MSCs can differentiate into several types of cells, including bone, cartilage, and muscle, and have anti-inflammatory and immunomodulatory properties that make them attractive for treating conditions such as osteoarthritis and autoimmune diseases [22, 23].
- Hematopoietic stem cells (HSCs) are found in the bone marrow and are responsible for generating all types of blood cells. HSCs are currently used in the treatment of certain blood disorders and cancers [24, 25].
- Adult stem cells (ASCs) are populations of undifferentiated cells found in several adult tissues and organs, including blood, intestine, skin, muscles, brain, heart, and tendons [26–28]. Clinical and pre-clinical studies have demonstrated these adult stem cells' structural and functional regeneration capabilities [29, 30].

The Mesenchymal and Tissue Stem Cell Committee of the International Society for Cellular Therapy (ISCT) has proposed minimal criteria that cells must exhibit to be defined as MSCs [31]. These criteria include: (a) polystyrene (i.e., plastic) adherence with spindle-shaped morphology in laboratory culture; (b) the capacity to differentiate into at least osteoblasts, adipocytes, and chondroblasts *in vitro*; and (c) expression of a characteristic set of nonspecific surface markers CD73, CD90, and CD105, and a lack of expression of CD34, CD45, CD11b, CD14, CD19, CD79a, and HLA- DR. Bone marrow aspirated (BMA) stem cells, the first source of MSCs identified, in particular, gained the scientific interest of the community since the discovery of their chondrogenic and osteogenic capacity, and so they became one of the more used types. In clinical practice, MSCs can be obtained from an autologous or allogenic source. Autologous cells are derived from and injected back into the same patient, while allogenic cells are collected from a donor(s) and injected into another person.

Applications of this therapy have garnered much interest since the late 1980s. The mechanisms by which stem cells exert their therapeutic effects in sports medicine are multifaceted, involving processes such as differentiation into specialized cell types, secretion of growth factors and anti-inflammatory molecules, and modulation of the immune response [32]. Overall, each type of stem cell has unique properties and potential therapeutic applications, and researchers are continuing to investigate their use in various areas of medicine. Usually, foreign stem cells can be implanted to take the role of resident cells. Despite the potential benefits of stem cell therapy, several challenges and limitations still need to be addressed. One of the main challenges is the lack of standardized protocols for stem cell therapy, leading to variations in the type and number of cells used and the methods of administration [32, 33]. This makes it difficult to compare results across studies and establish best practices for using stem cells in sports medicine. Additionally, there are concerns about the safety of stem cell therapy, including the risk of infection, tumor formation, and immune rejection [34].

This review will examine the current state of research on stem cell therapy in sports medicine, including its potential applications. We will also delve into the challenges and ethical considerations associated with stem cell therapy, and discuss the future directions of this promising field.

Potential applications

Stem cell therapy has been investigated as a potential treatment option for a variety of sports-related injuries, including those affecting muscles, tendons, ligaments, and cartilage (Table 1) [35].

These potential benefits are based on current research and are subject to further investigation and refinement.

Several clinical trials have shown promising results in the use of stem cells for treating these injuries, suggesting that this approach may offer an effective alternative to traditional treatments [35].

One area where stem cell therapy holds promise is the treatment of tendon disorders, such as rotator cuff tears. These are common injuries among athletes and traditional treatments such as surgery and physical therapy are not always effective in restoring full function [42]. However, stem cell therapy has been shown to promote tissue regeneration and reduce inflammation in the shoulder joint, leading to improved outcomes and faster recovery times. Indeed, several pre-clinical studies have evaluated the potential of these cells in animal models [43], while only

Table 1: Potential benefits of stem cells in sports medicine.

