Innovative Treatment Approaches for Knee Osteoarthritis: From Injections to Regenerative Surgery

(Review Article)

Abstract

Knee osteoarthritis (KOA) is a common degenerative joint disease that mostly impacts adults over 5 years of age. Its prevalence is considerably higher in women, individuals with excess body weight and people with prior joint trauma. Current treatment strategies primarily focus on symptom control, which underscores the urgent need for more effective and disease-modifying therapies. Recent advances in both nonsurgical and surgical modalities have introduced promising regenerative options. Therapeutic modalities notably mesenchymal stem cells (MSCs) and platelet-rich plasma (PRP) have demonstrated substantial potential in attenuating inflammatory responses and facilitating cartilage regeneration, particularly during the early pathological phases of knee osteoarthritis. Intra-articular hyaluronic acid (HA) injections provide only temporary symptomatic relief and show limited long-term efficacy. For advanced cases, surgical interventions including autologous chondrocyte implantation (ACI) and knee arthroplasty (TKA) remain viable options, with their associated risks and complications. Personalized treatment approaches based on disease severity, progression, and patient-specific factors are likely to yield optimal outcomes. Future directions in KOA management may include gene-edited MSCs, smart implants, and the integration of machine learning to enhance therapeutic precision and long-term success.

Keywords: Osteoarthritis of knee, regenerative medicine, mesenchymal stem cells, platelet-rich plasma, hyaluronic acid

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Introduction

Osteoarthritis (OA) is a disease of the joints that is very common and progresses over time, causing significant pain and functional limitations in millions of people worldwide. The articular cartilage is gradually eroded, osteophytes form, subchondral bone is remodeled, and the synovial membrane is altered due to inflammation, which are hallmark pathological features of the condition. As a heterogeneous and multifaceted disease process, OA involves all structural components of the joint and reflects a complex interplay of biomechanical, cellular, and biochemical determinants.[1] According to Cui et al. (2022), the prevalence of knee osteoarthritis in adults over 50 is estimated to range from 14% to 38% worldwide. Disease incidence increases with advancing age and shows a markedly higher frequency in women compared to men, with a prevalence ratio of approximately 1.69 .Contributing factors to this disparity include obesity (measured by body mass index, or BMI), aging, and possibly genetic predisposition, which result in variations in the incidence of the disease across different populations.[2] Knee osteoarthritis pain adversely affects patients' quality of life. It incurs substantial costs for healthcare systems through direct costs and indirect consequences, including reduced work output and early exits from the workforce.[3] Standard treatments for knee osteoarthritis (KOA) primarily aim to alleviate pain and enhance joint function, and typically encompass Physical therapy, NSAIDs, and corticosteroid injections are all part of the treatment plan. However, these treatments do not effectively prevent cartilage deterioration or repair the joint's structure.[4, 5]

Chronic administration of nonsteroidal anti-inflammatory drugs (NSAIDs) has been consistently linked to an elevated risk of gastrointestinal hemorrhage as well as a range of cardiovascular adverse events.[6, 7] Recently, advancements in regenerative medicine and surgical techniques have enabled the development of innovative therapies to alleviate symptoms and promote structural joint repair. PRP, also known as platelet-rich plasma, is a therapy that has been shown to be effective in managing pain and inflammation. However, its effectiveness can vary depending on the methods used in its preparation.[8, 9]

The exploration of mesenchymal stem cell (MSC) therapy is on the rise due to its ability to stimulate cartilage repair and enhance joint function, especially in individuals who are in moderate stages of knee osteoarthritis.[10, 11] Hyaluronic acid (HA) injections are utilized to transiently mitigate joint pain and improve functional performance; however, the clinical efficacy of these interventions is constrained by their inherently limited duration of action and rapid biodegradation within the synovial environment.[12, 13] Autologous chondrocyte implantation (ACI) is primarily employed to treating specific cartilage defects, rather than widespread Osteoarthritis, and has shown limited improvement in symptoms.[14] Total knee arthroplasty (TKA) is a viable option for severe knee osteoarthritis, offering substantial pain relief and improved function, though it carries risks of complications.[15, 16] The non-surgical innovative therapies are being assessed for their clinical outcomes and safety profiles in this review. Further research is, of course, crucial to improve these treatments and determine their long-term Effectiveness.[17]

Materials & Methods

To identify recent reviews, a comprehensive literature search was conducted in PubMed and Google Scholar and research articles on the management of KOA. Additionally, clinical trial data were extracted from ClinicalTrials.gov to support the comparative analysis. The search focused on non-surgical interventions, including PRP, MSCs, and HA, as well as surgical procedures such as ACI, and TKA.

