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Mesenchymal Stem Cell Potential in Preventing Osteolysis After Total Hip Replacement in Patients with Osteoarthritis

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ABSTRACT

Periprosthetic osteolysis is an important cause of bone loss and implant loosening after total hip arthroplasty (THA). Mesenchymal stem cells (MSCs) and their extracellular vesicles (EVs) have been investigated as biologic approaches to preserving the bone–implant interface. This narrative review examines the potential mechanisms and experimental evidence supporting MSC-based strategies for preventing osteolysis after THA in patients with osteoarthritis. The source literature search covered publications from 2015 to 2025 using terms related to MSCs, osteolysis, total hip replacement, and osteoarthritis. The reviewed evidence describes immunomodulatory and osteogenic actions, including macrophage polarization toward an anti-inflammatory phenotype, suppression of inflammatory cytokines and osteoclastogenesis, and promotion of osteoblast differentiation and mineralization. *In vitro* and murine studies of urine-derived stem cell EVs and umbilical cord MSC-derived EVs, including polymer-based delivery platforms, suggest protective effects against polyethylene particle-induced bone resorption. However, heterogeneity in cell preparation, dose, and delivery, together with limited clinical evidence and unresolved long-term safety questions, restricts translation. MSC-based therapies are promising experimental adjuncts for periprosthetic bone preservation, but well-designed human studies are required before routine clinical use.

Keywords: mesenchymal stem cells; periprosthetic osteolysis; total hip arthroplasty; osteoarthritis; extracellular vesicles

INTRODUCTION

Osteoarthritis (OA) is the most prevalent form of arthritis in adults, commonly leading to chronic pain and reduced mobility, and it remains the primary indication for total hip arthroplasty (THA). Osteoarthritis (Figure 1) is a chronic degenerative disease characterized by destructive changes in the articular cartilage, synovitis, subchondral bone sclerosis, and osteophyte formation [1]. THA is widely recognized as the standard of care for end-stage hip OA, offering substantial pain relief and functional improvement, and has been regarded as one of the most successful surgical procedures of the century. With an aging population and increasing expectations for mobility and quality of life, the global demand for THA is projected to rise significantly. For instance, Sloan et al. estimated, based on National Inpatient Sample (2000–2014) data, that the annual volume of primary THA could increase by 71%, reaching approximately 635,000 procedures by 2030 [2].

Despite its proven benefits, THA is not without risks, as complications may occur and should be considered in clinical practice.

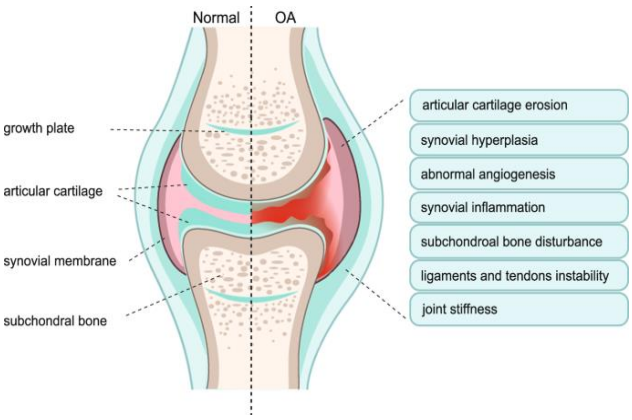


FIGURE 1: Osteoarthritis [3].

The process of bone loss or disintegration, known as osteolysis (Figure 2), is typically brought on by an excess of osteoclast activity. Although osteolysis is not a primary hallmark of osteoarthritis (OA), a degenerative joint disease, it can occur in specific circumstances and signal a worsening or complication of OA. Osteolysis is a biological, often progressive, reaction to wear particles or corrosion products generated by prosthetic implants.

It involves activation of macrophages by these particles, which in turn drive osteoclast differentiation and bone resorption at the implant–bone interface, potentially leading to prosthesis loosening or failure [4]. Once osteolysis occurs, the bone tissue undergoes erosion, leading to weakening of its load-bearing function and resulting in secondary fractures, prosthesis loosening, and other complications [5]. Even though osteoarthritis is typically defined by 1) Articular cartilage degradation, 2). The subchondral bone thickening, 3) the production of osteophytes, 4) subchondral cyst formation, at later stages or in certain circumstances, osteolysis may be brought on by: 1) osteoclast activation and chronic inflammation. Local inflammation in the synovium (mild synovitis) nevertheless happens even though OA is largely a non- inflammatory illness. Pro-inflammatory cytokines like these are released as a result of this inflammation: IL-1β, TNF-α, and IL-6.

