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# USE OF BIOLOGICAL THERAPIES IN THE TREATMENT AND MODULATION OF OSTEOARTHRITIS, A LITERATURE REVIEW

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**Abstract:** Knee chondral lesions and osteoarthritis represent a major clinical and public health challenge. According to the World Health Organization (WHO), osteoarthritis affects about 10% of the world's population. In addition, the Ministry of Health (MS) states that 6 to 12% of Brazilians live with this condition, especially individuals aged 65 years or older. Osteoarthritis and other chondral diseases significantly affect joint function and patients' quality of life. Given this, this study seeks to revisit existing biological therapies as relevant alternatives in the treatment of these conditions, reviewing in particular the use of cell therapies such as autologous chondrocyte implantation (ACI), mesenchymal stem cells (MSCs), stromal vascular fraction (SVF), and the use of blood products such as platelet-rich plasma (PRP). The discussion will focus on the possible effects of these interventions on pain, joint function, and the impact on cartilage preservation described in the most relevant and recent studies. In addition, it will be possible to analyze the advantages and limitations of each approach, as well as discuss the current difficulties for standardization of protocols and the need for new studies to consolidate these strategies. In this sense, the objective of this study is to offer a critical reflection on these therapies based on randomized clinical trials, meta-analyses, and consensus, contributing to the development of a critical bias within the academic community and ultimately encouraging evidence-based approaches to the management of knee joint diseases that affect not only the Brazilian population but also the global population.

**Keywords:** Osteoarthritis; biological therapies; mesenchymal stem cells; cartilage regeneration.

## INTRODUCTION

Knee osteoarthritis (OA) is a chronic and degenerative joint disease that represents one of the leading causes of pain and disability worldwide. With an estimated global prevalence of 22.9% in individuals aged 40 years or older (Dainese et al., 2022), and affecting between 6% and 12% of the Brazilian population, especially those over 65 years of age, OA places a significant burden on health systems and patients' quality of life. The condition is characterized by persistent musculoskeletal pain and progressive functional limitations, making it a major clinical and public health challenge (Dainese et al., 2022).

From a pathophysiological point of view, osteoarthritis is now understood as a disease that affects the joint as a whole, not just the cartilage (Dainese et al., 2022). Its pathogenesis is multifactorial and involves a complex cascade of biological and mechanical events that destabilize the balance between degradation and synthesis of the extracellular matrix of cartilage and subchondral bone. The process includes progressive destruction of hyaline articular cartilage, sclerotic changes in subchondral bone, formation of marginal osteophytes, and inflammation of the synovial membrane (synovitis). Synovitis, in particular, plays a crucial role, with the release of pro-inflammatory cytokines such as Interleukin-1 $\beta$  (IL-1 $\beta$ ) and Tumor Necrosis Factor Alpha (TNF- $\alpha$ ), which not only accelerate cartilage degradation but also activate nociceptors, directly contributing to the perception of pain (Dainese et al., 2022).

The etiology of OA is equally complex, with multiple risk factors contributing to its development and progression. Non-modi-

fiable factors, such as advanced age, female gender, and genetic predisposition, increase individual susceptibility. However, modifiable factors play a major role, including obesity, which imposes mechanical overload and contributes to a low-grade systemic inflammatory state; previous joint injuries (post-traumatic osteoarthritis); repetitive occupational stress; and weakness of the periarticular musculature, which compromises stability and shock absorption in the joint.

Traditional management of knee osteoarthritis follows a stepwise approach. The basis of treatment, as reinforced by guidelines such as those of the American Academy of Orthopaedic Surgeons (AAOS), consists of conservative measures such as physical therapy, muscle strengthening, weight loss, and the use of nonsteroidal anti-inflammatory drugs (NSAIDs) for pain control (Brophy; Fillingham, 2022). Intra-articular therapies, such as corticosteroid or hyaluronic acid injections, may offer temporary symptomatic relief but have not been shown to alter the course of the disease. For advanced and refractory cases, total knee arthroplasty (TKA) is the treatment of choice, although it is an invasive procedure with a limited lifespan and is less suitable for young and active patients.