Keywords used included: knee osteoarthritis; regenerative medicine; platelet-rich plasma; mesenchymal stem cells; hyaluronic acid; total knee arthroplasty. All duplicate records were eliminated, and predefined inclusion and exclusion criteria were applied to ensure the selection of unique, high-quality studies. Only full-text publications written in English were considered eligible for inclusion in the analysis.

Pathophysiology of Knee Osteoarthritis

KOA is driven by the combined effects of mechanical stress, inflammation, and metabolic dysregulation.[18, 19] Progressive cartilage degradation is predominantly driven by a dysregulation between anabolic and catabolic processes within the joint microenvironment. Proinflammatory cytokines such as IL-1<unk> and TNF-<unk> are responsible for this imbalance and matrix-degrading enzymes like MMP-13 and ADAMTS-5 are also elevated.[18, 21] Synovial inflammation and subchondral bone sclerosis play a critical role in joint degeneration, establishing a self-perpetuating and destructive cycle that exacerbates osteoarthritic progression.[21, 22]

Several risk factors exacerbate disease progression: Aging, which impairs chondrocyte function; obesity, which leads to excessive mechanical loading and increases inflammation from adipokines; and previous joint injuries that disrupt normal biomechanics.[23, 24] Genetic factors, such as polymorphisms in the COL2A1 gene, increase the susceptibility to cartilage damage.[25] A thorough insight into these underlying mechanisms plays a critical role in developing targeted interventions to repair structural joint damage rather than solely providing symptomatic relief.[26] Figure 1 illustrates highlights the role of some innovative treatments in cartilage repair and joint restoration.

Nonsurgical Treatment Approaches

Platelet-Rich Plasma (PRP)

PRP is an autologous blood-derived concentrate enriched with platelets. These platelets produce multiple bioactive mediators such as TGF-<unk>, VEGF, and platelet-derived growth factor (PDGF). These platelets secrete multiple bioactive mediators, such as transforming growth factor-beta (TGF-β), vascular endothelial growth factor (VEGF), and platelet-derived growth factor (PDGF).[27]These growth factors help to promote cartilage repair and maintain joint homeostasis by enhancing chondrocyte proliferation, enhancing extracellular matrix (ECM) synthesis, and providing anti-inflammatory effects.[28] A meta-analysis indicated that PRP significantly improved clinical outcomes in patients with Kallgren-Lawrence grades II to III, compared to HA injections administered over several months. PRP is most effective in the early to moderate stages of knee osteoarthritis, where cartilage damage may still be reversible.[29]

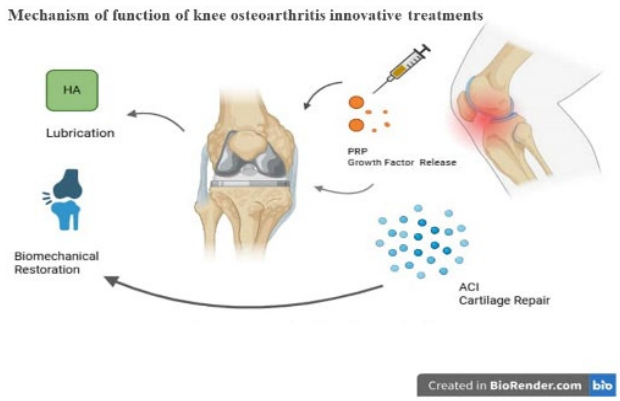

Figure 1: Mechanism of function of knee osteoarthritis innovative treatments, illustrating the roles of PRP (growth factor release), MSC (chondrocyte differentiation), ACI (hyaline cartilage formation), HA (lubrication), and TKA (joint replacement) in addressing cartilage thinning, synovial inflammation, and subchondral bone changes.

