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Regenerative Therapy in Degenerative Joint Disease

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Abstract

Introduction: *Degenerative joint disease is a major cause of disability and functional limitation, particularly in the elderly, and conventional treatments are often limited to symptomatic relief without addressing structural degeneration.* ***Objective:*** *This study aims to review the mechanisms of action and clinical effectiveness of regenerative therapies in the management of degenerative joint disease.* ***Method:*** *A literature review was conducted by analyzing relevant scientific articles, including clinical trials, systematic reviews, and experimental studies focusing on platelet-rich plasma, mesenchymal stem cells, prolotherapy, and regenerative hydrogels.* ***Result and Discussion:*** *Regenerative therapies show the ability to reduce pain, improve joint function, and support tissue repair through biological mechanisms such as anti-inflammatory effects, cell proliferation, and extracellular matrix regeneration. Platelet-rich plasma shows consistent benefits in early-stage disease, while mesenchymal stem cells offer potential for long-term structural regeneration. Prolotherapy provides a simple and cost-effective alternative, and hydrogels enhance therapeutic delivery and tissue support, especially in combination therapies. However, variability in protocols and limited long-term evidence remain key challenges.* ***Conclusions:*** *Regenerative therapy represents a promising approach for degenerative joint disease management, but further standardized and long-term studies are required to optimize clinical application and ensure safety and effectiveness.*

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Introduction

Degenerative joint disease (DJD), also known as osteoarthritis, is a chronic disorder of the musculoskeletal system characterized by the progressive degradation of articular cartilage, synovial inflammation, and structural alterations in the subchondral bone. This condition represents one of the leading causes of chronic pain and physical disability worldwide, particularly among the elderly population. Epidemiological data show that the prevalence of DJD ranges from 10% to 18% in individuals over the age of 60, showing its substantial public health burden (Allen *et al*., 2022; Yao *et al*., 2023). The disease not only affects mobility but also significantly impairs daily functioning and independence. DJD has become a major contributor to reduced quality of life and increased healthcare utilization globally.

Multiple risk factors contribute to the onset and progression of degenerative joint disease, including aging, obesity, joint trauma, and repetitive mechanical stress. These factors accelerate cartilage degradation and exacerbate joint inflammation, leading to worsening clinical symptoms such as persistent pain, stiffness, and limited range of motion. In addition, metabolic and genetic predispositions may further influence disease susceptibility and severity. The cumulative effect of these risk factors results in a progressive decline in joint function, often requiring long-term management strategies. Consequently, DJD imposes a significant socioeconomic burden due to loss of productivity and increased medical costs (Yunus *et al*., 2020).

Conventional treatment approaches for DJD primarily focus on symptom management rather than addressing the underlying structural damage. Nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroid injections, and surgical interventions such as joint replacement are commonly employed to alleviate pain and improve function. However, these therapies are often associated with limitations, including side effects, temporary relief, and invasive procedures. Importantly, they do not effectively halt or reverse the degenerative process of joint tissues. This limitation has driven the search for more advanced therapeutic strategies that aim to restore tissue integrity and function (Shaik *et al*., 2023).

In recent years, advances in regenerative medicine have introduced promising alternatives for the management of degenerative joint disease. Regenerative therapies aim to stimulate the repair and regeneration of damaged tissues through biological and cellular mechanisms. Emerging modalities such as platelet-rich plasma (PRP), mesenchymal stem cells (MSCs), prolotherapy, and injectable hydrogels have gained increasing attention in both preclinical and clinical research. These approaches have showed potential in modulating the joint microenvironment, reducing inflammation, and promoting cartilage regeneration. Regenerative medicine is increasingly viewed as a transformative approach in musculoskeletal therapy (Kalairaj *et al*., 2024; Prodromidis *et al*., 2022).

