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REVIEW ARTICLE

# Intra-articular Injection Therapy in Knee Osteoarthropathy: A Narrative Review

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**Abstract**

**Knee osteoarthropathy is a common degenerative joint disorder that can cause pain and functional impairment in affected individuals. Various intra-articular injection therapies have been explored as potential treatments for knee osteoarthropathy, including corticosteroid, hyaluronic acid, dextrose and platelet-rich plasma. Intra-articular corticosteroid injection is commonly used for short-term pain relief. Patients with higher baseline pain level and milder changes of degeneration on imaging may benefit more from corticosteroid injection. However, excessive use may lead to detrimental effects on joint tissues. Intra-articular hyaluronic acid injections have demonstrated positive effects in improving pain and function, as well as delaying the need for total knee replacement. The effects can be sustained for an extended period. Hypertonic dextrose injections may promote tissue repair and improve symptoms, but more research is needed to validate their efficacy. Platelet-rich plasma shows potential tissue growth-promoting effects. However, conflicting study results exist, and current clinical guidelines do not recommend its use due to limited evidence. When performing intra-articular injection, ultrasound-guided techniques have emerged as a superior alternative to landmark-guided methods, with improved accuracy, better clinical outcomes and potential cost-effectiveness.**

*Keywords:* Hyaluronic acid, Injections, Intra-articular, Osteoarthritis, Knee, Platelet-rich plasma, Prolotherapy

## 1. Introduction

Knee osteoarthropathy (OA) is a chronic degenerative joint disease and one of the common musculoskeletal problems.[1] Approximately 240 million people worldwide suffer from symptomatic and activity-limiting knee OA. Certain populations, such as those who have had previous injuries, are obese, older, and female, being more susceptible to developing this disease.[2] The diagnosis primarily relies on clinical symptoms. Knee pain, typically aggravated by weight-bearing and relieved during rest, is the most common symptom that patients complain about. Stiffness, usually happens when waking up in the morning. Joint swelling is also a clinical feature of knee OA, possibly related to the mechanisms of inflammation, reflecting synovial thickening or synovitis.

For a long time, knee OA has been regarded as a "wear and tear" disease of joint cartilage. However, with advances in

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cellular biology research, it is now widely believed that knee OA is not simply a wear and tear disease but rather a complicated inflammatory disease. Hence, therapeutic effects of certain medications mainly come from suppressing the inflammation, such as oral and topical nonsteroidal anti-inflammatory drugs. In recent years, with advancements in imaging techniques, intra-articular (IA) injections have become increasingly common in clinical practice. Corticosteroids, hypertonic dextrose, hyaluronic acid (HA), and platelet-rich plasma (PRP) are commonly used injectable formulations. The purpose of this review is to summarize the existing research of IA injections for knee OA, providing readers with a foundation for clinical management when treating knee OA.

## 2. Methods

A comprehensive literature search from 1997 to 2022 was conducted on the PubMed and Google scholar database to identify relevant studies investigating the intra-articular injection therapies of knee osteoarthritis. The following search terms were focused on but not limited to ("knee osteoarthritis" OR "knee osteoarthropathy") in combination with ("intra-articular") AND (("injection") OR ("treatment")) AND ("corticosteroid" OR "steroid" OR "hyaluronic acid" OR "viscosupplementation" OR "prolotherapy" OR "dextrose" OR "platelet-rich plasma" OR "PRP") AND ("ultrasound" OR "sonographic" OR "sonography" OR "ultrasonography" OR "ultrasound-guided" OR "landmark-guided"). Additional studies were identified by reviewing the reference lists in the pertinent articles. The results were further divided into several topics: corticosteroids, hyaluronic acid, dextrose, platelet-rich plasma and ultrasound-guided versus landmark injections."

