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Review Article

Potential Stem Cell Treatment for Common Hip Conditions: Osteoarthritis, Osteonecrosis and Gluteal Tendinopathy

Thomas J Caputo[1], Vincent S Gallicchio[2*]

[1]Department of Biochemistry, College of Science, Clemson University, Clemson, SC 29627, USA

[2]Department of Biological Sciences, College of Science, Clemson University, Clemson, SC 29627, USA

***Correspondence author:** Vincent S Gallicchio, Department of Biological Sciences, College of Science, Clemson University, Clemson, SC 29627, USA; Email: vsgall@clemson.edu

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Abstract

Hip pathology, encompassing common conditions such as Osteoarthritis (OA), Osteonecrosis (ONFH) and gluteal tendinopathy, presents significant challenges in clinical management which often necessitate innovative treatment modalities. Stem cell therapy has emerged as a promising approach for addressing these complex hip conditions by promoting tissue regeneration and modifying disease progression. This paper aims to review the current literature on stem cell therapy for hip pathology, focusing on its application in OA, ONFH and gluteal tendinopathy. A comprehensive review of relevant studies and clinical trials was conducted by examining the safety, efficacy and potential mechanisms of action of stem cell therapy in hip conditions. Studies investigating the use of Bone Marrow-Derived Mesenchymal Stem Cells (BMMSCs), Adipose-Derived Mesenchymal Stem Cells (ADMSCs) and Tendon-Derived Stem Cells (TDSCs) were included in the analysis. The reviewed studies demonstrate promising outcomes of stem cell therapy in improving pain, functionality and halting disease progression in patients with hip OA. Intra-articular injections of MSCs have shown sustained benefits and arrested the progression of osteoarthritis. Stem cell therapy has also shown effectiveness in delaying the progression of ONFH, reducing femoral head collapse and decreasing the need for total hip replacement. Furthermore, in cases of gluteal tendinopathy, stem cell therapy has exhibited significant improvements in pain and functionality in a limited number of studies on the topic and also offers sustained relief in patients unresponsive to conventional treatments. Stem cell therapy holds immense potential as a safe and effective intervention for hip pathology and offers disease-modifying effects and sustained clinical benefits in these prevalent conditions. Further research is warranted to optimize treatment protocols, clarify mechanisms of action and validate long-term efficacy in larger cohorts.

Keywords: Stem Cell Treatment; Osteoarthritis; Osteonecrosis; Gluteal Tendinopathy; Mesenchymal Stem Cells

Abbreviations

ADMSCs: Adipose-Derived Mesenchymal Stem Cells; ATI: Autologous Tenocyte Injection; AVN: Avascular Necrosis; BMAC: Bone Marrow Aspirate Concentrate; BMC: Bone Marrow Concentrate; BMMSCs: Bone Marrow-Derived Mesenchymal Stem Cells; ESWT: Extracorporeal Shockwave Therapy; GTPS: Greater Trochanteric Pain Syndrome; HA: Hyaluronic Acid; HHS: Harris Hip Score; IGA: Inferior Gluteal Artery; ITB: Iliotibial Band; LFCA: Lateral Circumflex Femoral Arteries; MFCA: Medial Circumflex Femoral Arteries; MSCs: Mesenchymal Stem Cells; NSAIDs: Nonsteroidal Anti-Inflammatory Drugs; OA: Osteoarthritis; ON: Osteonecrosis; ONFH: Osteonecrosis of the Femoral Head; PBMSCs: Peripheral Blood-Derived Mesenchymal Stem Cells; PRP: Platelet-Rich Plasma; SGA: Superior Gluteal Artery; TDSC: Tendon-Derived Stem Cells; TGF-B: Transforming Growth Factor B; UCMSC: Umbilical Cord-Derived Mesenchymal Stem Cells; VAS: Visual Analog Scale

Introduction

General Hip Anatomy

The hip joint is a ball-and-socket joint where the spherical head of the femur fits into a cup-shaped socket in the pelvis called the acetabulum [Fig. 1]. The acetabulum constitutes the articular socket of the hip joint and arises through the fusion of the three constituent bones of the pelvic girdle: the ilium, ischium and pubis [1]. Characterized by its cartilaginous lining, the acetabulum serves the pivotal function of providing a cushioning effect within the joint enabling the smooth and frictionless movement of the leg. The femoral head is the ball-shaped end of the femur that fits into the acetabulum which represents the ball portion of the ball-and-socket joint. The acetabular labrum lines the rip hip joint and is vital for biomechanics, stability and joint health [2]. Its functions include retaining fluid for lubrication, enhancing stability and reducing contact stress [2]. The hip joint relies on a group of ligaments to ensure stability and regulation of movement patterns. Among these ligaments, the iliofemoral ligament is recognized for its distinctive Y-shaped structure and stands out as the body's strongest ligament [1]. This ligament actively prevents hyperextension of the hip joint. Complementing this on the lower section, the pubofemoral ligament effectively limits excessive abduction which a movement away from the midline of the body [3]. Additionally, the ischiofemoral ligament works in the posterior of the hip by constraining excessive internal rotation and adduction or movement towards the center of the body [1]. The hip joint is enveloped by a fibrous capsule that includes both the joint and its synovial fluid. The synovial membrane cells that line the inner surface of the joint capsule actively produce synovial fluid [4]. This lubricating fluid serves to minimize friction within the joint space while also providing essential nutrients to nourish the articular cartilage [4]. Both the stability and mobility of the hip joint are supported by a multitude of surrounding muscles including hip flexors, extensors, abductors, adductors and rotators [3]. These muscles collectively act to stabilize the joint and enable a wide range of movements essential for daily function [1]. The principal vessels that contribute to the blood supply of the hip joint capsule are the Medial and Lateral Circumflex Femoral Arteries (MFCA and LFCA) which come from the profunda femoris artery [5]. Also, the Superior Gluteal Artery (SGA) is important for hip perfusion and stems from the posterior division of the internal iliac artery and the Inferior Gluteal Artery (IGA) stems from the anterior trunk of the internal iliac artery [5]. The combination of these arteries collectively establishes the necessary perfusion to the capsule.