These cytokines have the ability to raise RANKL expression, which promotes osteoclast activation and differentiation and causes bone resorption (osteolysis) 2). Subchondral Bone Microfractures & Biomechanical Alterations. High mechanical loads are applied to the subchondral bone beneath the articular cartilage. Repetitive stress, or microfractures, results in bone remodeling. The following happens if remodeling is excessively active or out of balance: Sclerosis on one side, Resorption-induced osteolysis on the opposite side. 3). Geode Formation Subchondral Cysts. Subchondral cysts are frequently seen on radiographs of advanced OA. These are cavities in the subchondral bone that are filled with fluid or necrotic tissue. They occur in isolated areas of osteolysis and are caused by either bone cell death or pressure from synovial fluid 4). Particulate matter complications (trauma or implants). Metal or polyethylene particles may cause osteolysis in OA patients having arthroplasty (TKR or THR, for example).

In total hip arthroplasty (THA), revision indications include osteolysis, aseptic loosening, infection, metallosis, periprosthetic fracture, instability, polyethylene bearing wear, mechanical implant failure, failed resurfacing, malposition, and unexplained pain.

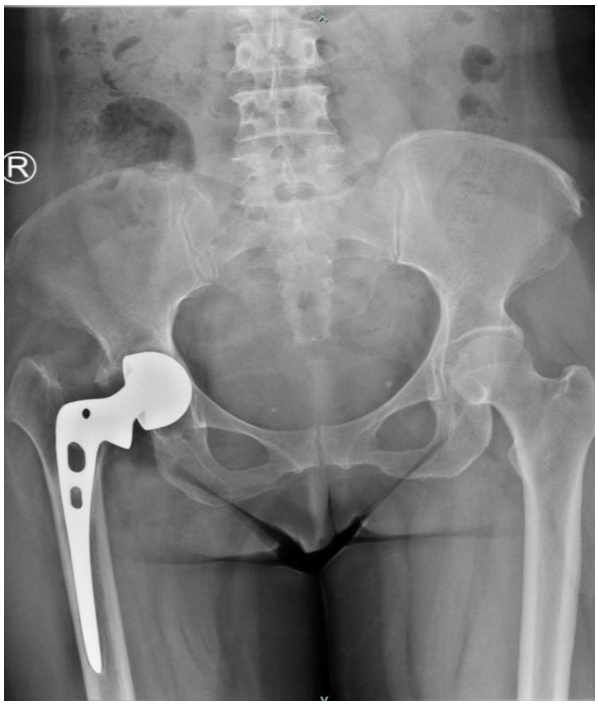


FIGURE 2: Aseptic Loosening After Hip Arthroplasty.

A large cohort study identified 1079 conditions contributing to THA failure, with 21.8% of patients having more than one reason for revision. Aseptic loosening was the most common indication (31.3%), followed by progressive osteolysis (21.8%). Among the 190 revisions for osteolysis, 54.7% involved the acetabular component only, 20% the femoral component only, and 25.3% both. All patients with available data had metal-on-polyethylene articulation. These findings illustrate the clinical importance of osteolysis as an indication for revision THA [6].

Osteolysis remains a major reason for revision THA, with projections estimating that approximately 10% of all revision THAs will be secondary to osteolysis, accounting for about 9700 revisions by 2030 [6]. This is due to several reasons, such as: 1) The Inflammatory Response Induced by Particles. Wear particles, such as polyethylene, metal, or ceramic debris, are produced over time by the implant's bearing surfaces, particularly in older metal-on-polyethylene designs. Macrophages phagocytose these tiny particles by a mechanism of release cytokines that promote inflammation (TNF-α, IL-1, IL-6), increase the expression of RANKL to activate osteoclasts, causes the bone surrounding the implant to resorb (osteolyze). Even if the patient is asymptomatic at the beginning, this causes progressive bone loss. 2) Loosening of Implants Owing to Bone Loss. Implant stability depends on the integrity of the bone-implant contact. The implant becomes loose as osteolysis worsens due to the bone that once held up the implant being gone. Wear is made worse by increased micromotion, creating a vicious cycle. Loosening impairs function and mobility and is frequently unpleasant.

