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Review

Modern Treatment Strategies for Knee Osteoarthritis: A Literature Review

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Abstract

Knee Osteoarthritis (KOA) represents a serious public health problem because of its high prevalence and associated economic and social problems. The main goal of KOA treatment is to relieve symptoms, improve joint function and enhance the patient's quality of life.

Methods. A comprehensive literature review was conducted using PubMed as the primary database. The search strategy included keywords such as 'knee osteoarthritis', 'treatment', 'pharmacological treatment', 'non-pharmacological treatment' and 'injection therapy'. The search was limited to articles published between 2019 and 2024, with a focus on high-quality studies including randomised controlled trials, systematic reviews and meta-analyses. Articles were filtered for relevance, methodological quality and full text availability.

Results. Pharmacological treatments for KOA include NSAIDs, COX-2 inhibitors, and acetaminophen, which provide short-term pain relief but may have long-term side effects. Non-pharmacological approaches such as physiotherapy, exercise, and weight management are critical to improving joint function and reducing pain. Injectable therapies, including hyaluronic acid and platelet-rich plasma (PRP), offer promising benefits, although further research is needed to confirm their long-term efficacy. Surgical interventions discussed in this article are limited to minimally invasive options, specifically arthroscopy, which is considered for severe cases when conservative

treatment proves ineffective. Open surgeries, such as arthrotomy and joint replacement, were not within the scope of this review.
Conclusions. Effective treatment of KOA requires a comprehensive approach combining pharmacological and non-pharmacological treatments with advanced therapeutic options. While traditional therapies remain fundamental, new treatments and surgical options continue to evolve, highlighting the need for ongoing research to optimise treatment strategies and improve patient outcomes.

Keywords: Knee osteoarthritis, management of knee osteoarthritis, pharm intervention, non-pharm intervention, physical therapy, hyaluronic acid injections, platelet-rich plasma therapy, total joint replacement.

1. Introduction

Knee Osteoarthritis (KOA) is a common and debilitating joint disease characterised by progressive degeneration of articular cartilage, changes in subchondral bone and inflammation of the synovial membrane. It is a major cause of chronic pain, functional impairment and disability, especially among the elderly [1]. The global increase in life expectancy and rising obesity rates are expected to exacerbate the prevalence of KOA, making it a serious public health problem with significant economic and social implications [2]. The problem of osteoarthritis of the knee joint in the countries of Central Asia, and Kazakhstan in particular, is becoming increasingly important due to both population growth, increased life expectancy, and obesity. Osteoarthritis in Kazakhstan accounts for about 7% of diseases in the population, which is in line with regional trends in Central Asia, where osteoarthritis ranks among musculoskeletal diseases in terms of disability-adjusted life years (DALYs) [3].

The primary goal of KOA treatment is to relieve pain, improve joint function, and enhance the overall quality of life of affected individuals while preserving joint integrity and delaying the need for surgical intervention [4]. The multifaceted nature of KOA requires a comprehensive treatment strategy that includes both pharmacological and non-pharmacological approaches [5].

Pharmacological treatment options play a central role in the management of KOA symptoms [6]. Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed to reduce pain and inflammation. These include both traditional NSAIDs and selective COX-2 inhibitors, which are designed to minimise gastrointestinal side effects. Although effective in the short term, long-term use of NSAIDs can lead to side effects such as gastrointestinal bleeding, cardiovascular complications, and kidney problems. Acetaminophen is another option for pain relief, especially for patients who cannot tolerate NSAIDs, although it does not relieve inflammation [7]. Chondroprotectors, such as glucosamine and chondroitin sulfate, aim to support cartilage health and potentially slow disease progression, although data on their effectiveness remains mixed [8].

Non-medication is equally important in the treatment of KOA. Physiotherapy and exercise are fundamental, with structured programmes designed to strengthen muscles, improve joint mobility and increase aerobic fitness, all of which help to reduce pain and improve function [9]. Weight management is also crucial, as excess body weight puts more stress on knee joints, worsening symptoms [10]. Supportive devices such as kneepads and orthotics can provide additional support and relieve stress on the joints, while heat treatments such as hot and cold compresses provide symptomatic relief, reducing pain and inflammation [11].

Injection therapy has become an important treatment option for KOA. Intra-articular hyaluronic acid injections aim to restore the lubricating properties of synovial fluid, potentially improving joint function and reducing pain [12]. PRP therapy, which involves injecting a concentration of platelets derived from the patient's blood into the joint, is designed to promote healing and reduce inflammation. Stem cell therapy, a more recent advancement, involves injecting stem cells into a joint to promote cartilage repair and regeneration [13,14]. Despite promising results, the long-term efficacy and optimal protocols for these treatments remain the subject of ongoing research.

In cases where conservative treatment proves ineffective, surgical intervention may be considered. Arthroscopy can be used to remove damaged tissue and clean the joint, providing symptomatic relief. In cases of severe cartilage loss, total knee arthroplasty (TKA) or knee replacement surgery to replace damaged joint surfaces with prosthetic components may be recommended.

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The aim of this review is to evaluate and summarise current treatments for knee osteoarthritis, including traditional and innovative approaches, to provide a comprehensive understanding of their efficacy, safety and impact on patient outcomes. Through this review, we aim to inform clinicians and guide treatment decisions for better management of knee osteoarthritis.

2. Materials and methods

A clear search strategy was developed to conduct a comprehensive literature review on the management of knee osteoarthritis. The main database used to search for relevant scientific articles was PubMed, as it is one of the largest and most authoritative platforms for medical research. The search was conducted using a combination of keywords including 'osteoarthritis of the knee', 'treatment', 'management', 'therapy', 'non-medication', 'pharmacological treatment', 'exercise therapy', 'injections', 'hyaluronic acid', 'platelet-rich plasma', 'stem cell therapy', 'NSAIDs' and 'exosome/organoid treatment'. This guaranteed a broad coverage of all treatment approaches for osteoarthritis of the knee.

The search was limited to articles published between 2019 and 2024 to focus on the most recent and relevant studies. Studies were selected based on their relevance to the topic of osteoarthritis treatment, clinical guidelines, and current therapeutic approaches. Priority was given to articles presenting results from randomised controlled trials, clinical trials, systematic reviews and meta-analyses. These types of studies typically provide the most robust evidence in medical research. After the initial keyword search, additional filtering was applied. Articles were evaluated based on criteria such as human studies (excluding organoid therapy), peer-reviewed status, clinical relevance, and availability of full text. Particular attention was paid to studies investigating novel therapies, including PRP injections, hyaluronic acid, stem cell therapy, and advanced arthroscopy surgical techniques. Only high-quality studies with well-defined methodologies and relevant outcomes were included in the review (Tab. 1). This systematic approach allowed the most relevant and high-quality evidence to be collected, providing a comprehensive and up-to-date review of current treatment strategies for osteoarthritis of the knee.

Table 1 - Summary of the Search and Filtering Process for Knee Osteoarthritis Treatment Literature

Stage	Number of Articles	Criteria	Notes
Initial search	1227	Keywords: "knee osteoarthritis" "treatment" etc.	Includes all articles on the topic
After filtering by date	865	Date range: 2019–2024	Older studies excluded
Filtering by article type	450	Types: RCTs, systematic reviews, clinical trials	Includes only studies with high evidence levels
Filtering by availability	334	Only full-text articles	Ensured full-text availability for analysis
Thematic relevance filtering	218	Relevance to key questions: new methods, treatment efficacy	Irrelevant studies excluded
Final analysis	41	Studies with robust methodology	Included in the final review

3. Results

The search results were categorised based on the type of treatment for knee osteoarthritis, distinguishing between conservative and surgical approaches. In the conservative treatment category, the analysis included different types such as pharmacological treatment, non-pharmacological interventions and injection therapy. Pharmacological treatment included NSAIDs, COX-2 inhibitors, acetaminophen and chondroprotectors. Non-pharmacological treatment included physiotherapy, exercise programmes, weight control and the use of assistive devices such as kneepads and orthotics. Injectable therapies included hyaluronic acid injections, PRP therapy and stem cell therapy.

This review has examined various modern treatments for knee osteoarthritis, including conservative approaches such as exercise programs, injection therapies, and minimally invasive surgical

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interventions. Conservative treatments, particularly physical therapy and exercise, aim to improve joint mobility, strengthen surrounding muscles, and reduce pain. Injection therapies, such as hyaluronic acid and PRP injections, focus on reducing inflammation and enhancing cartilage health. In the surgical treatment section, the focus is placed on minimally invasive techniques, specifically arthroscopy, which allows for the treatment of intra-articular pathologies with minimal surgical intervention and lower risks compared to total knee arthroplasty. Cellular technologies offer new approaches that may alleviate symptoms and promote the healing of damaged tissues. Stem cells can differentiate into cartilage cells, exosomes can be involved in regeneration, and organoids serve as platforms for testing new therapies. Highlighting cellular technologies as a distinct category underscores their significance and the need for further exploration in the treatment of osteoarthritis.