### 2.1. Corticosteroid

Intra-articular corticosteroid injection (IACS) has been performed in clinical practice for over sixty years.[3] Although knee OA is believed to have a degenerative origin, there is substantial evidence indicating the presence of inflammatory components at different stages of the disease. For example, oncoprotein and NF-kB expression have been observed in the synovium of osteoarthritic joints, both of which are transcription factors associated with the precursor genes of inflammation.[4] Additionally, increased levels of Toll-like receptors (TLR) have been found in the cartilage of OA joints.[5] There is also evidence of monocytes and proinflammatory mediators in the inflamed synovium, along with an upregulation of aggrecanases and collagenases.[6] Steroids exert a potent and complicated anti-inflammatory effect by reducing the inflammatory components in knee OA, and lead to an improvement in symptoms.[7]

Many clinical studies have proven the efficacy of IACS in short-term (≤12 weeks) pain reduction and functional improvement.[8,9] A 2015 Cochrane review included 27 randomized controlled trials involving a total of 1767 knee OA patients who received IACS or placebo. In terms of pain improvement, patients receiving IACS experienced a significant additional reduction of 1.0 cm on a 10-cm visual analogue scale (VAS) compared to the control group (steroid group: −2.8 cm vs. control group: −1.8 cm; 95 % confidence interval [CI] −1.5 to −0.6 cm). The most significant pain improvement was observed within the first six weeks after injection (1−2 weeks: −0.48 [95 % CI -0.70 to −0.27]; 4−6 weeks: −0.41 [95 % CI -0.61 to −0.21]), while there was no significant difference at 26 weeks after injection (−0.07 [95 % CI -0.25 to 0.11]). In terms of functional improvement, patients receiving IACS showed a significant additional 0.7 unit improvement on the standardized WOMAC disability score (ranging from 0 to 10 units) compared to the control group.[10] When it comes to comparing the efficacy of IACS with oral medication, a network meta-analysis conducted in 2015 found that IACS were more effective than oral medication in pain improvement of knee OA patients for at least three months.[11] Therefore, IACS in knee OA can be considered if the patient has had an inadequate response to nonpharmacologic therapies and oral medication. In addition to improving pain and function, research has also shown that IACS can enhance patients' compliance with physical therapy, possibly

due to the improvement in pain and mobility.[12]

Numerous studies have attempted to identify specific patient characteristics that may benefit more from IACS. A meta-analysis in 2016 found that patients with higher baseline pain levels (≥70 points on the 0–100 VAS scale) experienced more significant short-term pain improvement (<4 weeks) after the injection.[13] Another prospective clinical study reported that patients with higher baseline WOMAC pain scores showed better responses at one and six weeks after the injection.[14] Wu et al. also discovered that patients with higher initial pain scores (WOMAC pain score ≥5) had a 2.54-fold higher response rate compared to those with scores <5 after receiving IACS (44.8 % vs 17.6 %, $p < 0.001$).[15] Overall, these studies suggest that OA patients with more severe knee pain at the onset tend to respond better to short-term IACS. Furthermore, individuals with more advanced degenerative changes on images seem to exhibit poorer responses to IACS. In X-ray evaluations, Fatimah et al. found a negative correlation between the severity of degeneration assessed by the KL grade and the response to steroids ($r = -0.359$).[16] Regarding to MRI, Maricar et al. found that knee OA patients with more severe meniscal damage (odds ratio (OR) = 0.74; 95 % CI 0.55 to 0.98), higher KL grade (OR = 0.43; 95 % CI 0.23 to 0.82) and greater joint space narrowing (OR = 0.60; 95 % CI 0.36 to 0.99) on MRI were associated with a lower odds of long-term (6 months) response to steroid injections.[17] To sum up, knee OA patients who exhibit higher baseline pain levels or less severe imaging findings may potentially experience greater benefits from IACS treatment.

Various types of steroids such as methylprednisolone, triamcinolone, and betamethasone are commonly used for IA injections in clinical practice. All of these medications have shown benefits in relieving pain, but there is no consensus on which one is more effective.[9,18] Nevertheless, among different corticosteroids, betamethasone is known to be more toxic to chondrocytes and mesenchymal stem cells (precursors of chondrocytes and other musculoskeletal tissues) than other steroids in *in vitro* experiments due to its crystal structure and the presence of benzalkonium chloride. This may impact our clinical decision concerning the choice of steroids on knee OA patients.[19,20]

Several potential side effects of IACS should be cautious, including arthralgia, swelling, and joint stiffness. Besides, some may develop cutaneous pigmentation after the injection. Although the pigmentation does not adversely affect function, it significantly impacts patients' appearance and subsequent laser treatment may be needed.[21] Some cases of crystal-induced arthritis after steroid injections have also been reported, necessitating differentiation from infectious arthritis via joint fluid analyses.[22,23] Rarely, patients may develop infectious arthritis, which is a catastrophic complication requiring long-term antibiotic treatment or even surgical intervention. Therefore, cautious skin disinfection is crucial to avoid this complication. A questionnaire survey conducted in the United Kingdom in 2003 showed that most physicians (91.1 %) changed the needle after drawing the medication, but only 16.3 % of them used a sterile towel during the injection process. In this survey, 12.6 % of physicians encountered infectious arthritis after injections.[24] Based on these results, proper skin disinfection and needle change after drawing the medication can reduce the incidence of infectious arthritis and should be employed as routine.