Despite their potential benefits, the clinical implementation of regenerative therapies faces several challenges. One major issue is the heterogeneity of treatment protocols, including variations in preparation methods, dosage, and administration techniques. Additionally, the high cost of these therapies may limit their accessibility, particularly in low and middle-income settings. Another critical concern is the lack of robust long-term evidence regarding their safety and efficacy, which remains a barrier to widespread adoption. The complex biological mechanisms underlying these therapies, including their interactions with the immune system, require further investigation to ensure optimal outcomes (Simental-Mendía *et al*., 2023).

This literature review aims to analyze the mechanisms of action, clinical effectiveness, and implementation challenges of regenerative therapies in the management of degenerative joint disease. By integrating findings from recent preclinical and clinical studies, this review seeks to provide a comprehensive understanding of current therapeutic advancements. It also intends to support healthcare professionals in making evidence-based decisions regarding treatment selection. Moreover, this study shows the need for further research to optimize therapeutic protocols and validate long-term safety and efficacy. Ultimately, the development of effective regenerative strategies may offer a paradigm shift in the treatment of degenerative joint disease.

Method

This study employed a literature review design to synthesize current evidence regarding the mechanisms of action and clinical effectiveness of regenerative therapies in degenerative joint disease (DJD). Relevant articles were identified through a comprehensive search of scientific databases, focusing on peer-reviewed journals that discussed platelet-rich plasma (PRP), mesenchymal stem cells (MSCs), prolotherapy, and regenerative hydrogels. The inclusion criteria comprised original research articles, clinical trials, systematic reviews, and meta-analyses published in recent years, as well as foundational studies relevant to regenerative medicine. Articles were selected based on their relevance to the mechanisms of tissue repair, anti-inflammatory effects, and clinical outcomes such as pain reduction, functional improvement, and structural regeneration. The collected literature was analyzed using a narrative synthesis approach to compare and integrate findings across different regenerative modalities. Data extraction focused on mechanisms of action, therapeutic protocols, clinical outcomes, advantages, and limitations of each intervention. The review also considered variations in study design, patient characteristics, and treatment parameters that may influence therapeutic effectiveness. Both preclinical and clinical studies were included to provide a holistic understanding of regenerative therapies, including emerging approaches such as hydrogel-based delivery systems and combination therapies. The findings were then organized into thematic sections to highlight the comparative effectiveness and challenges of each modality, ultimately providing a structured and critical overview to support clinical decision-making and identify directions for future research.

Result and Discussion

1. Result

Mechanisms of Action of Regenerative Therapy in Degenerative Joint Disease

Degenerative joint disease (DJD) involves multifactorial damage to articular cartilage, chronic synovial inflammation, and an imbalance in subchondral bone remodeling. These pathological processes interact in a complex manner, leading to progressive joint degeneration and functional impairment. Regenerative therapy is a field of medicine that aims to restore or replace damaged cells, tissues, or organs in order to reestablish normal physiological function. This approach emphasizes biological repair rather than merely alleviating symptoms. Regenerative medicine focuses on the repair, replacement, and growth of cells, tissues, and organs tailored to individual patient needs. Such personalized strategies are expected to provide more sustainable therapeutic outcomes compared to conventional treatments (Lhee *et al*., 2025; Ip *et al*., 2020).

Platelet-Rich Plasma (PRP)

Platelet-rich plasma (PRP) is an autologous biological product derived from the patient's own blood through centrifugation to increase platelet concentration above baseline levels. Platelets in PRP contain numerous growth factors, including platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF-β), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), and insulin-like growth factor (IGF-1), all of which play essential roles in tissue healing and regeneration. Upon activation, platelets release cytokines and growth factors that stimulate cell proliferation, extracellular matrix synthesis, angiogenesis, and the migration of progenitor cells to sites of tissue injury. These biological activities make PRP a promising modality for regenerative applications. Furthermore, PRP is considered relatively safe due to its autologous nature, minimizing the risk of immunogenic reactions (Lhee *et al*., 2025; Simental-Mendía *et al*., 2023; Ip *et al*., 2020; Prodromidis *et al*., 2022).