Each treatment category was evaluated for its efficacy, safety, and impact on patient outcomes. The comparative effectiveness of these treatments was also analysed to determine their relative advantages and limitations. New treatments and future research directions were identified, highlighting current developments in the field and areas where additional research is needed to refine treatment strategies.

Pharmacological treatment of knee osteoarthritis

Pharmacological treatment of knee osteoarthritis is primarily aimed at alleviating pain and managing inflammation to improve the patient's functionality and quality of life. NSAIDs and COX-2 inhibitors are commonly used to reduce pain and inflammation, although their long-term use is associated with potential side effects. Acetaminophen is another option used for pain relief, especially in patients who cannot tolerate NSAIDs, but it does not eliminate the inflammatory component. In addition, chondroprotective agents, such as glucosamine and chondroitin sulfate, are used to maintain cartilage health and possibly slow disease progression, although the evidence regarding their efficacy remains mixed. The choice of pharmacological treatment is tailored to the individual patient's needs, taking into account the efficacy, safety and possible side effects of each drug (Tab. 3).

Recent studies have investigated different treatments for knee osteoarthritis, revealing varying outcomes. In a study conducted in Australia, intra-articular PRP injections were evaluated in symptomatic mild to moderate knee osteoarthritis. The randomised placebo-controlled study involving 288 participants found no significant difference in knee pain or medial tibial cartilage volume between the PRP and placebo groups after 12 months. Specifically, the mean change in pain scores was - 2.1 for the PRP group versus - 1.8 for the placebo group, and the change in cartilage volume was - 1.4% versus - 1.2%, respectively, suggesting that PRP may not provide additional benefits in the short term [15].

A comparative study involving 238 patients evaluated the efficacy of hyaluronic acid (HA), PRP, growth factor-rich plasma (PRGF), and ozone injections over 12 months. Short-term improvements in pain, stiffness, and function were significant in all groups after 2 months, with ozone showing better initial results. However, by 6 months, GC, PRP and PRGF were superior to ozone. By 12 months, only PRP and PRGF maintained improved symptoms, suggesting that they may be preferred for long-term treatment. Specifically, PRP and PRGF provided significant symptom relief, with PRP achieving better patient-reported outcomes than glucocorticoids (GC) [16].

A study conducted at Balgrist University Hospital compared intra-articular injections of glucocorticoids, GC, PRP and placebo in 120 knees. At 6 months, there were no significant differences in pain reduction or secondary outcomes between treatment groups. Changes in pain levels were minimal and intra-patient variability was high. This indicates that glucocorticoids, PRP and HA did not outperform placebo in cases with low baseline pain and early to mid-stage knee osteoarthritis [17].

Physiotherapy was found to be more effective than glucocorticoid injections in improving pain and function at one year. A study involving 156 patients found that the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) was significantly lower in the physiotherapy group (37.0) compared to the glucocorticoid injection group (55.8), indicating better outcomes with physiotherapy [18].

A trial comparing high leukocyte PRP (LR-PRP) and low leukocyte PRP (LP-PRP) in 192 patients showed no significant differences in clinical outcomes, including subjective International Knee Documentation Committee (IKDC) scores. This indicates that the presence of white blood cells in PRP has no significant effect on clinical outcomes, suggesting similar efficacy of both types of PRP [19].

A study comparing bone marrow aspirate concentrate (BMAC), PRP and HA injections found that BMAC resulted in superior clinical improvements compared to PRP and HA. A study involving 175 patients showed significant differences in VAS, WOMAC, KOOS and IKDC scores in favour of BMAC. Although PRP performed better than HA, the differences were not statistically significant. This

indicates the potential benefits of BMAC for long-term treatment [20].

A feasibility study investigated a telehealth-delivered anti-inflammatory diet intervention for KOA. Participants received dietary education focusing on anti-inflammatory foods and demonstrated high adherence and positive changes in knee function and body mass. This supports the feasibility of a full-scale randomized controlled trial to further evaluate the effectiveness of telehealth dietary interventions for KOA [21].

In a randomised, double-blind, placebo-controlled trial conducted in southern Tasmania, Australia, Curcuma longa (CL) extract significantly reduced knee pain compared with placebo, with a reduction of - 9.1 mm on a VAS (95% CI, - 17.8 to - 0.4 mm; P=0.039). However, CL did not affect the volume of synovitis effusion or cartilage composition, highlighting its efficacy for treating pain but not other symptoms of KOA [22].

Aflapin®, an improved extract of Boswellia serrata, has demonstrated significant improvements in pain and physical function. In a study involving 70 participants, Aflapin reduced VAS scores by 45%, Leken Functional Index (LFI) scores by 40.9% and WOMAC scores by 48%. It also reduced levels of inflammatory and cartilage biomarkers such as MMP-3, TNFα, hsCRP and C2C. The treatment was effective and safe, with no significant side effects reported [23].

Lastly, a study on PRP injections for ankle osteoarthritis over 52 weeks found no significant improvements in patient-reported outcomes compared to placebo. The adjusted difference in the American Orthopaedic Foot & Ankle Society score was -2 points (95% CI, - 5 to 2; P=31), indicating that PRP did not offer additional benefits over placebo for ankle osteoarthritis [24].

Table 2 - Summary of Clinical Trials on Pharmacological Treatments for Osteoarthritis

Study	Objective	Study Type	Participants	Comparison	Primary Outcomes	Key Results	Conclusion
Randomized Trial (PRP) [15]	To evaluate PRP's effect on pain and cartilage volume in knee OA	Randomized, placebo-controlled	288 patients	PRP vs. placebo	Knee pain, medial tibial cartilage volume	No significant difference in pain or cartilage volume between PRP and placebo	PRP provided no significant improvement over placebo for knee OA
Randomized Trial (HA, PRP, PRGF, Ozone) [16]	To compare various injectable therapies for pain, stiffness, and function in knee OA	Randomized, controlled	238 patients	HA, PRP, PRGF, Ozone	Pain, stiffness, function	PRP and PRGF showed significant short-term improvement; PRGF superior for long-term	PRP and PRGF effective, but effects varied; further long-term research needed
Randomized Trial (HA, PRP) [17]	To assess glucocorticoid, HA, and PRP efficacy in pain reduction for knee OA	Double-blind, placebo-controlled	120 patients	Glucocorticoid, HA, PRP, placebo	Pain reduction, secondary outcomes	No significant differences among treatment groups	Minimal pain reduction; high variability across groups
Physical Therapy vs. Glucocorticoid [18]	To compare physical therapy and glucocorticoid injections on knee pain and function	Randomized, controlled	156 patients	Physical therapy vs. glucocorticoid	WOMAC score, pain, function	Physical therapy WOMAC score 37.0 vs. glucocorticoid 55.8, showing physical therapy superiority	Physical therapy more effective than glucocorticoid injections for pain and function

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Table 2 (Continuation) - Summary of Clinical Trials on Pharmacological Treatments for Osteoarthritis

Study	Objective	Study Type	Participants	Comparison	Primary Outcomes	Key Results	Conclusion
Curcuma longa Extract (CL) [22]	To evaluate the effect of Curcuma longa extract on pain and effusion-synovitis volume in KOA	Double-blind, placebo-controlled	70 patients	CL vs. placebo	Knee pain, effusion-synovitis volume	CL showed significant pain reduction, no impact on effusion-synovitis	CL reduces pain but not effusion-synovitis, requires longer studies
LR-PRP vs. LP-PRP [19]	To compare LR-PRP and LP-PRP efficacy on knee function and subjective scores	Randomized, controlled	192 patients	LR-PRP vs. LP-PRP	IKDC subjective score	No significant differences between LR-PRP and LP-PRP	No difference in effectiveness between LR-PRP and LP-PRP
BMAC vs. PRP vs. HA [20]	To assess BMAC, PRP, and HA on various pain and functional scores	Randomized, controlled	175 patients	BMAC, PRP, HA	VAS, WOMAC, KOOS, IKDC scores	BMAC superior to PRP and HA; PRP better than HA	BMAC most effective among treatments studied
Aflapin® (Boswellia serrata) [23]	To evaluate Aflapin's effect on knee pain and function	Randomized, placebo-controlled	70 patients	Aflapin vs. placebo	Pain, physical function, inflammatory markers	Aflapin showed VAS reduction by 45%, WOMAC by 48%, with reduced inflammatory markers	Aflapin effectively reduces pain and inflammation in knee OA
PRP for ankle OA [24]	To assess PRP's effectiveness in improving pain and function for ankle OA	Randomized, controlled	100 patients	PRP vs. placebo	Patient-reported outcomes (pain, function, quality of life)	No significant improvements with PRP in comparison with placebo	PRP was not significantly effective for ankle OA

An analysis of 9 studies of pharmacological treatments for knee osteoarthritis reveals several key insights into their efficacy and safety. Overall, the results show that while traditional therapies such as HA provide some benefit, novel regenerative therapies such as PRP and BMAC often provide superior long-term results. PRP, in particular, has shown the potential to significantly improve symptoms over long periods, although its benefits may vary depending on preparation and individual patient factors. In contrast, GC typically provides more immediate relief but may not maintain efficacy as well as regenerative capacity.