Injury/ condition	Potential benefits of stem cells	Examples
Ligament injuries	Accelerated healing, increased tissue regeneration, reduced inflammation, improved biomechanical properties	MSC (adipose derived) – ACL injury – Matsumoto et al. [36]
Tendonitis	Improved tendon healing, reduced pain and inflammation, increased collagen production, improved tendon strength and flexibility	MSC (bone marrow) – rotator cuff disease – Gomes et al. [37]
Cartilage defects	Improved cartilage regeneration, reduced pain and inflammation, improved joint function, decreased risk of developing osteoarthritis	MSC (adipose derived) – knee osteoarthritis – Lamo-Espinosa et al. [38]
Muscle injuries	Improved muscle healing, increased muscle strength and function, reduced muscle atrophy, decreased risk of reinjury	MSC – muscle injuries – Mautner et al. [39]
Bone fractures	Improved bone healing, increased bone density and strength, reduced risk of nonunion or delayed union	MSC (bone marrow) – nonunion fractures – Hernigou et al. [40]
Neurological injuries	Improved nerve regeneration, increased motor function and sensory perception, reduced pain and inflammation	MSC (bone marrow) – peripheral nerve injury – Dezawa et al. [41]

Gomes et al. investigated the effects of bone marrow mononuclear cells (BMMCs) in 14 patients with complete rotator cuff tears, suggesting that BMMCs are a safe and promising alternative to other biological approaches to enhance tissue quality in affected tendons [37]. Stem cell therapy has also been investigated for the treatment of Achilles tendonitis, a common injury among runners and other athletes [44]. Usuelli et al. examined the efficacy of stromal vascular fraction (allo-ASC) injection vs. PRP injection in patients with non-insertional Achilles tendinopathy with a total follow-up of 6 months: level 3 evidence for a superior effect of allo-ASC injections for Achilles tendinopathy compared with PRP injections on PROMs at 15 and 30 days after injection, but no differences were observed at 60 days of follow-up [45].

Another area where stem cell therapy shows promise is in the treatment of knee osteoarthritis. This is a common condition among older athletes and can cause significant pain and functional limitations [46]. In a multicenter randomized controlled trial, Lamo-Espinosa et al. compared the use of bone marrow-derived stem cells with hyaluronic acid injections for the treatment of knee osteoarthritis (OA) in 30 patients. The results showed that stem cell therapy was superior in terms of pain relief, function, and cartilage regeneration [38]. However, according to a review paper on different types of stem cell injections for knee OA in 6 clinical trials involving 155 patients, five randomized controlled trials (RCTs)-Level 2 and one non-RCT with Level 3–4 evidence, all studies appeared to contain bias (selection, performance, findings, analysis, and results) [47].

Despite ligament injuries being quite common, there is limited knowledge on the basic science of cell differentiation toward developing ligamentous tissue. Stem cell therapy has been investigated for the treatment of anterior cruciate ligament (ACL) tears. In a study published in the American Journal of Sports Medicine, researchers used bone marrow-derived stem cells to treat ACL injuries in a group of 68 rabbits. The results showed significant improvements in knee stability and function, suggesting that stem cell therapy may be a promising treatment option for this type of injury [36].

In addition to these specific applications, stem cell therapy has the potential to be used in a wide range of sports-related injuries, including those affecting the hip, ankle, and other joints [48].

About cartilage disorders, stem cell therapy is a hot topic as researchers seek to understand the role of stem cells in regulating the pathomechanics of acute and chronic cartilage injuries. Case series studies have shown promising outcomes in patients treated with bone marrow-derived MSCs for chondral lesions as well as osteoarthritis, specifically about improvement in pain scores and function [49].

In muscle injuries treated with stem cell therapy, the results have been promising. Muscle injuries are common in athletes and can lead to significant downtime and loss of performance. Stem cell therapy has been shown to promote muscle regeneration and reduce inflammation, leading to faster recovery times and improved muscle function [39].