Given the limitations of conventional therapies in modifying disease progression, regenerative medicine has emerged as a promising frontier. Biological therapies, the focus of this review, represent a paradigm shift, seeking not only to alleviate symptoms but also to modulate the hostile intra-articular environment and stimulate intrinsic tissue repair. Approaches such as the use of mesenchymal stem cells (MSCs), stromal vascular fraction (SVF), platelet-rich plasma (PRP), and autologous chondrocyte implantation

(ACI) aim to restore joint homeostasis and regenerate damaged cartilage. This review, therefore, aims to critically analyze the current evidence on the efficacy and mechanisms of these biological therapies, synthesizing the findings of recent studies to contextualize their potential in the treatment of osteoarthritis and chondral lesions of the knee.

## METHODOLOGY

The present study was designed as a narrative review of the literature, with the aim of synthesizing the current evidence on the efficacy and mechanisms of biological therapies in the treatment of osteoarthritis and chondral defects of the knee.

### RESEARCH STRATEGY AND DATA SOURCES

A systematic search was conducted in the PubMed database for articles published between January 2015 and September 2025. The search strategy was designed to cover the main cellular and acellular therapies, using a combination of the following descriptors: (“Stem Cells” OR “Mesenchymal Stem Cells” OR “Stromal Vascular Fraction” OR “Autologous Chondrocyte Implantation” OR “Platelet-Rich Plasma”) AND (“Knee” OR “Knee Osteoarthritis” OR “Cartilage Defect”) AND (“Regeneration” OR “Repair”).

### INCLUSION AND EXCLUSION CRITERIA

The articles were selected in a two-step process, beginning with the analysis of titles and abstracts, followed by reading the full text. The inclusion criteria were: (1) type of study: meta-analyses, systematic

reviews, and randomized clinical trials; (2) focus: evaluation of the efficacy of biological therapies (mesenchymal stem cells, vascular stromal fraction, autologous chondrocyte implantation, and PRP) for osteoarthritis or chondral lesions of the knee; (3) outcomes: studies that reported clinical (e.g., WOMAC, VAS, Lysholm) and/or structural (e.g., MOCART, WORMS) results; and (4) language: articles published in English with full text available.

The following were excluded: (1) pre-clinical studies (animal or *in vitro* models); (2) case reports, letters to the editor, or conference abstracts; (3) articles whose main focus was not on joint tissue regeneration; and (4) publications in other languages. In addition, the *snowballing* technique was used, in which the reference lists of the selected articles were examined to identify relevant studies not captured in the initial search.

### DATA EXTRACTION

Data from eligible articles were extracted and organized to identify key findings on clinical efficacy, potential for structural disease modification, recurring methodological limitations in the literature (such as protocol heterogeneity), and future research directions. The information was synthesized narratively, consolidating the evidence to discuss the state of the art and the positioning of different biological therapies in the orthopedic therapeutic arsenal.

## RESULTS AND DISCUSSIONS

The aggregate analysis of studies on biological therapies for osteoarthritis and chondral lesions of the knee reveals a rapidly evolving field, with a growing body of evidence supporting their potential for both

symptomatic improvement and structural modification of the disease. Our results indicate that interventions such as the application of Mesenchymal Stem Cells (MSCs), Stromal Vascular Fraction (SVF), and Autologous Chondrocyte Implantation (ACI) are associated with improvements in patient pain and function. However, similar to other systematic reviews in emerging areas (DAINESE et al., 2022), a critical analysis of the data demonstrates remarkable heterogeneity among studies, which makes standardization and direct comparison between therapies a significant challenge.

The efficacy of cell therapies, especially CTMs and SVF, appears to be one of the most consistent findings in the literature. Studies such as those by Kim et al. (2015) and Zhang et al. (2017) reported consistent clinical and structural improvements, with significant reductions in pain scores (VAS) and functional improvement (WOMAC, Lysholm) in segments of up to 24 months. The meta-analysis by Yang et al. (2023) reinforces this observation, concluding that injections of adipose tissue-derived MSCs or SVF were superior to the control. The strength of these findings lies in the proposed dual mechanism of action: in addition to their chondrogenic differentiation potential, MSCs act as potent immunomodulatory agents, secreting anti-inflammatory molecules that modulate the hostile joint microenvironment, a critical factor in the pathophysiology of OA (Tran et al., 2019; LYONS et al., 2021).

