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Review

Physiotherapy for Osteoarthritis Following Orthobiological Injections – a Narrative Review of Recent Literature

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Abstract

The integration of orthobiologic injection modalities with structured physiotherapy regimens has emerged as a promising avenue for optimizing recovery trajectories in patients affected by osteoarthritis (OA). While these interventions demonstrate therapeutic potential, the existing research exhibits substantial variability in patient demographics, injection methodologies, study duration, and outcome assessment. Furthermore, despite the recognized importance of post-injection rehabilitation, comprehensive documentation of physiotherapy protocols remains scarce, precluding a definitive understanding of their complementary effects with orthobiologic treatments.

This study evaluates and synthesizes the current evidence on the therapeutic efficacy of orthobiologic injections, platelet-rich plasma (PRP) and other cell-based regenerative therapies when implemented alongside physiotherapeutic interventions in patients with knee OA. The absence of standardized post-injection physiotherapy protocols, coupled with inconsistent methodological frameworks, impedes the formulation of evidence-based rehabilitation guidelines. Accordingly, future research must prioritize longitudinal, well-controlled investigations that delineate the optimal integration of physiotherapy with orthobiologic therapies to maximize functional restoration and long-term symptom management in OA.

A structured literature search was conducted via PubMed, utilising a strategic combination of Medical Subject Headings (MeSH) and targeted keywords to

ensure thorough retrieval of relevant studies. A total of sixteen studies met the inclusion criteria, all of which reported favourable outcomes following orthobiologic injections. Interestingly, only one trial incorporated a general physiotherapy program, thus emphasizing the noticeable gap in literature regarding the integration of orthobiologic injections with standard rehabilitative strategies.

Introduction

Osteoarthritis (OA) is a multifactorial degenerative joint disorder characterised by the progressive degradation of articular cartilage, which leads to the involvement of surrounding joint structures such as the subchondral bone, ligaments, and synovium (1, 2). The management of OA requires a multimodal approach encompassing pharmacological, non-pharmacological, and surgical strategies (3). While conservative therapies are often effective in mitigating symptoms, certain cases progress to advanced stages where these interventions become insufficient, necessitating surgical options. It is therefore not surprising that the development of minimally invasive surgical techniques has transformed OA management by offering the potential to regenerate damaged joint structures, alleviate symptoms, and slow disease progression (4).

Among emerging non-surgical approaches, orthobiological products have gained prominence for their ability to enhance tissue repair and reduce pain across various musculoskeletal pathologies, including cartilage, ligament, tendon, and bone injuries. Frequently orthobiologic treatments applied in OA management include hyaluronic acid, platelet-rich plasma (PRP), mesenchymal stem cells (MSCs) delivered as bone marrow aspirate concentrate (BMAC), and stromal vascular fraction (SVF) (5).

The therapeutic effects of orthobiologic injections are closely linked to mechanobiology, as biomechanical processes play a key role in stimulating tissue repair and functional recovery (6). Physiotherapy works within the same framework, aiming to reduce pain, improve mobility, and enhance overall function by using targeted interventions (7). This includes manual therapy, thermotherapy, therapeutic ultrasound, laser therapy, and magnetotherapy, all of which support joint health and promote healing (8). To effectively integrate these treatments into a rehabilitation program, a thorough understanding of the biological/physiological mechanisms that drive musculoskeletal regeneration is essential, allowing interventions to be tailored for optimal recovery (6).

Methods

Review objective and eligibility criteria

The target population for this review includes adults aged 18 years and older diagnosed with osteoarthritis who have undergone orthobiologic injections, followed by recommended physiotherapeutic interventions such as exercise therapy, manual therapy, and physical agents to optimize clinical outcomes. To ensure the inclusion of high-quality, contemporary evidence, only randomized controlled trials published in English from 2014 to 2024 were considered.

Information sources and search strategy

A comprehensive literature search was conducted in PubMed utilising a combination of Medical Subject Headings (MeSH) and specific keywords to ensure thorough coverage. The search terms included: (Osteoarthritis) AND (Injection) AND ((Physiotherapy) OR (Rehabilitation)); (Osteoarthritis) AND (Injection) AND (Postinjection); (Physiotherapy) OR (Physical Therapy) OR (Exercise); (Orthobiologics) OR (Platelet-rich plasma); (Orthobiologics) OR (Stem cell) OR (Stromal vascular fraction); and (Orthobiologics) OR (Bone marrow aspirate) OR (Stem cell). The filters were applied to restrict results to randomized controlled trials published from 2014 to 2024, focusing on studies relevant to the scope of this review.

