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Review Paper

A Mini-review on the Role of Stem Cells in Orthopedics

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ABSTRACT

Stem cell therapy (SCT) has emerged as a promising approach in orthopedic medicine, offering regenerative solutions for bone, cartilage, and tendon injuries. Mesenchymal stem cells (MSCs), derived from bone marrow aspirate concentrate (BMAC) and stromal vascular fraction (SVF), promote tissue repair through differentiation, paracrine signaling, and immune modulation. While bone exhibits a natural regenerative capacity, challenges such as critical-sized defects and osteonecrosis necessitate the use of advanced therapies. Similarly, the limited self-repair ability of cartilage underscores the need for novel regenerative strategies, particularly in osteoarthritis. Despite promising preclinical and early clinical outcomes, the widespread adoption of SCT is hindered by regulatory challenges and a lack of large-scale randomized controlled trials (RCTs). This review explores the sources, mechanisms, and clinical applications of stem cells in orthopedics, highlighting their potential and the challenges that must be addressed for clinical translation.

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Introduction

Orthopedic medicine has historically progressed through innovations originating from various scientific disciplines. The advancements in metal and chemical engineering during the early 20th century significantly influenced modern orthopedic practices, leading to the development and clinical application of implants derived from newly engineered biomaterials. More recently, breakthroughs in regenerative medicine have introduced new possibilities in orthopedics, potentially transforming clinical approaches. Conditions that currently necessitate surgical intervention may, in the future, be managed more effectively and cost-efficiently through minimally invasive techniques, such as direct cell injections. The pursuit of novel therapeutic strategies for refractory and life-threatening diseases led to the emergence of stem cell research. Within orthopedics, stem cell therapy (SCT) has been explored as a potential solution for conditions where existing treatment options fail to provide satisfactory, efficient, or long-lasting outcomes [1, 2]. While bone injuries typically undergo complete regeneration, critical-sized defects in long bones necessitate either the harvest of a substantial autograft, which is associated with significant morbidity, or the implantation of an allograft, which carries the risk of various complications. Osteonecrosis of the femoral head, characterized by femoral head collapse and secondary osteoarthritis (OA) of the hip joint, frequently results in premature total hip arthroplasty (THA) in young patients.

Additionally, nonunion of long bones remains a challenging clinical issue, often complicating the achievement of successful bony union [3]. SCT holds promise as a novel treatment approach for these conditions. Unlike bone, which possesses intrinsic self-regenerative capacity, articular cartilage (AC) has a limited ability to repair itself. Consequently, damage to the AC often leads to the onset and progression of OA [4, 5]. Since AC defects are not effectively managed with conventional procedures such as microfracture, they represent a promising target for regenerative therapy through stem cell implantation.

Additionally, the more diffuse cartilage damage observed in OA may also benefit from SCT, as current treatment options lack regenerative potential. Degenerative tendon disorders, including advanced rotator cuff tears that do not respond favorably to conventional repair techniques, are also potential candidates for stem cell-based treatment [6, 7]. This passage provides a well-structured overview of the sources and applications of adult stem cells in orthopedics, highlighting both bone marrow aspirate concentrate (BMAC) and stromal vascular fraction (SVF) as key sources of mesenchymal stem cells (MSCs). It effectively explains the processes involved in obtaining these cell fractions and their relevance in musculoskeletal regenerative medicine. Additionally, it correctly emphasizes the challenges in clinical translation, particularly the scarcity of high-quality randomized controlled trials (RCTs) and the reliance on case reports and cohort studies.

To enhance the passage, consider these issues:

1) Clarifying the differences in MSC yield and potency between BMAC and SVF; 2) mentioning specific musculoskeletal conditions where these stem cell therapies have shown promise; 3) briefly discussing regulatory and ethical considerations in SCT, and 4) providing examples of notable clinical studies or meta-analyses that summarize current findings.

The majority of reported human studies on stem cell-based bone regeneration consist of cohort outcome studies or case reports, primarily due to the ethical and practical challenges associated with conducting RCTs. Published clinical studies and case reports have employed autologous, culture-expanded, non-genetically modified human MSCs for bone regeneration. Although the lack of control groups remains a significant limitation, these preliminary cohort studies provide insights into the safety and potential therapeutic efficacy of autologous SCT [3, 7-9].

