Current Pain and Headache Reports (2025) 29:64
https://doi.org/10.1007/s11916-025-01378-z

NON-PHARMACOLOGIC ASPECTS OF PAIN, MIGRAINE, AND HEADACHE (D BUSE, SECTION EDITOR)

The Current Status and Future Prospects of Intra-articular Injection Therapy for Hip Osteoarthritis: A Review

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Accepted: 5 March 2025

Abstract

Purpose of Review Hip osteoarthritis constitutes a prevalent condition among individuals aged 55 and above, serving as one of the primary triggers for joint discomfort and impairment, and marking a substantial origin of chronic pain particularly affecting the elderly population. Our article provides an exhaustive summary of the mechanisms of action, therapeutic efficacy, and potential adverse consequences associated with novel therapeutic modalities including glucocorticoids, hyaluronic acid, platelet-rich plasma, mesenchymal stem cells, and stromal vascular fraction. Concurrently, we conducted a comprehensive evaluation of the clinical efficacy and potential applications of various medications.

Recent Findings In comparison to physical therapy, oral analgesics, and other nonsurgical modalities, intra-articular injection therapy is characterized by enhanced safety and greater efficacy. Moreover, when contrasted with surgical intervention, intra-articular injection demonstrates a lower degree of invasiveness and incurs fewer adverse reactions.

Summary Intra-articular treatments have shown excellent local efficacy while significantly minimizing adverse reactions in patients. These methods hold significant potential for development but require comprehensive research and thorough discussion within the academic community.

Keywords Hip osteoarthritis · Intra-articular injection · Treatment · Prospect

Introduction

Osteoarthritis (OA) is a common degenerative joint disorder that affects millions of individuals globally, with a higher incidence among women. Approximately 300 million people are living with OA, and 242 million individuals experience pain due to hip/knee OA [1]. The incidence of OA is increasing with the number of elderly and obese individuals. OA destroys chondrocytes through inflammatory cytokines, metalloproteinases, and mechanical stress, narrowing joint space and forming osteophytes and subchondral cysts. OA is characterized by progressive degeneration of the articular cartilage, joint inflammation, and changes in the surrounding structure, resulting in joint pain, stiffness of joints, and functional limitations. Finally, it reduces the quality of life of patients, negatively affecting their psychological and social well-being [2–5].

Genetics, gender, mechanical stress, and past trauma are the primary factors that lead to OA development, and the weight-bearing joints of the body are often the first to be affected. Hip OA (HOA) is highly common among the elderly, and it is the most common form of OA after knee OA (KOA). Pain and dysfunction of the hip joint are the primary clinical manifestations and the common presenting complaints of patients during hospital visits [6, 7]. HOA progresses through the gradual loss of femoral acetabular cartilage, resulting in inflammation, a narrowing of the hip space, relaxation of the ligaments surrounding the joint, and muscle weakness [8, 9]. The loss of structural integrity of the extracellular matrix of articular cartilage is primarily due

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Published online: 18 March 2025

to aggrecan and collagen degradation, the two main proteins in the extracellular matrix of articular cartilage. Disintegrin and metalloproteinase with thrombospondin motifs are specific enzymes that contain aggrecanase activity and degrade aggrecan molecules. Matrix metallo- proteinases (MMPs) degrade collagen. The increased degradation and decreased synthesis of the matrix of articular chondrocytes precisely result in the irreversible destruction of articular cartilage, leading to OA.

HOA has been treated with different strategies. Conservative and surgical ap proachesare the mainstay treatment methods. Total hip arthroplasty is a prevalent surgical approach for HOA treatment. However, numerous postoperative complications often lead to suboptimal outcomes among patients. Furthermore, surgical interventions are frequently regarded as a last resort in the advanced stages of the disease. Conservative therapy is the preferred treatment option for HOA, according to the guidelines of the Osteoarthritis Society International and the National Institute for Health and Care Excellence. Non-surgical treatment is essential during the initial and intermediate phases of HOA [10]. The non-surgical treatments include fundamental physical therapy, oral non-steroidal anti-inflammatory drugs (NSAIDs), platelet-rich plasma (PRP), hyaluronic acid (HA), and corticosteroids (CS) [11]. Physical therapy aims to enhance biomechanics by diminishing the mechanical pressure imposed on the articular cartilage. This will slow the progression of hip OA, increase the range of motion of the hip, and alleviate pain while improving functionality [12–14]. Oral drug therapy includes NSAIDs and selective COX-2 inhibitors, which are medications known for their potent analgesic properties [15]. However, these systemically acting drugs are restricted among the elderly with OA due to the associated increased risk of cardiovascular, renal, and gastrointestinal adverse effects. Despite the reduced systemic side effects of topical NSAIDs and COX-2 inhibitors, their bioavailability is an unavoidable issue in clinical practice [16]. Therefore, intra-articular injection with an appropriate therapeutic dose may be a more effective mode of drug administration. It is a promising therapy that is essential in OA treatment because it is reliable and safe, can effectively improve the effect of local treatment, and can ameliorate systemic adverse reactions. Intra-articular injection has progressively emerged as the primary focus of clinicians. As a new treatment modality capable of delivering therapeutic agents directly and promptly to the target joint, it provides additional treatment options for healthcare professionals. Intra-articular injection of the corticosteroid is the sole intra-articular injection method recommended by the National Cancer Institute. Some studies have associated rapidly progressing OA with potentially severe complications, thus serving as an auxiliary to the primary treatment [17, 18]. Intra-articular injection is a promising intervention crucial in HOA management when administered at the appropriate therapeutic dosage. This method demonstrates high safety and reduces systemic adverse reactions by effectively enhancing local treatment efficacy [19, 20].

This review examines various treatment approaches for HOA, including CS, HA, PRP, mesenchymal stem cells (MSCs), stromal vascular fraction (SVF) and so on. Herein, we reviewed the most recent advancements, modes of action, and adverse effects of these therapies. After evaluating our findings, we summarized the assessment of the potential and value of intra-articular injections in HOA management.

Corticosteroids (CS)

Although osteoarthritis is a degenerative joint disease, a spectrum of inflammatory factors is produced during certain stages of it's progression. This furnishes an empirical and dependable theoretical foundation for the therapeutic management of hip osteoarthritis by intra-articular injections of the corticosteroids. It is widely recognized that corticosteroids serve as prevalent local anti-inflammatory agents in clinical settings, effectively combating the inflammatory progression of HOA by modulating the immune function of T cells and B cells [21]. Moreover, according to the most recent international standards, it is advised that patients afflicted with moderate to severe HOA be administered with intra-articular corticosteroid injections by medical professionals [22]. Specifically, in scenarios where oral non-steroidal anti-inflammatory drugs (NSAIDs) are contraindicated or ineffective, intra-articular injections of corticosteroids have been demonstrated to be efficacious in alleviating pain, with therapeutic effects often persisting for several weeks [23].

In contrast to natural CS, synthetic CS exhibits more significant anti-inflammatory action. They are predominantly categorized into crystalline and amorphous CS, and they typically require concurrent local anesthetic administration during the injection process. Crystalline triamcinolone (TA) and non-crystalline methylprednisolone acetate (MPA) are predominantly administered in clinical settings [19].