Study selection process and data synthesis

The initial screening process involved a review of titles and abstracts to identify potentially relevant

studies, which were then retrieved for comprehensive evaluation. Data extraction was conducted using a standardised approach, capturing key details such as study design, population characteristics, orthobiologic and physiotherapy interventions, and outcomes. A narrative synthesis was performed across all included studies, integrating critical characteristics, interventions, and observed outcomes into a cohesive summary.

Limitations

The search strategy lacked a standardized query instead of relying on multiple searches, which may have led to gaps or inconsistencies in the search results. Without a uniform approach, there is no certainty that all the relevant studies were identified, raising the possibility of missing key research or unintentionally introducing selection bias. Any such inconsistency in search methodology could ultimately impact the completeness and reliability of the review's findings.

Results

Sixteen articles met the inclusion criteria, each reporting positive effects of orthobiologic injections. Among them, only Mautner et al. implemented a general physiotherapy program that remained consistent regardless of the injection type. The remaining studies provided limited guidance, offering general recommendations on physiotherapy, physical activity, exercise, or therapeutic modalities following orthobiologic treatment. A comprehensive summary of the selected articles is presented in Table 1.

Discussion

Platelet-rich plasma (PRP)

Platelets, anucleate cell fragments circulating within the blood, play a fundamental role in haemostasis by forming haemostatic plugs and releasing coagulation factors at injury sites, a process orchestrated by a diverse array of proteins, cytokines, and bioactive factors. Simultaneously, they regulate wound healing through the secretion of growth factors such as PDGF, TGF-β, and VEGF, which drive angiogenesis, modulate inflammation, and recruit progenitor cells for tissue repair. Building on these biological properties, PRP has emerged as a therapeutic modality associated with enhanced tissue repair and regeneration. PRP is characterised by a platelet concentration significantly higher than baseline, requiring a minimum of 10^6 platelets per µL (or about 5 times the baseline) (25, 26).

Across multiple studies, PRP has consistently yielded significant improvements in VAS and WOMAC scores, indicating substantial reductions in pain, stiffness, and functional impairment (9 – 18). Notably, sustained benefits have been observed in both PRP and PRGF (Plasma Rich in Growth Factors) groups at 12 months, surpassing conventional treatments such as CST and HA. These outcomes are driven by the biologically active components of PRP, which modulate inflammation and facilitate tissue repair, offering not only immediate symptom relief but also long-term therapeutic effects. The additional evidence of lasting improvements in VAS and Lequesne scores with PRGF, alongside higher patient satisfaction compared to HA, demonstrate the potential of growth factor-rich therapies for managing chronic conditions (14, 15, 17). Beyond symptom relief, PRP improves functional capacity and overall well-being, as suggested by higher IKDC and SF-36 scores (9 – 12, 16, 19).

Importantly, a three-injection PRP protocol has shown superior efficacy over single-injection PRP or CST, further supporting the importance of optimising treatment regimens to maximise results of clinical outcomes (17).

Compared to AAT (Adipose Autologous Tissue), PRP differs in efficacy, with AAT demonstrating greater

Table 1. **Included articles**

Study	Population	OA grade	Study group	Injection time protocol [week]	Number of injections	Duration of study	Post-injection intervention	Outcome measures
Cole et al. 2017 (9)	111 patients	KL 1-3	G1: HA	0, 1, 2	3	52 weeks	Weight bearing restrictions, ice/cold therapy, exercise	VAS, WOMAC, IKDC, ELISA
			G2: PRP	0, 1, 2	3			
Elik et al. 2020 (10)	60 patients	KL 1-3	G1: PRP	0, 4, 24	3	6 months	No NSAID; paracetamol, exercise	VAS, WOMAC, SF-36, Ultrasonography
			G2: PL	0	1			
Kaszy´nski et al. 2022 (11)	60 patients	KL 1-3	G1: AAT	0, 1, 2	3	12 months	Weight bearing restrictions, exercise	VAS, KOOS, WOMAC, IKDC, EQ-5D-5L; TUG test, 5xSTS; 10mWT
			G2: PRP	0	1			
			G3: Control					
Raeissadat et al. 2015 (12)	160 patients	KL 2,3	G1: HA	0, 1, 2	3	12 months	Rest, No NSAID; paracetamol, ice/cold therapy, weight bearing restrictions, exercise	WOMAC, SF - 36
			G2: PRP	0, 4	2			
Raeissadat et al. 2020 (13)	23 patients (46 knees)	KL 1-3	G1: PRP	0, 4	2	8 months	No NSAID; paracetamol, exercise	VAS, WOMAC, MRI
			G2: EX					
Raeissadat et al. 2020 (14)	102 patients	KL 2,3	G1: HA	0, 1, 2	3	12 months	Rest, active knee flexion and extension after a 20-min rest for the injected fluid dispersion, no NSAID; acetaminophen, exercise	VAS, WOMAC, Lequesne index
			G2: PRGF	0, 3	2			
Raeissadat et al. 2021 (15)	238 patients	KL 2,3	G1: HA	0, 1, 2	3	12 months	Rest, active knee flexion and extension after a 20-min rest for the injected fluid dispersion, no NSAID; paracetamol, ice/cold therapy, exercise	VAS, WOMAC, Lequesne index
			G2: PRP	0, 3	2			
			G3: PRGF	0, 3	2			
			G4: OZ	0, 1, 2	3			
Rayegani et al. 2014(16)	62 patients	KL 1-4	G1: PRP, EX	0, 4	2	6 months	Rest, active knee flexion and extension after a 20-min rest for the injected fluid dispersion, no NSAID; acetaminophen, ice/cold therapy, exercise	WOMAC, SF-36, QOL
			G2: EX					