Types of stem cells

Stem cells are categorized based on their differentiation potential and potency into four main types: Totipotent, pluripotent, multipotent, and unipotent cells [10]. The most commonly utilized stem cells in orthopedics and sports medicine are MSCs and adipose-derived stem cells (ADSCs). MSCs, the most extensively studied stem cell type, possess the ability to differentiate into multiple cell lineages, including osteoblasts, chondrocytes, myocytes, and adipocytes. This multipotency makes them an ideal candidate for musculoskeletal regeneration and cell-based therapies [11]. ADSCs, obtained from adipose tissue, exhibit regenerative properties comparable to those of MSCs and are regarded as valuable candidates for bone and cartilage repair [12, 13]. Additionally, reprogrammed adult cells have shown promise due to their ability to differentiate into multiple cell types. Induced pluripotent stem cells serve as an alternative to embryonic stem cells for tissue engineering and regenerative

therapies, offering the advantage of reduced immunogenicity. The maintenance of their pluripotency is regulated by key transcription factors encoded by the *Oct4*, *Sox2*, and *Nanog* genes [14, 15].

Mechanisms of action

Stem cells exert their therapeutic effects through multiple mechanisms, including differentiation into specialized cell types, the secretion of bioactive molecules that modulate inflammation, promote angiogenesis, and stimulate tissue repair through paracrine signaling. They also influence the immune response, reduce inflammation, promote tissue regeneration, and facilitate the remodeling of the extracellular matrix, thereby enhancing tissue integrity and function [16-19].

MSCs and ADSCs are effective in promoting cartilage regeneration and alleviating symptoms of OA [20]. Stem cells can help regulate osteoblast activity, promoting the formation of new bone and preventing late-stage collapse in cases of avascular necrosis (AVN) [21]. BMAC is a rich source of MSCs and has become a popular treatment option for AVN of the femoral head [22]. For traumatic bone defects and nonunions of fractures, the combination of stem cells with scaffolds or growth factors (GFs) has been shown to enhance bone healing and promote the filling of bone defects [23]. Tendon and ligament injuries are common in sports and other activities. Stem cell injections have shown promise in promoting tissue repair and improving functional outcomes in these injuries [24]. SCT has been shown to improve the likelihood of successful spinal fusion by enhancing bone formation [25].

Use of stem cells in the treatment of bone and cartilage defects

Several studies have explored the application of stem cells in treating long bone defects, primarily through case reports with a level 4 evidence classification. Healey et al. investigated the use of autologous bone marrow aspirate in eight cases of diaphyseal nonunion following tumor resection, demonstrating its potential in bone regeneration [26]. In another study, Quarto et al. reported three cases where culture-expanded autologous MSCs were used to treat diaphyseal defects in the tibia, humerus, and ulna, with macroporous hydroxyapatite scaffolds serving as carriers to enhance bone integration [9]. Similarly, Krečič Stres et al. described a case involving a femoral diaphyseal defect that was treated using a combination of autologous cancellous bone and culture-expanded autologous MSCs, supported by porous calcium-triphosphate granules as an osteoconductive scaffold [27].

The application of MSCs has also extended to mandibular and maxillary defects. Hibi et al. documented a case in which a mandibular defect was reconstructed using culture-expanded autologous MSCs in combination with platelet-rich plasma (PRP), with calcium chloride and titanium mesh acting as structural supports [28]. Meijer et al. reported six cases where culture-expanded autologous MSCs were applied to alveolar cavitary defects, utilizing hydroxyapatite granules to facilitate bone regeneration [29]. In a similar approach, Mesimäki et al. presented a case involving maxillary defects treated with culture-expanded autologous ASCs, employing a titanium cage, bone morphogenetic protein (BMP), and β-tricalcium phosphate (β-TCP) to promote bone formation [30]. Likewise, Shayesteh et al. described seven cases in which culture-expanded autologous MSCs were used for maxillary sinus reconstruction, incorporating hydroxyapatite and β-TCP as scaffolding materials [31].

Dufrane et al. further investigated the therapeutic potential of ASCs by reporting six cases, three involving diaphyseal defects and three with pseudoarthrosis [8]. In these cases, culture-expanded autologous ASCs were applied using a scaffold-free three-dimensional technique, demonstrating an alternative regenerative approach. Collectively, these studies illustrate the diverse applications of stem cell-based therapies in bone regeneration, emphasizing their potential to enhance healing in both diaphyseal and craniofacial bone defects through the integration of various biomaterials and scaffolding techniques.