TA exhibits lower water solubility than methylprednisolone, constituting one of the least soluble injectable CS. Therefore, it is a more appropriate choice for patients with diabetes who are concerned about potential post-injection increases in blood sugar levels [24]. Previous studies have reported that TA requires approximately three weeks for absorption into the joints and up to six weeks for plasma detection. This indicates that TA has a relatively extended retention period and absorption rate that is relatively rapid within the body [25]. The mean retention time (MRT) of TA ranges from 2.5 to 4.3 days. The MRT of the medication varies based on the modification of the dosage. TA extended-release (TA-ER), a formulation based on microsphere

technology, has been approved by the US Food and Drug Administration (FDA) for managing OA-related painful symptoms through intra-articular injection. TA acetonide extended-release (FX006) can effectively maintain a stable drug concentration within the joint, with an MRT of approximately 19 days [26]. In a randomized, controlled, open-label, single-dose clinical trial, Alan reported that intra-articular injections of TA-ER formulations are efficacious in alleviating pain and are safe among patients with HOA [27]. When betamethasone disodium phosphate combined with betamethasone acetate is administered, betamethasone diminishes the MRT to approximately 2.8 days. MPA induces a substantial alleviation of pain symptoms in the initial phase of treatment. Peer-reviewed studies reported that the therapeutic efficacy of intra-articular- administered MPA injection reaches its peak approximately two weeks post-injection, with the palliative effects enduring up to 24 weeks [28]. The latest study reported that MPA can be retained within the human system for up to three months, potentially extending to an even longer period [29].

Previous studies have confirmed that intra-articular CS injections are efficacious in alleviating clinical symptoms for patients in the early stages of OA (Table 1). In 2007, Gibson demonstrated that hip injections possess therapeutic benefits and contribute to diagnosing the associated condition [30]. In a randomized, controlled, double-anony- mized clinical trial, Dorleijn reported that CS was efficacious in alleviating the pain associated with HOA and enhanced the hip mobility of patients [31]. The effects of CS extended for up to 12 weeks. A recent 2023 study proposed that intra-articular injection is an essential intervention in the conservative management regimen for symptomatic HOA [32]. This relie son the ability of intra-articular injections to alleviate pain effectively, increase range of motion, support patient ambulation, and reduce reliance on analgesic medications. However, symptom alleviation in cases of HOA was not long-lasting, without substantial benefits observed beyond six months. Additionally, a subset of patients exhibited mild adverse reactions following injection therapy [33]. Previous studies support the notion that the gene expression profile of chondrocytes can be altered due to the prolonged administration of glucocorticoids, which can increase oxidative stress. These modifications can accelerate HOA progression by precipitating chondrotoxicity and generating additional detrimental effects [34]. Wernecke demonstrated a causal relationship between the administration of high-dose, long-term CS and the onset of chondrotoxicity to a certain extent [35]. Therefore, up to four intra-articular corticosteroid injections should be administered annually to symptomatic joints [36]. Previous studies have demonstrated that injections of intra-articular CS provide modest and transient pain alleviation. Consequently, it is imperative for medical professionals, particularly surgeons, to exercise judicious skepticism regarding the long-term viability of this treatment modality within the context of future pharmaceutical interventions and its scope for advancement.

Hyaluronic Acid(HA)

HA is an efficacious alternative that clinicians frequently choose for HOA management in addition to CS administration into the joint cavity. β-Glucuronide and β-acetylglucosamine are the primary components of HA, a glycosaminoglycan and high molecular weight polysaccharide. This substance is abundant in all vertebrate tissues, particularly epithelial, neural, and connective tissues. HA is an essential component of synovial fluid within normal and osteoarthritic joints. Chondrocytes and synovial cells synthesize HA, enhancing lubrication and shock absorption functions in the articulating joints. As a major component of synovial fluid in the articular cavity, HA is distributed in the surface layer of articular cartilage at a depth of approximately 1–2 μm [45–48]. HA possesses a multifaceted array of biological attributes that explain its use in analgesia. Specifically, HA functions as an anti-inflammatory agent by inhibiting the synthesis and dispersion of inflammatory mediators while simultaneously exerting local immunoregulatory effects [49, 50]. Among patients with HOA, the concentration of HA typically decreased by 50% to 67% within case-specific observations. This reduction included a decrease in molecular size. Further research has confirmed that the pathological progression of OA results in substantial attenuation of molecular interactions. This results in a reduction of the elasticity and viscosity of the synovial fluid [51].

In 1997, the Food and Drug Administration (FDA) approved HA for OA treatment. Consequently, it has gained widespread acceptance in the medical community [52]. The findings indicate that the molecular weight and concentration of HA within the synovial fluid decrease with OA deterioration. This decrease results in the degradation of synovial fluid viscoelastic properties [53]. Joint symptoms can be alleviated using HA, which possesses exceptional viscoelastic properties [54]. Some researchers have emphasized that the efficacy of intra-articular HA injections for OA management is likely attributed to two primary mechanisms of action. First, HA increases the mechanical viscosity in a joint, facilitating lubrication, cushioning against impacts, and reducing friction, thereby providing protective benefits for the joint. Second, it assists in the restoration of internal stability of the joint by regulating HA secretion within the body. Previous studies have confirmed that an increase in HA concentration can lead to substantial pain alleviation and significant improvement in the OA symptoms by efficiently enhancing lubrication and reducing frictional resistance [55–57].

Table 1 Overview of included studies

Title	Authors	Country	Year	Study Type	Journal	Patient Number	Intervention	Outcome Assessment Methods	Follow-up Duration
Comparison of intra-articular injections of hyaluronic acid and corticosteroid in the treatment of osteoarthritis of the hip in comparison with intra-articular injections of bupivacaine. Design of a prospective, randomized, controlled study with blinding of the patients and outcome assessors [37]	Colen	Belgium	2010	Randomized Controlled Trial	BMC Musculoskelet Disord	315	Hyaluronic acid injections; corticosteroid injections with bupivacaine	VAS; Harris Hip Score; HOOS	6 months
Efficacy of a single ultrasound-guided injection for the treatment of hip osteoarthritis [38]	Atchia	UK	2011	Randomized Controlled Trial	Ann Rheum Dis	77	Intra-articular corticosteroid injection	NRS; WOMAC	3 months
Effectiveness of intramuscular corticosteroid injection versus placebo injection in patients with hip osteoarthritis: design of a randomized double-blinded controlled trial [39]	Dorleijn	Netherlands	2011	Randomized Controlled Trial	BMC Musculoskelet Disord	135	Corticosteroid injection vs placebo injection	Hip disability and Osteoarthritis Outcome Score (HOOS); WOMAC	3 months
Therapeutic hip injections: is the injection volume important? [40]	Young	UK	2012	Randomized Controlled Trial	Clin Radiol	110	Corticosteroid injection vs placebo injection	WOMAC; Oxford pain chart	3 months
Pilot study of ultrasound-guided corticosteroid hip injections by emergency physicians [41]	Anderson	USA	2014	Clinical Trial	West J Emerg Med	47	Corticosteroid injection vs local anaesthetic injection	Likert pain scale	1 months

Table 1 (continued)

Title	Authors	Country	Year	Study Type	Journal	Patient Number	Intervention	Outcome Assessment Methods	Follow-up Duration
Intramuscular glucocorticoid injection versus placebo injection in hip osteoarthritis: a 12-week blinded randomised controlled trial [31]	Dorleijn	Netherlands	2018	Randomized Controlled Trial	Ann Rheum Dis	106	Corticosteroid injection vs placebo injection	VAS, WOMAC	3 months
A randomised controlled trial of the clinical and cost-effectiveness of ultrasound-guided intra-articular corticosteroid and local anaesthetic injections: the hip injection trial (HIT) protocol [42]	Paskins	UK	2018	Randomized Controlled Trial	BMC Musculoskeletal Disorders	204	Corticosteroid injection vs local anaesthetic injection	NRS scores, Adverse events	6 months
Rapidly progressive idiopathic arthritis of the hip: incidence and risk factors in a controlled cohort study of 1471 patients after intra-articular corticosteroid injection [43]	Boutin	USA	2021	Controlled Clinical Trial	Skeletal Radiol	1471	Intra-articular corticosteroid injection	Croft score; Radiographs	10 years
Clinical effectiveness of one ultrasound guided intra-articular corticosteroid and local anaesthetic injection in addition to advice and education for hip osteoarthritis (HIT trial): single blind, parallel group, three arm, randomised controlled trial[44]	Paskins	UK	2022	Randomized Controlled Trial	BMJ	199	Ultrasound-guided corticosteroid injection	Numerical Rating Scal	6 months