3) Lack of symptoms until the process becomes advanced. Clinically, early osteolysis is frequently quiet. It's possible that significant bone loss has already taken place by the time symptoms like pain and instability manifest. Because of this, revision surgery is more intricate. This condition frequently necessitates augmentation procedures, unique implants, or bone grafts. More serious situations that need revision result from delayed detection. 4) Typical of Previous Implant Designs: The following were features of older THA designs, particularly traditional polyethylene liners, that could increase rates of wear and increase the production of particles. Osteolysis becomes clinically relevant in these patients, who are currently in the 15-25-year post-operative window. Revision THA for those patients has increased as a result.

Osteolysis after total hip arthroplasty (THA) is often asymptomatic and typically discovered through routine postoperative imaging. In mild, symptom-free cases, nonoperative management with regular clinical and radiographic monitoring is appropriate to detect progression or implant loosening. Surgical intervention is indicated when patients experience pain, functional decline, or implant instability related to aseptic loosening. Managing osteolysis can be complex, especially on the femoral side, where cemented components may crack or fragment, leading to significant bone loss or fracture. Revision surgery may involve extended femoral osteotomy for debridement and reimplantation with longer cementless stems. In cases of polyethylene debris–induced osteolysis around stable implants, addressing the bearing surface is essential, and bone grafting with allografts or cortical strut grafts may be required depending on the defect type. Severe bone loss may necessitate revision arthroplasty using structural allografts or prosthetic composites. For patients unsuitable for surgery, pharmacologic approaches such as bisphosphonates have been explored to slow bone loss, though their effectiveness in particle- induced osteolysis remains limited. These limitations emphasize the need for novel biologic strategies, such as mesenchymal stem cell (MSC) therapy, which offers potential in preventing osteolysis through both anti-inflammatory modulation and bone-regenerative mechanisms. Mesenchymal stem cells (MSCs) have emerged as a central focus in regenerative medicine, particularly for musculoskeletal disorders. While most fractures heal naturally, 10–20% result in delayed healing or nonunion, with hip fractures posing especially high risks, including a mortality rate of 15–25%. Fracture repair is a complex process involving osteogenesis and angiogenesis through sequential inflammatory, repair, and remodeling phases.

MSCs play a crucial role by migrating to fractured sites, differentiating into bone-forming cells, and modulating the healing environment. They secrete growth factors and anti-inflammatory cytokines, enhancing bone regeneration in both preclinical and clinical models. Experimental studies show MSCs can home to fracture sites via receptors such as CXCR4, improving biomechanical properties and callus formation. Beyond fracture repair, MSCs are also promising for critical-size bone defects and osteolysis. Notably, wear particles recruit MSCs through CCR1 signaling, where they help suppress osteolysis and increase bone mineral density. Thus, MSCs support bone repair not only through direct osteogenesis but also by regulating inflammation towards regeneration [7].

Mesenchymal stem cells (MSCs) possess both regenerative and immunomodulatory properties, making them promising candidates for translational therapies targeting inflammatory bone diseases. Clinical studies have explored MSC-based treatments across various inflammatory conditions such as graft-versus-host disease, diabetes, myocardial infarction, and osteoarthritis. In the context of osteolysis, MSCs contribute to bone preservation not only by differentiating into osteoblasts and enhancing bone regeneration but also by modulating immune responses. Specifically, MSCs facilitate the polarization of macrophages toward the anti-inflammatory M2 phenotype, which helps suppress wear-particle-induced inflammation and subsequent bone resorption. The objective is to analyze the effectiveness and potential mechanisms of mesenchymal stem cells in minimizing osteolysis after THA in osteoarthritis patients.

