



Stem Cell-Based Regenerative Therapy for Early-Onset Osteoarthritis

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ABSTRACT

Early-onset osteoarthritis (OA) is increasingly recognized in adolescents and young adults, particularly among individuals with prior joint injury or genetic susceptibility. Conventional management strategies such as physical therapy, anti-inflammatory medications, and joint replacement primarily provide symptom relief but do not address progressive cartilage degeneration. As a result, there is growing interest in regenerative therapies that target the underlying causes of joint damage. Stem cell-based therapy has emerged as a promising approach because of its ability to promote cartilage repair and reduce inflammation. This review examines the epidemiology and pathophysiology of early-onset osteoarthritis and explores stem cell sources, delivery methods, and recent clinical trials investigating regenerative treatment strategies. Overall, stem cell therapy may represent an important disease-modifying approach for preserving joint health in younger populations.

Keywords: Osteoarthritis, Early-onset osteoarthritis, Stem cells, Regenerative medicine, Mesenchymal stem cells

INTRODUCTION

Osteoarthritis, also referred to as OA, is the most common type of arthritis. It is estimated that 1 in 4 people develop symptomatic OA in their lifetime (Murphy *et al.*, 2010). OA results from an intricate interaction of regional and systemic factors (Loeser *et al.*, 2012). As a chronic joint disease, it has traditionally been viewed in middle-aged and older adults, but recent studies indicate that adolescents, especially those with a history of injury or repetitive joint stress, are increasingly diagnosed with early-onset OA (Glyn-Jones *et al.*, 2015; Abramoff and Caldera, 2014; Safiri *et al.*, 2020).

In this population, osteoarthritis can be disruptive to sports participation, school activities, and everyday living. A large epidemiological study estimates that approximately 305 per 100,000 individuals under the age of 18 are diagnosed with some form of arthritis, although the proportion specifically attributed to osteoarthritis is considerably smaller (Thierry *et al.*, 2023).



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Current management of early-onset osteoarthritis includes pharmacological therapy, physical therapy, injections, and joint replacement (Mayo Clinic, 2024). However, long-term outcomes remain concerning, as studies report that over half of patients who undergo joint replacement develop severe disease within four years, highlighting the limitations of standard treatment approaches (Evans *et al.*, 2018). These shortcomings emphasize that conventional therapies often fail to address the underlying progression of osteoarthritis. As a result, there is an urgent need for more effective treatments, such as stem cell therapy, which not only relieves symptoms but also aims to target the root causes of cartilage degeneration.

Stem cell-based therapy has emerged as a promising regenerative approach by supporting cartilage repair and modulating inflammation (Barry and Murphy, 2013). Various cell sources, including autologous bone marrow-derived and adipose-derived stem cells, as well as delivery methods such as injection and scaffold-based implantation, are currently under investigation (Makris *et al.*, 2015). Early clinical studies report improvements in pain, mobility, and inflammatory markers, suggesting that stem cell therapy may influence long-term disease progression rather than only providing short-term relief (ClinicalTrials.gov, 2024).

This review will discuss the epidemiology and pathophysiology of early-onset osteoarthritis in adolescents, examine stem cell sources and delivery methods, evaluate recent clinical trial findings, and explore future directions for regenerative treatment. Overall, the evidence highlights the growing potential

of stem cell therapy as a disease-modifying strategy for osteoarthritis.

Early-onset OA

Early-onset osteoarthritis challenges the traditional perception that OA is exclusively an age-related condition and demonstrates how joint degeneration can begin much earlier in life. Early-onset osteoarthritis develops in adolescents and is often associated with genetic predisposition or joint injuries resulting from repetitive mechanical stress. Although osteoarthritis is commonly linked to aging and long-term wear and tear, younger individuals can also experience early cartilage deterioration.

Early-onset osteoarthritis can arise from several additional risk factors, including obesity, joint malalignment, labral tears, and prior trauma. These conditions contribute to cartilage breakdown within the joint, leading to swelling and inflammation (National Library of Medicine, 2023). This inflammatory response is driven by pro-inflammatory cytokines, particularly tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6). These cytokines accelerate cartilage degradation by promoting chondrocyte apoptosis and matrix breakdown, creating a joint environment that limits natural tissue repair (Kapoor *et al.*, 2011; Tanaka *et al.*, 2014; Wojdasiewicz *et al.*, 2014). Although early-onset OA affects younger individuals, its prevalence still increases with age.