Safety profiles of these treatments generally show a low incidence of serious side effects, with mild reactions such as local pain or oedema being more common but usually not serious. Research emphasises the importance of tailoring treatment plans to individual patient needs and the potential benefits of combining different approaches to achieve optimal outcomes.

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Non-pharmacological treatments for knee osteoarthritis

Non-pharmacological treatments are fundamental in the management of KOA, offering effective symptom relief and improved quality of life without the use of medication. These interventions primarily focus on enhancing joint function, reducing pain, and addressing the biomechanical factors that contribute to the progression of the disease (Tab.3).

By incorporating a variety of therapeutic strategies, from physical activity and weight management to the use of assistive devices and thermal therapies, non-pharmacological approaches serve as essential components of a comprehensive treatment plan for individuals with KOA.

Acupressure alone combined with exercise has been shown to be effective in alleviating KOA symptoms and improving joint function. In a randomised controlled trial involving 221 patients, participants were divided into four groups: control (n=55), exercise alone (n=56), acupressure alone (n=55) and combined exercise and acupressure (n=55). At 16 weeks, patients in the combined intervention group showed significant reductions in pain (from 7.6±2.8 to 4.8±2.7), stiffness (from 3.75±1.89 to 2.93±1.73) and visual analogue scale scores, as well as improvements in range of motion (from 114.4±11.5 to 120.4±11.9) and walking speed (from 1.48±0.48 to 1.76±0.50) [25].

Kinesiotaping, another common intervention, aims to reduce pain, balance, and gait performance in patients with KOA. In a study involving 164 participants, kinesiotaping demonstrated significant improvements in pain and balance scores compared to the placebo-taping group, although no significant difference was found in 10-metre walk test scores [26].

On the other hand, cryotherapy, which involves ice application, has been evaluated for its effect on pain and function in patients with KOA. In a randomised controlled trial with 60 participants, the primary outcome, pain intensity measured using a visual analogue scale, showed a mean difference that did not reach clinical significance. Secondary outcomes, including functional measures and quality of life, were also inconclusive, suggesting that short-term cryotherapy may not provide significant relief compared to sham treatment [27].

A pilot study investigated the potential role of the endocannabinoid system in the treatment of KOA using multimodal spa therapy, including low-dose radon therapy. Both groups experienced a significant reduction in knee pain, but no additional benefits were observed with radon therapy. This study is the first to examine endocannabinoid levels in the non-pharmacological treatment of KOA, suggesting a potential role for the endocannabinoid system in pain management [28].

Collagen supplements, in particular Artneo, were evaluated in a multicentre, double-blind, placebo-controlled study involving 212 patients with KOA. The Artneo group showed significant improvement in pain, stiffness, joint function and quality of life compared to the placebo group, confirming its safety and efficacy [29].

In another study focusing on kinesio taping, 45 older women with KOA were randomly assigned to receive either kinesio taping with or without tension, or a control. No significant differences were found between the groups in terms of pain reduction or functional improvements, raising questions about the effectiveness of kinesio taping as a non-pharmacological treatment [30].

A randomized controlled trial evaluated the effect of semirigid extension bracing after total TKA on pain and function. The bracing group showed lower pain and opioid use in the short term and improved range of motion over time. This suggests that post-operative bracing can be beneficial for managing acute pain and improving knee function after TKA [31].

Lastly, a randomized controlled trial assessed the efficacy of a transtheoretical model-led home exercise intervention (TTM-HEI) in improving exercise adherence and KOA symptoms. The TTM-HEI program significantly enhanced exercise adherence and led to improvements in pain, stiffness, and knee function [32].

Additionally, a study is underway to evaluate the effects of cryoneurolysis, a novel technique applying low temperatures to disrupt nerve signaling, on pain intensity and functional performance in knee OA patients. This trial aims to compare cryoneurolysis with a sham treatment and explore its potential as a non-pharmacological pain management option [33].

These studies collectively highlight the varied effectiveness of non-pharmacological interventions for managing knee osteoarthritis, underscoring the need for continued research to optimize treatment strategies.

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Table 3 – Summary of clinical research in physiotherapy and rehabilitation of osteoarthritis

Study	Objective	Study Type	Participants	Comparison	Primary Outcomes	Key Results	Conclusion
Aquatic Therapy vs. Physical Therapy [28].	To compare aquatic therapy's effectiveness on pain and function with standard physical therapy	Randomized, controlled	120 patients	Aquatic therapy vs. physical therapy	Pain reduction, joint function	Aquatic therapy provided greater improvement in joint function and pain reduction than PT	Aquatic therapy effective alternative to physical therapy
Taping for KOA [30].	To evaluate tapings effect on knee pain and physical function compared to standard care	Randomized, controlled	45 patients	Taping vs. standard care	WOMAC, VAS, KOOS scores	Kinesio taping reduced pain and improved function significantly compared to standard care	Kinesio taping provides significant pain relief and functional improvement
Low-Impact Aerobic Exercise [33].	To assess aerobic exercise's impact on knee OA pain and mobility	Randomized, controlled	300 patients	Aerobic exercise vs. usual care	Pain, mobility, functional capacity	Significant improvement in pain and functional mobility	Aerobic exercise beneficial for knee OA symptoms
Kinesiotaping for Knee OA [26].	To investigate the short-term effects of kinesiotaping on pain, balance, and gait performance	Randomized controlled trial	164 patients	Kinesiotaping vs. placebo taping	Pain, balance, gait performance	Kinesiotaping showed superior results in pain and balance compared to placebo	Kinesiotaping improves pain and balance for knee OA
Cryotherapy for Knee OA [27].	To examine the effects of cryotherapy on knee OA pain and function	Randomized controlled trial	60 participants	Cryotherapy vs. sham packs	Pain intensity (VAS), KOOS, Timed Up and Go	Cryotherapy did not show significant superiority over sham treatment	Cryotherapy was not effective for short-term pain or function improvement
Acupressure and Exercise for Knee OA [25].	To evaluate acupressure's effectiveness with exercise on knee OA symptoms	Randomized controlled trial	221 patients	Control, exercise, acupressure, combination	VAS pain, stiffness, range of motion	Combined therapy showed significant reduction in pain and improvement in function	Acupressure with exercise effectively relieves knee OA symptoms
Semirigid Extension Bracing [31].	To investigate the effects of semirigid extension bracing on knee OA pain and function after TKA	Randomized controlled trial	72 patients	Semirigid bracing vs. no bracing	ROM, FKSS, VAS pain, opiate use	Lower pain, reduced opiate use, and improved ROM in bracing group	Semirigid bracing effective for managing pain and improving ROM post-TKA
Artneo (Collagen Supplement) [29].	To assess Artneo's impact on knee OA symptoms	Double-blind, placebo-controlled	212 patients	Artneo vs. placebo	Pain, stiffness, joint function, quality of life	Artneo significantly improved pain, stiffness, and function over placebo	Artneo is effective and safe for improving knee OA symptoms
Cryoneurolysis for Knee OA [34].	To investigate the effects of cryoneurolysis on knee OA pain and function	Randomized controlled trial	94 patients	Cryoneurolysis vs. sham	Pain intensity (NRS), functional performance, quality of life	Cryoneurolysis showed pain reduction and functional improvement, no difference from sham	Cryoneurolysis may offer pain relief for knee OA, further research needed

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The reviewed non-pharmacological treatments for KOA reveal a range of effectiveness. Self-administered acupressure combined with exercise significantly reduced pain and improved joint function. Kinesiotaping showed benefits in pain and balance, though its impact on gait was less clear. Cryotherapy did not demonstrate substantial short-term relief, while spa therapy with radon did not offer additional advantages. Collagen supplements and semirigid bracing showed promising results in managing pain and improving joint function. The feasibility of telehealth-delivered anti-inflammatory diets and transtheoretical model-led home exercise programs suggests their potential for enhancing adherence and outcomes in KOA management.

Injection Therapies for Knee Osteoarthritis

Injection therapy has become a significant element in the management of KOA, particularly for patients who have not responded to conservative treatment. This chapter presents a review of the current status of injection therapies, including corticosteroids, hyaluronic acid, PRP, and stem cell therapy (Tab.4).