Additionally, researchers have discovered that HA serves as a signaling molecule in addition to its role in tissue anatomical preservation. Specifically, HA is essential in regulating cell proliferation, differentiation, and migration by interacting with surface receptors on various cell types, including B-type synovial cells and chondrocytes. These treatments affect the extracellular matrix by reducing markers indicative of cartilage degradation and stimulating endogenous HA synthesis. HA simultaneously possesses substantial anti-inflammatory properties, effectively decreasing the secretion of in- flammatory mediators, including prostaglandins, leukotrienes, interleukin-1 (IL-1), and IL-6, while facilitating fibroblast metabolism, potentially engendering multiple physio- logical benefits, including analgesia, anti-inflammatory responses, and cartilage protection [58, 59]. Besides, HA, a viscoelastic natural glycosaminoglycan, is essential in the extracellular matrix of articular cartilage and actively contributes to maintaining the biomechanical integrity of healthy cartilage [60]. Consequently, intra-articular injections of HA are essential interventions capable of delaying the necessity for total hip arthroplasty, which is particularly important for the younger patient population. The indications, contraindications and complications of the HA were summarized in Table 2. Table 3 shows the different brand name approved by FDA that contains HA.

Numerous polymer HA products are available in the market, each with unique origins, structure, molecular weights, concentration, injection dosage, and number of injections

Table 2 Indications, Contraindications and Complications of the Intra-Articular Injection of HA

Indication for Intra-articular Hyaluronic Acid Injection	Description of Indication	Contraindications	Post-injection Complications
Osteoarthritis	Degenerative joint disease affecting the joint, causing pain and reduced mobility	Active joint infection; Allergy to hyaluronic acid;Bone deformity; Active skin infection or eczema; Bleeding disorders;	Pain at injection sit; Swelling; Joint stiffness; Synovitis
Post-traumatic Arthritis	Arthritis developed after joint injury, often affecting the knee, hip or ankle	Allergy to avian proteins (in some HA products); Compromised joint integrity	Effusion
Chondromalacia Patella	Softening and damage of the cartilage under the kneecap, leading to pain and inflammation	Active skin disease near the injection area	Skin redness and warmth
Rheumatoid Arthritis (as adjunct therapy)	Autoimmune disorder causing chronic joint inflammation and pain	Active systemic infection, Immune-compromised status	Infection
Synovial Fluid Replacement in Hemophilia Patients	Joint lubrication for patients prone to hemarthrosis (bleeding into joints)	Coagulation disorders, Ongoing anticoagulant therapy	Hemarthrosis
Pain Relief in Patients Intolerant to NSAIDs	Alternative pain management for patients unable to take nonsteroidal anti-inflammatory drugs	History of severe allergy or anaphylaxis to hyaluronic acid	Allergic reactions
Temporomandibular Joint (TMJ) Disorders	Degeneration or dysfunction of the TMJ, leading to jaw pain and dysfunction	Pregnancy; Breastfeeding; Severe systemic conditions	Bruising

Table 3 Information About Drugs Which Contain Hyaluronic Acid

Brand Name	Manufacturer	Country of Origin	Molecular Weight	Administration Route	Injection Dose
Synvisc-One	Sanofi	USA	High molecular weight	Intra-articular injection	6 mL (single injection)
Euflexxa	Ferring Pharmaceuticals	USA	High molecular weight	Intra-articular injection	2 mL (single injection)
Hyalgan	Fidia Pharma	Italy	Low molecular weight	Intra-articular injection	2 mL (single injection)
Orthovisc	Anika Therapeutics	USA	High molecular weight	Intra-articular injection	2 mL (single injection)
Durolane	Bioventus	USA	Non-crosslinked, high molecular weight	Intra-articular injection	3 mL (single injection)
Hylan G-F 20	Genzyme	USA	Crosslinked, high molecular weight	Intra-articular injection	2 mL (single injection)
Ostenil	TRB Chemedica	Switzerland	Medium molecular weight	Intra-articular injection	2.5 mL (single injection)

administered during the treatment regimen. Based on molecular weight, the different products available are divided into low molecular weight (MW: 0.5–1.5 million Da), medium molecular weight (MW: 1.5–6 million Da), and high molecular weight (MW: 6–7 million Da). Previous studies reported that HMW intra-articular HA (HMW-HA) exerts more profound effects on cartilage preservation, anti-inflammatory response modulation, proteoglycan interaction facilitation, rheological properties enhancement, pain alleviation, and mechanical properties improvement [61, 62].

Recently, clinical trials investigating HA therapy for HOA treatment have progressively garnered significant attention from numerous scholars (Table 4). In a 2021 clinical trial, Mihaela reported that 15 patients with HOA who received ultrasound-guided HA injections experienced a significant decrease in their visual analog scale (VAS) (Fig. 1) and Western Ontario and McMaster Universities Arthritis Index (WOMAC) scores after treatment, with a progressive downward trend [63]. Consequently, authorities maintain that the ultrasound- guided intra-articular injections (USGIAI) may serve as a treatment modality that is highly efficacious and safe for patients with moderate HOA, demonstrating consistent efficacy over short-term and medium-term periods. In addition, many scholars have focused on different molecular weights of HA and their clinical applications. In a clinical trial involving 80 overweight/obese patients with HOA, Professor Dalila demonstrated that a combined HA formulation exhibited superior anti-inflammatory, analgesic, and chondrogenic properties than high-molecular-weight HA [64]. Furthermore, experts from Japan reported advanced comparable research findings, indicating that administering Hylan G-F 20 via hip injection significantly alleviates pain experienced during ambulation, enhances the motor function of the hip, and elevates the quality of life of patients with HOA. The therapeutic benefits of this intervention have been observed to persist for up to 12 weeks [65]. HA was administered exclusively to patients with mild to moderate HOA in a one-year follow-up that was recently conducted. Individuals who have declined surgical intervention for advanced arthritis and are contemplating this treatment modality should be advised of the associated potential adverse effects [66].

Professor Wu comprehensively reviewed the safety of intra-articular HA injections in relation to articular injections. He maintains that higher molecular weight HAs administered for HOA management have exhibited superior efficacy than the various molecular weight HAs used to manage HOA six months post-treatment without a concomitant increase in the incidence of adverse reactions [78]. However, it is imperative to accumulate comprehensive datasets and acquire higher-quality evidence to validate these findings for future clinical medical research. However, research into the contraindications of intra-articular HA has not yielded distinct specificity. The contraindications of intra-articular HA are similar to those of intra-articular CS. However, a 2019 study conducted by Gualdi suggests that patients with scleroderma should be considered contraindicated for intra-articular HA injections due to the pro-inflammatory effects and the potential to exacerbate migrating keratinocytes and skin ulcers [79]. A previous low-risk clinical trial reported that the frequency of intra-articular injections of HA may increase from one in a single cycle to five after four cycles [80]. As a result, intra-articular HA injections may elicit a higher incidence of local adverse reactions, including self-limiting synovitis, joint hemorrhage, and myalgia, than intra-articular corticosteroid injections. This phenomenon is likely to be closely associated with the frequency of intra-articular injections [81]. Consequently, healthcare practitioners should prioritize the assurance of treatment safety and cost-effectiveness when administering intra-articular HA injections to individuals with mild to moderate HOA, and they should exercise increased vigilance towards possible complications.