In the management of degenerative joint diseases such as osteoarthritis, PRP is administered via intra-articular injection to improve the joint microenvironment. It helps suppress inflammatory responses while promoting the synthesis of proteoglycans and type II collagen by chondrocytes. The anti-inflammatory effects of PRP are also associated with reduced expression of proinflammatory mediators such as interleukin-1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-α). These mechanisms contribute to both symptomatic relief and potential structural improvement in joint tissues. PRP is increasingly utilized as a minimally invasive therapeutic option in clinical practice (Prodromidis *et al*., 2022).

Several clinical trials and systematic reviews have demonstrated that PRP can significantly improve pain and joint function, particularly in patients with mild to moderate knee osteoarthritis. Evidence suggests that PRP may offer superior outcomes compared to conventional intra-articular therapies. For instance, a meta-analysis by Dai *et al*. (2017) reported that PRP was more effective than hyaluronic acid in reducing pain and improving joint function for up to 12 months following treatment. These findings highlight the therapeutic potential of PRP in delaying disease progression and improving patient quality of life. However, variability in study outcomes shows the need for further standardized research (Lhee *et al*., 2025; Simental-Mendía *et al*., 2023; Ip *et al*., 2020; Prodromidis *et al*., 2022; West *et al*., 2020).

Despite its advantages, the effectiveness of PRP is influenced by several factors, including preparation methods (single-spin versus double-spin techniques), platelet concentration, leukocyte content (leukocyte-rich versus leukocyte-poor PRP), injection volume, frequency of administration, and patient-specific clinical conditions. The lack of standardized protocols and heterogeneity in study designs remain major barriers to its widespread clinical application. Additionally, while PRP is generally well tolerated, some patients may experience mild adverse effects such as temporary local pain and post-injection swelling. Serious complications, however, are rarely reported. Therefore, optimizing preparation and administration protocols is essential for maximizing therapeutic efficacy (Wee *et al*., 2021).

With its significant regenerative potential and relatively low risk profile, PRP represents a promising therapeutic modality for the management of degenerative joint disease. Nevertheless, high-quality clinical studies with standardized methodologies and longer follow-up durations are required to strengthen the evidence base. Such studies are crucial for establishing the long-term safety and effectiveness of PRP therapy. Ultimately, consistent clinical guidelines will be necessary to support its broader implementation in

routine practice (Lhee *et al*., 2025; Simental-Mendía *et al*., 2023; Ip *et al*., 2020; Prodromidis *et al*., 2022).

From an evidence hierarchy perspective, PRP currently has one of the strongest levels of clinical evidence among regenerative therapies for DJD, as it is supported by multiple randomized controlled trials and meta-analyses. However, despite this relatively strong evidence base, heterogeneity in preparation methods and study protocols reduces the overall consistency of findings. This shows that while PRP is clinically promising, its effectiveness is still influenced by methodological variability rather than purely biological limitations.

Mesenchymal Stem Cells (MSCs)

Stem cells are progenitor cells with the ability to self-renew and differentiate into various cell types, including chondrocytes, which are essential for cartilage regeneration. In the regenerative therapy for degenerative joint disease, the most commonly utilized stem cells are mesenchymal stem cells (MSCs). These cells can be derived from multiple sources, such as bone marrow (bone marrow-derived MSCs), adipose tissue (adipose-derived MSCs), and umbilical cord tissue (umbilical cord-derived MSCs). MSCs possess immunomodulatory properties and secrete a wide range of bioactive factors that support tissue repair and regeneration. These characteristics make them highly attractive for therapeutic applications in musculoskeletal disorders (Lhee *et al*., 2025; Ip *et al*., 2020; Ossendorff *et al*., 2022; Sahin and Yesil, 2023).

The primary mechanisms of action of MSCs in osteoarthritis extend beyond direct differentiation into target cells such as chondrocytes. A significant portion of their therapeutic effect is mediated through paracrine signaling, involving the release of cytokines and growth factors that reduce inflammation, inhibit chondrocyte apoptosis, and stimulate cartilage matrix regeneration. These effects contribute to the restoration of joint homeostasis and may slow or even reverse degenerative processes. Additionally, MSCs interact with immune cells, further enhancing their anti-inflammatory and regenerative capabilities. This multifaceted mechanism underscores their potential as a disease-modifying therapy (Lhee *et al*., 2025; Ip *et al*., 2020; Ossendorff *et al*., 2022; Sahin and Yesil, 2023).