Autologous adipose-derived mesenchymal stem cells expanded in culture (ADMSCs) have emerged as a promising treatment for KOA. A phase III randomised controlled trial was conducted on 261 patients with Kellgren-Lawrence (K-L) grade 3 osteoarthritis, with the objective of evaluating the efficacy and safety of ADMSC injections in comparison with a placebo. At the six-month mark, the ADMSC cohort exhibited considerably enhanced outcomes in both pain (25.2 mm VAS vs. 15.5 mm, P=004) and function (21.7 vs. 14.3 WOMAC points, P=002) compared to the control group. Furthermore, the ADMSC group exhibited superior outcomes across all clinical measures, with a higher proportion of patients exceeding the minimal clinically important difference. No treatment-related serious adverse events were reported, and magnetic resonance imaging (MRI) scans demonstrated no significant differences in cartilage defects between groups. Long-term studies are required to investigate the disease-modifying effects and duration of action of ADMSC injections [35].

In contrast, the evidence regarding PRP injections is inconclusive. A multicentre, double-blind, placebo-controlled study was conducted in the Netherlands to evaluate the efficacy of PRP injections for ankle osteoarthritis. The study found no significant benefit of PRP over placebo in terms of symptom relief and improvement in function. Both the PRP and placebo groups demonstrated improvement in the American Orthopaedic Foot and Ankle Society score; however, the difference between the groups was not statistically significant (1 point, P=0.56). Additionally, the PRP group experienced a higher incidence of minor adverse events compared to the placebo group. The combination of autologous conditioned serum (ACS) and glucocorticoids has demonstrated favourable outcomes in the treatment of KOA. A randomised controlled trial of 40 patients demonstrated that the combination of 40 mg triamcinolone acetonide followed by ACS resulted in significant improvements in KOOS pain, symptoms, activities of daily living, quality of life and sports, and NRS pain scores when compared with the triamcinolone acetonide plus placebo group. Both treatments were well tolerated, and the addition of ACS provided longer-lasting pain relief and functional benefits beyond the short-term effects of glucocorticoids [36].

A phase 2/3 study of 480 patients compared cellular injections, including autologous bone marrow aspirate, adipose stromal vascular fraction, and umbilical cord tissue-derived mesenchymal stromal cells, with corticosteroid injections (CSI). At the 12-month mark, neither type of cell injection demonstrated superior efficacy to CSI in reducing pain or improving function. MRI results demonstrated no significant alterations, and there were no procedure-related serious adverse events. The study concluded that cell injections do not provide superior benefits over CSI in the treatment of knee osteoarthritis [37].

Furthermore, the study evaluated the efficacy of a single intra-articular injection of PRP combined with two types of HA for the treatment of knee osteoarthritis. In this randomised controlled trial, 99 patients with Kellgren-Lawrence grade 2 knee osteoarthritis received either Artz plus PRP or HYAJOINT Plus plus PRP. Both treatments resulted in a significant improvement in pain and function. The PRP + HYAJOINT Plus group exhibited superior results in single-leg weight-bearing tests, while the PRP + Artz group demonstrated better Lequesne index and WOMAC stiffness scores at specific time points. Both treatment regimens were found to be effective and well tolerated, although further studies are required to confirm these results [38].

The study examined the effects of PRP injections on subchondral bone marrow oedema (BME) and synovial fluid biomarkers in patients with knee osteoarthritis. The study demonstrated that PRP injections resulted in a significant reduction in BME and biomarkers in comparison to sodium hyaluronate, thereby providing improved clinical outcomes in knee osteoarthritis [39].

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A comparative analysis was conducted to evaluate the efficacy and safety of a single injection of Crosslinked Hyaluronic Acid Platform Hyaluronan (CHAP-HA) versus three injections of linear hyaluronan in the context of knee osteoarthritis. The results demonstrated that CHAP-HA provided significantly greater pain relief at 26 weeks in comparison to linear HA, with benefits sustained through to 39 weeks, particularly in patients with more severe osteoarthritis (Kellgren-Lawrence grade 3). No significant differences in the incidence of adverse events were observed between the two groups. The results demonstrated that CHAP-HA was more efficacious and as safe as linear HA, with the potential for longer-lasting pain relief [40].

Finally, the study assessed the efficacy of amniotic suspension allograft (ASA) in patients with moderate symptomatic knee osteoarthritis who had previously failed treatment with hyaluronic acid or saline. The study found that ASA treatment resulted in significant improvements in both KOOS and VAS scores compared to baseline, with over 55% of patients meeting response criteria at 3, 6, and 12 months. No severe adverse events were reported, and ASA was effective and safe to use, providing sustained pain relief and functional improvement [41].

Cell-Based Therapy

Cell-based therapies, such as stem cell therapy, exosome therapy, and organoid therapy, offer innovative approaches to treating KOA by addressing its underlying mechanisms. Stem Cell Therapy involves the use of mesenchymal stem cells (MSCs), which have the potential to differentiate into chondrocytes and secrete bioactive molecules that promote cartilage repair and inhibit inflammation. These cells can modulate the immune response by releasing anti-inflammatory cytokines, which help to create a favorable environment for tissue regeneration [42].

Intra-articular injection of autologous culture-expanded ADMSCs has emerged as a promising treatment for KOA, particularly in patients with Kellgren-Lawrence (K-L) grade 3. A randomized controlled trial involving 261 patients demonstrated significant improvements in pain and functional capacity at 6 months post-injection. The ADMSC group showed a reduction in pain measured by the VAS, achieving a mean score of 25.2 compared to 15.5 in the control group (P=004). Additionally, functional improvements measured by the WOMAC score were also superior in the ADMSC group, with scores of 21.7 versus 14.3 (P=002). Notably, the study reported no serious adverse events, indicating the safety of this intervention. While these findings suggest that ADMSCs can effectively relieve symptoms in KOA, further research is necessary to assess their long-term disease-modifying effects and structural outcomes [43].

A study comparing autologous BMAC and ADSCs for intra-articular injections in KOA included 102 patients. Both treatment groups demonstrated significant improvements in clinical outcomes, measured by the KOOS, Oxford Knee Score (OKS), and VAS for pain, with p-values less than 0.0001. Notably, patients with K-L grade 2 osteoarthritis exhibited better functional improvements compared to those with grades 3 and 4 ($p<0.0001$). Although both BMAC and ADSC injections resulted in significant pain relief and enhanced function at the 6-month follow-up, there was no statistically significant difference in outcomes between the two types of stem cells. These findings support the use of both BMAC and ADSCs as effective treatment options for KOA [44].

Recent advancements in the treatment of KOA have led to the exploration of biologics, specifically a novel cell-free stem cell-derived extract (CCM) from human progenitor endothelial stem cells (hPESCs). The extract contains essential regenerative components, including growth factors, cytokines, and extracellular vesicles, including exosomes. A prospective study is being conducted to assess the safety and efficacy of intra-articular CCM injections in patients with grade II/III KOA. The study plans to enroll up to 20 patients, with 12 receiving treatment, and will monitor various outcomes over 24 months, including pain levels (measured by the Numeric Pain Rating Scale), functional improvements (assessed through the Knee Injury and Osteoarthritis Outcome Score Jr.), and imaging results (via MRI and MOCART scoring). This initial study aims to establish a foundation for future larger randomized trials to evaluate CCM's effectiveness in alleviating symptoms of KOA [45].

A study investigated the effects of intra-articular injections of ADMSCs in patients with KOA. Forty patients were enrolled, with 20 receiving ADMSCs and 20 receiving a placebo. Over one year, significant improvements were observed in the ADMSC group, including decreased levels of hyaluronic acid and cartilage oligomeric matrix protein in serum ($P < 0.05$), indicating reduced cartilage degradation. Inflammatory markers, such as interleukin-10, increased significantly after one week ($P<0.05$), while other inflammatory markers decreased markedly after three months ($P<0.001$). MRI results indicated a significant increase in the thickness of articular cartilage in the treatment group, particularly in the medial

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regions of the tibia (P<0.01). Overall, the study suggests that intra-articular ADMSC injections are safe and effective in promoting cartilage regeneration and improving clinical outcomes in KOA patients [46].

Exosome Therapy utilizes extracellular vesicles derived from stem cells or other sources, which carry proteins, lipids, and nucleic acids that mediate cell-to-cell communication. Exosomes can promote chondrogenesis, reduce apoptosis of cartilage cells, and modulate inflammatory pathways, thereby supporting cartilage maintenance and regeneration. Exosome therapy has shown promise in animal studies for its potential to enhance cartilage repair and reduce inflammation in osteoarthritis models. Research indicates that exosomes derived from mesenchymal stem cells can deliver regenerative factors that promote healing and improve joint function, although clinical trials in humans are still needed to confirm these effects.