Although PRP injections are generally regarded as safe, the risks of temporary mild, pain, swelling, bruising, redness, and skin irritation at the injection site are present. Joint infections, being a dreadful side-effect may occur if sterile procedures are not followed meticulously. Rarely, allergic reactions may happen, particularly in individuals with a history of allergies to blood-derived products. Some more serious complications, such as nerve or tissue damage, may rarely happen from improper needle placement or poor injection techniques, producing numbness, weakness, or tissue damage. To minimize these potential risks, injections can be performed using image-guided techniques, with strict adherence to established protocols to ensure precise and safe administration.[30] A systematic review and meta-analysis of 26 randomized controlled trials, including a total of 1,650 knees, demonstrated that platelet-rich plasma (PRP) provides superior clinical outcomes compared to hyaluronic acid (HA) at 6- and 12-month follow-ups, as assessed by WOMAC and VAS scores. The therapeutic effect of PRP was most pronounced when platelet concentrations ranged between 750,000 and 1,250,000 platelets/μL. These findings, representing level 1 evidence, support the potential of PRP as a more effective medium-term intervention for knee osteoarthritis than HA. However, caution is warranted due to variability in PRP preparation methods, which may influence treatment efficacy.[31] Raeissadat et al. have recommended PRP as the preferred option in moderate KOA, considering its cost-effectiveness and utility.[32] A systematic review by Chahla et al.[33] examining PRP preparation protocols and composition found that only 10% of the included studies provided a comprehensive description of the preparation process, while merely 16% reported detailed information regarding the composition of the PRP. These authors concluded that lack of standardization hampers the ability to make effective comparisons between PRP products and strongly advocated the inclusion of comprehensive, step-by-step protocols in future studies. Dhurat and Sukesh, have offered valuable recommendations specifying the essential components that should be incorporated into a standardized PRP protocol.[34] A significant limitation of injection-based techniques remains the "limited duration of sufficient drug dosage within the joint" required to achieve sustained therapeutic effects. To overcome this challenge, several novel nanotechnological approaches and nanocarriers have been developed and are currently under investigation.[35]

While PRP injections can provide symptomatic relief in certain regions of the knee, their effectiveness appears reduced in areas severely impacted by medial osteoarthritis. This highlights the necessity for additional studies to better understand PRP's role in cartilage repair and to refine treatment strategies for optimal clinical outcomes in knee osteoarthritis.[36]

Mesenchymal Stem Cell (MSC) Therapy

Mesenchymal stem cells (MSCs), sourced from bone marrow, adipose tissue, and umbilical cord, exhibit potent immunomodulatory effects and possess significant anti-inflammatory and tissue-repairing capabilities.[37, 38] These cells contribute to cartilage repair by differentiating into chondrocytes, secreting trophic factors such as transforming growth factor-beta (TGF-β) and insulin-like growth factor-1 (IGF-1), and modulating the inflammatory environment through mediators like interleukin-10 (IL-10) and prostaglandin E2 (PGE2).[37, 39, 40]

Bone marrow-derived mesenchymal stem cells (BM-MSCs) have been extensively investigated due to their high proliferative capacity and their potential to differentiate into chondrogenic lineages.[40] The relative simplicity of obtaining these cells from a patient's own bone marrow renders them a more economical source compared with other MSC types. Clinical studies demonstrate that both intra-articular administration and surgical delivery of BM-MSCs result in beneficial therapeutic outcomes in individuals with KOA.[41, 42] Nonetheless, limitations include donor site discomfort, the low proportion of retrievable cells (≈0.001% of nucleated bone marrow cells), and a decline in differentiation potential with advancing donor age.[43] Performing bone marrow aspiration from the anterior or posterior iliac crest under local anesthesia, with the assistance of ultrasound or fluoroscopic guidance, significantly

improves procedural accuracy and enhances overall efficiency.[44]