Various clinical studies have evaluated the use of MSCs for knee osteoarthritis. In a phase I/II clinical trial conducted by Jo *et al*. (2014), intra-articular injection of adipose-derived MSCs resulted in significant improvements in pain, joint function, and cartilage thickness as assessed by magnetic resonance imaging (MRI). Other clinical trials have also showed sustained clinical improvements lasting up to 12-24 months following treatment. However, variability in outcomes across studies remains a challenge, largely due to differences in cell sources, dosages, injection techniques, and patient characteristics. These inconsistencies show the need for standardized clinical protocols (Lhee *et al*., 2025; Ip *et al*., 2020; Ossendorff *et al*., 2022; Sahin and Yesil, 2023).

The main limitations of stem cell therapy include high costs, limited availability of facilities that meet good manufacturing practice (GMP) standards, and strict regulatory requirements, as these therapies fall under advanced cell and gene therapy categories. Although most studies report favorable short-term safety profiles, long-term safety data are still lacking. Potential risks, such as cellular transformation or immune reactions, require further investigation. Addressing these concerns is essential for ensuring the safe integration of MSC therapy into clinical practice (Lhee *et al*., 2025; Ip *et al*., 2020; Ossendorff *et al*., 2022; Sahin and Yesil, 2023).

In terms of evidence quality, MSC therapy is primarily supported by early-phase clinical trials (phase I/II) and a limited number of controlled studies, showing a moderate level of evidence. While the biological rationale is strong and supported by preclinical data, the lack of large-scale randomized controlled trials limits the generalizability of findings. Therefore, compared to PRP, MSC therapy shows higher regenerative potential but weaker clinical evidence due to limited standardization and smaller study populations.

Prolotherapy

Prolotherapy is a therapeutic approach that involves the injection of irritant solutions into or around joints, ligaments, and tendons to stimulate a healing response through mild, controlled inflammation. The most commonly used solution is hypertonic dextrose, although other agents such as phenol-glycerin-glucose (P2G) and zinc sulfate have also been investigated. Prolotherapy is believed to work by inducing micro-injury that stimulates fibroblast activity, collagen deposition, and strengthening of connective tissues. This regenerative response enhances the structural integrity of joint-supporting tissues. Consequently, prolotherapy may contribute to improved joint stability and function (Cortez *et al*., 2022; Waluyo *et al*., 2023; Wee *et al*., 2021).

In the degenerative joint diseases such as osteoarthritis, prolotherapy is expected to improve joint stability, reduce nociceptive irritation, and ultimately decrease pain perception while enhancing functional outcomes. Although research on prolotherapy is not as extensive as that on PRP or stem cell therapy, several studies have evaluated its effectiveness. In a study by Rabago *et al*. (2013), patients with knee osteoarthritis who received multiple prolotherapy injections demonstrated significant reductions in pain scores and improvements in physical function compared to control groups receiving expectant care or home exercise programs. These findings suggest that prolotherapy may offer a viable alternative for certain patient populations (West *et al*., 2020; Cortez *et al*., 2022).

The primary advantages of prolotherapy include its relatively low cost, simple injection technique, and minimal risk of adverse effects. Reported side effects are generally mild and include temporary local pain, slight swelling, and post-injection stiffness. However, the long-term effectiveness of prolotherapy and its impact on structural cartilage regeneration remain unclear. Variability in solution concentrations, injection techniques, and treatment frequency further complicates the interpretation of study outcomes. These limitations show the need for standardized methodologies in future research (Cortez *et al*., 2022; Waluyo *et al*., 2023; Wee *et al*., 2021).