Table 1. **Included articles**

Study	Population	OA grade	Study group	Injection time protocol [week]	Number of injections	Duration of study	Post-injection intervention	Outcome measures
Uslu Güvendi et al. 2018 (17)	50 patients	KL 3	G1: CST	0	1	6 months	Immobilization, rest, ice/cold or heat therapy, paracetamol, exercise	VNS, WOMAC, Lequesne index, HAD
			G2: PRP	0	1			
			G3: PRP	0, 1, 2	3			
Xu et al. 2024 (18)	48 patients	KL 1-3	G1: PRP	0, 1, 2 (months)	3	12 weeks	Low-frequency PEMFs irradiation therapy with a frequency of 30 Hz and intensity of 1.5 mT, once daily, 5 times a week for 12 weeks	VAS, WOMAC, Lequesne Index, ROM
			G2: PEMF					
			G3: PRP, PEMF	0, 1, 2	3			
Anz et al. 2020 (19)	90 patients	KL 1-3	G1: PRP	0	1	12 months	No NSAID, weight bearing restrictions, physiotherapy	WOMAC, IKDC
			G2: BMAC	0				
Freitag et al. 2019 (20)	30 patients	KL 2,3	G1: control			12 months	Weight bearing restrictions, crutches, exercise	NPRS, KOOS, WOMAC, MRI
			G2: ADMS	0 (months)	1			
			G3: ADMS	0, 6 (months)	2			
Garza et al. 2020 (21)	39 patients	KL 2,3	G1: hd SVF	0	1	12 months	Weight bearing restrictions, exercise	WOMAC, MRI
			G2: ld SVF	0	1			
			G3: PL	0	1			
Hong et al. 2018 (22)	16 patients (32 knees)	KL 2,3	G1: SVF, HA	0	1	12 months	Weight bearing restrictions, physical activity, Celebrex	WOMAC, ROM, MRI
			G2: HA, SVF	0	1			
Mautner et al. 2023 (23)	480 patients	KL 2-4	G1: BMAC	0	1	12 months	Weight bearing restrictions, physiotherapy	VAS, KOOS, EQ-5D, PROMIS-29 scores
			G2: SVF	0	1			
			G3: UCT	0	1			
			G4: CST	0	1			
Zhang et al. 2022 (24)	126 patients	KL 2,3	G1: SVF	0, 1, 2 (months)	3	5 years	Weight bearing restrictions, physical activity	VAS, WOMAC, Radiography, MRI
			G2: HA	0, 1, 2 (months)	3			

AAT – Autologus adipose tissue, ADMS – Adipose-derived mesenchymal stem cell, BMAC –Bone marrow aspirate concentrate, CST – Corticosteroids, ELISA – Enzyme-linked Immunosorbent Assay, EQ-5D-5L – Health Questionnaire EQ-5D-5L, HA – Hyaluronic acid, HAD – Hospital Anxiety and Depression Scale, hd, PRP –High dose stromal vascular fraction, IKDC – International Knee Documentation Committee, KL – Kellgren–Lawrence, KOOS – Knee Injury and Osteoarthritis Outcome Score, ld PRP – Low dose stromal vascular fraction, 10mWT –10 m Walk Test, NPRS – Numeric pain rating scale, OZ – Ozone, PEMF – Pulsed electromagnetic fields, PL – Placebo, PRGF-PRP – derived growth factor, PRP – Platelet-rich plasma, QOL – Quality of life score, ROM – Range of motion, SF 36 – Short Form Health Survey, 5*STS – 5 Times Sit to Stand Test, SVF – Stromal vascular fraction, TUG – The Timed Up and Go test, UCT – Allogeneic human umbilical cord tissue-derived mesenchymal stromal cells, VAS – Visual analog scale, VNS – Visual numeric scale, WOMAC – Western Ontario and McMaster Universities Osteoarthritis Index, G1– Group 1, G2 – Group 2; G3 – Group 3; G4 – Group 4.

improvements in functional assessments such as TUG (Timed Up and Go), STS (Sit-to-Stand), and MWT (6-Minute Walk Test). This suggests that AAT may be more appropriate in cases where mobility restoration is the primary concern, either as a standalone treatment or in conjunction with PRP. To that degree, the adaptability of biological therapies in alleviating pain and inflammation while enhancing physical function points to the necessity of more tailored and patient-specific treatment approaches (11).