A systematic review and meta-analysis comprising 15 randomized controlled trials and four observational studies, involving a total of 584 individuals with knee osteoarthritis, demonstrated significant reductions in pain (VAS) and improvements in functional outcomes (WOMAC) within 6 to 12 months post-treatment ($p < 0.001$). Importantly, the incidence of adverse events did not differ significantly between participants receiving MSC therapy and control groups ($p > 0.05$), supporting a favorable safety profile.[45, 46]

Intra-articular administration of bone marrow-derived mesenchymal stem cells (BM-MSCs) has been associated with substantial improvements in pain relief, enhanced joint function, and overall quality of life in patients with knee osteoarthritis, particularly those with Kellgren-Lawrence grade II–III disease. Optimal clinical outcomes are generally observed with a median dose of approximately 40×10^6 cells. In contrast, individuals with advanced osteoarthritis (grade IV) exhibit only limited therapeutic benefits, highlighting the influence of disease severity on treatment efficacy.[47, 48]

The findings suggest PRP may provide slightly superior short-term benefits over MSC therapy. Nevertheless, the scarcity of studies and the presence of potential biases underscore the necessity for larger, high-quality clinical trials.[49] Despite promising clinical outcomes, MSC therapy still faces challenges, including inconsistent results, variable dosing and administration methods, limited cell survival at injection sites, and the risk of heterotopic ossification. More large-scale randomized controlled trials are warranted to refine protocols and confirm long-term efficacy.[47, 48]

Hyaluronic Acid (HA) Injections

Hyaluronic acid (HA) is a naturally occurring glycosaminoglycan found in the synovial fluid of the knee, playing a crucial role in joint lubrication and the protection of cartilage against mechanical stress. In osteoarthritic knees, HA concentrations are diminished, resulting in compromised lubrication, reduced shock absorption, and consequently, increased pain and restricted joint mobility.[50, 51] Intra-articular HA injections can restore these functions and provide symptom relief for several months; however, their effectiveness is limited due to rapid degradation. Novel HA-based hydrogels with enhanced stability have been developed to improve therapeutic outcomes in slowing the progression of Osteoarthritis. Although HA is generally safe, clinical results vary, and combining HA with PRP has shown superior effects.[50] HA is produced with a high molecular weight but progressively undergoes enzymatic degradation within the joint environment, leading to a decrease in its molecular size.[52] In arthritic knees, altered regulation of hyaluronic acid (HA) synthesis, degradation, and clearance results in a concurrent reduction in both the concentration and molecular weight of HA within the synovial fluid.[53] These changes detrimentally affect the viscoelastic properties of synovial fluid, thereby increasing mechanical load on the articular cartilage and accelerating joint degeneration.[54] A systematic review on randomized controlled trials with a total of 3,851 participants relative to the therapeutic efficacy of intra-articular HA injections with placebo in patients with knee osteoarthritis concluded that in 2 to 4 weeks a more significant improvements in pain and stiffness subscales of the WOMAC was evident among HA recipients.[54] Follow-up evaluations conducted 5 to 8 weeks after the initial intervention demonstrated a significant reduction in resting pain, favoring treatment with hyaluronic acid (HA). These results indicate that intra-articular HA injections can provide effective short-term pain relief in patients with knee osteoarthritis.[54]

Surgical Treatment Approaches:

Autologous Chondrocyte Implantation (ACI)

The principle of autologous chondrocyte implantation (ACI) involves harvesting a small biopsy of healthy cartilage from the knee, expanding the isolated chondrocytes ex vivo, and subsequently re-implanting millions of cultured cells into the damaged joint surface as a graft. In 2000, ACI was not recommended for routine management of localized knee cartilage defects within the NHS due to the absence of randomized controlled trial (RCT) evidence at that time.[54] The functional units of cartilage, chondrocytes, serve a pivotal role in cartilage preservation and regeneration, and the formation of a new layer of hyaline-like cartilage to restore the joint surface is the idea behind ACI.[55] Articular cartilage is avascular and possesses a limited capacity for self-repair. While isolated cartilage loss is defined as a cartilage defect, combined cartilage and bone loss is referred to as an osteochondral defect. Over time, three major generations of ACI have been developed: The first-generation autologous chondrocyte implantation (ACI) technique involves the placement of cultured and expanded chondrocytes beneath a periosteal flap. This approach has been associated with complications such as periosteal contracture, donor site morbidity, and graft failure resulting from hypertrophy or delamination.[56, 57] A major milestone was the commercialization of Carticel® (Genzyme),