Various studies have investigated the application of stem cells for treating osteonecrosis, with most focusing on BMAC and culture-expanded bone marrow-derived stem cells (BMSCs). Hernigou and Beaujean conducted a case series involving 116 patients (186 hips) and found that THA was required in 9 of 145 hips at stage I or II and in 25 of 44 hips at stage III or IV [32]. In a prospective controlled study by Gangji et al. which included 19 patients (26 hips) at Stage I or II, 8 of 11 hips in the control group progressed, whereas only 3 of 13 hips in the graft group showed progression [33]. Hernigou et al. extended their investigation in a case series of 342 patients (534 hips), reporting that THA was needed in 94 of the 534 Stage I or II hips [34].

Sen et al. conducted a prospective, randomized trial involving 40 patients (51 hips) at stage I or II, demonstrating that clinical scores and hip survival were significantly better in the BMAC-treated group after 12 and 24 months [35]. Similarly, Ma et al. studied 45 patients (53 hips) in a randomized trial where both groups received autologous bone grafts [36]. The results demonstrated a 100% non-progression rate in the treatment group compared to 66.7% in the control group. Zhao et al. (2012) conducted a prospective, randomized trial involving 100 patients. They found that, after five years, only 2 of 53 hips treated with culture-expanded BMSCs progressed, compared to 10 of 44 hips in the control group [37].

In a case-control study by Lim et al. involving 128 patients (190 hips), fibrin glue was used in the stem cell-treated group, while the control group received autologous bone grafts [38]. The success rate was higher for stage I and II lesions, though stage III lesions had similar outcomes to the control group. Kang et al. examined 52 patients (61 hips) treated with BMAC and autologous bone grafts. They found high failure rates in stage III and IV cases, particularly in large or laterally located lesions [39]. Persiani et al. conducted a case series with 29 patients (31 hips) treated with culture-expanded BMSCs, reporting symptom relief and resolution of osteonecrosis in 25 hips. In contrast, 6 hips, including those at stages II, III, and IV, showed progression [40].

Martin et al. studied 77 hips at Stage I or II and observed that 16 hips (21%) progressed, but 86% of patients reported significant pain relief [41]. Mao et al. reported in a case series of 62 patients (78 hips) treated with intra-arterial BMAC injection that 72 of 78 hips achieved satisfactory clinical results, whereas 6 hips progressed and required THA [42]. In a prospective, randomized trial by Mao et al., involving 55 patients (98 hips) with stages I to III, peripheral blood stem cells were used in conjunction with porous tantalum rod implantation [43]. The overall collapse rates were 15.15% (5/33 hips) in the control group and 8.11% (3/37 hips) in the combination treatment group.

Hernigou et al. reported a single case where complete repair of osteonecrosis was observed after four years [44]. Daltro et al. conducted a cohort study on 89 patients at stage I or II, showing significant improvement in symptoms and radiological findings in 86 cases [45]. Kawate et al. studied 45 patients at stage III or higher, using culture-expanded autologous BMSCs combined with a free fibular graft and β-TCP granules, demonstrating halted disease progression and early bone regeneration [46]. Similarly, Aoyama et al. treated 10 stage III patients using culture-expanded autologous BMSCs with vascularized iliac bone graft and β-TCP granules [47]. Of the 9 patients who completed the protocol, 7 remained at stage III, while 2 progressed to stage IV, with an overall increase in bone volume.

These studies collectively highlight the potential of stem cell-based therapies in managing osteonecrosis, with varying degrees of success across different stages of the disease. The use of BMAC and culture-expanded BMSCs, often in combination with additional grafting techniques, has shown promising results, particularly in the early stages of osteonecrosis. At the same time, advanced-stage cases still present therapeutic challenges.

Several studies have investigated the use of various cellular therapies for bone healing and fracture treatment. Connolly et al. conducted a case series involving 20 patients with ununited tibial fractures, demonstrating that 19 out of 20 cases achieved clinical and radiological union within an average of 2.95 months using autologous bone marrow aspirate [48]. Similarly, Garg et al. reported that 17 out of 20 cases of ununited long bone fractures achieved union within 3 to 7 months with the same treatment [49].

Ateschrang et al. explored the use of cancellous allogenic bone grafts revitalized with autologous bone marrow injection in 15 cases of infected tibial nonunions [50]. They achieved infection control in 14 patients and bone union in 11. Dallari et al. conducted a prospective, randomized trial involving 33 patients undergoing tibial osteotomy. Their findings indicated significantly improved osseointegration in groups treated with platelet gel or platelet gel combined with culture-expanded autologous BMSCs compared to the control group [51].