Stem cell therapy has also been explored for the treatment of bone fractures. Fractures are a common sports injury, and while most heal with traditional treatments, some fractures can lead to complications such as nonunion or delayed union. Stem cell therapy has been shown to promote bone healing and increase bone density and strength, potentially reducing the risk of these complications. In a study by Hernigou et al., patients with nonunion fractures were treated with concentrated bone marrow aspirate, which contains stem cells. The results showed a high rate of fracture healing, suggesting that stem cell therapy may be an effective treatment for this condition [40].

Lastly, stem cell therapy has been investigated for the treatment of neurological injuries, such as peripheral nerve damage. These injuries can lead to significant functional impairment and disability. Stem cell therapy has been shown to promote nerve regeneration and improve motor function and sensory perception. In a study by Dezawa et al., mice with peripheral nerve injuries were treated with bone marrow stromal cells, which resulted in improved nerve regeneration and functional recovery [41].

With ongoing research and development, stem cell therapy may become a standard part of sports medicine treatment in the future.

Challenges and limitations

While stem cell therapy holds promise for the treatment of sports injuries, several challenges and limitations need to be addressed before it can become a standard part of sports medicine treatment [50] (Table 2).

One of the major concerns is the lack of standardized protocols for stem cell therapy. There is currently no agreement among researchers and clinicians regarding the optimal type and number of cells to use, and the most effective method of administration is still being defined. Furthermore, current researches on this topic have several limitations, such as small sample sizes or short follow-up periods making their results difficult to be generalized. This variability makes it difficult to compare results across studies and establish best practices for using stem cells in sports medicine [51].

Another challenge is the safety of stem cell therapy. While stem cells are generally considered safe, there are

Table 2: Potential risks and harms of stem cells in sports medicine.

Risk/harm	Potential risks and harms of stem cells
Unproven efficacy	Stem cell therapy is still experimental and lacks standardized protocols, which may lead to inconsistent results and unpredictable outcomes
Adverse effects	Stem cell therapy may cause adverse effects such as infection, bleeding, pain, and tissue damage
Tumor formation	The use of stem cells may increase the risk of tumor formation, particularly if the cells are not fully differentiated or if they have genetic mutations
Ethical concerns	The use of certain sources of stem cells, such as embryonic stem cells, raises ethical concerns regarding the destruction of embryos

concerns about the risk of infection, tumor formation, and immune rejection [52]. These risks are particularly relevant when using allogeneic (donor-derived) stem cells, as they can trigger an immune response in the recipient. Additionally, there is a risk of tumor formation when using pluripotent stem cells due to their ability to form any type of tissue in the body [53]. Finally, also the genetic stability of MSCs, which can be altered during *in vitro* manipulation, should be considered: indeed, genetic stability has the potential to influence the transformation and the therapeutic effect of these cells and therefore it is an important aspect to consider when manipulating these therapies [54].

Ethical considerations

The field of regenerative medicine, particularly stem cell therapy, has been a subject of intense debate and scrutiny over the past few decades. This scrutiny has been fueled by ethical controversies, increasing regulatory oversight by the Food and Drug Administration (FDA), and significant media attention.

Informed consent is a critical ethical consideration in the use of stem cells in sports medicine. Athletes must have a comprehensive understanding of the risks and benefits of stem cell therapy before deciding on their treatment [55]. This includes providing patients with information about the experimental nature of the treatment, the potential for adverse effects, and the lack of long-term data on the safety and efficacy of stem cell therapy. Clinicians must ensure that patients have access to accurate and understandable information about the treatment. They should also provide an opportunity for patients to ask questions and receive clear answers.

The use of embryonic stem cells raises significant ethical concerns due to the destruction of human embryos required for their use [56]. Many researchers have turned to alternative sources of stem cells, such as induced pluripotent stem cells or adult stem cells, which do not raise the same ethical concerns. However, these alternative sources also come with their own set of challenges and limitations, which need to be considered [57].