One of the most promising aspects highlighted in this review is the potential of biologic therapies to promote structural modification, rather than just symptomatic relief. Evidence of cartilage regeneration and improvement in MRI scores, such as WOR-

MS and MOCART, suggests that these therapies may, in fact, alter the trajectory of joint degradation (Kim et al., 2015; Yang et al., 2023). This ability to impact joint structure fundamentally differentiates biological approaches from conventional treatments and represents the main goal of regenerative medicine. However, the correlation between the structural improvement observed in images and the clinical outcomes reported by patients is not always direct, requiring further investigation into which structural changes are most relevant to the patient experience.

The main limitation that permeates the literature and, consequently, this review, is the marked methodological heterogeneity, a challenge also pointed out by Dainese et al. (2022) in the context of inflammatory markers. There is wide variation in cell sources (bone marrow vs. adipose tissue), preparation methods (isolated CTMs vs. SVF), dosages, delivery vehicles (with or without scaffolds), and patient populations (different degrees of OA). This lack of standardization, often criticized in reviews in the field (Jacob et al., 2020; Epanomeritakis et al., 2022), limits the strength of conclusions and prevents the performance robust meta-analyses, making it difficult to establish the superiority of one technique over another.

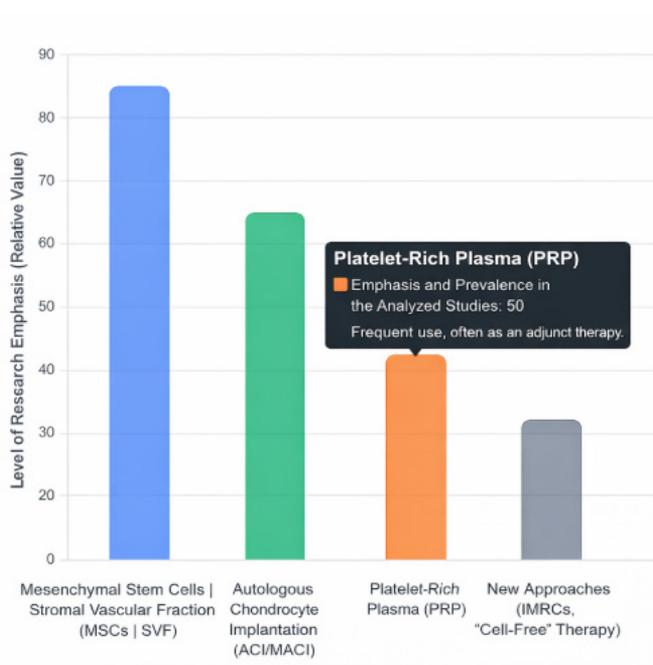
The choice of optimal therapy appears to depend on the nature of the injury and the patient's goals. For focal chondral defects in active patients, ACI, particularly matrix-associated ACI (MACI), demonstrates consistent results in graft integration and clinical improvements (Epanomeritakis et al., 2022). For these patients, outcomes such as return to sport are crucial. The meta-analysis by Robinson et al. (2020) indicated a high rate of return to sport (80%), with

particularly promising results for therapies combining stem cells with PRP, suggesting a beneficial synergistic effect. The use of PRP as an adjuvant appears to modulate the joint environment, providing growth factors that optimize the regenerative response (Pak et al., 2017; Richter et al., 2015).

The frontiers of research continue to expand with the development of new approaches, such as IMRC cells, which have demonstrated superior immunomodulatory capacity in initial trials (Huang et al., 2023), and cell-free strategies, which seek to recruit endogenous cells to the site of injury (Zaffagnini et al., 2015). These innovations may overcome some of the logistical and regulatory barriers associated with cell manipulation. For clinical practice, current evidence supports a personalized approach. For future research, it is imperative to conduct multicenter, randomized, controlled clinical

trials with long-term follow-up to consolidate the safety, efficacy, and cost-effectiveness of these therapies. The standardization of preparation and application protocols is a fundamental step toward enabling valid comparisons and translating the promise of regenerative medicine into reliable clinical treatments.