Platelet-Rich Plasma (PRP)

Platelet-rich plasma (PRP) has emerged as a favored option within the realm of innovative biological therapies for the management of a diverse spectrum of orthopedic disseases. Clinical trials have yielded substantial results in the treatment of external humeral epicondylitis and osteoarthritis; however, outcomes for other conditions, such as rotator cuff injury and Achilles tendon injury, exhibit variability [82–86]. This treatment regimen is appealing due to its simplicity in production, relative affordability, customization for individual patients, ease of administration, and low occurrence of adverse reactions.

PRP is a biological substance derived from an individual's blood. The platelet count in PRP is between 150,000 and 300,000 platelets per mL, significantly higher than those in routine plasma (Fig. 2) [87]. The primary benefits of PRP derive from anabolic factors, which are particularly abundant in alpha and dense granules [88]. Insulin-like growth factor 1 (IGF-1), transforming GF-β (TGF-β), platelet-derived GF (PDGF), vascular endothelial GF (VEGF), and fibroblast GF-β (FGF-β) are the primary growth factors that platelet alpha granules release [89]. These factors can significantly facilitate MScs and autologous chondrocyte proliferation and augmentation. Collectively, these factors facilitate cellular chemotaxis, migration, mitosis, extracellular matrix synthesis, and angiogenesis, thereby alleviating symptoms and potentially initiating tissue healing processes. Moreover, they increase extracellular matrix constituents, including proteoglycans and types I and II collagen [90, 91]. The expression levels of cytokines, including FGF-β, VEGF, PDGF, and IGF-1, exhibit a progressive increase at different time intervals following the PRP administration via an

Table 4 Study characteristics of the included studies

Title	Authors	Country	Year	Study Type	Journal	Patient Number	Intervention	Outcome Assessment Methods	Follow-up Duration
Efficacy of intraarticular hyaluronic acid injection through a lateral approach under fluoroscopic control for advanced hip osteoarthritis [67]	Eyigör	Turkey	2010	Clinical Trial	Agri	21	Intra-articular hyaluronic acid injection	Lequesne index; visual analog scale VAS	6 months
Kinematic and kinetic modifications in walking pattern of hip osteoarthritis patients induced by intra-articular injections of hyaluronic acid [68]	Paoloni	Italy	2012	Clinical Trial	Clin Biomech (Bristol, Avon)	20	Intra-articular hyaluronic acid injection	Pain relief (VAS); Functional improvement (WOMAC)	6 months
Efficacy of ultrasound-guided intra-articular injections of platelet-rich plasma versus hyaluronic acid for hip osteoarthritis [48]	Battaglia	Italy	2013	Randomized Controlled Trial	Orthopedics	100	Hyaluronic acid vs platelet-rich plasma (PRP) injection	Harris Hip Score (HHS) and visual analog scale (VAS)	12 months
Femoroacetabular impingement: is hyaluronic acid effective? [69]	Abate	Italy	2014	Clinical Trial	Knee Surg Sports Traumatol Arthrosc	20	Ultrasound-guided injections of hyaluronic acid	Pain score; Lequesne Index; Harris Hip Score	12 months
Duration of symptom relief after intra-articular injection of hyaluronic acid combined with sorbitol (anti-ox-vs) in symptomatic hip osteoarthritis [70]	Migliore	Italy	2014	Clinical Trial	Int J Immunopathol Pharmacol	20	Intra-articular injection of hyaluronic acid combined with sorbitol	Lequesne index, Health Assessment Questionnaire (HAQ), pain reduction, Global Patient Assessment (GPA), Global Medical Assessment (GMA)	12 months
Intra-articular hyaluronic acid vs platelet-rich plasma in the treatment of hip osteoarthritis [71]	Sante	Italy	2016	Randomized Controlled Trial	Med Ultrason	43	Hyaluronic acid vs platelet-rich plasma (PRP) injection	VAS; WOMAC	4 months

Table 4 (continued)

Title	Authors	Country	Year	Study Type	Journal	Patient Number	Intervention	Outcome Assessment Methods	Follow-up Duration
Efficacy of a single intra-articular injection of ultra-high molecular weight hyaluronic acid for hip osteoarthritis: a randomized controlled study [72]	Clementi	Italy	2018	Randomized Controlled Trial	Eur J Orthop Surg Traumatol	54	Ultrasound-guided injections of hyaluronic acid	Lequesne index, VAS and WOMAC score	12 months
Evaluating the use of intra-articular injections as a treatment for painful hip osteoarthritis: a randomized, double-blind, multicenter, parallel-group study comparing a single 6-mL injection of hylan G-F 20 with saline [73]	Brander	USA	2019	Randomized Controlled Trial	Osteoarthritis Cartilage	357	Intra-articular injection of hylan G-F 20	NRS; WOMAC score; Patient Global Self-Assessment (PTGA)	6 months
Randomized, double-blind, controlled trial, phase III, to evaluate the use of platelet-rich plasma versus hyaluronic acid in hip coxarthrosis [74]	Villanova-López	Spain	2020	Clinical Trial	Rev Esp Cir Ortop Traumatol (Engl Ed)	74	Hyaluronic acid vs platelet-rich plasma (PRP) injection	VAS score, HHS and WOMAC	12 months
Open-label phase 3 study of diclofenac conjugated to hyaluronate (diclofenac etalhyaluronate: ONO-5704/SI-613) for treatment of osteoarthritis: 1-year follow-up [75]	Nishida	Japan	2021	Clinical Trial	BMC Musculoskelet Disord	166	Intra-articular (IA) injection of DF-HA	Adverse events;X-ray; 11-point numerical rating scale	12 months

Table 4 (continued)

Title	Authors	Country	Year	Study Type	Journal	Patient Number	Intervention	Outcome Assessment Methods	Follow-up Duration
Diclofenac-hyaluronate conjugate (diclofenac etalhyaluronate) intra-articular injection for hip, ankle, shoulder, and elbow osteoarthritis: a randomized controlled trial [76]	Kubo	Japan	2022	Randomized Controlled Trial	BMC Musculoskelet Disord	75	Intra-articular (IA) injection of DF-HA	Adverse events;X-ray; 11-point numerical rating scale	12 months
Comparison between the effects of ultrasound guided intra-articular injections of platelet-rich plasma (PRP), high molecular weight hyaluronic acid, and their combination in hip osteoarthritis: a randomized clinical trial [77]	Nouri	Iran	2022	Randomized Controlled Trial	BMC Musculoskelet Disord	105	Hyaluronic acid vs platelet-rich plasma (PRP) injection	Lequesne index, VAS and WOMAC score	6 months