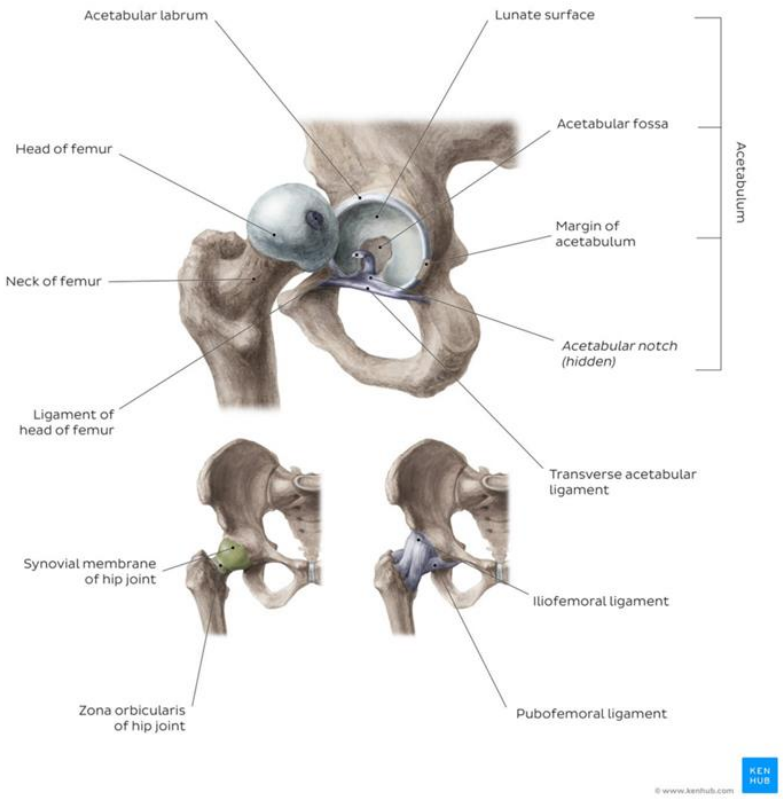

Figure 1: Hip joint from different perspectives [6].

Common Hip Conditions and Associated Pathology

Osteoarthritis (OA), commonly known as "wear-and-tear" arthritis or degenerative joint disease, affects more than 27 million Americans and is the most prevalent form of joint disorder in the United States [7]. It primarily involves the articular cartilage and surrounding tissues with the hip joint being commonly affected. Hip OA can be categorized into primary and secondary types with primary OA being idiopathic and usually affecting multiple joints in the elderly population while secondary OA typically develops due to a defined disorder affecting the joint's articular surface, such as trauma [8]. The pathophysiology of hip OA involves progressive loss of articular cartilage narrowing the joint space, subchondral cysts, osteophyte formation, ligamentous laxity, muscle weakness and synovial inflammation (Fig. 2) [7]. Risk factors for hip OA include age, gender, obesity and genetics [9]. Non-radiographic factors such as BMI >29 and increased age at presentation with hip pain are known to be significant predictors of hip OA [9]. Hip OA can significantly impair mobility and lead to disability which emphasizes the importance of early diagnosis and appropriate treatment.

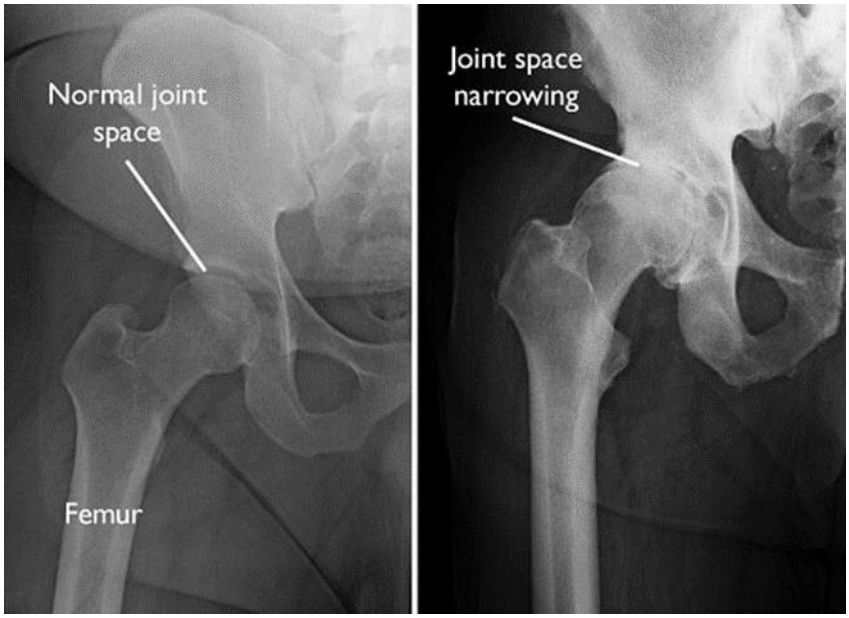

Figure 2: (Left) In this X-ray of a normal hip, the space between the ball and socket indicates healthy cartilage. (Right) This X-ray of an arthritic hip shows severe loss of joint space [10].