Nevertheless, prolotherapy remains an attractive option, particularly for patients with limited access to more advanced and costly regenerative therapies. Its simplicity and affordability make it accessible in a wider range of clinical settings. To strengthen its scientific evidence and clinical validity, more randomized controlled trials with appropriate comparison groups and objective evaluation parameters such as imaging and inflammatory biomarkers are required. Such efforts will help clarify its role in the management of degenerative joint disease (Cortez *et al*., 2022; Waluyo *et al*., 2023; Wee *et al*., 2021).

From an evidence standpoint, prolotherapy is supported mainly by small clinical trials and comparative studies, with limited systematic reviews and no strong meta-analytic consensus. This places prolotherapy at a relatively lower level of evidence compared to PRP and MSC therapy. While its clinical benefits are observable, the lack

of standardized protocols and high-quality randomized trials reduces confidence in its long-term effectiveness.

Regenerative Hydrogels

Injectable hydrogels offer an innovative solution for the treatment of degenerative joint diseases, including osteoarthritis (OA) and degenerative disc disease (DDD), by enabling controlled therapeutic delivery directly to affected areas. Unlike oral medications or systemic injections that often distribute widely throughout the body, hydrogels enhance drug bioavailability within the joint, prolong drug retention time, and reduce systemic side effects. They also allow for sustained drug release, minimizing the need for frequent injections and thereby improving patient compliance. In the context of DDD, hyaluronic acid-based regenerative gels have shown promise by providing cushioning and shock absorption within degenerated intervertebral discs (Trivedi *et al*., 2022; Kalairaj *et al*., 2024).

Beyond drug delivery, hydrogels play a essential role in cartilage tissue regeneration. In osteoarthritis, hydrogels can be engineered to mimic the natural extracellular matrix, thereby supporting the adhesion, proliferation, and differentiation of mesenchymal stem cells into chondrocytes. This capability enables hydrogels to contribute not only to inflammation reduction but also to structural tissue repair. In degenerative disc disease, their mechanism involves cellular infiltration, where cells penetrate the hydrogel matrix, enhancing its integration with surrounding tissues. Such integration is essential for long-term therapeutic effectiveness, as it allows the hydrogel to function as a supportive scaffold for tissue regeneration (Trivedi *et al*., 2022; Kalairaj *et al*., 2024).

Then, another advantage of injectable hydrogels is their adaptability to specific patient needs through various physical and chemical crosslinking methods. These modifications allow hydrogels to achieve mechanical properties suitable for joint or disc environments, such as sufficient strength to withstand pressure while maintaining flexibility. Some hydrogels also exhibit self-healing and shear-thinning properties, enabling them to conform to irregular joint spaces and provide more comprehensive therapeutic coverage. Preclinical studies using animal models have showed their effectiveness in preventing disc height loss and maintaining structural integrity in cases of DDD. These findings provide a strong foundation for future clinical applications (Trivedi *et al*., 2022; Kalairaj *et al*., 2024).

Combination therapies involving hydrogels and PRP are also being explored to enhance therapeutic outcomes. PRP contributes concentrated platelets and growth factors that support tissue repair and pain reduction. This combined approach offers a multifaceted strategy for managing degenerative joint and disc diseases by addressing both symptoms and underlying pathology. With ongoing advancements in hydrogel formulation and processing techniques, hydrogel-based therapies are approaching broader clinical implementation. They serve not only as drug delivery systems but also as regenerative platforms for restoring damaged joint and disc tissues (Kalairaj *et al*., 2024).

The development of injectable hydrogels for the treatment of degenerative joint and disc diseases represents a significant advancement in regenerative medicine. By leveraging the properties of hyaluronic acid and integrating biological components such as PRP or growth factors, these hydrogels provide both immediate pain relief and long-term tissue regeneration. As research continues to evolve, this innovative therapy holds

great potential to transform the management of degenerative musculoskeletal conditions and improve overall patient quality of life (Trivedi *et al*., 2022; Kalairaj *et al*., 2024).

However, most of the current evidence for regenerative hydrogels remains at the preclinical stage, with limited translation into human clinical trials. This shows that, despite strong mechanistic and experimental support, hydrogels currently have the lowest level of clinical evidence among the therapies discussed. Their potential is high, particularly as delivery systems or combination therapies, but their clinical effectiveness still requires validation through well-designed human studies.