Aside from local side effects, studies have shown that steroids have adverse reactions on bones which include accelerated OA progression, subchondral insufficiency fracture, osteonecrosis, and rapid joint destruction.[25] Experiments including *in vitro* human chondrocytes and animal articular cartilage have shown that IACS may cause chondrotoxicity, especially at higher doses (>3mg/dose or 18–24 mg per cumulative dose).[26] The mechanisms underlying chondrotoxicity are complicated and involve the loss of cellular organelles, changes in cell shape, promoted turnover of aggrecan and increased markers of cartilage loss, leading to damage of cartilage proteins.[27] The destructive effects on cartilage observed in animal experiments are also evident in clinical imaging. For instance, a clinical randomized controlled study in 2017 used magnetic resonance imaging (MRI) every 12

weeks to track changes in cartilage thickness after injections for 2 years. The results revealed a greater loss of cartilage thickness in the steroid (triamcinolone) group compared to the saline group (steroid group: −0.21 mm vs. saline group: −0.10 mm; between-group difference, −0.11 mm [95 % CI -0.20 to −0.03 mm]).[28] Another cohort study in 2019 showed that IACS group, when compared to a controlled group, was associated with more severe KL grade worsening (HR 3.02, 95 % CI 2.25 to 4.05) and joint space width worsening (HR 2.92, 95 % CI 2.18 to 3.90).[29] As a result, patients with knee pain, who do not exhibit or only show mild OA on radiography, should actively exclude other potential causes of knee pain to prevent unnecessary cartilage loss following corticosteroid injections. Another concern is whether IACS can lead to elevated blood sugar levels. It is well-established that intravenous or oral use of steroids commonly causes blood sugar elevation in clinical practice, and IA injection is no exception. Habib et al. pointed out that in OA patients with well-controlled diabetes (HbA1c < 7 %), almost all experienced a significant increase in blood sugar after receiving IA triamcinolone injections. The blood sugar peaked at 24−32 h after injection and returned to normal range within 2.5−4 days.[30] The median peak level of blood sugar elevation is usually less than 300 mg/dL. Therefore, while diabetes is not a contraindication for receiving IACS, it is recommended to closely monitor blood sugar in the first 1−3 days after injection.[31] This is especially important in patients with poorly controlled diabetes to avoid complications related to hyperglycemia.[30,31]

Intramuscular corticosteroid injections (IMCS) have become a potentially viable alternative because of the adverse reactions associated with IACS mentioned above. The advantages of intramuscular injections include simple administration, reduced risk of infections and decreased toxicity to the articular cartilage. A randomized controlled trial in 2022 compared IMCS with IACS (40 mg triamcinolone) in knee OA patients and followed for 24 weeks.[32] In terms of safety, the study showed that IMCS had fewer side effects compared to IACS (42 % vs. 33 %). The most frequently reported adverse events of IMCS were hot flushes and headaches, and all of these events were categorized as not serious. IMCS has also shown some degree of pain improvement in knee OA patients, which was inferior to IACS at 4 weeks and similar to IACS at 8 and 24 weeks. The underlying mechanism for this difference may be related to pharmacokinetics, as IM steroids generally require 8 weeks (while IA steroids take 4 weeks) to reach peak effect. This study suggests IMCS might be a feasible treatment alternative for knee OA patients and requires further research to validate its use.