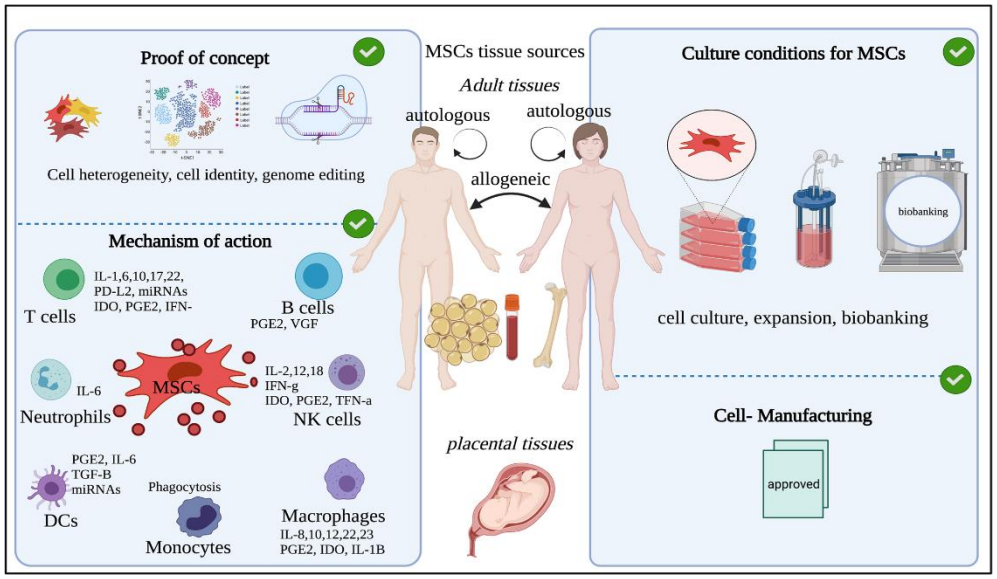


FIGURE 3: Schematic illustration of MSC sources and four focusing areas. Along with immune cells, MSCs isolated from various tissues show immune-modulating functions. MSCs heterogeneity, application of single cell RNA sequencing, and gene editing are three proofs of concepts used as advanced technologies in deciphering MSC uniqueness (central and right). Cell culture, expansion, and biobanking are standard procedures to establish good laboratory practices for further use in clinical practice (left). [8].

Mesenchymal stem cells (MSCs) derived from dental tissues have been thoroughly characterized for their dual regenerative and immunomodulatory properties, including robust osteogenic potential and strong anti-inflammatory secretomes [9, 10, 11]. Dental MSC populations such as dental pulp stem cells (DPSCs), stem cells from exfoliated deciduous teeth (SHED), periodontal ligament stem cells (PDLSC), and others express canonical MSC markers, secrete osteoinductive growth factors (e.g., BMPs, TGF-β, VEGF), and release paracrine mediators (PGE2, IL-10, HGF) that both promote osteoblast differentiation and polarize macrophages toward an anti-inflammatory M2 phenotype [10, 11]. These combined functions, stimulating bone formation while dampening particle-driven inflammation, are precisely the therapeutic actions needed to interrupt the pathogenic cascade that leads from wear debris to osteolysis and implant loosening [7, 12, 13].

Dental-derived mesenchymal stem cells (MSCs) have shown significant regenerative and immunomodulatory potential in oral and maxillofacial models, providing a relevant biological framework for their use in orthopedic implant preservation. Studies on dental MSCs, including dental pulp stem cells (DPSCs), stem cells from exfoliated deciduous teeth (SHEDs), and periodontal ligament stem cells (PDLSCs), demonstrate their ability to differentiate into osteoblast-like cells, modulate macrophage polarization, and secrete cytokines such as IL-10 and TGF-β that suppress inflammatory bone loss [10, 11]. Dental-derived MSCs provide a valuable model for understanding MSC-mediated bone regeneration relevant to arthroplasty. These cells, including DPSCs, PDLSCs, and SHEDs, are accessible, exhibit rapid proliferation, and secrete osteogenic and anti-inflammatory mediators that drive dentin and alveolar bone repair [9, 10, 11]. This paracrine mechanism parallels the protective pathway observed in MSC-derived extracellular vesicle (EV) therapy for periprosthetic osteolysis, where immunomodulation and osteogenesis act synergistically to prevent implant loosening [14, 15, 16]. Their signaling profiles, particularly the release of BMPs, IL-10, and VEGF, mirror the molecular effects seen in orthopedic MSC-EV studies that inhibit osteoclast activity and restore bone formation around implants [14, 15, 16]. This convergence highlights a shared regenerative mechanism across tissues: MSCs act not only as progenitors for new bone but also as paracrine modulators that preserve structural integrity under chronic mechanical and inflammatory stress.