Osteonecrosis (ON) or Avascular Necrosis (AVN), is characterized by bone cell death resulting from altered blood flow, either due to traumatic or non-traumatic causes or associated risk factors. Each year in the United States, there is a range of 10,000-20,000 new cases reported [11]. Traumatic causes include physical trauma, decompression sickness or radiation while non-traumatic cases may involve intravascular coagulation or extravascular compression [12]. The pathophysiology of ON involves vascular impairment, altered bone-cell physiology and genetic factors. Trauma is a significant risk factor due to direct injury to vessels supplying the subchondral bone [13]. Vascular impairment, intravascular occlusion and intraosseous extravascular compression contribute to ischemia and subsequent ON with factors such as sickle cell disease, coagulation abnormalities, corticosteroid use, excessive alcohol consumption and Gaucher disease playing prominent roles in disrupting blood flow to the femoral head (Fig. 3) [13]. Regardless of the cause, ON of the Femoral Head (ONFH) is associated with blood flow impairments which lead to histological changes, inflammatory responses and potential collapse of the bone structure.

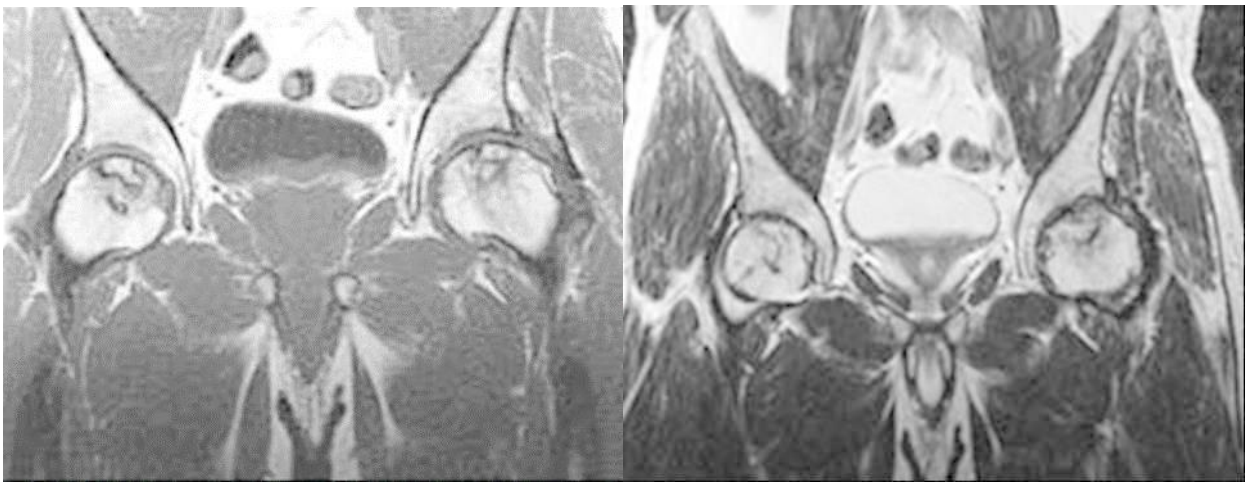

Figure 3: Patient 39 years old with use of high dose of corticosteroids and visible ONFH with MRI. (Left) Cor T1 and T2-weighted MRI image of the pelvis shows a stage B (blood-like) at the level of right femoral head with increased signal on T1W and T2W. (Right) AVN stage C (fluid-like) in left femoral head, with decreased signal intensity on T1W and increased signal on T2W [14].

Tendinopathy, encompassing conditions like reactive tendinitis and tendinosis, poses a challenge in understanding its pathophysiology due to a multitude of intrinsic and extrinsic factors contributing to tendon injury [15]. The tendinopathy that will be looked at in closer detail in this study will be gluteal tendonitis. Gluteal tendonitis, characterized by lateral hip pain and tenderness over the greater trochanter, is a significant cause of pain and disability with quality of life and levels of disability comparable to end-stage hip osteoarthritis [16]. Predominantly affecting women over 40 years old, with reports indicating a prevalence of up to 23.5% in women and 8.5% in men aged 50 to 79 years, gluteal tendinopathy stands as the most prevalent lower limb tendinopathy [16]. Repeated rubbing between the greater trochanter and the Iliotibial Band (ITB) results in microtrauma at the insertion point of the gluteal tendons, causing local inflammation, tendon degeneration and heightened tension in the ITB [17]. In Figure 4, the general anatomy is shown as the ITB tensioners would be what is rubbing against the trochanteric abductors to cause this inflammation and tension (Fig. 4). Chronic gluteal tendonitis is thought to stem from collagen bundle disorganization, elevated cell count, heightened proteoglycan synthesis and the development of new blood vessels [17]. Tendinopathy involves a decrease in type 1 collagen and an increase in type 3 collagen, resulting in diminished mechanical tendon strength due to the latter's fewer cross-links [18].