### 2.2. Hyaluronic acid

HA is a linear polysaccharide in synovial fluid, synthesized by chondrocytes and synovial cells through the polymerization of glucuronic acid and N-acetylglucosamine.[33] The average molecular weight of HA in normal synovial fluid of human ranges from 6000 to 7000 kiloDalton (kD), with concentrations of 2−4 mg/mL.[34] HA in the joint have several characteristics. First, it acts as a lubricant during slow movements under low shear rates, and as an elastic solid providing cushion during rapid movements under high shear rates. Second, HA has cartilage-protective and anti-inflammatory properties. High-molecular-weight HA can interact with CD44, toll-like receptor-2, and toll-like receptor-4 to exert anti-inflammatory effects.[35] Third, HA can bind to receptors on joint cells and stimulate synovial fibroblasts to increase synthesis of endogenous HA.[36] Among knee OA patients, researchers have observed a decreasing trend in the concentration and molecular weight of HA in the synovial fluid, resulting in reduced mechanical and viscoelastic properties of the synovial fluid.[37] IAHA injections may help restore higher average molecular weight and concentration of HA in the synovial fluid, thereby improving the symptoms.

Clinical results demonstrate that IAHA can be used to improve long-term pain and function in knee OA patients. A study conducted by Navarro-Sarabia et al., which included 306 knee OA patients, found that more patients in the IAHA group responded favorably according to the Osteoarthritis Research Society International (OARSI) 2004 criteria for pain, function and patient global assessment, showing a significant

difference 40 weeks after the injection (RR: 1.22, 95 % CI 1.07 to 1.41, $p = 0.004$).[38] Another meta-analysis indicated that in terms of pain reduction, IACS performed better than IAHA within four weeks, but at six months, IAHA was superior to IACS.[39] Regarding to the function (WOMAC score), no difference was found at three months. However, the IAHA group exhibited a better response after six months (three months, $p = 0.29$; six months, $p = 0.005$), suggesting that IAHA may provide long-term and stable analgesic effects in clinical settings.[39]

Furthermore, IAHA can delay the interval for knee OA patients to receive total knee replacement (TKR). A retrospective study by Altman et al. demonstrated that among 182,022 knee OA patients who underwent TKR, those who received IAHA had a significantly longer time to TKR compared to those without injections (1.4 years longer; median time-to-TKR, HA cohort 484 days vs. non-HA cohort 114 days, $p < 0.0001$). Besides, IAHA is associated with a dose-dependent increase in time-to-TKR (median time-to-TKR, one course HA cohort 1.4 years vs. five courses HA cohort 3.6 years, $p < 0.0001$).[40] This result is also consistent with another retrospective study, demonstrating its clinical importance.[41]

Recently, with advancements in biotechnology, crosslinked HA has emerged in the market. Theoretically, crosslinking can produce HA of higher molecular weight, stability and viscosity, providing a more durable effect with fewer injection sessions. There are some studies supporting the use of crosslinked HA.[42,43] Based on the results, crosslinked HA appears to be a promising therapeutic approach; however, existing literature has yet to reach a consensus, and further research in this area is warranted.

Besides its clinical efficacy, the reason why HA is currently more widely used is its high safety profile. A meta-analysis showed that compared to saline, IAHA had slightly more local adverse reactions (14.5 % vs. 11.7 %), but the difference was not statistically significant. The most common local adverse reactions included injection site pain, joint pain, joint swelling and effusion. Most of which resolved within 2−3 days.[44] Rare severe complications, such as livedo reticularis caused by HA embolism, have been reported, emphasizing the need to inform patients fully about these associated risks.[45]

Overall, IAHA can improve pain and function in knee OA patients and delay the need for surgery. Nonetheless, some researchers argue that IAHA may not improve symptoms of knee OA, or the observed improvements may not reach the clinical significance (minimal clinically important difference [MCID] between group difference should have an expected VAS improvement $\geq$15 mm on a 100-mm VAS).[46] A meta-analysis conducted by Arrich et al. showed that IAHA could significantly improve pain during movements at 10−14 weeks and 22−30 weeks (mean difference on a 100-mm VAS, −3.8 mm after 2−6 weeks, −4.3 mm after 10−14 weeks, and −7.1 mm after 22−30 weeks), but none of these differences reached clinical significance, and IAHA did not improve knee function. Furthermore, the involved studies lacked appropriate endpoint assessments and intention-to-treat analyses.[47] As a result, whether IAHA injection truly benefits knee OA patients still relies on more evidence-based research, including studies with coherent preparation methods, extended follow-up periods and adequate blinding methods.