Translating these dental MSC insights into orthopedic applications could enhance early prophylaxis and long-term prevention of periprosthetic osteolysis. Integrating these dental MSC insights suggests that MSC-based strategies after THA could function not only as regenerative therapies but also as proactive biologic modulators that maintain bone–implant homeostasis.

In both dental and orthopedic tissue models, MSCs exhibit strong anti-inflammatory and osteogenic effects. Dental MSCs, such as DPSCs and SHEDs, demonstrate *in vitro* osteoblastic differentiation and release of growth factors (BMPs, VEGF, IGF-1) that enhance mineralization and angiogenesis [10, 11]. MSCs are multifunctional agents capable of promoting osteogenesis while attenuating periprosthetic inflammation, reinforcing their potential as adjunctive biologics for preventing osteolysis after THA.

METHODS

This study was conducted as a narrative literature review focusing on the role of mesenchymal stem cells (MSCs) in preventing periprosthetic osteolysis following total hip arthroplasty (THA). A comprehensive literature search was performed across PubMed and Scopus, together with publisher platforms including MDPI, Elsevier, and BMC, covering publications from 2015 to 2025. The search used the keywords “mesenchymal stem cell”, “osteolysis”, “total hip replacement”, and “osteoarthritis.” Earlier publications were used for background context.

A total of 189 records were initially identified. After removal of duplicates, 158 articles remained for screening. Titles, keywords, and abstracts were assessed for relevance, yielding 102 articles for initial review. Based on inclusion criteria, English language, full-text availability, and original or review articles related to MSC therapy in bone loss or osteolysis after arthroplasty, 72 full-text articles were evaluated. Of these, 37 articles were excluded due to non-relevance or insufficient data. Subsequently, 35 full-text articles were reviewed in detail, and 24 studies were finally included in this narrative synthesis. No additional articles were obtained through reference list searching.

The selected studies were analyzed to identify key findings related to MSC mechanisms, delivery methods, and therapeutic outcomes in both *in vitro* and *in vivo* models of osteolysis and periprosthetic bone preservation.

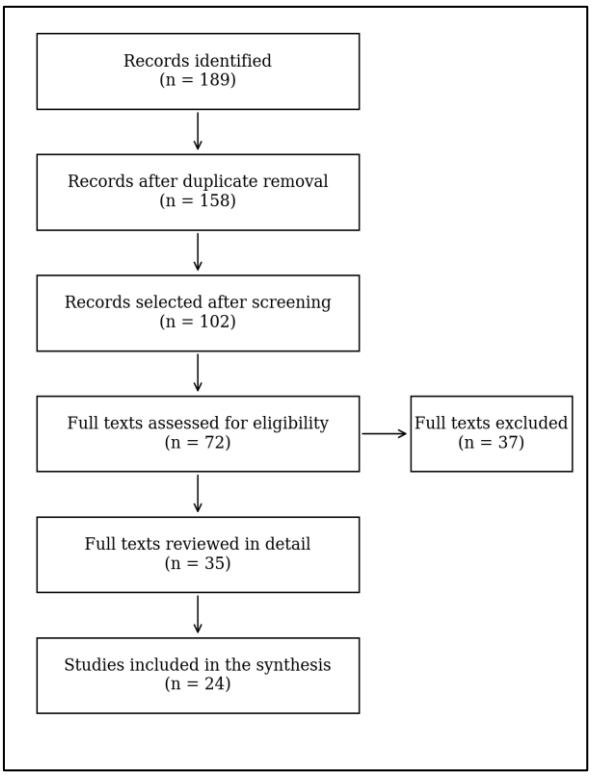


FIGURE 4: Literature Search and Study Selection.