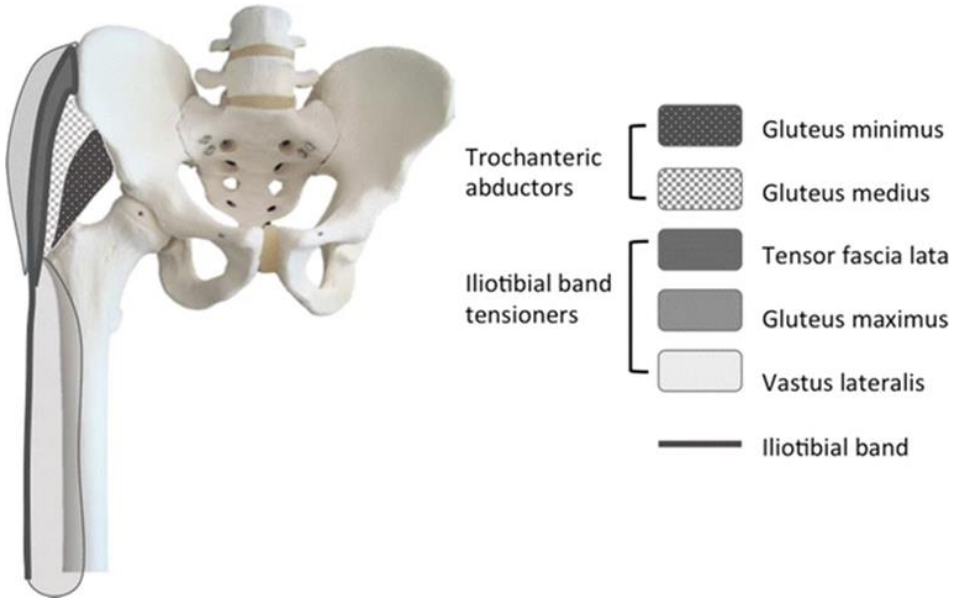

Figure 4: Trochanteric abductors versus iliotibial band tensioners [16].

Current Treatment for Common Hip Conditions

The choice of treatment for all these hip conditions emerges from a range of different treatments and depends on many factors including the severity of symptoms, the patient's age, overall health and lifestyle factors. Treatment options for hip osteoarthritis range from lifestyle modifications and physical therapy to medications. Exercise therapy is universally recommended as the first-line treatment for OA of the hip by major international guidelines including the National Institute for Health and Care Excellence (United Kingdom) and the American Academy of Orthopedic Surgeons [19]. This recommendation is supported by extensive evidence from over 80 randomized controlled trials conducted over the past 40 years [19]. The pharmacological management of OA encompasses oral and topical treatments. Acetaminophen and Oral Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) are commonly utilized as the initial pharmacotherapeutic options due to their popularity and affordability [20]. NSAIDs are typically administered orally or topically on an as-needed basis initially, but have potential for gastrointestinal, renal and cardiovascular adverse effects in the long-term [20]. For patients unable to take NSAIDs or who do not respond to them, intra-articular corticosteroid injections can provide temporary pain relief with hip injections typically guided by imaging [21]. However, corticosteroid injections may not offer significant pain relief compared to placebo after three months and could be less effective than physical therapy after one year [21]. Intra-articular Hyaluronic Acid (HA) injections present an alternative for persistent pain despite NSAIDs, but while their efficacy is comparable to NSAIDs, the highest quality trials demonstrate weaker effects [21]. Newer orthobiologic therapies like Platelet-Rich Plasma (PRP) or stem cell hip injections are also becoming more commonly seen in treatment for hip OA. These injections aim to alleviate pain and improve joint function in individuals with hip OA by harnessing the regenerative properties of the injected substances [22]. Studies investigating hip injections, particularly PRP and cell-based therapies, have shown promising results in reducing hip pain and enhancing joint function [22]. However, the evidence is still evolving with limitations including heterogeneity in injected products and the need for further high-quality research to establish their efficacy and optimize treatment protocols [22]. Severe cases call for surgical interventions including hip arthroscopy, total hip arthroplasty or osteotomy. Each year, more than 1 million individuals worldwide undergo total hip arthroplasty primarily due to end-stage hip OA with over 90% of cases falling into this category [23]. Long-term studies indicate that most implanted hips remain functional even after 10 to 25 years post-surgery and this procedure is especially effective especially for individuals who have not responded to conservative management strategies [23]. Assistive devices, like walkers and nutritional supplements can also be implemented to help with hip OA.

The treatment options for hip osteonecrosis also include the common pain and inflammation medicines seen within the OA possible treatments. Physical therapy is also recommended while protective weightbearing is commonly applied to preserve the hip as long as possible before collapse [24].

Several surgical options are available for individuals with femoral head osteonecrosis, categorized as either joint preservative or joint reconstructive procedures [11]. Joint preservation interventions include core decompression, bone grafting, biologics, cellular therapies and osteotomy aiming to alleviate pressure and improve perfusion in pre-collapse stages [11]. Core decompression is the most used clinical technique during pre-collapse stages [25]. It relieves bone marrow pressure and reduces pain further slowing joint degradation but is contraindicated after collapse occurs [25]. Bone grafting, especially vascularized grafts, can aid revascularization and potentially revitalize necrotic zones in larger lesions without early collapse [26]. Osteotomy alters weight distribution within the joint which potentially delays disease progression [27]. Arthroplasty is reserved for extensive damage or collapse of the femoral head and hip joint. Emerging therapies such as stem cell therapy and PRP injections mentioned are also being implemented to assist in slowing avascular necrosis. These treatments are commonly seen alongside the popular core decompression treatment, but significant findings are yet to be found which increases the for more successful trials [28].