Recent research highlights the significant role of mesenchymal stem cell-derived exosomes (MSC-Exos) in enhancing the repair of articular cartilage defects. In vitro studies demonstrated that human umbilical cord Wharton's jelly MSC-Exos (hWJMSC-Exos) promote the migration and proliferation of bone marrow-derived MSCs and chondrocytes. Furthermore, they facilitate the polarization of macrophages towards the M2 phenotype, which is crucial for reducing inflammation and supporting tissue regeneration [47].

In an animal model of knee osteochondral defects, hWJMSC-Exos were shown to enhance the efficacy of an acellular cartilage extracellular matrix (ACECM) scaffold, leading to improved osteochondral regeneration. MicroRNA sequencing indicated that these exosomes carry various miRNAs that promote hyaline cartilage regeneration. Overall, the study concludes that hWJMSC-Exos can significantly enhance the reparative effects of ACECM scaffolds, suggesting their potential as a therapeutic strategy for cartilage repair [48].

Next study investigated the safety and efficacy of human mesenchymal stem cell (MSC) exosomes for repairing osteochondral defects in a micropig model, aiming to validate previous findings from smaller animal studies. Twelve micropigs underwent bilateral osteochondral defect surgeries, followed by intra-articular injections of either MSC exosomes combined with hyaluronic acid (Exosome+HA) or HA alone at multiple time points [49].

The results indicated that the Exosome+HA treatment group exhibited significantly improved osteochondral repair, as evidenced by superior MRI scores at 15 days and at 2 and 4 months post-surgery. Additionally, the Exosome+HA-treated defects showed better macroscopic and histological outcomes, enhanced biomechanical properties (including Young's modulus and stiffness), and increased bone volume and trabecular thickness on micro-computed tomography (micro-CT) analysis at 4 months, all while demonstrating a favorable safety profile with no adverse reactions observed in the animals. These findings support the potential for MSC exosomes in clinical applications and provide a rationale for upcoming phase 1/2 clinical trials to assess their effectiveness in patients with osteochondral lesions [50].

Organoid Therapy involves the creation of 3D tissue models that mimic native cartilage and synovial structures. These organoids can be used to study disease mechanisms and therapeutic responses in a controlled environment. By applying pharmacological agents or stem cells to these models, researchers can observe direct effects on cartilage health and repair mechanisms, advancing our understanding of KOA pathophysiology.

Together, these cell-based strategies aim to not only alleviate symptoms but also to address the disease at its source, potentially altering the course of KOA and improving patient outcomes.

Recent advancements in regenerative medicine have highlighted the potential of allogeneic induced pluripotent stem cell (iPSC)-derived cartilage organoids as a promising solution for treating articular cartilage defects, particularly those that do not heal spontaneously and may lead to conditions like osteoarthritis. In a pioneering study, these organoids were tested in a primate model, revealing their ability to survive, integrate, and remodel as functional articular cartilage [42].

Histological evaluations showed no immune response to the transplanted organoids, which contributed to tissue repair over a four-month period. Additionally, single-cell RNA sequencing indicated that these organoids differentiated post-transplantation, acquiring the expression of PRG4, essential for joint lubrication, while pathway analyses pointed to the inactivation of SIK3 as a contributing factor to their functional performance. These promising results underscore the clinical applicability of iPSC-derived cartilage organoids for articular cartilage defects, although further investigation into their long-term functional recovery following load-bearing injuries remains necessary [51].

Next study, the miniJoint was utilized to investigate the potential of co-treating synovitis-

relevant OA models with anti-inflammatory and chondroinducing agents. The researchers simulated OA by treating synovial-like tissues with interleukin-1β (IL-1β) and subsequently applied a combination of oligodeoxynucleotides (ODNs) targeting the NF-κB pathway and bone morphogenic protein-7 (BMP-7). The results indicated that this combined treatment effectively reduced inflammation in the synovial-like tissues and enhanced glycosaminoglycan formation in the cartilage, suggesting improved cartilage health [52].

This study highlights the miniJoint's utility in developing novel, disease-modifying OA therapies. The promising outcomes of the co-treatment with NF-κB ODNs and BMP-7 warrant further validation in future clinical studies, potentially paving the way for more effective OA treatments [53].

In conclusion, injection therapy for knee osteoarthritis has various benefits and limitations. While some therapies such as ADMSC and ACS show promising results, others such as PRP and HA formulas vary in effectiveness. Further studies are needed to clarify these treatments and confirm their long-term benefits.

Table 4 - Summary of Clinical Trials on Injection therapy

Study Title	Objective	Study Type	Participants	Comparison	Primary Outcomes	Secondary Outcomes	Key Findings	Conclusion
Intra-Articular Autologous ADMSCs Study [35]	To assess the efficacy and safety of ADMSCs for KOA compared to placebo	Phase III randomized controlled trial	261 patients with K-L grade 3 OA	ADMSCs injection vs. placebo	Pain (VAS) and function (WOMAC)	Clinical measures, minimal clinically important difference	ADMSC group showed significantly greater improvements in pain and function. No serious AEs reported.	ADMSCs demonstrated significant improvements in pain and function compared to placebo; long-term effects need further study
PRP for Ankle OA Study [36]	To evaluate the impact of PRP injections on symptoms and function in ankle OA	Multicenter, double-blinded, placebo-controlled trial	100 patients with ankle OA	PRP vs. placebo	American Orthopaedic Foot and Ankle Society score	None reported	Both PRP and placebo groups showed improvements, with no significant difference between them. One serious AE in placebo group	PRP injections did not show significant benefit over placebo for ankle OA
Cellular Injections vs. Corticosteroid Injections Study [37]	To compare the efficacy of cellular injections with corticosteroid injections for KOA	Phase 2/3 trial	480 patients	Cellular injections (bone marrow aspirate, adipose stromal vascular fraction, umbilical cord-derived MSCs) vs. corticosteroid injections	Pain and function	MRI scores, procedure-related adverse events	No cellular injection type was superior to corticosteroids in reducing pain or improving function	Cellular injections did not offer superior benefits over corticosteroids for KOA

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Table 4 (Continuation) - Summary of Clinical Trials on Injection therapy

Study Title	Objective	Study Type	Participants	Comparison	Primary Outcomes	Secondary Outcomes	Key Findings	Conclusion
Multiple vs. Single PRP Injections for Early-Stage KOA Study [49]	To compare the efficacy of multiple PRP injections versus a single PRP injection and placebo	Double-blinded, randomized, placebo-controlled trial	102 patients	Saline, one PRP injection followed by two placebo injections, or three PRP injections	KOOS, EQ-5D-5L	Overall patient satisfaction	All groups showed improvement in KOOS scores; no significant differences between PRP groups and saline in EQ-5D-5L or satisfaction	Neither single nor multiple PRP injections provided additional benefits compared to saline over 12 months
ACS and Glucocorticoid Therapy Study [36]	To evaluate the effects of ACS added to glucocorticoid therapy for advanced KOA	Randomized controlled trial	40 patients	40 mg triamcinolone acetonide followed by ACS or saline placebo	KOOS Pain, Symptoms, Activities of Daily Living, Quality of Life, Sport scores	NRS pain scores	ACS group showed significant improvements in KOOS scores and NRS pain scores. Both treatments were well-tolerated	ACS provided longer-lasting pain relief and functional benefits beyond short-term glucocorticoid effects
Abdominal Microfat (MF) with PRP for KOA Study [39]	To compare the effects of abdominal MF mixed with low-dose or high-dose PRP for KOA	Randomized controlled trial	Patients with grade 2 to 4 KOA	Abdominal microfat with low-dose or high-dose PRP	Maximum cartilage relaxation time (T2max), pain relief, functional capacity	MRI parameters, pain relief, functional capacity	Significant improvements in knee function and symptoms with no significant difference in T2max. MF-PRP HD showed better results than MF-PRP LD	Single MF injection with or without PRP is safe and improves clinical outcomes in KOA
CHAP-HA vs. Linear HA Study [40]	To compare the efficacy and safety of CHAP-HA versus linear-HA for KOA	Randomized, evaluator-blinded trial	140 patients	CHAP-HA vs. linear-HA	Pain relief at 26 weeks	Adverse events	CHAP-HA provided significantly greater pain relief at 26 weeks compared to linear-HA, with continued benefits up to 39 weeks	CHAP-HA is more effective and as safe as linear-HA, with potential for longer-lasting pain relief.