RESULTS

Mesenchymal stem cells (MSCs) play pivotal roles in preserving bone integrity after total hip replacement by mitigating inflammation caused by wear particles, promoting osteoblastogenesis, and restoring a healthy bone microenvironment. When debris from prosthetic components accumulates, macrophages are activated and adopt a pro-inflammatory phenotype (M1), releasing cytokines such as TNF-α, IL-1β, and IL-6 that drive osteoclast activation and bone resorption.

MSCs counter this by encouraging macrophage polarization toward the anti-inflammatory M2 state, via release of soluble mediators like IL-10, TGF-β, PGE2, and exosomes, thus reducing inflammatory damage (for example, in 3D co-culture models with polyethylene particles, MSCs + M2 macrophages enhance osteogenic marker expression compared with MSCs alone or MSCs with M1 macrophages).

In addition, M2 macrophages release growth factors (e.g., BMP-2, VEGF) that stimulate osteoblast differentiation from MSCs, while limiting osteoclast formation and activity, helping to maintain bone mass. Through these actions, immune regulation, fostering new bone deposition, and curbing bone resorption, MSCs help heal the peri-implant bone microenvironment, potentially preventing the progression of osteolysis in osteoarthritis patients after THA.

In vitro assays provide mechanistic evidence for the protective role of MSC-derived extracellular vesicles (EVs) against wear particle–induced osteolysis. Li et al. [14] tested human urine-derived stem cell EVs (USC-EVs) using: 1. Macrophage assays: RAW264.7 macrophages stimulated with polyethylene (PE) particles. USC-EVs significantly reduced secretion of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6), measured by ELISA and qPCR. 2. Osteoblast differentiation assays: Bone marrow stromal cells treated with USC-EVs showed increased alkaline phosphatase (ALP) activity and enhanced mineralization (Alizarin Red staining), demonstrating a direct osteogenic effect. Xie et al. [15] evaluated human umbilical cord MSC-EVs (hUCMSC-EVs), including a PLGA- encapsulated delivery system, using: 1. Macrophage uptake & inflammatory assays: FITC-labeled EVs confirmed internalization by RAW264.7 macrophages. Inflammatory cytokine expression (TNF-α, IL-6) was reduced after particle stimulation, assessed by qPCR and ELISA. 2. Osteoclastogenesis assays: Bone marrow–derived monocytes (BMMs) cultured with RANKL ± PE particles showed reduced differentiation into TRAP-positive multinucleated osteoclasts when treated with PLGA-EVs, indicating suppression of osteoclast formation. These assays collectively show that MSC-EVs suppress macrophage-driven inflammation, downregulate osteoclast differentiation, and promote osteogenesis *in vitro*. This provides a mechanistic foundation for their *in vivo* protective effects against periprosthetic osteolysis.

Recent animal studies provide strong evidence that mesenchymal stem cell–derived extracellular vesicles (MSC-EVs) can attenuate particle-induced periprosthetic osteolysis. Li et al. [14] demonstrated that extracellular vesicles derived from human urine stem cells (USC-EVs) significantly reduced polyethylene particle–induced osteolysis in murine calvarial models. USC- EVs not only suppressed macrophage-mediated inflammation and osteoclastogenesis but also promoted osteoblast differentiation and new bone formation, suggesting a preventive and regenerative effect.

Complementary findings were reported by Xie et al. [15], who engineered human umbilical cord MSC-derived EVs encapsulated in poly(lactic-co-glycolic acid) (PLGA) nanoparticles. In a similar murine osteolysis model, PLGA-EVs provided sustained anti- inflammatory and anti-osteoclastic effects, markedly reducing bone resorption and osteoclast numbers compared with controls. The nanoparticle system enhanced EV stability and enabled prolonged release, indicating potential for long-term suppression of progressive osteolysis.

Together, these studies underline the therapeutic promise of MSC-based vesicles in mitigating wear particle–induced osteolysis *in vivo*, with USC-EVs showing early preventive and osteogenic potential, while PLGA-EVs offer durable anti-resorptive effects.