Gan et al. examined spine fusion in 41 patients treated with autologous bone marrow MSCs combined with β-TCP, reporting favorable spinal fusion results in 39 cases after 34.5 months [52]. Kitoh et al. performed a prospective case-control study on distraction osteogenesis in 24 long bones (12 femora and 12 tibiae), demonstrating significantly accelerated bone healing in the MSC/PRP-treated group compared to the control [53].

Neen et al. assessed 50 patients undergoing spine fusion with autologous bone marrow and a type 1 collagen/hydroxyapatite matrix [54]. Their study found comparable outcomes to autogenous bone grafting in posterolateral lumbar fusion but significantly lower success rates in lumbar interbody fusion. Rodriguez-Collazo and Urso conducted a case-control study on 20 patients

with bimalleolar fractures treated with BMAC and PRP in combination with Ilizarov device fixation, reporting a significantly faster healing rate (16±1.6 weeks) compared to the control group (24±1.3 weeks) [55].

Desai et al. conducted a cohort study on 39 patients with tibial nonunion treated with BMAC, demineralized bone matrix (DBM), and or recombinant human BMP-2 (rhBMP-2) [56]. Their results indicated that rhBMP-2 had a lower healing rate compared to DBM. Murena et al. (2014) presented a case report of two patients with humeral nonunion treated with cortical allograft, BMP-7, and BMAC, showing complete healing at 4 and 8 months postoperatively [57].

Liebergall et al. conducted a prospective, randomized trial involving 24 patients with distal tibial fractures who were treated with sorted autologous BMSCs, PRP, and DBM [58]. Their study found a median union time of 1.5 months in the intervention group compared to 3 months in the control group. Finally, Qu et al. reported on nine cases of long bone nonunion treated with either BMAC (3 cases) or umbilical cord MSCs (6 cases), finding that the mean clinical healing time was comparable between the two treatment groups [59].

Studies have explored the use of stem cells in treating osteochondral defects, demonstrating promising outcomes across various clinical settings. Wakitani et al. reported a case series involving three patients (level 4 evidence), where culture-expanded autologous bone marrow-derived MSCs (BMSCs) were implanted into the patellofemoral joint using a collagen gel combined with autologous periosteum or synovium [60]. One year post-transplantation, the defect was completely covered. Similarly, Kuroda et al. documented a single case (level 4 evidence) in which autologous BMSCs were used to treat a medial femoral condyle defect, supported by an autologous periosteum and collagen gel. At seven months, the defect was filled with hyaline-like cartilage tissue [61].

Haleem et al. presented a case series of five patients (level 4 evidence) treated with culture-expanded autologous BMSCs in femoral condyles, supplemented with platelet-rich fibrin glue and a periosteal flap, while one patient also underwent ACL reconstruction and microfracture [62]. After 12 months, three patients exhibited complete defect filling with full surface congruity, whereas two showed incomplete congruity. In another case report, KasemkiJwattana et al. treated two patients (level 4 evidence) with culture-expanded autologous BMSCs in the lateral femoral condyles, combined with ACL reconstruction and a collagen scaffold [63]. A follow-up of 30–31 months showed good defect filling, stiffness, and integration with the adjacent cartilage.

Nejadnik et al. conducted a case-control study (72 patients, level 3 evidence) comparing autologous BMSCs with autologous chondrocyte implantation (ACI) in knee defects [64]. Their findings indicated no significant difference in outcomes between the two approaches. Giannini et al. reported on 48 patients (level 4 evidence) treated with BMAC for talar osteochondral lesions, with a minimum follow-up of 24 months, revealing varying degrees of tissue remodeling; however, none exhibited purely hyaline cartilage [65]. In a subsequent study, Giannini et al. (2010) compared three treatment techniques—open ACI (10 patients), arthroscopic ACI (46 patients), and arthroscopic BMAC transplantation (25 patients)—in a case-control study involving 81 patients (level 3 evidence) [66]. After one year, all techniques showed a similar pattern of clinical improvement, demonstrating the potential of BMAC as an alternative therapeutic option.