In contrast to commonly used outcome measures such as VAS and WOMAC, measure like MRI offers a detailed visualisation of joint structures, enabling the detection of early osteoarthritic changes and the assessment of cartilage integrity (27). A trial conducted by Raeissadat et al. (13) demonstrated the positive effects of PRP on MRI findings, including increased patellofemoral cartilage volume and reduced synovitis, whereas Elik et al. (10) found no statistically significant difference in distal femur cartilage thickness via ultrasonography. Additionally, biochemical methods analyse metabolic processes in OA, aiding in the identification of molecular markers associated with disease progression (27). Biochemical analyses showed reduced pro-inflammatory cytokine levels in the PRP-treated group, which may account for the symptomatic improvements in clinical outcomes (9).

Mesenchymal stem cells (MSCs)

Mesenchymal stem cells (MSCs) are multipotent progenitor cells capable of differentiating into a variety of mesenchymal lineages (7, 28). These cells exhibit remarkable self-renewal capacity and plasticity, possessing notable immunosuppressive and anti-inflammatory properties. MSCs can be derived from a range of tissue sources, including bone marrow, adipose tissue, peripheral blood, and synovial membranes (29). Among these sources, bone marrow is a well-established source of MSCs. Its extraction typically involves aspirating marrow, which is then processed to yield BMAC, a concentrated formulation of bone marrow-derived cells (30). Similarly, adipose tissue serves as a significant source of regenerative and immunomodulatory cells, primarily contributing to the SVF (31).

Given the potential of MSCs in regenerative medicine, extensive investigations into the efficacy and safety of intra-articular cellular injections have been conducted. Mauetner et al. evaluated 480 patients with KL grades 2 – 4 OA. Following the injection, all trial groups adhered to a physiotherapy protocol. One year later, VAS and KOOS assessments revealed significant pain reduction across all groups, where none of the orthobiologic injections demonstrated superior efficacy compared to CST, and no serious adverse events related to the procedure were reported (23).

Cellular preparations derived from SVF have shown significantly better outcomes compared to hyaluronic acid injections (22, 24). Moreover, repeated injections have proven more effective than control treatments in enhancing joint function, relieving pain, and slowing OA progression (20, 21).

Despite these clinical improvements, MRI assessments have provided inconsistent findings regarding structural changes in the joint. Muetner et al. observed no significant differences in joint health or cartilage condition among groups treated with BMAC, SVF, UCT, or CST after one year (23). However, other studies reported mixed results; while SVF injections led to functional improvements, MRI evaluations revealed no measurable changes in the modified Outerbridge classification or chondral thickness, a limitation that may stem from the resolution constraints of MRI imaging (21).

SVF treatment improved cartilage repair and reduced bone marrow abnormalities in some cases, but the results were worse in knees with severe cartilage damage, making advanced structural degeneration difficult to treat. Control groups, especially those receiving HA, showed little effect on cartilage repair (22).

While SVF treatment led to functional improvements, its long-term impact on structural changes remains unclear. Zhang et al. found no improvements in bone marrow lesions (BMLs) after SVF injections, suggesting that the therapy may relieve symptoms or aid superficial repair, but it does not address deeper bone-related changes in OA. A five-year follow-up showed no significant differences in BMLs between SVF-treated groups and controls, indicating its limitations in reversing bone damage. Final radiological evaluations showed that total cartilage volume loss was reduced in both the SVF and HA groups. More patients in the SVF group maintained or improved full-thickness cartilage defects, with fewer experiencing progression compared to the HA group (24).

A study comparing injection regimens found that two injections were most effective, with 89% of partici-

pants maintaining or improving cartilage health and no osteophyte progression. Single injections provided moderate benefits, while the control group experienced significant cartilage loss and osteophyte development. Synovitis, meniscus damage, and popliteal cysts remained unchanged across all groups, showing the complexity of OA and the need for more targeted treatments (20).