Current treatments for hip tendinopathy include rest, activity modification and physical therapy to strengthen the hip muscles and improve biomechanics [29]. Pain relief is frequently achieved through medications like NSAIDs, corticosteroid injections or alternative therapies such as Extracorporeal Shockwave Therapy (ESWT). ESWT is utilized in the management of tendinopathy and soft tissue disorders across various anatomical regions [30]. Evidence suggests that higher frequency and dosage of ESWT may enhance its efficacy, though further high-quality studies are needed to establish optimal treatment protocols [30]. Surgical intervention for gluteal tendinopathy is typically reserved for cases resistant to nonoperative treatments especially in the presence of high-grade tendon tears [31]. Both open and endoscopic repairs have shown clinically significant improvements in

patient-reported outcomes and pain up to 5 years post-surgery [31]. Various fixation techniques, including transosseous sutures and suture anchors, have been employed while the impact of gluteal muscle atrophy and fatty degeneration on surgical outcomes remains debated [31]. Overall, operative management serves as a viable last-resort option when conservative measures fail to alleviate symptoms adequately and most cases can be effectively managed with a combination of conservative measures [32].

Stem Cell Therapy Alternative for Hip Conditions

Common hip conditions including osteoarthritis, osteonecrosis and gluteal tendinopathy represent a significant burden on individuals and healthcare systems worldwide. Current treatment options frequently focus on symptomatic relief and fail to address the underlying pathophysiology. This leads to a result of suboptimal outcomes and the lingering potential for disease progression. As previously mentioned, orthobiologic therapies, more specifically stem cell treatment, is becoming increasingly prevalent in treatment pathways for these conditions. Somatic or adult stem cells are undifferentiated cells dispersed throughout the body among specialized cells post-development [33]. These cells play a vital role in facilitating the repair, growth and replenishment of cells lost during daily turnover processes [33]. The current literature highlights promising outcomes from animal studies in bone, tendon and cartilage repair with early clinical results primarily available for bone and cartilage repair [34]. However, data on tendon repair is mostly confined to animal models and the efficacy of these techniques across all three areas remains inconsistent which is possibly due to varied application methods ranging from simple stem cell injections to complex tissue engineering [34]. Over the past three decades, Mesenchymal Stem Cells (MSCs) have garnered extensive interest due to their unique biology and potential therapeutic applications in tissue engineering [35]. MSCs possess inherent differentiation capabilities and secrete various growth factors and cytokines making them promising candidates for tissue repair [35]. They are derived from various sources including the umbilical cord, amniotic fluid, placenta, adipose tissue and joint synovium [36]. They exhibit multipotency meaning that they can differentiate into numerous mesenchymal cell types and recent research suggests they may also differentiate into nonmesodermal cells (Fig. 5) [36]. Bone Marrow-Derived Mesenchymal Stem Cells (BMMSCs) and Adipose-Derived Mesenchymal Stem Cells (ADMSCs) are two promising options for bone repair therapies and similar orthopedic issues. BMMSCs, considered the gold standard osteoprogenitors, have shown promise in clinical studies for enhancing bone repair rates, but challenges such as impure cell preparations and invasive isolation methods hinder their widespread therapeutic use [37]. In contrast, ADMSCs offer advantages including ease of isolation, higher proliferative capacity and resistance to senescence [37]. Tendon-Derived Stem Cells (TDSCs) are also emerging as a potential therapy for tendinopathy. Compared to other stem cell sources, like BMMSCs, TDSCs offer advantages in terms of their higher tenocytic gene expression profile and better mechanical strength [38]. While clinical studies have shown promising results in terms of pain relief and functional improvement, further research is needed to fully understand the efficacy and mechanism of action of TDSC therapy before widespread clinical implementation can be achieved [38]. BMMSCs and ADMSCs are far more reliable and clinically tested compared to TDSCs, but they may be used in the future if scientists can harness them correctly.

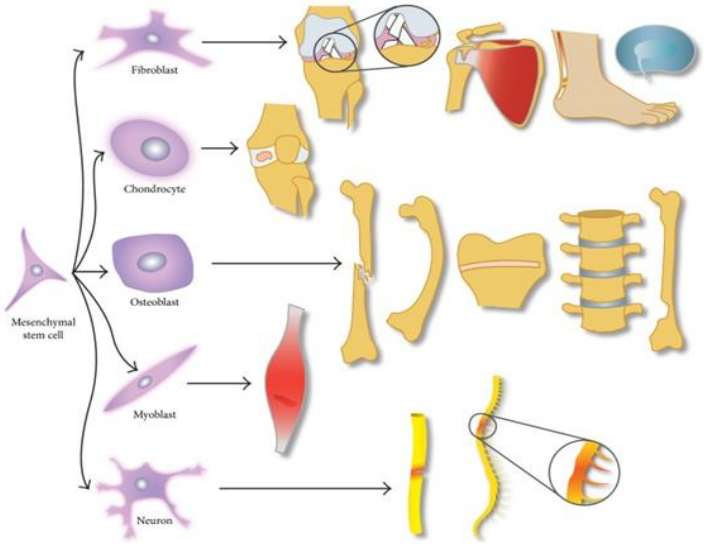

Figure 5: Mesenchymal Stem Cells (MSCs) are broadly applicable to the field of orthopedics. MSCs can be stimulated to differentiate into several cellular lineages with various clinical applications [36].

Discussion

Stem Cell Treatment for Hip Osteoarthritis

Stem cell therapy is an emerging treatment for the common hip pathology discussed throughout this paper. In this discussion, we will review the effects of stem cell treatment on these prevalent issues and specific cases where it has been applied. The primary challenge in cartilage tissue engineering lies in crafting a viable replacement for natural cartilage, as underscored by Langer and Vacanti's definition of tissue engineering in 1993, which emphasizes interdisciplinary approaches to enhance tissue function [39]. The potential of regenerative therapy, particularly leveraging stem cell advancements, holds promise in addressing osteoarthritis progression and facilitating joint tissue repair [39]. The pivotal role of MSCs in OA joint regeneration primarily lies in their ability to stimulate the local microenvironment through paracrine signaling [39]. Studies have demonstrated that MSCs facilitate tissue regeneration by releasing paracrine signals derived from mesenchymal stem cells themselves [39].