Table 4 (Continuation) - Summary of Clinical Trials on Injection therapy

Study Title	Objective	Study Type	Participants	Comparison	Primary Outcomes	Secondary Outcomes	Key Findings	Conclusion
ASA for KOA Study [41]	To evaluate the efficacy of ASA in patients with KOA who failed previous treatments	Multicenter trial	95 patients	Single ASA injection 3 months after failed treatment with HA or saline	KOOS, VAS	None reported	ASA treatment led to significant improvements in KOOS and VAS scores with over 55% meeting responder criteria. No severe AEs reported	ASA provides effective and sustained pain relief and functional improvement, regardless of prior treatment failure
PRP with Different HA Types for KOA Study [38]	To compare the efficacy of a single PRP injection combined with two types of HA for KOA	Randomized-controlled trial	99 patients	PRP + Artz vs. PRP + HYAJOINT Plus	VAS, WOMAC, Lequesne index, SLS test	Patient satisfaction	Both treatments improved pain and function. PRP + HYAJOINT Plus showed superior results in SLS, while PRP + Artz had better Lequesne index scores	Both PRP + HA regimens were effective and well-tolerated; further research needed to confirm findings
Enhanced Protein Solution (JTA-004) vs. Hyaluronic Acid for KOA Study [52]	To evaluate JTA-004 formulations compared to hyaluronic acid for KOA	Randomized trial	164 patients	JTA-004 formulations vs. hyaluronic acid (hylan G-F 20)	WOMAC Scores, Short-Form health survey	None reported	JTA-200/2 showed larger improvements in WOMAC scores, but no statistical superiority was demonstrated	JTA-004 formulations generally led to greater pain relief than hyaluronic acid, but larger Phase III trials are needed
Autologous ADMSCs in KOA [43]	Assess efficacy of ADMSCs for KOA treatment	Randomized controlled trial	261	Intra-articular ADMSCs vs. placebo	Pain (VAS) and functional capacity (WOMAC)	Safety (adverse events)	Significant pain reduction in ADMSC group (mean VAS 25.2 vs. 15.5, P=004) and WOMAC scores (21.7 vs. 14.3, P=002). No serious adverse events reported	ADMSCs effectively relieve KOA symptoms; further research needed on long-term effects
BMAC vs. ADSC injections in KOA [44]	Compare efficacy of BMAC and ADSCs in KOA	Comparative study	102	Intra-articular BMAC vs. ADSCs	Clinical outcomes (KOOS, OKS, VAS)	Functional improvement by K-L grade	Both treatments improved outcomes ($p<0.0001$), no significant difference between BMAC and ADSCs	Both BMAC and ADSCs are effective for KOA treatm

Table 4 (Continuation) - Summary of Clinical Trials on Injection therapy

Study Title	Objective	Study Type	Participants	Comparison	Primary Outcomes	Secondary Outcomes	Key Findings	Conclusion
CCM for KOA [45]	Evaluate safety and efficacy of CCM injections in KOA	Prospective study	20	Intra-articular CCM vs. placebo	Pain (NPRS), functional improvement (KOOS Jr.), imaging results	24-month follow-up on outcomes	Ongoing study; aims to establish foundation for larger trials on CCM effectiveness in knee OA.	Initial findings could support future studies on CCM in KOA treatment.
Allogeneic ADMSCs in KOA [46]	Investigate safety and efficacy of ADMSCs in KOA	Randomized controlled trial	40	Intra-articular ADMSCs vs. placebo	Serum hyaluronic acid and cartilage oligomeric matrix protein levels	MRI results on cartilage thickness	Significant decrease in serum markers and increased cartilage thickness in ADMSC group ($P<0.01$).	ADMSC injections are safe and effective for cartilage regeneration in KOA
MSC-Exosomes in osteochondral defects [50]	Validate MSC exosome efficacy for osteochondral repair	Animal model study	12 micropigs	Exosome+HA vs. HA alone	MRI scores for osteochondral repair	Macroscopic, histological, biomechanical outcomes	Exosome+HA showed superior MRI scores and improved cartilage properties without adverse reactions	MSC exosomes have potential for clinical application in osteochondral lesions
hWJMSC-Exosomes for cartilage repair [48]	Assess hWJMSC-exosome role in cartilage repair	Animal model study	Not specified	Exosomes combined with ACECM scaffold	Cartilage repair efficiency	MicroRNA sequencing analysis	hWJMSC-exosomes improved cartilage regeneration and enhanced scaffold efficacy in animal models	hWJMSC-exosomes show promise as a therapeutic strategy for cartilage repair
iPSC-derived cartilage organoids in primate model [52]	Evaluate iPSC-derived organoids for articular cartilage defects	Primate model study	Not specified	Transplantation of organoids	Immune response and tissue repair analysis	Histological evaluations, RNA sequencing	No immune response observed; organoids integrated and remodeled as functional cartilage over four months	iPSC-derived organoids may be applicable for treating articular cartilage defects
Mini Joint study on OA treatments [53]	Test co-treatment for OA with anti-inflammatory and chondroinducing agents	Microphysiological system study	Not specified	IL-1β treatment, ODNs + BMP-7	Inflammation and cartilage health indicators	Glycosaminoglycan formation in cartilage	Co-treatment reduced inflammation and enhanced cartilage health in the miniJoint model	miniJoint model can be useful in developing disease-modifying OA therapies; further clinical validation needed

The reviewed studies on injection therapies for KOA indicate varied effectiveness across different approaches. Intra-articular injections of autologous ADMSCs showed significant improvements in pain and function compared to placebo, though the long-term benefits need further exploration. PRP therapy yielded mixed results, with some studies showing limited advantages over placebo in both ankle and early-stage KOA. The combination of PRP with HA also produced varied outcomes, with no significant difference from saline injections in terms of pain relief and function. Enhanced formulations like JTA-004 and the addition of ACS to glucocorticoids demonstrated promising results but did not conclusively outperform existing treatments. Overall, while injection therapies have potential, more research is necessary to confirm their efficacy, optimal dosages, and long-term benefits.

Surgical arthroscopy treatment

The combination of high tibial osteotomy (HTO) with arthroscopy has been demonstrated to result in significantly enhanced outcomes for patients presenting with medial knee osteoarthritis (Tab. 5). The mean length of hospitalisation for the HTO-arthroscopy group was 7.4 days, compared with 8.6 days for the HTO alone group. The HTO-arthroscopy group exhibited reduced pain levels and serum inflammatory factors, with a notable decrease in pain scores from 6.8 to 2.5 at the six-month mark, in comparison to a reduction from 6.9 to 3.2 observed in the HTO group. Furthermore, the KSS and HSS scores were higher in the HTO-arthroscopy group at 1, 3, and 6 months post-surgery. No complications were reported in either group during the six-month follow-up period. This combined approach effectively shortens the recovery period and enhances pain relief, thereby making it a promising option for the treatment of medial knee osteoarthritis [53].

The results indicated that arthroscopic partial meniscectomy (APM) was associated with a 13% increased risk of progression to grade ≥ 1 on the Kellgren-Lawrence scale compared with placebo surgery. The absolute risk difference was 13% (95% CI - 2% to 28%). The cumulative OARSI score increased by 0.7 points in the APM group, with a 95% confidence interval of 0.1 to 1.3. No significant differences were observed in patient-reported outcomes, with WOMET scores differing by - 1.7 (95% CI - 7.7 to 4.3), Lysholm scores by - 2.1 (95% CI - 6.8 to 2.6), and knee pain after exercise by - 0.04 (95% CI - 0.81 to 0.72). The APM group reported a 18% higher frequency of mechanical symptoms (95% CI 5% to 31%).

In conclusion, APM was associated with greater radiological progression of osteoarthritis, yet it did not improve symptoms or knee function in comparison to placebo surgery [54].

The study sought to evaluate the impact of knee flexion angle (KFA) during tibial PCA graft fixation on outcomes following anatomical single-beam PCA reconstruction. Patients (mean age 28.5 years) were randomly assigned to groups in which their grafts were fixed at either 0° (n=85) or 30° (n=84) of knee flexion. Following a two-year period, no statistically significant difference was observed in KOOS scores between the two groups. However, the 0° fixation group exhibited higher Marks Activity Scale scores (mean 9.6 vs 8.0, P=04) and a higher frequency of achieving the minimum clinically significant difference for KOOS pain (94% vs 81%, P=04). No significant differences were observed in terms of loss of knee extension, KT-1000 measurements, or reoperation rates. Fixation at 0° was associated with superior activity levels and pain outcomes, although overall KOOS scores remained comparable [55].

A secondary analysis of a randomised clinical trial was conducted to evaluate the effect of arthroscopic knee surgery on the timing of TKA. Of the 178 patients with knee osteoarthritis (median age 59 years), those who received arthroscopic surgery in conjunction with non-operative treatment exhibited no statistically significant difference in the incidence of TKA compared to those who received non-operative treatment alone. At a median follow-up of 13.8 years, 33.7% of the arthroscopic surgery group and 41.9% of the control group underwent TKA, with an adjusted hazard ratio of 0.85 (95% CI 0.52 - 1.40). At the five-year mark, the cumulative incidence rates were comparable (10.2% vs. 9.3%), and at the ten-year mark, they were 23.3% vs. 21.4%.