Physiotherapy and co-interventions

Physiotherapy treatment should be structured according to the phases of the regenerative process: inflammation, proliferation, and maturation. While these phases have general timeframes, their duration varies between individuals. Age, sex, comorbidities, and the extent of structural damage influence the progression of each phase (6). Treatment is personalized, with goals and plans developed in collaboration with the patient to match their functional needs and priorities (8).

Orthobiological injections often cause inflammation and pain, requiring immobilization or support, the application of ice, elevation, and medication for management (17). It is commonly advised to avoid taking NSAIDs before and after treatment in the early stages, as they interfere with platelet function and reduce growth factor release. Other analgesics can be prescribed instead. Cryotherapy may help manage pain, but concerns remain that reduced blood flow could slow healing (9-24).

Swelling can be addressed through lymphatic drainage, which improves circulation, intercellular signalling mechanisms, and the release of growth factors. Additionally, the injection site needs to be protected by reducing the load on the treated segment through rest or immobilization. Although initial immobilization is recommended, small range-of-motion movements can be performed after the first day of treatment (9, 11, 19 – 22, 32).

The resolution of inflammation marks the transition into the second phase of healing, typically occurring between 3 and 14 days following treatment (32). During this phase, it is recommended to focus on increasing the range of motion, enhancing circulation in the treated area, and improving tissue resilience through therapeutic exercises. The intensity and type of physiotherapy interventions during this period should be guided by the patient's tolerance to activity. A practical guideline is to avoid exercises or activities that elicit pain exceeding 3/10 on a numerical rating scale either during or after the activity (10, 33).

As healing progresses, controlled mechanical loading through therapeutic exercises becomes essential for collagen reorganization and tissue recovery. Strengthening and stretching exercises performed in water are particularly beneficial during this phase (32). Water-based exercises minimise mechanical stress on the joints while providing resistance to support muscle strengthening. For intra-articular injections, strengthening programmes may be initiated earlier than for tendons or ligaments, given the differences in healing dynamics (33).

To optimize healing and rehabilitation outcomes, incorporating physical agents into treatment may be beneficial. For instance, pulsed electromagnetic fields (PEMF) have been shown to enhance the bioavailability of PRP growth factors by stimulating cellular uptake and activation, thereby improving tissue repair and functional recovery. Xu et al. investigated the use of PEMF applied five times per week over 12 weeks, reporting significant improvements in pain measured via VAS, function via WOMAC, and mobility compared to standalone PRP or PEMF therapy (18). Additionally, extracorporeal shock wave therapy (ESWT) has shown promising results in treating OA combined with intraarticular injections, as a non-invasive therapy that applies mechanical force to tissue cells by passing through different mediums. When subjected to mechanical force, cells generate biological signals that stimulate anti-inflammatory responses, angiogenesis, immune modulation, cell proliferation, and cartilage protection (34 – 36).

During healing, exercise programs should progress from single-joint to multi-joint movements. Isometric contractions are the safest option at this stage due to restricted joint mobility and provide short-term pain relief. In knee OA, the focus is on strengthening the locomotor chain, including the hip, knee, and ankle joints (32). Raeissadat et al. proposed a protocol with multi-angle isometric strengthening exercises for the quadriceps femoris, hip adductors, and abductors, along with hamstring stretching. Participants performed these exercises three times daily, holding each stretch for 10 seconds and repeating it 10 times (13). As patients progress, simple knee flexion and extension exercises can be advanced to more complex movements such as lunges, squats, and seated holds (33).

Stretching exercises are recommended between 24 hours and one week post-treatment, but the optimal modality, whether dynamic, static, or proprioceptive neuromuscular facilitation (PNF), remains unclear. Stretching improves flexibility and joint range of motion. Exercises should be pain-free and adapted to the patient's needs and tolerance (37).

Eccentric contractions are typically avoided in the early stages of healing due to concerns that they may impair the healing cascade by reducing vascularisation. Consequently, eccentric exercises are more appropriately introduced during the late proliferative or remodelling phases (37). To manage pain alongside exercise, transcutaneous electrical nerve stimulation (TENS) may be employed. By the end of the second phase, low-impact aerobic activities such as cycling, swimming, and walking can be gradually introduced to maintain or improve cardiorespiratory fitness (23, 32).

In the early third phase (weeks 3 to 4), pain typically subsides, and full joint range of motion should be restored. The focus shifts to increasing activity levels, progressively building muscle strength and endurance. If not started earlier, eccentric strengthening exercises begin at this stage, along with proprioceptive and stability training. Water-based exercises should increase in duration and intensity to improve aerobic capacity.

In the later third phase (weeks 5 to 10), exercises become more complex, incorporating multi-plane movements and adjusting loads based on progress. High-intensity resistance training may be introduced when appropriate. Aerobic activities such as cycling, swimming, and running continue to support overall fitness. Monitoring pain, joint mobility, and motor control ensures safe and effective progression (32).