Mardones, et al., performed a cohort study in Chile in 2017 that aimed to assess the safety and efficacy of intra-articular infusion of *ex-vivo* expanded autologous BMMSCs in patients with hip osteoarthritis and articular cartilage defects [40]. Ten patients with evidence of hip osteoarthritis were included in the study receiving three weekly doses of BMMSCs (60 × 106 cells per dose) [40]. Evaluations before and after the treatment showed improvements in hip scores for pain, stiffness, physical function and range of motion, indicating the treatment's clinical effectiveness and safety [40]. This improvement was sustained over time without major complications or side effects during the follow-up period [40]. Additionally, radiographic scores of the hip joint assessed between 7 to 30 months post-infusion showed a cessation in the progression of osteoarthritis [40].

In a 2018 study in the United States, Darrow, et al., investigated whether treating hip OA with multiple Bone Marrow Concentrate (BMC) injections would be more effective than a single injection [41]. Drawing on findings from a previous knee OA study, the authors suggested that spacing injections approximately 14 days apart could leverage growth factor secretion, particularly Transforming Growth Factor β (TGF-β) known for MSC growth and osteogenic differentiation [41]. They hypothesized that this approach would lead to superior symptomatic relief compared to a single treatment. The results of this case series demonstrate significant improvements in pain reduction and functionality among all patients following BMC injections for hip OA. Notably, patients experienced substantial decreases in pain and improvements in functionality scores with one patient reporting an 80% decrease in resting pain and another a 67% decrease in active pain [41]. Additionally, patients showed an average increase in total overall improvement percentage and functionality score after successive treatments with none of the patients considering surgery post-treatment [41]. This study highlights the potential efficacy of BMC injections in improving symptoms of hip OA comparable to findings in knee OA treatment studies. However, the study is limited by its small sample size, short follow-up duration and absence of nucleated cell counts suggesting the need for further randomized controlled studies with larger sample sizes and longer follow-ups to validate these results [41].

A retrospective study in 2019 by Carlo, et al., assessed the feasibility of using intra-articular injections of autologous ADMSCs in treating hip osteoarthritis [42]. Six consecutive patients that were unresponsive to conservative treatments and graded 0-2 on the Tönnis grading scale were included [42]. The Tönnis grading scale assesses the degree of osteoarthritis in the hip based on radiographic findings. It ranges from Grade 0, indicating no osteoarthritis, to Grade 3, indicating severe osteoarthritis [43]. Grade 1 is characterized by increased sclerosis and slight joint-space narrowing, Grade 2 by small cysts and moderate joint-space narrowing and Grade 3 by large cysts, joint-space obliteration, severe deformity or evidence of necrosis [43]. Preoperative evaluations and assessments at the 6-month post-operative mark were conducted for all patients [42]. This study found that the injection of autologous and micro-fragmented adipose tissue is a safe treatment option for early-stage hip osteoarthritis yielding positive clinical outcomes measured by the Harris Hip Score (HHS) and Visual Analog Scale (VAS) for pain [42]. This treatment demonstrated safety with no treatment-related adverse events. The injection's benefits include its anti-inflammatory properties, mechanical lubricating effect and the potential of MSCs to secrete bioactive molecules that support tissue repair [42]. The study suggests a potential role of MSCs in restoring joint equilibrium and mediating inflammation [42].

The emerging field of stem cell therapy holds promise in addressing the challenges of hip OA through regenerative approaches. Studies by Mardones, et al., and Darrow, et al., demonstrated the safety and efficacy of intra-articular injections of MSCs and BMC in improving pain and functionality in hip OA patients [40,41]. These treatments showed sustained benefits and halted the progression of osteoarthritis highlighting their potential as disease-modifying therapies. Additionally, a retrospective study by

Carlo, et al., explored the use of autologous ADMSCs which indicated promising outcomes in terms of pain relief and functional improvement [42]. These findings underscore the potential of stem cell therapies as safe and effective interventions for early-stage hip OA offering hope for improved management of this debilitating condition.

Stem Cell Treatment for Hip Osteonecrosis

ONFH is a painful and progressive condition characterized by bone cell death which often leads to articular cartilage collapse and subsequent osteoarthritis [44]. It primarily affects individuals aged 30 to 40 years with bilateral hip involvement in 75% of cases [44]. Total hip arthroplasty is a common treatment, but its durability in young and active patients is limited [44]. Therefore, early interventions such as core decompression and stem cell treatment are gaining attention for preserving native joint function. Bone marrow serves as the predominant source of stem cells utilized in treating ONFH. Within an appropriate setting, BMMSCs possess the capacity to differentiate into various cell types within the musculoskeletal system, including trabecular bone, articular cartilage and tendons [45]. Adipose tissue also acts as a dependable source of stem cells for addressing ONFH. ADMSCs or AMSCs as seen in Fig. 6, offer several benefits including ease of access, increased productivity and comparable differentiation capabilities to BMSCs (Fig. 6) [45].