which introduced standardized protocols for chondrocyte expansion and processing.[56] Furthermore, the establishment of Good Manufacturing Practice (GMP)-compliant facilities facilitated longitudinal evaluation of repair tissue, where imaging (MRI) and histological biomarkers emerged as predictors of long-term clinical outcomes.[56, 58] Additional investigations of constituents of the extracellular matrix (ECM), including glycosaminoglycans (GAGs) and collagen, provided deeper insights into the biological processes of tissue regeneration.[59, 60]

Table 1. Summary of Key Randomized Controlled Trials on Non-Surgical and Surgical Treatments for Knee Osteoarthritis

Treatment	Number of Participants	Condition/KL	Intervention	Main Efficacy Outcomes	Safety	Follow-up	ClinicalTrials.gov ID
PRP	52	KL 1–3	3 weekly IA injections (4 mL, LP-PRP)	VAS ↓44; WOMAC 3.0; IKDC 65.5	No AEs	1 year	NCT02588872
HA	59	KL 1–3	3 weekly IA injections (2 mL HA)	VAS 57; WOMAC 4.0; IKDC 55.8	No AEs	1 year	NCT02588872
QS-TKA	45	Not specified	Quadriceps-sparing TKA	Better HSS recovery vs MIS-TKA	No AEs	6 months	NCT02160977
Allogenic MSCs	15	KOA	IA 40M donor MSCs	WOMAC −13; VAS −21; SF-12 ↑21	No serious AEs	1 year	NCT01586312
ACI-C	21	Not specified	Collagen-based ACI	KOOS +10; Lysholm +17; VAS −19	No serious AEs	2 years	NCT01458782
TKA Traditional	22	Not Specified	Traditional TKA	Similar to Min-TKA	No serious AEs	12 weeks	NCT00710840

Second-generation ACI: To overcome limitations associated with the periosteal flap, a porcine-derived type I/III collagen membrane (Chondro-Gide™, Geistlich) was introduced. This improvement enhanced surgical handling and reduced donor-site complications. Despite superior clinical outcomes, a proportion of patients continued to require secondary surgical interventions.[61, 62]

Third-generation ACI (MACI™): Matrix-assisted ACI involves embedding autologous chondrocytes within a biodegradable scaffold. This approach offers greater control over cell distribution, facilitating the repair of larger defects. It has been associated with lower graft failure rates compared with earlier generations.[63, 64]

Despite significant advancements, several challenges persist. One of the primary limitations is the propensity of chondrocytes to undergo dedifferentiation during in vitro expansion, which diminishes their ability to regenerate hyaline-like cartilage effectively.[56] Recent evidence suggests that chondrons—defined as chondrocytes together with their pericellular matrix—exhibit superior regenerative potential; however, their low yield limits widespread clinical use.[65]

Ongoing clinical research is exploring novel strategies such as spheroidal aggregates of expanded chondrocytes with their native ECM (Spherox), currently under investigation for lesions measuring 4–10 cm². Although promising, definitive data from this trial remain unavailable.[66] Although autologous chondrocyte implantation (ACI) has not yet been approved for the treatment of osteoarthritis, ongoing advancements in tissue engineering and regenerative medicine indicate its potential as an alternative to arthroplasty for managing degenerative joint diseases.[56] The gene-editing technologies such as CRISPR-Cas9 have emerged as potential adjuncts to enhance the regenerative function of chondrocytes.[67] Beyond cartilage repair, CRISPR-based approaches

may also be applied in OA to mitigate catabolic activity following cell reinsertion.[68, 69]

Total Knee Arthroplasty (TKA)