Clinical Effectiveness of Regenerative Therapy in Degenerative Joint Disease

The clinical effectiveness of regenerative therapies is generally evaluated using parameters such as pain reduction, improvement in joint function, and structural repair of damaged tissues. These outcomes are commonly measured through validated clinical scoring systems and imaging modalities. Regenerative approaches aim not only to alleviate symptoms but also to modify disease progression by promoting tissue healing and regeneration. As such, assessing both functional and structural outcomes is essential to determine their overall therapeutic value.

Platelet-Rich Plasma (PRP)

Platelet-rich plasma (PRP) has become one of the most extensively studied regenerative therapies for degenerative joint disease (DJD), particularly in knee and hip osteoarthritis (OA). Prodromidis *et al.* (2022), in a systematic review and meta-analysis of 14 studies involving 1,099 patients, evaluated the effect of platelet-rich plasma (PRP) injections on articular cartilage content in knee osteoarthritis. The meta-analysis showed that PRP treatment was not associated with a statistically significant increase in cartilage thickness or volume compared with control interventions. These findings suggest that, although PRP may provide clinical symptom improvement in osteoarthritis, its chondrogenic or structural regenerative effects remain uncertain. The authors further emphasized substantial heterogeneity in PRP preparation protocols and study designs, which limits the strength of definitive conclusions regarding cartilage regeneration. Zhao *et al.* (2020), in a systematic review and meta-analysis of seven studies involving 941 patients, reported that intra-articular injection of PRP combined with HA resulted in greater improvements in pain and functional outcomes compared with PRP alone. Specifically, the combination therapy showed superior reductions in VAS scores and improvements in WOMAC and Lequesne Index scores at mid- to long-term follow-up. However, no significant difference in adverse events was observed between combination therapy and monotherapy groups, indicating a comparable safety profile. These findings suggest that combined PRP and HA may enhance symptomatic outcomes, although further high-quality trials are needed to confirm its superiority over single-agent therapy.

A study Li *et al.,* (2023) reported that multiple intra-articular PRP injections provide better clinical outcomes compared to multiple hyaluronic acid injections in knee osteoarthritis, particularly in improving pain and functional scores over short- and mid-term follow-up. However, the long-term safety and consistency of repeated PRP applications still require further large-scale studies (Li *et al*., 2023). Despite this variability, PRP remains an attractive therapeutic option due to its favorable safety profile, with adverse effects generally limited to mild local pain and temporary swelling. These findings show that intra-articular PRP may yield enhanced clinical outcomes when combined with hyaluronic acid (HA), particularly in terms of pain reduction and

functional improvement in knee osteoarthritis. However, further high-quality studies are still required to confirm the superiority of combination therapy over PRP alone and to optimize treatment protocols and patient selection (Zhao *et al*., 2020).

Mesenchymal Stem Cell (MSC) Therapy

Mesenchymal stem cell (MSC) therapy offers a promising regenerative approach for DJD, particularly in moderate to advanced stages of the disease. MSCs, typically isolated from bone marrow or adipose tissue, exert their effects through both direct differentiation into chondrocytes and the secretion of anti-inflammatory paracrine factors such as interleukin-10 (IL-10) and TNF-α stimulated gene-6 (TSG-6). These factors inhibit proinflammatory signaling pathways, including nuclear factor kappa B (NF-κB), thereby reducing inflammation and promoting tissue repair (West *et al*., 2020).

A study by Hoi Ip *et al*. (2020) reported that high-dose MSC injections (50×10^6 cells) improved the Knee Injury and Osteoarthritis Outcome Score (KOOS) by 60% within 12 months in patients with grade II-III knee OA. This improvement was accompanied by an increase in cartilage thickness of approximately 0.3 mm, as measured by magnetic resonance imaging (MRI). Additionally, autologous chondrocyte implantation (ACI) has been shown to delay the need for arthroplasty in patients with femoral condyle defects, although its outcomes are less favorable in patellar lesions (Migliorini *et al*., 2016).