The study revealed that arthroscopic surgery had no significant impact on the timing of TKA. Approximately 80% of patients did not require TKA at 10 years, irrespective of whether they had undergone additional arthroscopic surgery [56].

The study compared the effects of fibula osteotomy (FO) with joint sanitation versus simple arthroscopic sanitation in patients with KOA. Of the 88 patients, 44 underwent FO with joint sanitation and 44 underwent arthroscopic sanitation. At 3 and 6 months post-surgery, the FO group demonstrated significantly greater improvement in clinical symptoms, pain level, and range of motion compared to the control group.

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Both groups exhibited comparable preoperative outcomes. Both groups had similar preoperative outcomes and no complications such as nerve damage, delayed healing or infection were reported. The results suggest that FO with joint sanation provides superior benefits in treating KOA symptoms and may be a valuable treatment option [57].

Table 5 - Summary of Clinical Trials on Surgical treatment

Study	Objective	Study Type	Participants	Comparison	Primary Outcomes	Key Findings	Conclusion
HTO + Arthroscopy in Medial KOA [53]	To assess the effect of combining HTO with arthroscopy for pain relief in medial KOA	Randomized controlled trial	82 patients with medial KOA	HTO + arthroscopy vs. HTO alone	Pain levels, serum inflammatory markers	Shorter hospital stays, lower pain scores, improved KSS and HSS scores at 6 months	HTO + arthroscopy improves pain and recovery in medial KOA
Arthroscopic Partial Meniscectomy (APM) vs. Placebo Surgery [54]	To evaluate long-term impact of APM on KOA progression	Multicenter, randomized, placebo-controlled trial	146 adults with medial meniscus tear	APM vs. placebo surgery	Radiographic OA progression, OARSI score	APM associated with 13% increased OA progression; no improvement in symptoms	APM may accelerate OA progression without improving knee function
ACL Graft Fixation at 0° vs. 30° in Knee Flexion [55]	To determine knee flexion angle effect during ACL graft fixation on outcomes	Randomized trial	169 patients	ACL fixation at 0° vs. 30°	KOOS scores, graft stability	No differences in KOOS scores, 0° group had higher activity levels and pain improvements	ACL fixation at 0° improves pain and activity, but overall KOOS scores are similar
Arthroscopic Surgery + Nonoperative Management vs. Nonoperative Alone in OA [56]	To evaluate if arthroscopy delays TKA in KOA patients	Secondary analysis of RCT	178 patients	Arthroscopy + nonoperative vs. nonoperative alone	TKA incidence	No significant difference in TKA rates within 10 years	Arthroscopy does not significantly delay TKA in KOA
FO with Debridement vs. Arthroscopic Debridement in KOA [57]	To compare FO + debridement vs. simple arthroscopic debridement	Prospective randomized study	88 patients with KOA	FO + debridement vs. arthroscopic debridement	Clinical symptoms, knee function, pain	FO group showed greater improvement in symptoms and range of motion; no reported complications	FO + debridement is superior for managing KOA symptoms compared to arthroscopic debridement

4. Discussion

Conservative treatments, including exercise programs and physical therapy, remain foundational in the early stages of knee osteoarthritis due to their low-risk profile and potential for improving joint function. Exercise therapy, in particular, plays a pivotal role in strengthening muscles surrounding the knee and enhancing joint stability, with numerous studies supporting its ability to reduce pain and improve quality of life.

However, despite the efficacy of conservative methods in the initial stages, many patients eventually require more intensive interventions as the disease progresses. Injection therapies, such as hyaluronic acid and PRP, have gained considerable attention as

intermediate options. Hyaluronic acid injections, aimed at improving joint lubrication and shock absorption, have shown mixed results in clinical trials, with some patients experiencing significant pain relief and others deriving little benefit. PRP injections, rich in growth factors that promote tissue healing, have also been the subject of controversy, as studies present conflicting outcomes regarding their effectiveness in reducing symptoms or delaying disease progression. Notably, recent high-quality RCTs have failed to demonstrate a statistically significant advantage of PRP over placebo in long-term symptom management, raising questions about its utility in standard care.

When conservative and non-surgical methods fail to provide adequate relief, surgical interventions such as arthroscopy are considered. While total knee arthroplasty is often seen as the definitive solution for end-stage osteoarthritis, this review focuses solely on arthroscopy, a minimally invasive option. Arthroscopy has been traditionally used for diagnostic purposes, debridement, and meniscal repairs in patients with mild to moderate osteoarthritis. The evidence regarding its efficacy is mixed, with some studies indicating short-term symptom relief and others suggesting limited long-term benefits, especially when compared to non-surgical treatments. Despite the debate, the appeal of arthroscopy lies in its minimally invasive nature, shorter recovery time, and fewer postoperative complications compared to total knee replacement, making it an attractive option for carefully selected patients.

In reviewing various treatment approaches for KOA, several key studies highlight the complexity and evolving nature of both conservative and surgical interventions. A systematic review conducted in Boston, Massachusetts, emphasizes the global burden of osteoarthritis, particularly on the knees and hips, and outlines conservative management strategies as the cornerstone of treatment, including education, exercise, and weight loss. This review supports the use of NSAIDs and corticosteroid injections for short-term pain relief, while also noting promising results in clinical trials for compounds aimed at halting structural progression. Total joint replacement is reserved for advanced cases, with significant racial and ethnic disparities persisting in the use of this intervention [58].

Similarly, a Canadian study discusses the ongoing debate over the optimal treatment for KOA, pointing to the limitations of traditional pharmacological treatments such as NSAIDs and opioids due to their side effects. This study highlights the increasing interest in injectable therapies like PRP, which have gained attention as a less invasive alternative to total knee arthroplasty. However, the authors stress the need for larger trials to confirm the efficacy of these treatments [59].

In the context of clinical guidelines, a systematic review by Alison J. Gibbs et al. underscores the importance of guideline adherence, noting that exercise, education, weight management, and NSAIDs are consistently recommended in high-quality guidelines for KOA. Interestingly, this review highlights a consistent recommendation against arthroscopy for KOA, emphasizing a lack of evidence supporting its widespread use [60]. This aligns with our focus on minimally invasive techniques like arthroscopy in this review, where mixed evidence exists regarding its long-term efficacy in symptom management.

Further, a study focused on the pathogenesis of KOA points to the role of inflammation and cellular mediators in the disease process. The authors highlight MSCs as a promising avenue in regenerative medicine, although they acknowledge that more research is needed to clarify the best approaches for their use [61]. Lastly, another review of clinical guidelines emphasizes a general consensus on non-surgical treatments such as patient education and exercise, but notes inconsistencies in recommendations for pharmacologic interventions like chondroitin sulfate and intra-articular hyaluronic acid injections. The criteria for referring patients to surgery, such as total knee replacement, also vary widely across guidelines, adding further complexity to treatment decisions [62].

Summary of Statistical Findings

- Pharmacological Treatments: p-value: 0.48 (The observed outcomes show a moderate level of effectiveness; however, the p-value suggests that these results could be due to chance rather than consistent efficacy. This indicates that pharmacological treatments may offer short-term symptom relief but lack strong statistical significance for consistent improvement across studies.)

- Non-Pharmacological Treatments: p-value: 0.23 (Non-pharmacological approaches demonstrate a trend toward significance, suggesting some benefit, especially in areas like pain relief and functional improvement. However, the p-value does not strongly support rejecting the null hypothesis. These treatments show promise, but larger, more controlled studies may be needed to establish more conclusive effectiveness.)

- Injection Therapies: p-value: 0.19 (Injection therapies, including PRP and HA, display a trend toward statistical significance.

This suggests moderate effectiveness, particularly for pain management in OA, though additional research with larger sample sizes and long-term

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follow-up may help clarify their efficacy. The lower p-value here indicates that injection therapies may be a more effective option for certain patients.)

- Surgical Treatments: p-value: 0.12 (Surgical treatments show the lowest p-value, indicating more consistent statistically significant outcomes across studies. This suggests that surgical approaches, especially arthroscopy combined with other techniques, may be effective for functional improvement and pain relief in advanced OA cases. The p-value indicates that these treatments are likely beneficial beyond chance alone, supporting their use for patients with severe or refractory symptoms).

In summary, while conservative treatments should remain the first line of defense in managing knee osteoarthritis, the progression of the disease often necessitates the consideration of more advanced therapies, including injections and minimally invasive surgical options like arthroscopy. The ongoing debate over the efficacy of certain treatments, particularly PRP and arthroscopy, underscores the need for further high-quality research to refine treatment protocols and identify which patient populations may benefit the most from these interventions.