Fig. 1 Diagram of Visual Analogue Scale (VAS) pain score

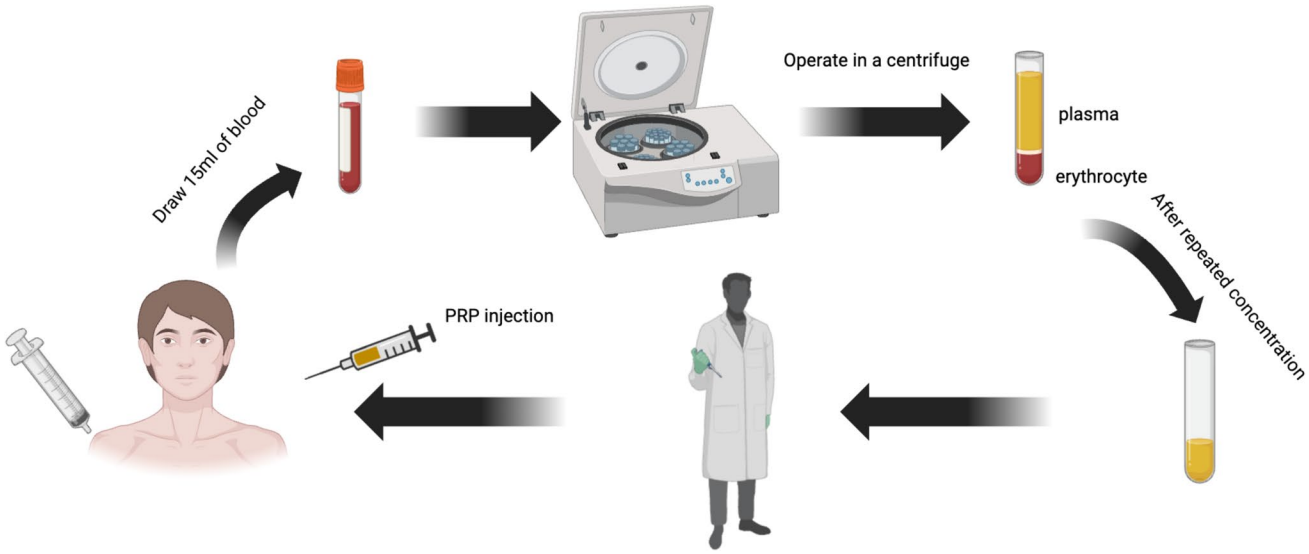

Fig. 2 Preparation Process Flowchart of Platelet-Rich Plasma (PRP)

intra-articular route. This pattern indicates that PRP does not merely increase the concentration of these cytokines; instead, it facilitates their biosynthesis and secretion by activating the endogenous regulatory pathways governing cytokine function [92]. In addition, in actual applications, PRP can reduce the inflammatory response throughout the course of OA by inhibiting the activation of nuclear factor kappa-light-chain enhancer by IL-1, thereby decreasing the levels of pro-inflammatory cytokines [93]. This study demonstrated that TGF-β enhances osteoblast mitotic activity [94].

Similar to HA, PRP lacks sufficient high-level clinical evidence to substantiate its efficacy. The indications for PRP are not covered by most insurance providers despite its widespread use in clinical settings as a standard treatment modality in knee and HOA [95]. PRP intra-articular injection therapy is gaining attention as a new biological treatment. PRP has several variations arising from the heterogeneity in platelet isolation and activation techniques, differential centrifugation speeds, diverse collection apparatuses, and disparate classification methodologies [96]. One significant categorization of PRP is its difference in leukocyte content, divided into high-leukocyte PRP and low-leukocyte PRP. While low-leukocyte PRP concentration is below baseline, high-leukocyte PRP exceeds it [97]. Purified PRP maintains physiological concen- trations of platelets and growth factors across various preparation methodologies. Its comprehensive anti-inflammatory response and promotional impact on chondrogenesis indicate its potential as a viable therapeutic modality for OA management [98].

Clinical investigations into the therapeutic applications of PRP for HOA management have recently been uninterrupted. Dr. Nouri headed a clinical trial that compared the long-term efficacy of intra-articular injections of PRP, HA, and their combined administration in managing patients with HOA [77]. The findings of the trial indicated that the PRP injection and the combined treatment group exhibited superior long-term outcomes than HA treatment alone based on functionality enhancement, disability reduction, and activities of daily living. Additionally, HA integration with PRP did not exhibit any significant therapeutic enhancement. In a 2022 study, Mazzotta compared the clinical efficacy of autologous PRP derived from peripheral blood with cord-derived platelet-rich PRP for HOA treatment [99]. The findings indicate that cord-derived platelet-rich PRP is more effective than autologous PRP for patients with early and middle stages of HOA, based on safety and efficacy, conferring more substantial therapeutic benefits. The Luan repository published a clinical trial that substantiated the therapeutic efficacy and safety of PRP injections and extracorporeal

shock wave therapy (ESWT) for managing patients with femoral head necrosis [100]. Besides, ESWT demonstrated limited efficacy in the treatment of patients with symptomatic ONFH, while PRP injection was more effective in alleviating pain and promoting functional restoration. These studies may offer a comprehensive research trajectory for the subsequent advancement of PRP applications.

Based on the analysis mentioned above, PRP is a new medicinal product with significant developmental potential and market value. However, the absence of standardized parameters, including consistent centrifugation speeds and durations during PRP preparation, may result in the generation of variants with varying proportions of white blood cells [101]. Pain at the injection site, joint stiffness, dizziness, headaches, nausea, and tachycardia are potential adverse reactions. Accordingly, further standardized and high-caliber clinical trials are imperative to confirm the efficacy of PRP utilization in therapeutic practices.

Mesenchymal Stem Cells (MSCs)

MSCs, a type of adult stem cell in numerous tissues, exhibit numerous functions, including anti-inflammatory, paracrine, and immunoregulatory effects, which have been confirmed across multiple studies [102]. Extensive research has confirmed the considerable potential of MSCs in mitigating pain and facilitating cartilage regeneration (Table 5). Therefore, scholars have attempted to reverse the progressive cartilage degeneration trend by applying cellular regenerative technologies [103]. Bone marrow, adipose tissue, peripheral blood, muscle, amniotic fluid, umbilical cord, and placenta are the primary sources of MSCs. In 1999, Pittenger achieved an initial milestone by successfully isolating and characterizing bone marrow MSCs (BMMSCs). He proposed that stem cells can differentiate into various lineages, including adipocytes, osteoblasts, and chondrocytes [104]. Ongoing study advancements revealed that MSCs can be derived from bone marrow and the placenta, umbilical cord blood, perivascular cells of the umbilical cord, cartilage tissue, adipose tissue, and skeletal muscle. BMSCs and adipose-derived MSCs (ADSCs) have emerged as common clinical interventions and have progressively been integrated into routine OA treatment regimens [105].

The underlying mechanism of the function of BMMSCs is unclear. However, the production of chemical mediators is widely recognized as an essential mechanism facilitating the in vivo role of BMMSCs. This mechanism can be divided into two primary categories: the first category pertains to their anti-inflammatory actions, while the second category pertains to their involvement in the tissue repair or regeneration process [106]. Numerous academic studies have demonstrated that BMMSCs can enhance growth factor secretion and modulate the tissue microenvironment [107]. These factors, including cell migration, proliferation, differentiation, and extracellular matrix synthesis, contribute to the repair and regeneration of cartilage tissue. BMMSCs can mitigate tissue injury and enhance the proliferative potential of stem cells, thereby catalyzing stromal vasculature regeneration and repair by modulating TGF-β, VEGF, MMPs, tissue inhibitors of metalloproteinases (TIMPs), and other essential growth factors [108].

The clinical application of BMMSCs is a continuous endeavor, in addition to the rigorous exploration of their underlying mechanisms (Table 6). In 2017, researchers, including Rodrigo, initiated a comprehensive series of studies to evaluate the therapeutic efficacy of BMMSCs in the clinical management of HOA. They found that three successive intra-articular injections of autologous BMMSCs exhibited safety and reliability in clinical applications for patients with hip cartilage defects. This resulted in the restored hip function and increased range of motion [109]. In a 10-year prospective, double-anonymi- zed, randomized controlled clinical trial, Li employed MSCs to treat patients with femoral head necrosis [110]. The study included 43 patients who received stem cell injections, followed by a ten-year observation period. The findings indicated that the integration of stem cell therapy with core decompression results in more substantial clinical benefits than decompression treatment alone. Canadian scholars conducted a research initiative examining the safety and efficacy of stem cell therapy in treating HOA. The study demonstrated that the maximal enhancement of the clinical manifestations of patients was achieved within the 3- to 6-month interval after the injectable therapy administration while concurrently maintaining a low incidence of adverse events [111]. In 2023, Dr. Natali et al. conducted a clinical trial of 55 patients. They found that intra-articular injections exhibited favorable clinical outcomes in patients with early to moderate HOA, with outcome scores ranging from 48 to 30 and a relatively low incidence of adverse reactions [112]. In the recently published literature, Dr Ehioghae provides a comprehensive and profound examination of the domain of stem cell therapy for knee and hip OA [113]. He highlighted the immense and associated constraints of stem cell therapy in OA management. Besides, previous studies highlighted the importance of ongoing inquiry to determine the long-term efficacy of pertinent treatments and to identify the most appropriate stem cell varieties to formulate standardized treatment protocols.