However, several challenges limit the widespread application of MSC therapy. These include high treatment costs (approximately IDR 50-100 million per injection) and variability in cell viability (70-90%), depending on the source and isolation methods. Bone marrow-derived MSCs exhibit approximately 30% greater regenerative capacity compared to adipose-derived MSCs, but they also carry a risk of abnormal differentiation into fibrotic tissue or osteophytes if the microenvironment is not adequately controlled. A preclinical study by Kalairaj *et al*. (2024) demonstrated that combining MSCs with hyaluronic acid-based hydrogels increased cartilage regeneration by 40% in animal models. While promising, further standardization of protocols, optimal dosing strategies, and long-term monitoring are necessary to ensure the safety and clinical effectiveness of this therapy (Kalairaj *et al*., 2024).

Prolotherapy

Prolotherapy is a regenerative injection technique that utilizes irritant solutions, such as hypertonic dextrose, to stimulate healing in damaged connective tissues. The therapy works by inducing mild localized inflammation, which activates fibroblasts, promotes collagen deposition, and facilitates structural repair of joint-supporting tissues. Prolotherapy contributes to improved joint stability and functional outcomes.

The effectiveness of prolotherapy varies depending on the injection site and the severity of osteoarthritis. In patients with advanced knee OA (Kellgren-Lawrence grade III-IV), its benefits are relatively limited, with pain reduction of approximately 15-20% (West *et al*., 2020). However, combining prolotherapy with other interventions, such as strengthening exercises, has been shown to enhance therapeutic outcomes. A study by West *et al*. (2020) showed that the combination of prolotherapy and physical exercise improved joint function by approximately 20% more than prolotherapy alone.

The main challenges associated with prolotherapy include the lack of standardized protocols regarding solution concentration, injection volume (typically 2-5 mL), and administration intervals (weekly or monthly). Additionally, this therapy is not

recommended for patients with dextrose allergies or active infections at the injection site. Despite these limitations, its favorable safety profile and ease of administration make prolotherapy a potential adjuvant therapy for DJD, particularly in settings where access to advanced biological therapies is limited.

Regenerative Hydrogels

Hydrogels based on hyaluronic acid (HA) or collagen are designed to mimic the structure and function of the natural extracellular matrix of articular cartilage. These materials provide a three-dimensional microenvironment that supports the proliferation, differentiation, and activity of regenerative cells such as mesenchymal stem cells (MSCs) and chondrocytes. The combination of hydrogels with biological therapies, such as PRP or MSCs, aims to enhance cartilage regeneration through controlled release of growth factors and mechanical support (Trivedi *et al*., 2022).

A preclinical study by Kalairaj *et al*. (2024) using a rabbit OA model demonstrated that HA-based hydrogels combined with PRP increased cartilage thickness by 40% within 12 weeks. This effect was primarily mediated by the sustained release of transforming growth factor-beta 3 (TGF-β3), which plays a essential role in stimulating proteoglycan and type II collagen synthesis. These findings show the potential of hydrogels as effective bioactive delivery systems in regenerative joint therapy (Kalairaj *et al*., 2024).

In a phase I clinical trial by Richards *et al*. (2017), the use of HA hydrogels infused with MSCs in 50 patients with knee OA resulted in a 30% improvement in Short Form Health Survey (SF-36) scores after six months. However, approximately 20% of patients experienced temporary post-injection swelling, which did not require additional intervention. Technical advantages of hydrogels include their ability to conform to joint cavity shapes, maintain mechanical stability (elastic modulus of 10-50 kPa), and support integration with surrounding tissues (Richards *et al*., 2017).

Despite these advantages, the long-term effectiveness of hydrogels remains a challenge. The duration of therapeutic effects is generally limited to 6-12 months, particularly in patients with high mechanical joint loads who are at risk of recurrent degeneration. Additional challenges include high production costs, the need for advanced 3D printing technologies for customized applications, and the lack of international standards regarding optimal hydrogel composition. Future research is focused on developing next-generation hydrogels with self-healing properties, improved bioavailability of active molecules, and long-term safety for clinical use (Trivedi *et al*., 2022).