Gobbi et al. reported a case series of 15 patients (level 4 evidence) utilizing BMAC combined with a collagen I/II matrix. Significant clinical improvements were observed at the final follow-up, and MRI confirmed lesion coverage with hyaline-like tissue in all patients [67]. Finally, de Windt et al. conducted a prospective cohort study (9 patients, level 2 evidence) using allogeneic MSCs mixed with 10% or 20% recycled autologous chondrocytes embedded in fibrin glue. At 12 months, the study demonstrated significant clinical improvement, complete defect filling with regenerated cartilage, and the formation of hyaline-like tissue with high proteoglycan and type II collagen content [68].

These studies collectively underscore the potential of stem cell-based therapies for osteochondral defects, demonstrating varying degrees of cartilage regeneration, integration, and clinical improvement.

Research on the use of stem cells for treating OA has demonstrated promising results, including improvements in clinical outcomes, reduced pain, and cartilage regeneration. Centeno et al. reported a single case (level 4 evidence) where culture-expanded autologous BMSCs were injected into a knee with OA, along with hyaluronic acid and pulsed ultrasound. The patient exhibited an increase in meniscus volume and a decrease in modified visual analog scale (VAS) pain scores [69]. Similarly, Centeno et al. described another case (level 4 evidence) in which autologous BMSCs, combined with

platelet lysate and dexamethasone, resulted in a reduction of cartilage defects on the medial femoral condyle and a decrease in VAS pain scores [70].

Davatchi et al. followed four patients (level 4 evidence) treated with culture-expanded autologous BMSCs for knee OA, observing improved clinical parameters at six months, which remained better than baseline even after five years [71]. in a high-level prospective randomized trial (Level 1 evidence), Wakitani et al. treated 24 patients with medial femoral knee OA using culture-expanded autologous BMSCs combined with a collagen sheet and periosteal cover, alongside high tibial osteotomy (HTO) [72]. The cell-transplanted group showed superior arthroscopic and histological grading scores compared to the control group.

Another prospective randomized trial by Wong et al. (56 patients, Level 1 evidence) demonstrated that patients receiving cultured autologous BMSCs in combination with microfracture, medial opening-wedge HTO, and hyaluronic acid exhibited significantly better clinical and MRI scores than the control group [73]. Similarly, Vangsness et al. conducted a randomized trial (55 patients, level 1 evidence) using allogeneic BMSCs in knee OA patients undergoing partial meniscectomy. The study reported a significantly increased meniscal volume following MSC injection and a notable reduction in pain compared to the control group [74].

Pak presented a case series (level 4 evidence) involving four patients (two with knee OA and two with hip OA) who received autologous adipose tissue-derived stem cells. MRI scans indicated an increased medial meniscus height in knee OA patients, suggesting a regenerative effect [75]. In a prospective cohort study (18 patients, level 2 evidence), Jo et al. administered intra-articular injections of 1.0×10^8 autologous adipose tissue-derived stem cells into OA-affected knees. The treatment improved joint function, reduced pain, and decreased cartilage defects [76].

These findings highlight the potential of stem cell-based therapies in OA management, demonstrating improvements in pain relief, cartilage regeneration, and functional outcomes across various clinical trials.

Conclusion

SCT holds significant potential for advancing orthopedic treatments, particularly in addressing bone defects, osteonecrosis, cartilage injuries, and tendon disorders. The regenerative capacity of MSCs, whether derived from bone marrow, adipose tissue, or induced pluripotent stem cells, has demonstrated encouraging results in musculoskeletal applications. Despite these advances, the clinical translation of stem cell-based therapies remains limited due to regulatory challenges, ethical concerns, and the lack of large-scale RCTs providing definitive evidence of efficacy. Future research should focus on optimizing cell sources, delivery methods, and scaffold integration to enhance therapeutic outcomes. Additionally, well-designed clinical trials are crucial for establishing standardized protocols and ensuring the safe and effective implementation of stem cell therapies in routine orthopedic practice.

Ethical Considerations

Compliance with ethical guidelines

There are no ethical considerations to be considered in this research.

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Authors' contributions

Conceptualization and study design: Morteza Nakhaei Amroodi; Investigation and data analysis: Mojtaba Baniasadi; Writing the original draft: Pouria Tabrizian and Saedreza Amiri; Review and editing: Saedreza Amiri, Morteza Nakhaei Amroodi and Pouria Tabrizian; Supervision: Saedreza Amiri; Final approval: All authors.

Conflict of interest

The authors declared no conflict of interest.

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