Conclusion

Orthobiologic injections have shown positive results in OA management, with most studies evaluating outcomes using VAS and WOMAC scores, where these measures consistently indicate pain relief and functional improvement. However, MRI findings remain inconsistent, suggesting that structural changes may not always align with symptomatic benefits. Variability in patient populations, OA severity, injection protocols, and administration intervals further complicates comparisons. Multiple injections are administered at intervals ranging from weeks to months, with no clear consensus on the optimal dosing schedule.

Despite the potential benefits of orthobiologic therapies, post-injection rehabilitation protocols are poorly defined. While many studies acknowledge the importance of physiotherapy, this review identifies one study that provides guidelines on exercise selection, progression, or timing relative to injection administration. Most rehabilitation programs are briefly mentioned or entirely undocumented, limiting the ability to assess their role in treatment outcomes, which shows a significant gap in the literature.

The relationship between orthobiologic injections and physiotherapy remains unclear due to the lack of standardized rehabilitation protocols. Future research should focus on developing evidence-based post-injection rehabilitation strategies and establishing standardized outcome measures beyond self-reported pain and function scores. More comprehensive assessments, including objective imaging and long-term follow-up studies, are needed to determine the true impact of orthobiologic therapies following physiotherapy on OA progression and recovery.

Author Contributions

Conceptualization (IČ, AI, MF); Data Curation (DK), Formal Analysis (IČ, DK); Writing – Original Draft (IČ), Writing – Review & Editing (IČ, AI, MF, DK). All authors reviewed and approved the final version of the manuscript.

Conflict of Interest

The authors declare no conflicts of interest.