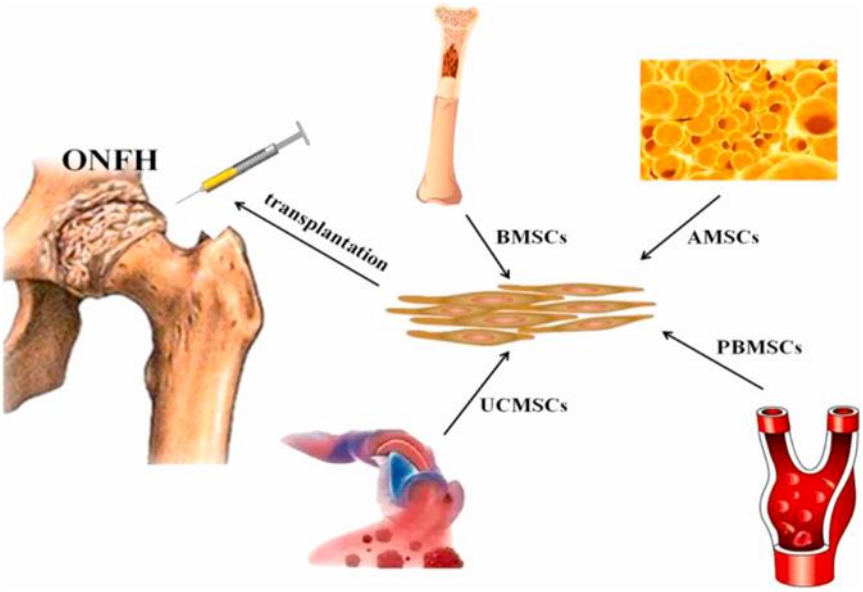

Figure 6: The main source of stem cells for transplantation [45].

The first to investigate this therapy was Hernigou and Beaujean in 2002 where they looked at the efficacy of injecting MSCs combined with standard core decompression for ONFH [46]. The study involving 189 hips (116 patients) utilized concentrated iliac crest bone marrow injected through core decompression tracts into necrotic areas [46]. Results at 5 years showed favorable outcomes for patients with early-stage disease with only a small percentage requiring total hip arthroplasty [46]. The study also found that the amount of injected MSCs and the underlying cause of ONFH were associated with disease progression with patients having lower stem cell concentrations or a history of certain risk factors being at higher risk of disease advancement [46].

In 2020, Mao, et al., comprehensively assessed the long-term effectiveness and safety of stem cell therapy for early-stage ONFH through rigorous randomized controlled trials [47]. Evaluation criteria included the occurrence of femoral head collapse, the need for total hip replacement and hip survival rates [47]. Additionally, the study aimed to determine the most suitable age group and optimal dosage of stem cell therapy based on existing randomized controlled trial findings [47]. The analysis of this study revealed that stem cell therapy significantly delays the progression of ONFH and improves hip survival rates in the long term [47]. Notably, stem cell therapy effectively reduces the occurrences of femoral head collapse and the need for total hip replacement over extended follow-up periods [47]. The analysis suggests that patients under 40 years old benefit more from stem cell therapy and an optimal stem cell quantity of approximately 108 magnitude offers superior long-term benefits [47].

Mechanistically, stem cells may promote tissue repair, angiogenesis and osteogenesis through various biological factors. Stem cell therapy presents a promising avenue for managing ONFH, particularly in younger patients, with further research needed to elucidate its therapeutic effects and mechanisms [47].

A study done by Papakostidis, et al., in 2016 conducted a meta-analysis evaluating whether implanting autologous bone marrow aspirate containing MSCs into the core decompression tract would enhance clinical and radiological outcomes in ONFH compared to conventional core decompression alone [48]. The study focused on primary outcomes including structural failure of the femoral head and conversion to total hip replacement [48]. The results demonstrated a significant reduction in disease progression to femoral head collapse and a decreased need for total hip arthroplasty with the combined therapy [48]. Core decompression, although effective in early-stage ONFH, often fails in advanced cases which prompted this investigation of alternative therapies involving MSCs. These cells play a crucial role in ONFH pathogenesis with reduced activity observed in osteonecrotic femoral heads [48]. The effectiveness of autologous cell therapy depends on disease stage and the number of MSCs transplanted with earlier intervention and higher MSC concentrations leading to better outcomes [48]. Subgroup analysis confirmed the superiority of autologous cell therapy over core decompression, particularly in early-stage disease, using highly concentrated bone marrow aspirates containing abundant MSCs [48].

A recent study done by Gun-Il Im in 2018 brought attention to a meta-analysis examining stem cell therapy for ONFH found a minimal complication rate of 2.8% with all reported complications being minor, such as hematoma, wound infection and pain at the bone marrow aspiration site [49]. The author mentions that while the transformation of implanted cells poses a potential serious risk, there have been no major complications associated with stem cell implantation for ONFH reported thus far [49]. Im emphasizes the importance for treating physicians to be familiar with methods for quantifying and characterizing cells, as well as the efficiency of harvest, processing and delivery procedures [49]. Additionally, the author recommends that established measures should not be disregarded until stem cell therapy has been proven safe, effective and cost-effective [49].

Stem Cell Treatment for Gluteal Tendinopathy

Tendon pathologies encompass various musculoskeletal conditions including traumatic, degenerative and overuse-related tendinopathies [50]. Despite their prevalence, conventional treatments frequently yield inconsistent results. Tendinopathy's exact causes remain elusive, but histopathological features like fat cell accumulation and tissue calcification suggest a potential for multi-phenotypic cell involvement beyond tenocytes [50]. Current treatments like NSAIDs, corticosteroid injections and surgery have limitations, prompting exploration of MSC therapy which has been backed by promising results in other medical fields [50].