As illustrated in Figure 1, early-onset osteoarthritis does not result from a single cause but rather from the interaction of mechanical stress, metabolic factors, and inherited susceptibility, which together accelerate cartilage breakdown at a younger age.

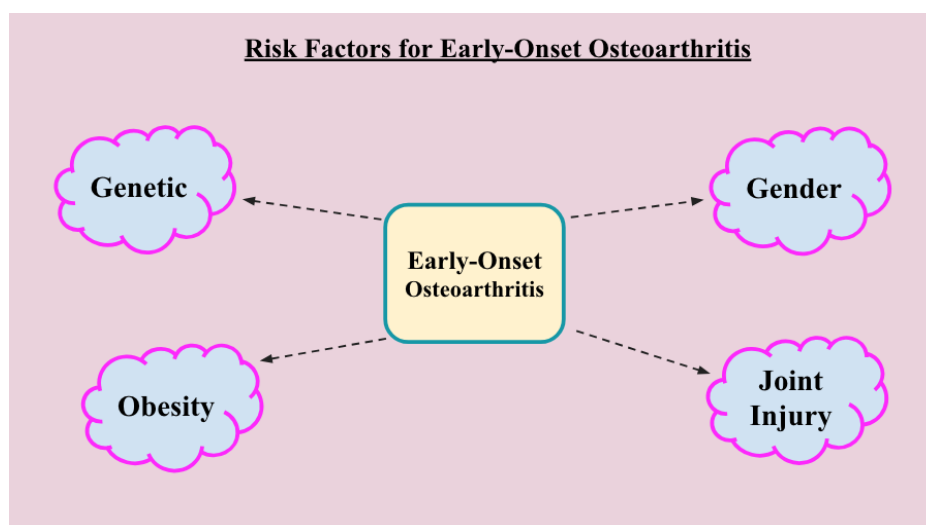


Figure 1. Risk factors associated with early-onset osteoarthritis

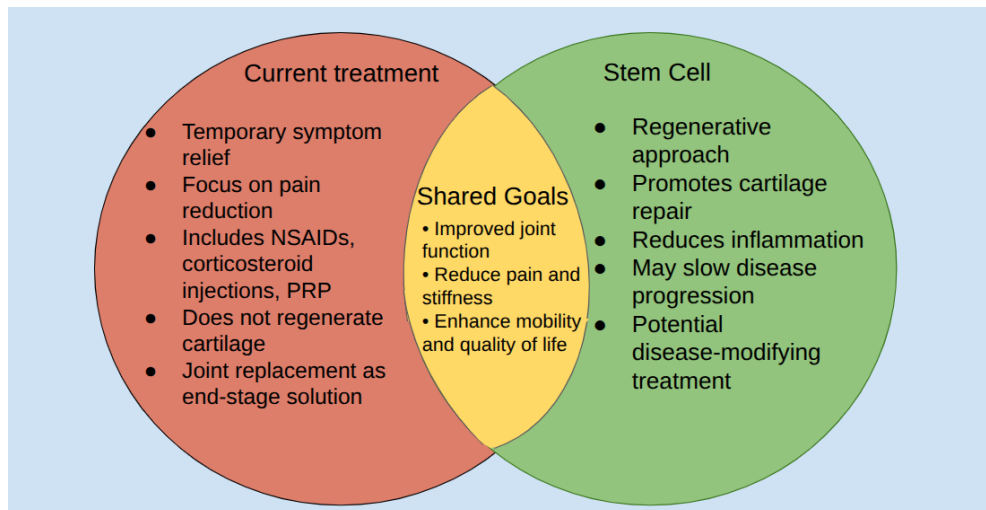


Figure 2. Comparison of conventional osteoarthritis treatments and stem cell-based regenerative therapy.

Common symptoms include knee pain, instability, and swelling, which may worsen with increased body weight (Hunter and Felson, 2006; Loeser, 2017). Globally, early-onset OA is becoming more prevalent, with over half of newly diagnosed OA cases occurring in individuals under the age of 55 (Safiri *et al.*, 2020). This rise parallels increasing rates of obesity and sports-related joint injuries, suggesting that the incidence of early-onset OA is likely to continue growing proportionally (Vos *et al.*, 2017).