DISCUSSION

Mesenchymal stem cells (MSCs) have demonstrated considerable promise in preventing osteolysis following total hip arthroplasty (THA), largely due to their dual ability to modulate inflammation and stimulate osteogenesis. Wear particle–induced osteolysis is primarily driven by macrophage activation and subsequent osteoclastogenesis, leading

to progressive bone loss and implant loosening [4, 5]. Experimental findings consistently show that MSCs are able to counteract these processes by promoting macrophage polarization toward the M2 anti-inflammatory phenotype and releasing soluble mediators such as IL-10, TGF-β, and prostaglandins, which dampen local inflammation [7, 12, 17, 18]. In parallel, MSCs contribute to bone regeneration through osteoblast differentiation and secretion of pro-osteogenic growth factors, thereby restoring the balance between bone resorption and deposition [7, 12, 19]. These characteristics support the potential of MSCs as an adjuvant therapy after THA, aimed at reducing the risk of implant loosening and prolonging prosthesis longevity. In particular, the application of MSC-derived extracellular vesicles has shown efficacy in both *in vitro* and *in vivo* models: USC-EVs have demonstrated strong preventive and osteogenic effects [14], while PLGA-engineered hUCMSC-EVs offer sustained protection against particle-induced osteolysis and inhibition of osteoclastogenesis [15]. Such results highlight their translational value as biologic adjuncts to current surgical and pharmacologic strategies. Nevertheless, several challenges remain before clinical translation.

First, there is no consensus regarding standardization of MSC dose, preparation, and delivery method, which complicates reproducibility across studies and settings [13]. Second, the long-term safety profile of MSC therapy is not yet fully understood, particularly in relation to potential immune reactions, tumorigenicity, or adverse effects of biomaterial carriers [20, 21]. Finally, while preclinical evidence is strong, clinical evidence remains limited: most findings are derived from small-scale or animal studies, and robust randomized controlled trials in humans are lacking [2, 6]. Thus, while MSC-based therapies present an exciting biologic alternative for mitigating periprosthetic osteolysis, future research should aim to optimize delivery platforms, establish safe and effective dosing protocols, and conduct large-scale clinical trials to validate their role as a standard adjunctive therapy in THA.

CONCLUSIONS

Mesenchymal stem cells (MSCs) show significant potential in preventing osteolysis following total hip arthroplasty (THA) through their dual anti-inflammatory and osteogenic effects. By modulating macrophage polarization from the pro-inflammatory M1 to the anti- inflammatory M2 phenotype, MSCs effectively suppress the cytokine-driven osteoclast activation that underlies bone resorption. Concurrently, MSCs promote osteoblast differentiation and bone matrix deposition, thereby restoring balance within the bone remodeling microenvironment. Experimental evidence from *in vitro* and *in vivo* models supports MSCs' ability to mitigate wear particle–induced inflammation, inhibit osteoclastogenesis, and enhance new bone formation around the prosthetic interface. These findings collectively highlight MSC-based therapy as a promising biologic strategy to address one of the most persistent complications in long-term THA outcomes, periprosthetic osteolysis, offering a regenerative and immunomodulatory alternative to conventional management approaches.

While preclinical studies have provided encouraging evidence of mesenchymal stem cells (MSCs) in preventing wear-particle–induced osteolysis, most findings to date are derived from *in vitro* experiments and *in vivo* models in mice. Although these studies have clarified the cellular mechanisms, such as macrophage modulation, osteoblast differentiation, and suppression of osteoclast activity, their translation into human applications remains uncertain due to differences in immune response, bone remodeling dynamics, and implant biomechanics between species. Therefore, large-scale and well-designed clinical trials are essential to validate the safety, efficacy, and long-term outcomes of MSC-based therapy in humans. Such evidence is necessary before MSCs can be routinely implemented as a standard preventive or therapeutic strategy for periprosthetic osteolysis following total hip replacement.

Looking ahead, mesenchymal stem cell–based therapies hold great promise as a regenerative and immunomodulatory strategy to prevent or even reverse periprosthetic osteolysis. Future research should focus on optimizing delivery methods, enhancing MSC survival and integration within the periprosthetic environment, and clarifying the molecular mechanisms underlying their interaction with immune and bone cells. With further preclinical and clinical validation, MSCs could redefine the standard of care in preserving implant longevity and bone health following total hip replacement.

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