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References

1. Hawkins T, Bar A. Osteoarthritis: pathophysiology and diagnosis. Clin Pharm, CP. 2015;7(3). https://doi.org/10.1211/PJ.2015.20068288
2. Khon MD, Sasson AA, Navin FD. Classifications in Brief: Kellgren-Lawrence Classification of Osteoarthritis. Clin Orthop Relat Res. 2016;474(8):1886-93. https://doi.org/10.1007/s11999-016-4732-4
3. Grazio S, Ćurković B, Babić-Naglić Đ, Anić B, Morović-Vergles J, Vlak T, et al. Guidelines of the Croatian Society for Rheumatology for the treatment of knee and hip osteoarthritis. Reumatizam. 2010;57(1):36-47.
4. Chen T, Weng W, Liu Y, Aspera-Werz RH, Nüssler AK, Xu J. Update on Novel Non-Operative Treatment for Osteoarthritis: Current Status and Future Trends. Front Pharmacol. 2021;12:755230. https://doi.org/10.3389/fphar.2021.755230
5. Graeff JJ, van den Bekerom MPJ, van Meer BL, Zijl JAC. Orthobiologics and hyaluronic acid usage in the Netherlands: an electronic survey of 265 orthopaedic surgeons and sports physicians. J Exp Orthop. 2021;8(1):66. https://doi.org/10.1186/s40634-021-00380-9
6. Centeno CJ, Pastoriza SM. Past, current and future interventional orthobiologics techniques and how they relate to regenerative rehabilitation: A clinical commentary. Int J Sports Phy Ther. 2020;15(2):301-25.
7. Margiana R, Markov A, Zekiy AO, Hamza MU, Al-Dabbagh KA, Al-Zubaidi SH, et al. Clinical application of mesenchymal stem cell in regenerative medicine: a narrative review. Stem Cell Res Ther. 2022;13(1):366. https://doi.org/10.1186/s13287-022-03054-0
8. HKF. Kliničke smjernice za fizikalnu terapiju kod osteoartritisa kuka i koljena, Hrvatska komora fizioterapeuta. In: Grubišić M, Hofmann G, Jurinić A, editors. Kliničke smjernice u fizikalnoj terapiji. Zagreb: HKF: 2018. Croatian.
9. Cole BJ, Karas V, Hussey K, Pilz K, Fortier LA. Hyaluronic acid versus platelet-rich plasma: a prospective, double-blind randomized controlled trial comparing clinical outcomes and effects on intra-articular biology for the treatment of knee osteoarthritis. Am J Sports Med. 2017;45(2):339-46. https://doi.org/10.1177/0363546516665809
10. Elik H, Dogu B, Yılmaz F, Begoglu FA, Kuran B. The efficiency of platelet-rich plasma treatment in patients with knee osteoarthritis. J Back Musculoskelet Rehabil. 2020;33:127–38. https://doi.org/10.3233/BMR-181374
11. Kaszyński J, Bąkowski P, Kiedrowski B, Stołowski Ł, Wasilewska-Burczyk A, Grzywacz K, et al. Intra-Articular Injections of Autologous Adipose Tissue or Platelet-Rich Plasma Comparably Improve Clinical and Functional Outcomes in Patients with Knee Osteoarthritis. Biomedicines. 2022;10(3):684. https://doi.org/10.3390/biomedicines10030684
12. Raeissadat SA, Rayegani SM, Hassanabadi H, Fathi M, Ghorbani E, Babaee M, et al. Knee osteoarthritis injection choices: Platelet-rich plasma (PRP) versus hyaluronic acid (A one-year randomized clinical trial). Clin Med Insights Arthritis Musculoskelet Disord. 2015;8:1-8. https://doi.org/10.4137/CMAMD.S17894
13. Raeissadat SA, Ghorbani E, Sanei Taheri M, Soleimani R, Rayegani SM, Babaee M, et al. MRI Changes After Platelet Rich Plasma Injection in Knee Osteoarthritis (Randomized Clinical Trial). J Pain Res. 2020;13:65-73. https://doi.org/10.2147/JPR.S204788
14. Raeissadat SA, Gharooee Ahangar A, Rayegani SM, Minator Sajjadi M, Ebrahimpour A, Yavari P. Platelet-Rich Plasma Derived Growth Factor vs Hyaluronic Acid Injection in the Individuals with Knee Osteoarthritis: A One Year Randomized Clinical Trial. J Pain Res. 2020;13:1699-711. https://doi.org/10.2147/JPR.S210715
15. Raeissadat SA, Ghazi Hosseini P, Bahrami MH, Salman Roghani R, Fathi M, Gharooee Ahangar A, et al. The comparison effects of intra-articular injection of Platelet Rich Plasma (PRP), Plasma Rich in Growth Factor (PRGF), Hyaluronic Acid (HA), and ozone in knee osteoarthritis; a one year randomized clinical trial. BMC Musculoskelet Disord. 2021;22(1):134. https://doi.org/10.1186/s12891-021-04017-x
16. Rayegani SM, Raeissadat SA, Taheri MS, Babaee M, Bahrami MH, Eliaspour D, et al. Does intra articular platelet rich plasma injection improve function, pain and quality of life in patients with osteoarthritis of the knee? A randomized clinical trial. Orthop Rev. 2014;6(3):112-7. https://doi.org/10.4081/or.2014.5405
17. Uslu Güvendi E, Aşkin A, Güvendi G, Koçyiğit H. Comparison of efficiency between corticosteroid and platelet rich plasma injection therapies in patients with knee osteoarthritis. Arch Rheumatol. 2017;33(3):273-81. https://doi.org/10.5606/ArchRheumatol.2018.6608
18. Xu RD, Li JH, Zhang H, Liang HR, Duan SY, Sun M, et al. The combined application of pulsed electromagnetic fields and platelet-rich plasma in the treatment of early-stage knee osteoarthritis: A randomized clinical trial. Medicine (Baltimore). 2024;103(35):e39369. https://doi.org/10.1097/MD.0000000000039369
19. Anz AW, Plummer HA, Cohen A, Everts PA, Andrews JR, Hackel JG. Bone marrow aspirate concentrate is equivalent to platelet-rich plasma for the treatment of knee osteoarthritis at 2 years: a prospective randomized trial. Am J Sports Med. 2022;50(3):618-29. https://doi.org/10.1177/03635465211072554
20. Freitag J, Bates D, Wickham J, Shah K, Huguenin L, Tenen A, et al. Adipose-derived mesenchymal stem cell therapy in the treatment of knee osteoarthritis: a randomized controlled trial. Regen Med. 2019;14(3):213-30. https://doi.org/10.2217/rme-2018-0161