Stem cell therapy

As the limitations of conventional osteoarthritis treatments become more evident, regenerative therapies have gained attention for their potential to address cartilage damage at its source. Current management strategies range from lifestyle modifications and physical therapy to platelet-rich plasma (PRP) injections and joint replacement surgery (Campbell *et al.*, 2015). While these approaches may relieve pain and improve function, they do not restore damaged cartilage. In contrast, stem cell therapy represents a regenerative treatment strategy that aims to reduce inflammation while promoting tissue repair (Wang *et al.*, 2023).

Conventional osteoarthritis treatments primarily focus on symptom management through anti-inflammatory medications, corticosteroid injections, platelet-rich plasma (PRP), and joint replacement surgery. In contrast, stem cell therapy represents a regenerative approach that promotes cartilage repair, reduces inflammation, and may slow disease progression. Stem cells are unique because of their ability to self-renew and differentiate into specialized cell types.

Through differentiation, stem cells can become cells involved in tissue repair and regeneration, and they are naturally found in various tissues throughout the body (Caplan, 2017). In osteoarthritis treatment, stem cell therapy is used to repair and replace damaged cartilage within affected joints, targeting the underlying tissue degeneration that contributes to inflammation and pain (Barry, 2007).

Cell sources

The therapeutic effectiveness of stem cell treatment for osteoarthritis is strongly influenced by the origin of the stem cells used. Rather than serving interchangeable roles, different stem cell sources vary in regenerative potential, accessibility, and immune behavior, making source selection clinically significant for early-onset osteoarthritis. Stem cells can be obtained from multiple tissues, but the primary cells used in this therapy are mesenchymal stem cells (MSCs), which are commonly derived from bone marrow and adipose tissue (Pittenger *et al.*, 1999). Each MSC source presents distinct advantages and limitations that influence both clinical feasibility and long-term joint preservation. Studies report that adipose tissue can yield up to 100–500 times more MSCs per gram than bone marrow while maintaining similar differentiation potential, making it an efficient and scalable source for clinical use (Fraser *et al.*, 2006).

The left chart shows the distribution of clinical trials by study phase, while the right chart illustrates the proportion of stem cell sources used in these trials, including adipose-derived, bone marrow-derived, and umbilical cord-derived mesenchymal stem cells.

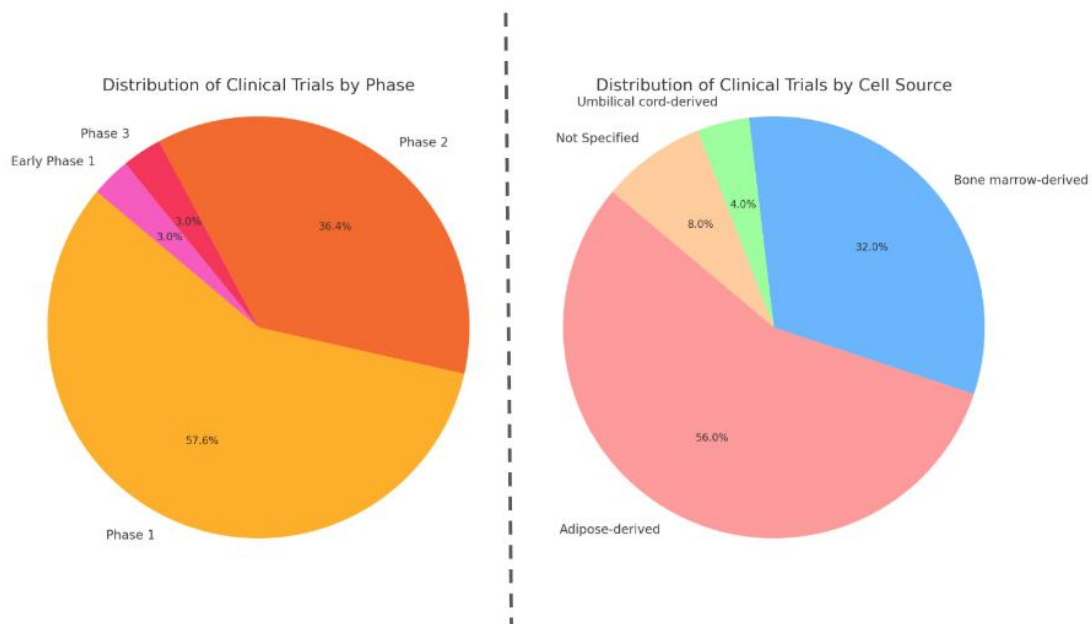


Figure 3. Distribution of clinical trials investigating stem cell therapy for osteoarthritis.