### 2.3. Dextrose

Dextrose injection is another potential treatment for knee OA. Physicians use multiple injections of a mildly irritating solution which are administered to various painful ligaments, tendons, and adjacent joint spaces to achieve symptom relief. The injection involves the entire joint, including IA injection (into the synovial cavity) and peri-articular (PA) injection (at soft tissue-bone attachments) (Table 1). Nowadays, the most commonly used solution in clinical practice is a hypertonic dextrose solution (typically 12.5%−25 %).[48] Although the underlying mechanisms are not fully understood, it is currently believed that the injection of a hypertonic solution in injured or weakened ligaments and tendon tissues can provoke a mild inflammation by dehydrating cells, which causes local tissue trauma. The mild inflammatory response can consequently help the body release cytokines and growth factors, thereby

*Table 1. Summary of dextrose concentration and injection techniques.*

| Study | Site (Approach/Injection points) | Concentration | Guidance |
|---|---|---|---|
| Reeves et al., 2000[81] | Intra-articular (inferomedial approach) | 9 mL 10 % dextrose | Landmark |
| Dumais et al., 2012[82] | Intra-articular (anterior approach) | 5 mL 20 % dextrose | Landmark |
| | Peri-articular (8 points): | 1 mL 15 % dextrose | |
| | Right medial collateral ligament (2 points) | | |
| | Right lateral collateral ligament (2 points) | | |
| | Left lateral collateral ligament (2 points) | | |
| | Left lateral collateral ligament (2 points) | | |
| Rabago et al., 2012[54] | Intra-articular (inferomedial approach) | 6 mL 25 % dextrose | Landmark |
| | Peri-articular (6 points): | 1.5 mL 15 % dextrose | |
| | Medial collateral ligament | | |
| | Pes anserine attachment | | |
| | Tibial tuberosity | | |
| | Coronary ligaments | | |
| | Patella | | |
| | Lateral collateral ligament | | |
| Rabago et al., 2013[83] | Intra-articular (inferomedial approach) | 6 mL 25 % dextrose | Landmark |
| | Peri-articular (6 points): | 1.5 mL 15 % dextrose | |
| | Medial collateral ligament | | |
| | Pes anserine attachment | | |
| | Tibial tuberosity | | |
| | Coronary ligaments | | |
| | Patella | | |
| | Lateral collateral ligament | | |
| Rahimzadeh et al., 2014[84] | Intra-articular (not mentioned approach) | 5 mL 25 % dextrose | Fluoroscopy |
| Eslamian et al., 2015[52] | Intra-articular (lateral approach) | 8 mL 20 % dextrose | Landmark |
| Hashemi et al., 2015[85] | Intra-articular (inferomedial approach) | 7 mL 12.5 % dextrose | Ultrasound |
| Eroğlu et al., 2016[86] | Intra-articular (inferomedial approach) | 6 mL dextrose (unknown concentration) | Landmark |
| | Peri-articular (not mentioned site) | 1.5 mL dextrose (unknown concentration) | |
| Soliman et al., 2016[87] | Intra-articular (inferomedial or an inferolateral approach) | 5 mL 25 % dextrose | Landmark |
| | Peri-articular (not mentioned site) | 0.5 mL 15 % dextrose | |
| Topol et al., 2016[51] | Intra-articular (lateral approach) | 10 mL 12.5 % dextrose | Ultrasound |
| Farpour et al., 2017[57] | Intra-articular (inferolateral approach) | 6 mL 25 % dextrose | Landmark |
| | Peri-articular (tender points) | 2 mL 25 % dextrose | |
| Rahimzadeh et al., 2018[88] | Intra-articular (upper outer quadrant approach) | 7 mL 25 % dextrose | Ultrasound |