21. Garza JR, Campbell RE, Tjoumakaris FP, Freedman KB, Miller LS, Santa Maria D, et al. Clinical efficacy of intra-articular mesenchymal stromal cells for the treatment of knee osteoarthritis: A double-blinded prospective randomized controlled clinical trial. Am J Sports Med. 2020;48(3):588-98. https://doi.org/10.1177/0363546519899923
22. Hong Z, Chen J, Zhang S, Zhao C, Bi M, Chen X, et al. Intra-articular injection of autologous adipose-derived stromal vascular fractions for knee osteoarthritis: a double-blind randomized self-controlled trial. Int Orthop. 2019;43(5):1123-34. https://doi.org/10.1007/s00264-018-4099-0
23. Mautner K, Gottschalk M, Boden SD, Akard A, Bae WC, Black L, et al. Cell-based versus corticosteroid injections for knee pain in osteoarthritis: a randomized phase 3 trial. Nat Med. 2023;29(12):3120–36. https://doi.org/10.1038/s41591-023-02632-w
24. Zhang S, Xu H, He B, Fan M, Xiao M, Zhang J, et al. Mid-term prognosis of the stromal vascular fraction for knee osteoarthritis: a minimum 5-year follow-up study. Stem Cell Res Ther. 2022;13(1):105. https://doi.org/10.1186/s13287-022-02788-1
25. Rahman E, Rao P, Abu-Farsakh HN, Thonse C, Ali I, Upton AE, et al. Systematic review of platelet-rich plasma in medical and surgical specialties: quality, evaluation, evidence, and enforcement. J Clin Med. 2024;13(15):4571. https://doi.org/10.3390/jcm13154571
26. Foster TE, Puskas BL, Mandelbaum BR, Gerhardt MB, Rodeo SA. Platelet-rich plasma: from basic science to clinical applications. Am J Sports Med. 2009;37(11):2259-72. https://doi.org/10.1177/0363546509349921
27. Illingworth KD, El Bitar Y, Siewert K, Scaife SL, El-Amin S, Saleh KJ. Correlation of WOMAC and KOOS scores to tibiofemoral cartilage loss on plain radiography and 3 Tesla MRI: data from the osteoarthritis initiative. Knee Surg Sports Traumatol Arthrosc. 2014;22(7):1649-58. https://doi.org/10.1007/s00167-013-2402-6
28. Copp G, Robb KP, Viswanathan S. Culture-expanded mesenchymal stromal cell therapy: does it work in knee osteoarthritis? A pathway to clinical success. Cell Mol Immunol. 2023;20(6):626-50. https://doi.org/10.1038/s41423-023-01020-1
29. Giuseppe F, Francesco P, Alice R, Maurilio M, Elizaveta K. Stem cells in articular cartilage regeneration. J Orthop Surg Res. 2016;11:42. https://doi.org/10.1186/s13018-016-0378-x
30. Her YF, Kubrova E, Martinez AGA, D'Souza RS. The analgesic efficacy of intradiscal injection of bone marrow aspirate concentrate and culture-expanded bone marrow mesenchymal stromal cells in discogenic pain: A systematic review. J Pain Res. 2022;15:3299-318. https://doi.org/10.2147/JPR.S373345
31. Shanmugasundaram S, Vaish A, Chavada V, Murrell WD, Vaishya R. Assessment of safety and efficacy of intra-articular injection of stromal vascular fraction for the treatment of knee osteoarthritis-a systematic review. Int Orthop. 2021;45(3):615-25. https://doi.org/10.1007/s00264-020-04926-x
32. McKay J, Frantzen K, Vercruyssen N, Hafsi K, Opitz T, Davis A, et al. Rehabilitation following regenerative medicine treatment for knee osteoarthritis-current concept review. J Clin Orthop Trauma. 2019;10(1):59-66. https://doi.org/10.1007/10.1016/j.jcot.2018.10.018
33. Sussman WI, Gruner MP, Bakal DR, Mautner KR. Rehabilitation principles for interventional orthopedics and orthobiologics. In: George TK, Mostoufi SA, Tria JrAJ, editors. Orthopedic Rehabilitation. Cham: Springer; 2023. https://doi.org/10.1007/978-3-031-32026-2_1
34. Kou D, Chen Q, Wang Y, Xu G, Lei M, Tang X, et al. The application of extracorporeal shock wave therapy on stem cells therapy to treat various diseases. Stem Cell Res Ther. 2024;15(1):271. https://doi.org/10.1186/s13287-024-03888-w
35. Li J, Li J, Li D, Jin X, Liu S, Zhang L. The efficacy of extracorporeal shock wave combined with platelet rich plasma in the treatment of knee osteoarthritis with meniscus injury: A retrospective analysis. Pak J Med Sci. 2024;40(3Part-II):382-7. https://doi.org/10.12669/pjms.40.3.8670
36. Mingwang Z, Zhuanli D, Changhao W, Lufang F, Xiaoping W, Haiping L, et al. Efficacy and safety of extracorporeal shock wave therapy combined with sodium hyaluronate in treatment of knee osteoarthritis: a systematic review and Meta-analysis. J Tradit Chin Med. 2024;44(2):243-50. https://doi.org/10.19852/j.cnki.jtcm.20231226.002
37. Lippi L, Ferrillo M, Turco A, Folli A, Moalli S, Refati F, et al. Multidisciplinary rehabilitation after hyaluronic acid injections for elderly with knee, hip, shoulder, and temporomandibular joint osteoarthritis. Medicina (Kaunas). 2023;59(11):2047. https://doi.org/10.3390/medicina59112047