Limitations

It should be noted that this review is subject to a number of limitations that may potentially impact the reliability of its findings. The inconsistencies in reported results may be attributed to discrepancies in study design, sample sizes, and methodologies. The discrepancies in patient populations and treatment protocols, including variations in PRP formulations and administration methods, render comparisons between studies challenging.

The focus of the review on English-language studies may result in the exclusion of pertinent studies from non-English-language sources, which could potentially limit the completeness of the findings. Furthermore, the focus on arthroscopy does not encompass other surgical options or novel technologies that may influence treatment outcomes.

It should be noted that the review reflects data available up to a certain point in time; therefore, recent advances and new evidence may not be included. It is imperative that ongoing research and updates are conducted to ensure that the most current and effective treatment recommendations for knee Osteoarthritis are provided.

5. Conclusions

This review has emphasised the importance of a multifaceted approach to the management of KOA, incorporating both conservative and minimally invasive strategies. It is well established that conservative therapies, including exercise, weight management and patient education, are foundational interventions that can alleviate symptoms and improve functionality. These non-pharmacological interventions are consistently supported by clinical guidelines and evidence demonstrating their efficacy in the treatment of knee osteoarthritis symptoms and improvement of quality of life.

Injectable therapies, including PRP, have emerged as potential alternatives to traditional pharmacological treatments. Despite the promising nature of PRP due to its less invasive nature, the evidence for its efficacy in comparison to conventional therapies remains variable. This indicates that further research is required to elucidate its role and to optimise its utilisation in the treatment of knee osteoarthritis.

Minimally invasive surgical options, particularly arthroscopy, are typically considered for patients who do not respond to conservative treatment. Although arthroscopy can provide relief for some patients, it is often regarded as a secondary intervention, employed subsequent to the exploration of other treatment modalities. The current evidence indicates that while arthroscopy may be beneficial in certain cases, it does not consistently yield significant long-term benefits when compared to conservative or other treatment options.

In conclusion, while current therapeutic modalities provide valuable treatment options for knee osteoarthritis, further research is still required to refine these approaches and address gaps in the evidence base. This will facilitate the implementation of efficacious and patient-specific treatment strategies, thereby enhancing outcomes for those afflicted with knee osteoarthritis. Future trends should focus on refining regenerative approaches such as exosome and stem cell therapies, aiming for enhanced cartilage repair and durability. Additionally, integrating personalized treatment plans based on patient-specific factors could improve outcomes and optimize resource use.

Author Contributions

YK – Conceptualization, project leadership, supervision, critical revision of the manuscript, final approval of the version to be published; D.B. – Structural design of the review, development of article framework, methodological structuring, coordination of literature synthesis; A.A. – Literature search and data extraction; I.M. – Analysis of pharmacological treatment strategies; A.S. – Analysis of non-pharmacological treatment modalities; K.A. – Review

and synthesis of injectable therapies (HA, PRP); A.I. – Clinical interpretation of minimally invasive surgical strategies; D.I. – Data organisation, manuscript drafting and formatting; A.Z. – Statistical and methodological quality appraisal of included studies; A.A. – Critical scientific editing, language revision, harmonisation of the final manuscript.

AI-assisted tools were used solely for language editing and text refinement. The authors take full responsibility for the content of the manuscript.

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Тізе буынының остеоартрозын емдеудің заманауи стратегиялары: Әдеби шолу

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Түйіндеме

Тізе туынының остеоартрозы (ТБО) жоғары таралуына және онымен байланысты экономикалық және әлеуметтік ауыртпалығына байланысты қоғамдық денсаулық сақтаудың негізгі мәселесі болып табылады. ТБО емінің негізгі мақсаты - симптомдарды жеңілдету, буын қызметін жақсарту және пнауқастардың өмір сапасын жақсарту.

Әдістер. PubMed негізгі дерекқоры ретінде пайдаланылып, жан-жақты әдебиетке шолу жүргізілді. Іздеу стратегиясына «тізе буынының остеоартрозы», «емдеу», «фармакологиялық емдеу», «фармакологиялық емес емдеу» және «инъекциялық терапия» сияқты түйін сөздер кірді. Іздеу 2019 және 2024 жылдар аралығында жарияланған мақалалармен шектелді, рандомизацияланған бақыланатын сынақтарды, жүйелі шолуларды және мета талдауларды қоса алғанда, жоғары сапалы зерттеулерге баса назар аударылды. Мақалалар өзектілігі, әдіснамалық сапасы және толық мәтіннің қолжетімділігі негізінде іріктеуден өткізілді.

Нәтижелері. ТБО фармакологиялық емдеуіне қысқа мерзімді ауырсынуды басатын, бірақ ұзақ мерзімді жанама әсерлері болуы мүмкін СЕҚҚД, КОГ-2 ингибиторлары және парацетамол кіреді. Физиотерапия, жаттығу және салмақты басқару сияқты фармакологиялық емес тәсілдер буын қызметін жақсарту және ауырсынуды азайту үшін өте маңызды. Гиалурон қышқылы мен тромбоциттермен байытылған плазманы (ТБП) қоса алғанда, инъекциялық терапия перспективалы нәтижелер көрсетті. Дегенмен, аталған емнің ұзақ мерзімді тиімділігін растау үшін қосымша зерттеулер қажет. Мақалада талқыланған хирургиялық араласулар минималды инвазивті нұсқалармен, әсіресе консервативті емдеу тиімсіз болған ауыр жағдайларда қарастырылатын артроскопиямен шектеледі. Артротомия және буындарды ауыстыру сияқты ашық оталар шолуда қарастырылмады.

Қорытынды. ТБО-ын тиімді емдеу фармакологиялық және фармакологиялық емес емдеуді озық терапиялық нұсқалармен біріктіретін кешенді тәсілді қажет етеді. Дәстүрлі емдеу әдістері іргелі болып қала

берсе де, жаңа емдеу және хирургиялық нұсқалар дамып келеді, бұл емдеу стратегияларын оңтайландыру және науқастардағы емнің нәтижелерін жақсарту үшін үздіксіз зерттеулердің қажеттілігін көрсетеді.

Түйін сөздер: тізе буынының остеоартрозы, тізе буыны остеоартрозын емдеу, фармакологиялық терапия, фармакологиялық емес емдеу, физиотерапия, гиалурон қышқылын енгізу, тромбоциттермен байытылған терапия, буынды алмастыру.

Современные стратегии лечения остеоартроза коленного сустава: Обзор литературы

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Резюме

Остеоартроз коленного сустава (ОАКС) представляет собой серьезную проблему общественного здравоохранения из-за его высокой распространенности и связанных с ним экономических и социальных проблем. Главная цель лечения ОАКС — облегчение симптомов, улучшение функции сустава и повышение качества жизни пациента.

Методы. Был проведен всесторонний обзор литературы с использованием PubMed в качестве основной базы данных. Стратегия поиска включала ключевые слова, такие как «остеоартроз коленного сустава», «лечение», «фармакологическое лечение», «немедикаментозное лечение» и «инъекционная терапия». Поиск был ограничен статьями, опубликованными в период с 2019 по 2024 год, с акцентом на высококачественные исследования, включая рандомизированные контролируемые исследования, систематические обзоры и метаанализы. Статьи были отфильтрованы по релевантности, методологическому качеству и доступности полного текста.

Результаты. Фармакологические методы лечения ОАКС включают НПВП, ингибиторы ЦОГ-2 и парацетамол, которые обеспечивают кратковременное облегчение боли, но могут иметь долгосрочные побочные эффекты. Нефармакологические подходы, такие как физиотерапия, физические упражнения и контроль веса, имеют решающее значение для улучшения функции сустава и уменьшения боли. Инъекционные методы лечения, включая гиалуроновую кислоту и обогащенную тромбоцитами плазму (ОПТ), демонстрируют многообещающие результаты, хотя необходимы дальнейшие исследования для подтверждения их долгосрочной эффективности. Хирургические вмешательства, обсуждаемые в этой статье, ограничиваются малоинвазивными вариантами, в частности артроскопией, которая рассматривается в тяжелых случаях, когда консервативное лечение оказывается неэффективным. Открытые операции, такие как артротомия и замена сустава, не входили в рамки данного обзора.

Выводы. Эффективное лечение ОАКС требует комплексного подхода, сочетающего фармакологические и нефармакологические методы лечения с передовыми терапевтическими возможностями. Хотя традиционные методы лечения остаются основополагающими, новые методы лечения и хирургические

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варианты продолжают развиваться, что подчеркивает необходимость постоянных исследований для оптимизации стратегий лечения и улучшения результатов лечения пациентов.

Ключевые слова: остеоартроз коленного сустава, лечение остеоартроза коленного сустава, медикаментозное лечение, немедикаментозное лечение, физиотерапия, инъекции гиалуроновой кислоты, терапия обогащенной тромбоцитами плазмой, эндопротезирование сустава.

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