Stem cell therapy for osteoarthritis mainly utilizes MSCs because of their ability to differentiate into cartilage, bone, and fat cells. The three most commonly studied sources are bone marrow-derived MSCs, adipose-derived MSCs, and umbilical cord-derived MSCs. Bone marrow-derived MSCs demonstrate strong regenerative potential but require invasive harvesting procedures, whereas adipose-derived MSCs can be collected more easily and in larger quantities. (Fraser *et al.*, 2006). This contrast illustrates a trade-off between regenerative potency and procedural invasiveness, which is especially relevant when treating adolescent patients. Umbilical cord-derived MSCs are a newer and increasingly promising source due to their youthful and immune-privileged properties, which reduce rejection risk and may enhance cartilage regeneration (Wang *et al.*, 2020). Bone marrow-derived MSCs are often favored for their strong chondrogenic differentiation, adipose-derived MSCs for their abundance and ease of collection, and umbilical cord-derived MSCs for their enhanced proliferative capacity and reduced immunogenicity. (Wang *et al.*, 2020)

Despite differences in harvesting methods and cellular characteristics, all three MSC sources demonstrate comparable therapeutic potential when appropriately applied. A recent review confirmed that MSCs from these sources can improve pain, stiffness, and cartilage thickness in osteoarthritic joints, making them particularly suitable for early-onset cases where joint

preservation is preferred over replacement. Clinical studies investigating these MSC sources have been conducted internationally, including in the United States, South Korea, and Iran, reflecting growing global interest in regenerative approaches for osteoarthritis. (Pas *et al.*, 2023).

Delivery

Beyond stem cell selection, the method by which these cells are delivered to the joint plays a critical role in treatment success. Intra-articular injection, which introduces a concentrated dose of stem cells directly into the joint space, is the most widely used technique in stem cell therapy. This minimally invasive approach allows cells to localize to injured cartilage, reduce inflammation, and initiate tissue repair (ClinicalTrials.gov, 2024). To further enhance cartilage regeneration, some experimental approaches use scaffold-based implantation, in which stem cells are combined with biomaterials such as collagen or hyaluronic acid gels before being surgically placed into the joint. For more severe structural injuries or deeper cartilage lesions, advanced techniques such as chondrocyte pellet cultures and arthroscopic implantation are also under investigation (Madry *et al.*, 2010).

Due to its repeatability, safety profile, and relatively short recovery time, injection-based therapy remains the most commonly applied delivery method for early-onset osteoarthritis (Makris *et al.*, 2015).

Advantages and disadvantages

Evaluating stem cell therapy requires examining both its regenerative benefits and the practical challenges that limit widespread clinical adoption. The primary advantage of stem cell treatment lies in its regenerative capacity. By restoring cartilage and improving joint structure, stem cells address the underlying causes of osteoarthritis, in contrast to conventional therapies such as pain relievers, corticosteroid injections, or joint replacement surgery. Clinical studies report measurable improvements in WOMAC, VAS, and SF-36 scores, indicating enhanced mobility and reduced pain (Vega *et al.*, 2015).

Stem cell therapy may also delay or even prevent the need for joint replacement surgery in cases of early-onset osteoarthritis. However, limitations remain, including high treatment costs, variability in outcomes depending on stem cell quality, and a lack of long-term follow-up data. Additional challenges involve the need for standardized protocols in cell preparation, dosing,

and post-treatment monitoring (ClinicalTrials.gov, 2024).

Despite these drawbacks, growing evidence supports the safety of stem cell therapy and its potential to modify disease progression rather than simply masking symptoms.

Recent Clinical Trials

Clinical trial outcomes provide essential evidence for determining whether stem cell therapy can meaningfully improve osteoarthritis progression and patient function. Of the 52 clinical trials investigating stem cell therapy for osteoarthritis conducted worldwide, seven have been completed and analyzed; these studies primarily focus on knee and hip osteoarthritis. Adipose-, bone marrow-, and umbilical cord-derived mesenchymal stem cells (MSCs) were used in these trials, most commonly delivered through intra-articular injection.

Table 1. Summary of completed clinical trials investigating stem cell therapy for osteoarthritis, including cell source, enrollment size, location, and primary outcome measures used to evaluate treatment effectiveness.