Generally, when comparing the strength of evidence across therapies, PRP shows the most robust clinical support due to the availability of meta-analyses and multiple randomized trials. MSC therapy shows promising regenerative capacity but is still limited by early-phase clinical evidence and high variability. Prolotherapy presents moderate but less consistent clinical evidence, while regenerative hydrogels remain largely supported by preclinical studies. This comparison shows the importance of distinguishing between biological potential and clinically validated effectiveness when evaluating regenerative therapies for DJD.

2. Discussion

Regenerative therapies for degenerative joint disease (DJD) continue to evolve as alternatives or complements to conventional treatments, aiming not only to reduce symptoms but also to repair damaged joint structures. The four approaches discussed

PRP, mesenchymal stem cells (MSCs), prolotherapy, and hydrogels that offer diverse mechanisms of action, clinical effectiveness, and implementation challenges (Lhee *et al*., 2025; Ip *et al*., 2020).

PRP remains one of the most widely used therapies due to its autologous nature, relatively simple application technique, and favorable safety profile. Clinical evidence supports its effectiveness in reducing pain and improving joint function, particularly in early-stage osteoarthritis. However, patient responses vary significantly, and there is no consensus regarding optimal protocols in terms of concentration, centrifugation methods, or injection frequency (Cortez *et al*., 2022).

MSC therapy offers long-term structural regenerative potential through both direct differentiation and anti-inflammatory paracrine effects. Studies demonstrate significant clinical improvements and increased cartilage thickness following intra-articular injections. Nevertheless, its use is limited by high costs, strict regulatory requirements, and technical challenges related to cell isolation and viability. The combination of MSCs with biomaterials such as hydrogels represents a promising strategy to enhance therapeutic efficacy and cell retention at target sites (Ip *et al*., 2020; Sahin and Yesil, 2023; Lhee *et al*., 2025; Ossendorff *et al*., 2022).

Prolotherapy is a simple and cost-effective injection therapy that stimulates connective tissue healing through mild inflammatory induction. It is particularly suitable for mild to moderate DJD cases, especially in patients with limited access to advanced biological therapies. However, its effectiveness is more limited in advanced osteoarthritis, and long-term data remain insufficient (Lhee *et al*., 2025).

Meanwhile, hydrogels serve as supportive matrices capable of delivering cells or bioactive molecules in a targeted manner. The combination of hydrogels with PRP or MSCs has shown improvements in cartilage thickness and clinical outcomes, although the effects are typically temporary (6-12 months) and more suitable for patients with lower joint loading. Challenges include manufacturing complexity, cost, and the lack of standardized formulations (Kalairaj *et al*., 2024).

No single therapy is superior in all aspects. Treatment selection should be tailored to disease stage, clinical objectives, patient characteristics, and resource availability. Multimodal approaches such as PRP-MSC or MSC-hydrogel combinations that hold significant potential to enhance therapeutic effectiveness and durability. Furthermore, more long-term comparative studies with standardized methodologies are needed to ensure the safety, efficacy, and cost-effectiveness of these modalities in clinical practice (Kalairaj *et al*., 2024).

Conclusion

Regenerative therapy offers a promising approach in the management of degenerative joint disease, not only by alleviating symptoms but also by promoting structural and functional restoration of the joints. Platelet-rich plasma (PRP) shows significant benefits in mild to moderate osteoarthritis with a favorable safety profile, while mesenchymal stem cells (MSCs) provide potential for long-term structural regeneration despite challenges related to cost and regulatory constraints. Prolotherapy represents a simple and cost-effective adjuvant treatment, particularly in the early stages of the disease. Meanwhile, hydrogels function as bioactive delivery systems that offer mechanical support and a conducive microenvironment for tissue regeneration, especially when combined with PRP or MSCs. A multimodal approach appears to enhance overall therapeutic effectiveness; however, further well-designed and standardized studies are

required to establish optimal protocols, evaluate long-term efficacy, and ensure the clinical safety of each regenerative modality.

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