Equity and access to care are also important ethical considerations in the context of stem cell therapy. The cost of stem cell therapy can be prohibitive for many athletes, creating disparities in access to care. While some insurance plans may cover the cost of stem cell therapy for certain injuries, it remains expensive for others. This financial barrier can prevent athletes without adequate resources from receiving this potentially beneficial treatment. Researchers and clinicians should explore ways to ensure that stem cell therapy is available to all patients who can benefit from it, regardless of their financial situation [58].

Regulation of stem cell therapy is another ethical concern [59]. As this treatment is still in the experimental stage, there is a lack of clear regulatory guidelines for its use. This can lead to confusion and inconsistencies in the administration and regulation of stem cell therapy across different countries and healthcare systems. Researchers and clinicians should collaborate to establish clear regulatory frameworks to ensure the safety and efficacy of stem cell therapy in sports medicine.

Moreover, the use of stem cell therapy in sports medicine has the potential to create a doping problem in athletic competitions. Stem cell therapies can enhance tissue repair and regeneration, resulting in faster recovery times and improved athletic performance. However, as the use of stem cells in sports medicine is still in its early stages, limited regulation and oversight exist to prevent the abuse of these therapies for performance enhancement. Some athletes may be tempted to use stem cell therapies to gain an unfair advantage over their competitors. Additionally, the use of stem cells obtained from other individuals or animals can pose a risk of transmitting diseases, raising potential health and safety concerns within the sports community [60]. These ethical considerations highlight the need for careful monitoring and regulation of stem cell therapy in sports medicine to maintain fairness and athlete safety [61].

Future directions

Despite the challenges and limitations of stem cell therapy in sports medicine, there is significant potential for future advancements in this field [62–64]:

(1) Standardization of Protocols: Future research should focus on identifying the optimal type and number of cells to use, as well as the most effective method of administration. This would enable clinicians to establish best practices for the use of stem cells in sports medicine and make it easier to compare results across studies.
(2) Safety Improvements: Future research should focus on developing new methods to improve the safety of stem cell therapy, such as enhancing cell delivery methods, reducing the risk of infection, and minimizing the risk of immune rejection.
(3) Ethical Sourcing of Stem Cells: As the field continues to evolve, researchers and clinicians must continue to explore alternative sources of stem cells that do not raise ethical concerns.
(4) Expansion of Applications: While stem cell therapy has shown promise in the treatment of several sports injuries, researchers and clinicians should explore new applications for this treatment. For instance, stem cell therapy could potentially be used to enhance muscle regeneration or to improve joint function in patients with osteoarthritis. This would require extensive research and clinical trials to establish the efficacy and safety of these new applications.
(5) Regulatory Oversight: As stem cell therapy continues to develop, it will be important to establish clear regulatory frameworks to ensure the safety and efficacy of this treatment. Future research should focus on identifying the most effective methods of regulation and ensuring that these regulations are implemented consistently across different countries and healthcare systems.
(6) Enhanced Rehabilitation Strategies: Stem cell therapy can be combined with other rehabilitation strategies to optimize the outcomes for athletes.

Continued research and development will be essential to establish best practices, improve safety, expand applications, and ensure regulatory oversight of this promising treatment. With further advancements, stem cell therapy has the potential to revolutionize the field of sports medicine and improve outcomes for athletes.

Conclusions

In conclusion, stem cell therapy represents a promising avenue for the treatment of sports injuries, such as muscle, tendon, and nerve injuries [65–67], offering the potential to enhance outcomes and expedite recovery in athletes. However, several challenges and limitations must be addressed before its widespread adoption in sports medicine. Overcoming these obstacles is imperative to ensure the safe and effective utilization of stem cell therapy in sports medicine. Collaborative efforts among researchers and clinicians are essential to establish best practices, identify alternative ethical sources of stem cells, and develop enhanced safety measures. As we move forward, we must continue to evaluate the efficacy and safety of stem cell therapy, while also considering the ethical implications and ensuring equitable access to this potentially transformative treatment.

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