Clinical investigations have thoroughly substantiated the safety and tolerability of MSCs, and no adverse events (AEs) have been documented. The probability of adverse reactions associated with joint injections is as low as 3.1%, primarily as pain and swelling. Moreover, the carcinogenicity of MSCs has not been definitively established at the theoretical level [118–121]. However, the malignant transformation

Table 5 Summary of the Information About Stem Cell Acquired from Several Common Sources

Stem Cell Type	Source Tissue	Characterization Markers	Potential Applications	Advantages	Disadvantages
Mesenchymal Stem Cells (MSCs)	Bone Marrow	CD73+, CD90+, CD105+, CD45-, CD34-, low-affinity nerve growth factor receptor (LNGFR)	Orthopedic applications, bone and cartilage regeneration, autoimmune diseases	Easy to harvest and culture, multipotent, immunomodulatory properties	Limited proliferation potential, invasive harvesting procedure
Mesenchymal Stem Cells (MSCs)	Adipose Tissue	CD73+, CD90+, CD105+, CD45-, CD31-, CD34+ (in some populations)	Regenerative medicine, particularly for cartilage repair and wound healing	Abundant source, less invasive to obtain than bone marrow, high yield	Potential donor site morbidity, variability in cell yield and function
Hematopoietic Stem Cells (HSCs)	Bone Marrow	CD34+, CD45+, CD38-, Lin-	Blood disorders, leukemia treatment, bone marrow transplants	Well-established clinical use, effective for hematological conditions	Risk of graft-versus-host disease (GVHD), limited differentiation potential outside hematopoietic lineage
Hematopoietic Stem Cells (HSCs)	Peripheral Blood	CD34+, CD45+, CD133+	Hematopoietic stem cell transplantation for blood disorders	Less invasive collection via apheresis, suitable for autologous and allogeneic transplants	Requires mobilization, lower yield compared to bone marrow
Hematopoietic Stem Cells (HSCs)	Umbilical Cord Blood	CD34+, CD45+, CD133+	Pediatric transplants, blood disorders. Limited by cell quantity	Rich source of primitive stem cells, lower risk of GVHD	Limited cell quantity, often requires multiple donors for adults
Induced Pluripotent Stem Cells (iPSCs)	Adult Somatic Cells	OCT4, SOX2, NANOG, TRA-1–60, TRA-1–81, SSEA-4	Disease modeling, drug screening, potential future cell therapy	Avoids ethical issues associated with ESCs, pluripotent, patient-specific	Risk of tumorigenicity, reprogramming efficiency varies, potential for genetic instability
Embryonic Stem Cells (ESCs)	Blastocyst (Early Embryo)	OCT4, SOX2, NANOG, SSEA-3, SSEA-4, TRA-1–60	Research and regenerative medicine; ethical concerns limit clinical use	Pluripotent, unlimited proliferation capacity, robust differentiation potential	Ethical concerns, risk of teratoma formation, immunogenicity in allogeneic settings
Neural Stem Cells (NSCs)	Brain Tissue (Subventricular Zone)	Nestin, SOX2, GFAP (in some cases)	Neurological disease treatment, brain injury repair	Potential for neural differentiation, targeted applications in neurodegenerative diseases	Difficult to isolate, ethical concerns, limited proliferation
Amniotic Fluid Stem Cells (AFSCs)	Amniotic Fluid	CD29+, CD44+, CD73+, CD90+, CD105+	Regenerative medicine, prenatal therapies	Multipotent, less ethical concerns than ESCs, low risk of tumorigenicity	Limited differentiation potential compared to ESCs, variable cell quality
Perinatal Stem Cells	Placenta, Umbilical Cord Tissue	CD73+, CD90+, CD105+, CD34-, CD45-	Regenerative medicine, tissue repair	Abundant and ethically acceptable source, immunomodulatory properties	Limited pluripotency, less studied compared to other stem cell types

Table 6 Study characteristics of the included studies

Title	Authors	Country	Year	Study Type	Journal	Patient Number	Intervention	Outcome Assessment Methods	Follow-up Duration
Long-Term Follow-up of Intra-articular Injection of Autologous Mesenchymal Stem Cells in Patients with Knee, Ankle, or Hip Osteoarthritis [114]	Emadedin	Iran	2015	Clinical Trial	Arch Iran Med	18	Intra-articular (BM)-derived mesenchymal stem cells (MSCs) injection	VAS; WOMAC; MRI	30 months
Mesenchymal stem cell therapy in the treatment of hip osteoarthritis [109]	Mardones	Chile	2017	Clinical Trial	J Hip Preserv Surg	10	Intra-articular autologous bone marrow-derived mesenchymal stem cells (BM-MSC) injection	Harris Hip (HHS), Visual Analog (VAS), Vail Hip and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)	36 months
Short-Term Outcomes of Treatment of Hip Osteoarthritis With 4 Bone Marrow Concentrate Injections: A Case Series[115]	Darrow	USA	2018	Clinical Trial	Clin Med Insights Case Rep	4	Intra-articular injection of mesenchymal stem cells	VAS; WOMAC	6 months
Mesenchymal Stem Cells injection in hip osteoarthritis: preliminary results[116]	Dall'Oca	Italy	2019	Clinical Trial	Acta Biomed	6	Ultrasound-guided injections of hyaluronic acid	WOMAC; Harris Hip Score	12 months
The safety and effectiveness of bone marrow concentrate injection for knee and hip osteoarthritis: a Canadian cohort [111]	Burnham	Canada	2021	Clinical Trial	Regen Med	112	Intra-articular injection of bone marrow concentrate	WOMAC; VAS;HHS	6 months
Clinical use of autologous adipose-derived stromal vascular fraction cell injections for hip osteoarthritis[117]	Onoi	Japan	2023	Clinical Trial	Regen Ther	42	Intra-articular injection of adipose-derived stromal vascular fraction	HHS; Japanese Orthopaedic Association Hip Disease Evaluation Questionnaire (JHEQ) score; VAS;MRI	6 months

of cells remains a potential risk in stem cell therapy; over one-third of systematic reviews conducted in 2017 reported inaccuracies in their safety evaluation methodologies [122]. Moreover, recent studies have not agreed on the optimal sources, isolation, identification, and cultivation conditions of BMMSCs. Extensive and prolonged clinical trials are imperative to facilitate the dissemination and utilization of mesenchymal stem cell injection technology and to establish it as a conventional clinical treatment modality for OA.

Stromal Vascular Fraction (SVF)

Studies have unequivocally established the safety and efficacy of ADSCs and MSCs in the therapeutic management of OA. However, isolating, culturing, and proliferating these stem cell types commonly takes several weeks in well-equipped laboratories, potentially extending the treatment timeline of patients [123, 124]. Autologous SVF is considered a more efficacious approach. Additionally, during the application of liposuction techniques, collagenase enzymes present within the adipose tissue are activated, leading to the hydrolysis of fats. Consequently, the fat cells are dislodged and undergo emulsification. Subsequently, centrifugation differentiates the cellular components from the resulting emulsified fat. The residue that settles at the bottom of the centrifuge tube is referred to as SVF [125]. SVF cells encompass a heterogeneous population of various cell types, including MSCs, hematopoietic cells, macrophages, fibroblasts, pericytes, endothelial cells, smooth muscle cells, and progenitor cells (Fig. 3) [126, 127]. Compared to other varieties of stem cells, including BMMSCs, procuring adipose-derived stem cells (ASCs) is significantly less complex [128]. ADSCs compositions demonstrate significant variation, ranging from < 1% to > 15% across diverse samples because of the discrepancies in the extraction methods. Within the extant literature, eight studies examined liposuction procedures performed one day before the surgery, while four investigations focused on liposuction performed on the day of the surgery [129–136]. SVF significantly saves more time (weeks) than ADSCs and MSCs in cell culture and proliferation with superior efficiency.