Trial Number	Cell Source	Conditions	Enrollment	Location	Primary Outcome Measures	Phase	Industry
NCT03990805	Adipose-derived	Knee Osteoarthritis, Degenerative Arthritis	260	Multiple sites in South Korea	WOMAC score, VAS score	Phase 3	Industry
NCT03818737	Adipose-derived, Bone marrow-derived, Umbilical cord-derived	Osteoarthritis	475	Multiple sites in USA	VAS-pain, KOOS-pain, KOOS-total	Phase 3	Other
NCT01626677	Umbilical cord blood-derived	Degenerative Osteoarthritis, Articular Cartilage Defect	103	Multiple sites in South Korea	IKDC, VAS, WOMAC	Phase 3	Industry
NCT01873625	Bone marrow-derived	Rheumatoid Arthritis (Knee Osteoarthritis)	60	Royan Institute, Tehran, Iran	VAS, WOMAC, MRI	Phase 2 3	Other Gov
NCT01041001	Umbilical cord blood-derived	Cartilage Injury, Osteoarthritis	104	Multiple sites in South Korea	ICRS grade, VAS, WOMAC, IKDC	Phase 3	Industry
NCT03289416	Bone marrow-derived	Knee Osteoarthritis	90	Florida, USA	WOMAC, IKDC	Phase 4	Other
NCT03467919	Adipose-derived	Knee Osteoarthritis, Knee Pain	40	Stanford University, California, USA	KOOS, Lysholm score	Phase 3	Other

Abbreviations:

WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

VAS: Visual Analog Scale

KOOS: Knee Injury and Osteoarthritis Outcome Score

IKDC: International Knee Documentation Committee (Subjective Knee Evaluation Form)

MRI: Magnetic Resonance Imaging

ICRS: International Cartilage Repair Society (Cartilage Repair Assessment Score)

Across the seven completed trials, enrollment ranged from 40 to 475 participants, including both adult and adolescent populations. Four studies (NCT01873625, NCT03818737, NCT03289416, and NCT03467919) were university- or government-sponsored Phase 2/3 to Phase 4 trials, while three were industry-funded Phase 3 trials (NCT03990805, NCT01626677, and NCT01041001).

In one of the largest studies, adipose-derived MSCs were evaluated in 260 South Korean patients (NCT03990805), demonstrating significant reductions in pain and stiffness after 24 weeks based on WOMAC and VAS scores (ClinicalTrials.gov, 2024). Another study involving adolescent participants with osteoarthritic knee injuries (NCT01873625) reported MRI-confirmed cartilage repair. (ClinicalTrials.gov, 2024) Additional Phase 3 trials, including NCT01626677 (umbilical cord-derived MSCs) and NCT03467919 (adipose-derived MSCs from Stanford University), further support the safety of stem cell therapy and its potential to improve cartilage structure and function over time. (ClinicalTrials.gov, 2024).

Collectively, these findings indicate that stem cell therapy not only provides symptomatic relief but may also contribute to structural repair and slow disease progression, highlighting its potential as a disease-modifying strategy rather than a purely palliative treatment.

Future direction

Although current findings are promising, continued research is necessary to refine stem cell therapy and expand its applicability to adolescent patients. Future research should focus on improving treatment consistency and accessibility through standardized protocols, multicenter clinical trials, and long-term studies in younger populations to better evaluate safety, cost-effectiveness, and the durability of cartilage repair. Further investigation into how age, activity level, and genetic background influence outcomes may also enable more personalized regenerative therapies. Advances in stem cell-based cartilage repair could extend beyond osteoarthritis to other degenerative and inflammatory joint conditions, broadening its overall clinical impact (Pas *et al.*, 2023; Wang *et al.*, 2020; Galipeau and Sensébé, 2018).

From a clinical and practical perspective, improving cost accessibility, regulatory standardization, and streamlined manufacturing processes will be essential for integrating stem cell therapy into routine orthopedic care. Establishing clear treatment guidelines and ensuring equitable access will ultimately determine whether these regenerative strategies can transition from experimental trials to real-world application.

CONCLUSION

Early-onset osteoarthritis represents a growing clinical concern because of its long-term impact on joint function and quality of life in adolescents. While conventional treatments primarily focus on symptom management, stem cell therapy offers a regenerative strategy that addresses both inflammation and cartilage repair. As scientific understanding and clinical research continue to advance, stem cell-based therapies may become an important approach for preserving joint health and modifying disease progression in younger populations.

Conflict of interest

The authors declare no competing interests.

Data Availability Statement: Not applicable.

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