TKA is the standard surgical therapeutic intervention for patients with advanced-stage knee osteoarthritis and is considered the ultimate therapeutic option for severe joint degeneration.[70] While clinically effective in alleviating symptoms and improving joint function, TKA is associated with certain adverse events, including periprosthetic joint infection, implant loosening, and periprosthetic fractures.[71-73] Revision surgeries, often required in such cases, tend to have higher costs and suboptimal outcomes in comparison to primary procedures. Despite advancements in surgical techniques and prosthetic design, approximately 20% of patients report dissatisfaction after TKA, from residual pain, limited function, malalignment, or complications. Since predicting dissatisfaction remains challenging, combining various risk factors, may support more individualized care to improve satisfaction.[74]

Nevertheless, TKA generally yields high satisfaction rates; one study reported that 96% of patients were satisfied, and 86% would choose to undergo the procedure again, emphasizing its positive impact on quality of life.[75] Technological advancements have contributed to better outcomes. Smart knee implants equipped with sensor technologies that enable real-time monitoring of recovery and function, robot-assisted TKA and superior surgical precision and prosthetic alignment, potentially leading to better long-term results.[76, 77] TKA is also increasingly used in very elderly populations, including those aged 90 and above, such as nonagenarians and centenarians with comparable outcomes are to younger patients.[78] However, individuals with prior septic arthritis are at greater risk of complications following TKA compared to those with osteoarthritis.[79] Furthermore, the growing adoption of minimally invasive surgical techniques in TKA has been linked to reduced soft tissue trauma and faster recovery, further enhancing the appeal of this procedure.[80]

Comparative Evaluation of Non-Surgical and Surgical Treatments for Knee Osteoarthritis

A comparative assessment of various interventions for KOA, including PRP, MSCs, hyaluronic acid HA, ACI, and TKA, was performed using data extracted from ClinicalTrials.gov. The efficacy, safety, and follow-up outcomes for each treatment are summarized in Table 1, with corresponding NCT IDs provided for reference.

This comprehensive evaluation highlights the differential benefits and limitations of non-surgical versus surgical approaches, offering clinicians evidence-based insights for personalized treatment selection.

Future Directions

Innovations have the potential to improve the treatment landscape for knee osteoarthritis significantly. By standardizing PRP formulations through enhanced centrifugation protocols and the use of biomaterials, therapeutic efficacy can be increased by an impressive 15 to 20%.[81] Evidence further suggests that MSC optimization helps chondrogenic differentiation through strategies such as gene editing.[82, 83]

The combination of PRP and HA delivers impressive clinical benefits.[84] Advancements in ACI, including the development of scaffold-free platforms and three-dimensional bioprinting technologies, aim to reduce procedural costs while maintaining treatment efficacy. In the context of TKA, the implementation of sensor-equipped smart implants holds the potential to decrease the necessity for reoperation by 10 to 15 percent. This is achieved through enhanced load monitoring and the early detection of implant failure.[85] The utilization of biomarker-based precision medicine, specifically the assessment of synovial fluid indicators such as COMP and CTX-II, has the potential to enhance patient selection and optimize treatment outcomes by 20-25%.[86] Nonetheless, it is essential to conduct well-powered randomized trials to validate the sustained clinical benefits and cost-effectiveness of these emerging strategies.[87, 88] Innovative methodologies, including microRNA-based therapies and the development of engineered cartilage constructs, are currently being investigated for early intervention in disease management.[89, 90, 91] In addition, machine learning algorithms are being explored to predict individual treatment responses, offering new avenues for personalized management of knee osteoarthritis.[92]

Conclusion

While this review consolidates current knowledge and highlights the promise of emerging regenerative therapies and surgical innovations, it underscores the importance of establishing standardized protocols, extended follow-up periods, and robust clinical trials to validate the long-term clinical safety and effectiveness of these treatments. The integration of patient-centered outcomes and economic evaluations will be equally important to ensure that these advancements translate into meaningful improvements in patient care and accessibility.

Addressing these limitations will lay the foundation for further personalized and effective management strategies for knee osteoarthritis.

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Conflict of interest

The authors declare that they have no conflicts of interest.

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