In 2021, a research study in Brazil by Rosário, et al., investigated the effectiveness of Bone Marrow Aspirate Concentrate (BMAC) compared to corticosteroid injections which is a standard treatment for gluteal tendinopathies [51]. BMAC, prepared in a standardized manner with FDA and KFDA approval, offers a feasible one-stage option for cartilage repair that provides easy control of MSCs and reduced risk of disease transmission [52]. However, despite containing various beneficial components such as hematopoietic stem cells, platelets, growth factors and cytokines, BMAC yields only a small fraction of MSCs, potentially limiting its efficacy and particularly in elderly patients who may have lower levels of MSC differentiation and chondrogenicity [52]. It involved 48 patients diagnosed with gluteal tendinopathy which were randomly assigned to either BMAC or corticosteroid injection groups [51]. After six months, both groups exhibited improvements with patients treated with BMAC showing significantly higher VAS scores and Lequesne index scores compared to corticosteroid recipients [51]. However, there was no statistically significant difference in the improvement of quality of life between the two groups [51]. The study is situated within a context where tendinopathy research remains limited with only a few studies focusing on this condition. Early research on cell therapy for tendinopathies, including gluteal tendinopathy, emerged in the early 2010s with BMAC being explored in various mammalian and *in-vitro* studies to understand its mechanisms of action [53]. Corticosteroid injections, a common treatment, have shown short-term benefits but with the risk of long-term complications such as tendon weakening [51]. Multidisciplinary approaches including lifestyle modifications, physical therapy and comorbidity management are considered crucial for managing Greater Trochanteric Pain Syndrome (GTPS) which is often closely associated with gluteal tendinopathy [54]. BMAC has shown promise in treating various tendon disorders including patellar tendinopathy and rotator cuff injuries indicating its potential as a viable alternative to corticosteroid injections for GTPS and gluteal tendinopathy [51].

This review from Mirghaderi, et al., in 2022 addresses the safety and efficacy of cell therapy in treating tendon disorders [55]. It underscores the generally positive safety profile of cell injection with minor adverse events reported in some cases [55]. Various treatments, including cell therapy with MSCs have shown promising results in tendon healing, but previous studies have encountered limitations such as non-randomized allocation and short-term follow-ups [55]. The exact mechanism of action of MSCs in tendon healing is not fully understood, but studies suggest various possibilities including differentiation into tenocytes and secretion of regenerative factors [55].

Chen, et al., condensed the challenges and differing perspectives on tendon-derived cell therapy for tendinopathies including gluteal tendinopathy in 2022 [38]. Recent advancements have unveiled the presence of TDSCs which offers a promising new avenue for treatment [38]. This review explores the potential TDSC-based therapies have by highlighting their superiority over non-homologous treatments such as BMMSC and ADMSC therapies [38]. The authors reference studies demonstrating TDSCs' superior tenocytic gene expression profile, mechanical strength and regenerative capabilities [38]. Moreover, TDSC-based therapies have shown remarkable efficacy in repairing tendon defects across various anatomical sites which can offer hope for improved outcomes in late-stage tendinopathy and tears [38]. These therapies work through mechanisms such as replenishing local tendon cell populations, promoting tissue regeneration and stimulating growth factor production showcasing their potential as a transformative approach in tendinopathy treatment. One study referenced uses these TDSCs in a procedure called Autologous Tenocyte Injection (ATI) to treat gluteal tendinopathy in twelve female patients who did not respond to conventional treatments including multiple corticosteroid injections [56].

The study revealed significant improvement in early clinical patient-reported outcomes sustained up to 24 months post-treatment [56]. All patients showed improvement in the Oxford Hip Score with a notable change in pain scores and physical component subscale of the SF-36 [56]. Despite previous steroid injections, which demonstrated short-term efficacy, patients in the ATI trial displayed sustained pain relief [56]. Animal studies have also suggested potential mechanisms of action for ATI including the incorporation of tenocytes into the tendon matrix and the production of growth factors [56].

Conclusion

In conclusion, the exploration of stem cell therapy for common hip conditions provides a compelling glimpse into the future of orthopedic treatment. Through review of the literature addressing hip osteoarthritis, osteonecrosis and gluteal tendinopathy, this paper underscores the transformative potential of stem cell therapy in mitigating the progression of these debilitating conditions. By analyzing the application of stem cell therapy in musculoskeletal disorders, this paper sets the stage for understanding its relevance in addressing hip pathologies. Key findings from recent important studies highlight the safety and efficacy of intra-articular mesenchymal stem cell injections for hip OA as well as the long-term benefits of stem cell therapy in delaying the progression osteonecrosis of the femoral head and improving hip survival rates. Moreover, the comparison between bone marrow aspirate concentrates and corticosteroid injections for gluteal tendinopathy underscores the versatility of stem cells across various tendinopathy disorders. Looking forward, future applications of stem cell application in hip conditions hold significant promise. The potential combination between stem cells and conventional treatments including corticosteroid injections and physical therapy present exciting avenues for further research and clinical practice. However, it is essential to acknowledge the need for more extensive research before widespread implementation. Areas requiring more in-depth investigation include optimizing stem cell application protocols and conducting larger scale randomized controlled trials with longer follow-up durations. As we continue to refine our understanding of stem cell treatment and its applications in hip conditions, there is a tangible prospect for enhanced patient outcomes and improved quality of life for individuals suffering from these prevalent orthopedic conditions.

Conflict of Interest

The authors have no conflict of interest to declare.

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