| | | | |
|---|---|---|---|
| Hosseini et al., 2019[89] | Peri-articular (4 points):<br>Superolateral of patella (2 points)<br>Medial knee joint line (1 points)<br>Anterior fibular head (1 points) | 2.5 mL 12.5 % dextrose | Ultrasound |
| Pishgashi et al., 2020[90] | Intra-articular (supralateral approach) | 5 mL 20 % dextrose | Ultrasound |
| Rezasoltani et al., 2020[91] | Intra-articular (not mentioned approach) | 8 mL 20 % dextrose | Ultrasound |
| Sert et al., 2020[53] | Intra-articular (supralateral approach)<br>Peri-articular (10 points):<br>Medial collateral ligament (2 points)<br>Lateral collateral ligament (2 points)<br>Superior patellar pole (1 points)<br>Patellar tendon (2 points)<br>Coronary ligaments (2 points)<br>Pes anserinus tendon (1 points) | 5 mL 25 % dextrose<br>1 mL 15 % dextrose | Landmark |
| Sit et al., 2020[92] | Intra-articular (not mentioned approach) | 5 mL 25 % dextrose | Ultrasound |
| Baygutalp et al., 2021[93] | Intra-articular (lateral approach)<br>Peri-articular (10 points):<br>Coronary ligament (2 points)<br>Medial collateral ligament (2 points)<br>Lateral collateral ligament (2 points)<br>Quadriceps tendon region of patella (1 points)<br>Patellar tendon (2 points)<br>Pes anserine tendon (1 points) | 5 mL 12.5 % dextrose<br>1 mL 12.5 % dextrose | Landmark |
| Hsieh et al., 2022[94] | Intra-articular (lateral suprapatellar approach) | 7 mL 25 % dextrose | Ultrasound |
| Mishra et al., 2022[95] | Intra-articular (not mentioned approach) | 5 mL 12.5 % or 25 % dextrose | Landmark |
| Topol et al., 2022[96] | Intra-articular (suprapatellar approach) | 10 mL 12.5 % dextrose | Ultrasound |
| Medin Ceylan et al., 2023[97] | Peri-articular (not mentioned site) | 0.5 mL 5 % dextrose | Landmark |

promoting soft tissue recovery.[49] Animal and *in vitro* studies have shown that IA dextrose injections can induce cartilage synthesis.[50] Some researchers have used arthroscopy to observe the effects of IA dextrose injections, and the results revealed that in knee OA with severe radiographic changes, IA dextrose injection can induce cartilage formation over exposed subchondral bone, revealing the chondrogenic effect of prolotherapy.[51]

Clinical studies have shown significant short-term (four weeks and eight weeks) improvements in pain and function for IA dextrose injection in knee OA patients.[52] A randomized controlled study in 2020 compared the effects of IA and PA dextrose injection, saline injection, and controlled group (home exercises) on pain and function. Within these groups, the dextrose group showed more benefits at 18 weeks than the other two.[53] Rabago et al. also reported that IA and PA dextrose injections showed more improvement in WOMAC score at 52 weeks compared to the saline and controlled groups (15.3 ± 3.5, 7.6 ± 3.4, and 8.2 ± 3.3 points, respectively, $p < 0.05$).[54] The benefits in knee pain, function, and stiffness scores could even be sustained up to 2.5 years.[55] Despite its long-term efficacy, it is worth noting that some studies have indicated that the therapeutic effect of dextrose injection plateaued at 8–12 weeks.[52,54] One possible reason is that patients may overuse the knee after experiencing improvement in pain and function and may not follow the recommendation of gradual increase in knee loading. Therefore, it is important for clinical physicians to inform patients about the principle of progressive loading in order to mitigate the risk of suboptimal therapeutic outcomes.

As for the comparison between PA and IA injections, Rezasoltani et al. found that PA injection provided better pain relief (VAS), especially two months after injection, but there was no difference in morning stiffness and difficulty in rising from sitting between the two methods.[56] On the other hand, Farpour et al. concluded that there is no difference in pain and function improvement between PA and IA injections (both groups showed improvement).[57] In short, there is currently no consensus of whether PA or IA injections are more beneficial and additional research is required in this regard.

In terms of safety profile, there have been no reports of severe or systemic side effects, indicating that the administration of dextrose injections is a safe therapeutic approach. Following the injection, some patients might undergo local adverse reactions, which include knee swelling, bruising, and post-injection discomfort. These effects typically resolve within a few days.

In a nutshell, dextrose injection appears to be a safe and potentially effective treatment option for knee OA. However, there is still a lack of standardized treatment guidelines, including dextrose concentration, injection sites, and frequency. Besides, the sample sizes in the studies are generally small, and there is a lack of well-designed research in this area. Therefore, further research is needed to validate the application of dextrose injection in knee OA.

### *2.4. Platelet-rich plasma*

PRP is an autologous preparation derived from the patient's own blood, typically extracted in approximately 7–10 mL or more. The blood is then centrifuged in specialized tubes to separate platelets and blood cells, creating the PRP formulation. There are two main types of PRP based on the amount of leukocytes, known as leukocyte-poor PRP (Lp-PRP) and leukocyte-rich PRP (Lr-PRP), determined by the selection of different blood layers during centrifugation.[58] Some PRP products will contain exogenous substances such as thrombin or calcium chloride to activate platelets.