The investigation demonstrated that the origin of adipose tissue or the identity of the donor does not entirely determine the SVF. This fraction can exert anti-inflammatory effects on chondrocytes and synoviocytes by secreting several anti-inflammatory mediators, including IL-1 receptor antagonist, indoleamine-2,3-dioxygenase, TGF-β, and prostaglandin E2 [137]. Moreover, the research indicates that ASCs in adipose tissue can detect the local microenvironment of OA and react appropriately to such environmental alterations. In addition, in actual applications, the regulatory functions of SVF on preadipocytes, vascular pericytes, macrophages, red blood cells, fibroblasts, and regulatory T cells facilitate tissue regeneration and renewal [138]. Studies have demonstrated that the safety and efficacy of ADSCs in remodeling hypertrophic scars, nerve regeneration, therapeutic interventions

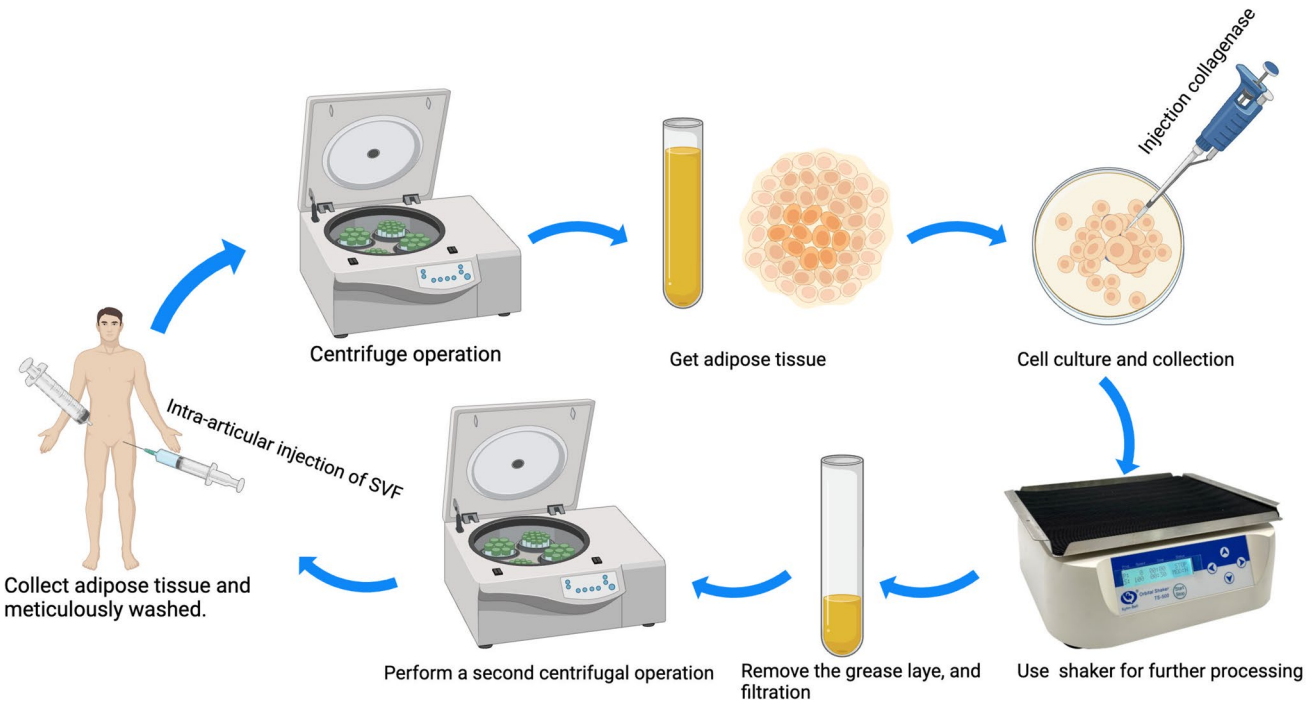

Fig. 3 Preparation Process Flowchart of Stromal Vascular Fraction (SVF)

for acute myocardial infarction, and cartilage regeneration are non-significantly different from other types of stem cells under specific conditions [139–142]. In orthopedic clinical practices, SVF cells exhibit a beneficial impact on OA, particularly in the case of knee OA [143, 144]. However, clinical research into the SVF treatment of HOA remains understudied.

In 2020, the research team led by Dr. Mehling initiated a clinical trial designed for patients with HOA. The trial included 106 participants who underwent SVF as a therapeutic intervention for their hip joints. In stark contrast to the outcomes observed 7 days post-transplantation, the findings unequivocally demonstrated a significant decrease in pain levels and improved joint mobility at 3, 6, and 12 months following SVF graft injections. SVF intra-articular injections have demonstrated an exceptional safety profile without serious AEs or complications. Furthermore, SVF cell therapy demonstrated enhanced efficacy in patients with stage III arthritis than in those with stages I, II, and IV OA [145]. In 2023, a Japanese academician conducted a similar investigation that included 42 individuals in stem cell-based vascular fat (SVF) therapy over six months. The study revealed a significant improvement in hip joint health, as indicated by the Hip Joint Health Score (HHS), the Hip Joint Health Questionnaire (JHEQ), and the VAS for pain following SVF treatment. However, radiological assessments, including the central marginal angle, the acetabular index, and T2-weighted imaging, failed to identify any significant changes between the pre-therapeutic and six-month post-therapeutic follow-up. SVF cell therapy constitutes an innovative and efficacious medical intervention, demonstrating promising short-term clinical outcomes in HOA management [117].

Extensive clinical trial data and comparative research on therapies such as intra-articular hormone injections or PRP are rare. Only a few studies have reported that the intra-articular injection of adipose-derived cellular populations (SVF) can alleviate OA symptoms and facilitate articular cartilage regeneration. The findings of the study indicated that patients with OA experienced substantial symptom alleviation between one month and two years after treatment with ADSC injection, also known as SVF. This improvement contributed to a significant enhancement in the quality of life of patients and did not introduce an elevated risk of adverse reactions. Few patients initially experienced mild swelling and discomfort within a few days, with no significant complications detected in the donor region [134, 146]. SVF has demonstrated efficacy in point-of-care contexts for managing several clinical conditions, and it is now commonly administered globally, with numerous documented successful treatment outcomes. The procurement of SVF is a simple process that is easily accessible and predominantly derived from abdominal or gluteal adipose tissue without requiring complex steps, including cellular culture and proliferation. These inherent benefits suggest that SVF may be a safe and efficacious minimally invasive treatment modality for OA, holding considerable promise for widespread utilization. However, this hypothesis requires validation through extensive clinical investigation.

Other Therapies

An imbalance may arise between catabolic and anabolic factors during OA progression. This theory introduces a new perspective for investigating the use of biological agents in OA treatment [147]. The anaerobic bacterium Clostridium botulinum produces botulinum toxin (BT), composed of a light chain of 50,000 Da connected to a heavy chain of 100,000 Da through disulfide bonds. Research has identified an independent anti-inflammatory effect of BT injections in addition to its well-established application in muscle hyperactivity and certain autonomic disorders treated with BT type A (BT-A) [148, 149]. Numerous studies have demonstrated that BT-A administration potently inhibits neurotransmitters and neuropeptide secretion at the central axon terminals of injured sensory neurons, thereby diminishing central nervous system sensitization. Consequently, BT-A exhibits a targeted analgesic action and has been implemented in pain research [150, 151]. Therefore, it is recommended that the Botox injection administration into the joints can alleviate pains associated with OA. In Mathilde's investigation, the research team noted that BT-A injections in the joint provided transient relief for patients with HOA. Moreover, there was a significant decline in pain scores in some patients with intractable joint pain, with the alleviating effects lasting up to six months post-therapy [152]. Concurrently, researchers have demonstrated that BT-A injections in the joint cavity and therapeutic exercises yield more significant effects [153].