In order to visually summarize the main findings of this review, a comparative chart was created that organizes the different groups of biological therapies applied to osteoarthritis and chondral lesions of the knee. The chart highlights the emphasis given in studies to cell therapies, such as Mesenchymal Stem Cells (MSCs) and Stromal Vascular Fraction (SVF), noted for their dual mechanism of action and consistent clinical results. Next are structural therapies, represented by ACI/MACI, recognized for their regenerative potential in focal defects.



Graph 1 - Comparative Analysis of the Emphasis of Studies on Biological Therapies for Knee Osteoarthritis

Source: Prepared by the author (2025)

Biological adjuvants, such as Platelet-Rich Plasma (PRP), are also included, mainly for their synergistic effect when combined with cell therapies. New frontiers in research, such as IMRC cells and cell-free strategies, reflect innovative perspectives that are still in the early stages of evidence. Finally, the graph includes the category of outcomes and limitations, which encompasses reported clinical and structural improvement, but also the methodological heterogeneity that permeates the literature. Thus, the visual resource presented in “Graph 1” reinforces the understanding of current trends, as well as the gaps that still require investigation, demonstrating the prevalence and focus of research on different therapeutic approaches, reflecting their stage of development and perceived effectiveness.

## CONCLUSION

Detailed analysis of the findings allows for an initial stratification of efficacy. Therapies such as microfracture, although historically relevant, seem to offer less lasting results, functioning more as an initial biological stimulus than a robust regenerative solution. In contrast, for focal chondral defects in young and active patients, OAT and, especially, matrix-associated ACI (MACI) demonstrate more consistent and lasting results, with evidence of tissue integration and hyaline-like cartilage formation. The success of these surgical approaches highlights the importance of careful patient selection, where accurate indication is a determining factor for clinical outcome.

Biological therapies are establishing themselves as a transformative frontier in the management of knee osteoarthritis and cartilage defects, marking a paradigm shift

from purely symptomatic relief to an approach with real potential for disease modification and tissue regeneration. The evidence gathered in this review consistently demonstrates that interventions such as Autologous Chondrocyte Implantation (ACI), autologous osteochondral transplantation (AOT), and injections of Stromal Vascular Fraction (SVF) or Mesenchymal Stem Cells (MSCs) can promote significant improvements in pain and function, as well as, in documented cases, induce positive structural changes as assessed by imaging. However, a critical analysis reveals that the field is marked by substantial heterogeneity in methodologies, cell sources, and protocols, which prevents the crowning of a single therapy as universally superior and requires caution in the interpretation of data.

In the spectrum of injectable therapies, approaches based on MSCs, whether through cultured cells or SVF, emerge with great potential, especially for the treatment of diffuse osteoarthritis. The mechanism of action of these cells transcends simple chondrogenic differentiation; their main virtue seems to lie in their potent ability to modulate the joint microenvironment. By secreting an arsenal of anti-inflammatory cytokines, growth factors, and extracellular vesicles, CTMs actively combat the catabolic and inflammatory environment that perpetuates cartilage degradation, creating conditions conducive to homeostasis and endogenous repair. Innovations such as IMRC cells, with enhanced immunomodulatory capacity, exemplify the promising future of this line of research, aiming at an even more precise and effective biological intervention.

Future clinical practice, therefore, should evolve toward a model of careful patient stratification, where therapeutic choi-

ce will be guided not only by radiographic severity but also by patient age, activity level, lesion size and location, and possibly by biomarkers of joint inflammatory status. The journey to translate the promise of biological therapies into standardized and widely accessible treatments, however, still faces significant obstacles. It is imperative that future research focus on conducting randomized, controlled, multicenter clinical trials with long-term follow-up. Such studies are crucial for directly comparing the efficacy and cost-effectiveness of different approaches, establishing standardized protocols for cell preparation and application, and ultimately generating the high-quality evidence needed to solidify the role of these therapies in the therapeutic arsenal of modern orthopedics, offering hope and reliable treatments to millions of patients affected by osteoarthritis.

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