PRP is widely used in the treatment of chronic musculoskeletal diseases, including rotator cuff tears, elbow epicondylitis, patellar tendinopathy, Achilles tendinopathy (in one trial) and acute muscle injuries.[59,60] Moreover, PRP can be utilized as a postoperative treatment to promote tissue repair, for instance, in ACL reconstruction.[59] Due to its high concentration of platelets and the presence of various growth factors, it is theoretically believed to have tissue growth-promoting effects.[61] Through these growth factors, PRP has shown positive

effects on cartilage growth and mesenchymal stem cell proliferation *in vitro* and in animal experiments. It can also mediate inflammatory factors and reduce inflammation.[61] As a result, PRP holds potential benefits for treating knee OA patients, and its trend of clinical use is increasing.[62]

Although the use of PRP is becoming increasingly prevalent, the current evidence supporting the clinical benefits of PRP remains limited. Some studies have indicated that PRP can improve pain and function in knee OA patients.[63−66] PRP has also been showed to benefit more than HA and saline in the aspect of functional outcomes (WOMAC) and pain improvement (VAS).[67,68] As for the clinical efficacy between Lp-PRP and Lr-PRP, a randomized controlled trial in 2022 showed that both injections produced similar clinical improvement in a 12-month follow-up of 192 patients, with no intergroup difference.[69] However, there are some studies having conflicting results. For example, a large and well-designed randomized controlled trial in 2021 enrolled 288 knee OA patients with KL grade 2 or 3.[70] These patients received either IA injections of 5 mL of Lp-PRP with US guidance (three IA injections at weekly intervals) or a placebo of 5 mL of normal saline. After twelve months of follow-up, both groups showed improvements in pain compared to baseline (PRP group $-2.1 \pm 2.7$ vs. placebo group $-1.8 \pm 2.5$), surpassing the MCID. Nonetheless, there was no significant between-group difference in pain improvement (between-group pain change: −0.4 [95 % CI, −0.9 to 0.2]). Regarding the aspect of function, the PRP group exhibited more global improvement in function at the twelve-month follow-up compared to the placebo group (PRP group 42.8 % vs. placebo group 32.1 %; risk ratio 1.36 [95 % CI, 1.00 to 1.86], $p = 0.05$). In terms of structural imaging, which is more objective, there was no significant difference in observable cartilage changes on MRI between the two groups (between-group medial tibial cartilage volume change −0.2 % [95 % CI, −1.9 % −1.5 %]). This study therefore concluded that it does not support the use of PRP for the management of knee OA. On the other hand, a study conducted by Raeissadat et al. demonstrated significant improvements in patellofemoral cartilage volume and synovitis on MRI after multiple PRP injections (two sessions with a four-week interval) at an eight-month follow-up.[66] Based on the aforementioned studies, it remains uncertain whether PRP injections can induce structural changes in imaging.

The inconsistent results in the aforementioned studies may be related to different methodologies, including different PRP preparation methods, injection regimens, patient characteristics and outcome measures. The lack of adequate blinding methods may also lead to patients' reported symptom improvements. Therefore, a larger-scale study is necessary to standardize PRP preparation methods and conduct comparisons between different preparations, as well as to identify the specific knee OA population that may benefit the most from PRP injections.

Similar to the previously mentioned dextrose injection, PRP is also considered a treatment with high safety. Local adverse reactions, such as knee swelling, hematoma, mild synovitis, and post-injection pain may occur, but they usually resolve on their own within a few days.[68,71] Some systemic side effects have been reported, including nausea, tachycardia, headache, and fainting; however, these symptoms are temporary and typically subside within a few days.[68] Severe adverse events have not been reported so far.

### *2.5. Ultrasound-guided injection vs. landmark-guided injection*

In an era when US was not as widely available, physicians mostly relied on landmark-guided techniques for injection. However, with advanced technology in recent years, US imaging has significantly improved in both image quality and portability. The development of portable US devices has further enhanced the accessibility of US imaging. Via US scanning, the precise location of the lesion can be visualized, thereby improving the accuracy of injection.