The pathogenesis of chronic pain and its precursor role in pain perception are complexly associated with nerve growth factor (NGF). Clinical trials confirm the efficacy of NGF-targeted mechanisms in alleviating OA pain, thereby affirming the critical role of NGF-blocking antibodies in therapeutic interventions [154–159]. Ongoing clinical trials examining the effectiveness of monoclonal antibodies targeting NGF remain uninterrupted. For instance, Marc et al. have conducted studies to evaluate the long-term safety of intramuscular injections of tanezumab in patients with OA and its efficacy at the 16-week mark. The researchers have clarified the potential therapeutic efficacy of tanezumab in HOA management, particularly in patients who have not responded favorably to conventional treatments, have developed an intolerance to the medication, or have other contraindications, including hypersensitivity to NSAIDs [160].

The inflammatory cytokine cascade is essential for the onset or progression of varying degrees of local inflammation, particularly synovial inflammation, bone resorption, and the degradation and loss of cartilage. Previously, OA was not considered a systemic inflammatory condition. Specifically, the significant production of IL-1 and tumor necrosis factor-alpha (TNF-alpha) in osteoarthritic joints exerts a substantial effect on synovial cells and chondrocytes, stimulating the production and secretion of mediators and effectors derived from bone and synovial tissue [161, 162]. Consequently, anti-TNF biologics are anticipated to be a potent potential therapeutic modality for hip arthritis management. Infliximab and etanercept are the most extensively employed inhibitors of TNF. Although relevant research has preliminary verified the safety of infliximab, its application via intra-articular administration for OA management remains in the early phase of investigation and experimentation. In clinical trials that compared HA with etanercept, participants who received etanercept exhibited higher VAS scores during the initial one to two weeks than those who received HA injections. However, the discrepancy in the efficacy of the two therapeutics diminished progressively beyond the fourth week [163].

Discussion

HOA is characterized by a complex equilibrium between articular tissue degeneration and regeneration, culminating in gradual anatomical and functional capacity depletion, potentially manifesting as clinical symptoms, including pain and impairment. The scientific community has encountered numerous obstacles in OA treatment, including the complex interplay of pathological processes, the heterogeneity in the pathogenic profiles of OA, and the variability in the rate of disease progression among different demographic groups [164, 165]. Drug safety is of utmost importance to the elderly population, as they require lifelong treatment.

Intra-articular injection therapy can enhance the local therapeutic effect while ensuring the safety of the treatment process. Furthermore, this method can substantially reduce the risk of systemic exposure and adverse reactions. Several intra-articular medications have been employed in HOA management, including glucocorticoids, HA, platelet-rich plasma, MSCs, and stromal vascular fraction. However, the number of randomized controlled trials investigating these medications for OA remains relatively low.

In 2017, Giulio employed the precise magnetic resonance imaging technique known as T2 mapping to quantitatively evaluate the impact of intra-articular HA injections on chondral morphology and investigate its correlation with clinical symptoms [166]. The findings indicate that T2 mapping is an efficacious tool for assessing the therapeutic effects of HA intra-articular injections in patients with HOA. However, conducting a series of histological investigations is imperative to gain a more comprehensive understanding of the correlation between HA and T2 mapping. Long et al. evaluated the safety and efficacy of ultrasound-guided injections of high molecular weight HA in patients with mild to moderate HOA. A previous study of 87 patients with HOA demonstrated the safety and efficacy of a single injection of HA [167]. The pain relief and functional capacity enhancement observed post-treatment demonstrated statistically significant improvements. The latest research further reveals that HA injections within the joint demonstrate reduced adverse effects and more significant symptom alleviation than CS injections for the treatment of patients with early-stage OA [168]. In a study published in 2022, Nouri et al. comparatively assessed the therapeutic efficacy of intra-articular injections containing PRP and HA and their combined application in the management of patients with HOA [77]. The authors reported that the efficacy of PRP therapy and its combination with other modalities was significantly more enduring (up to six months) than HA injections. However, all three interventions demonstrated pain alleviation and functional enhancement. This resulted in amplified functional recovery, diminished disability, and increased capability of daily living. Moreover, HA incorporation into PRP treatment did not significantly improve therapeutic outcomes. Based on a 2023 meta-analysis, there is low-to-moderate quality evidence that PRP therapy is efficacious in alleviating pain symptoms and improving functional performance in patients with HOA, particularly within a follow-up duration of 1 to 2 months [169]. Besides, the researchers emphasized that a single administration of PRP yielded a more substantial pain reduction than repeated injections. Research on treating HOA via the intra-articular injection of stem cells is scarce in clinical practice. In 2023, a scholarly team headed by Professor Zhu conducted a meta-analysis that included 20 relevant studies, which revealed a consistent positive correlation between stem cell therapy combined with core decompression and enhanced clinical efficacy [170]. However, the efficacy of cellular therapies and other treatments in the management of hip pathologies requires more stringent design in clinical trials to ensure the high quality of prospective studies and randomized controlled trials. Sufficient sample sizes are essential for affirming their genuine efficacy.

This literature review comprehensively examined different intra-articular injectable medications employed in HOA management. Despite the prevalent use of sodium hyaluronate and glucocorticoids as intra-articular treatment modalities, it is advisable to exercise caution and refrain from recommending intra-articular HA and CS for patients with advanced stages of OA. Since symptoms may not be significantly alleviated, an increase in the frequency of injections may result in adverse reactions. Recently, regenerative

medicine therapies, including PRP, MSCs, and SVF, have been used for OA management. Concurrently, extensive research on these therapies has yielded promising clinical outcomes. However, it is premature to make conclusive assessments regarding the efficacy and safety of these regenerative medical products in cartilage regeneration. Furthermore, there is a prevalent need for more extensive patient samples and sophisticated radiological and histological evidence to corroborate the rational usage of PRP, MSCs, and SVF in OA treatment in clinical practice. This is essential to provide reliable data that supports the widespread clinical applications of these methods.

Conclusion

The intra-articular approach offers superior local efficacy and mitigates adverse patient responses, particularly in regenerative medical treatments. The application of minimally invasive techniques for pain alleviation is efficacious and has significant potential for further development, necessitating additional comprehensive study and scholarly discourse.

Key References

Its citation number is a rough indicator of the article's quality and significance. This study found that the publication "Pharmaceutical treatment of osteoarthritis (2022)" by Richard et al. in Osteoarthritis and Cartilage, reviewing the status of recommendations for pharmacological treatment of osteoarthritis management, was the most frequently cited article on osteoarthritis in the last three years [171]. "The Efficacy of Bone Marrow Stem Cell Therapy in Hip Osteoarthritis: A Scoping Review" which was published in 2024 by Perez et al. was the most important literature on stem cell therapy for hip osteoarthritis, with 55 citations, in the last three years [172]. The authors found that the efficacy of using BM-MSC therapy for HOA was beneficial and improved clinical symptoms in patients.

Acknowledgements We thank the participants of the study

Author Contributions Fengxian Wang initiated and coordinated the study. Li Li, Xiaofan Dou and Xueliang Song were responsible for study selection and data collection. All authors read and approved the final manuscript. All authors contributed to the article and approved the submitted version.

Funding None.

Data Availability No datasets were generated or analysed during the current study.

Compliance with Ethical Standards

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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