Research has shown that the accuracy of landmark-guided injections averages around 79 %, which varies depending on the approach used.[72] Image-guided injections have shown to have a significant improvement in accuracy, with knee injections

*Table 2. Summary of knee osteoarthritis intraarticular treatment recommendations from major professional organizations.*

| Recommendation | AAOS 2022[98] | ACR 2019[79] | EULAR 2003[99] | OARSI 2019[78] |
|---|---|---|---|---|
| Corticosteroid | △ | ○ | △ | △ |
| Hyaluronic acid | □ | □ | △ | △ |
| Dextrose | – | □ | – | × |
| Platelet-rich plasma | △ | × | – | × |

○: strongly recommended; △: conditionally recommended; □: conditionally recommended against; ×: strongly recommended against; —: not shown.
Abbreviations: AAOS, American Academy of Orthopaedic Surgeons; ACR, American College of Rheumatology; EULAR, European League Against Rheumatism; OARSI, Osteoarthritis Research Society International.
* In this table, the latest recommendations regarding the intraarticular treatment of knee osteoarthritis from the major professional organizations were included. Any recommendation derived from moderate or limited evidence of AAOS is regarded as conditionally recommended; any recommendation of EULAR that possesses a level of evidence of 1 (out of 4) and a level of agreement of 8 (out of 10) or higher is considered to be strongly recommended.

achieving up to 98 % accuracy using US guidance (1100 injections).[73] Overall, landmark-guided injections still provide good results, but US guidance offers additional advantages.[73] For instance, in the case of IACS, US-guided procedures have demonstrated reduced injection pain, increased synovial fluid aspiration and better pain relief compared to conventional palpation-guided methods.[74] With regards to HA injections, in order to effectively restore HA molecules and their concentration within the synovial fluid of the joint, exogenous HA needs to be administered into the IA space rather than into the fat pad or sub-synovial tissue. If inadvertently injected outside the joint, the efficacy of such treatments may be compromised.[72] By using fluoroscopic imaging, Varlotta et al. have observed that US-guided IAHA injections can accurately target the ideal locations, from the suprapatellar recess into the tibiofemoral and patellofemoral joint. Kianmehr et al. have also reported that patients who received US-guided IAHA injections experienced better pain relief and functional improvement compared to those receiving landmark-guided injections.[75,76] Moreover, US-guided injections have been shown to be a more cost-effective option than landmark-guided injections, possibly due to the enhanced precision of US-guidance, resulting in better responses to pain relief and reduced follow-up costs.[77] With the widespread adoption of US, it is important to establish a comprehensive US protocol to assist in guiding IA knee injections. Current clinical physicians also need to become more familiar with the manipulation and the utilization of US to achieve improved clinical outcomes.

### *2.6. Current guideline on steroid, HA, dextrose, and PRP*

To date, major professional organizations have developed guidelines for injection treatments of OA management (Table 2). The majority of clinical guidelines recommends the use of IACS for its short-term (<6 weeks) effectiveness. As for IAHA, only OARSI guideline in 2019 conditionally recommends its use in providing long-term pain relief (≥12 weeks). The use of dextrose injection has not been endorsed by major clinical guidelines and requires further validation. Some OA clinical guidelines, including those from the American College of Rheumatology (ACR) in 2019 and OARSI in 2019, do not recommend the use of PRP due to the relatively low evidence.[78,79] Recently, Eymard et al. have presented an expert consensus for PRP injections in knee OA at the European Congress of Rheumatology (EULAR) annual meeting in 2020, stating that PRP injection demonstrates efficacy in addressing early or moderate knee OA and could be regarded as a viable second-line treatment option.[80] Given that PRP is more expensive than other injectable formulations, further rigorous research is necessary to determine its clinical efficacy and corresponding indications.

## 3. Conclusion

Knee OA is a highly prevalent and widely impacting chronic degenerative joint disease. In addition to exercise and oral medications, IA injections (corticosteroids, HA, hypertonic dextrose, PRP) can also offer some degree of pain relief and functional improvement, and may even delay the need for surgery. Among

them, US-guided injections enhance accuracy and safety. However, there is still no consensus on the effectiveness of certain treatments, as indicated by various guidelines and research findings. Moreover, the preparation methods and concentrations of injectants lack standardized clinical criteria. Future efforts should focus on conducting more large-scale studies to establish and provide reliable reference benchmarks.

## Conflicts of interest

None.

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