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Review

Hyaluronic acid, platelet-rich plasma, bone marrow aspirate concentrate, the stromal vascular fraction, or mesenchymal stem cells: which is the best candidate for treating knee osteoarthritis?

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ABSTRACT

Regenerative medicine-based therapies are considered promising for some chronic diseases, such as osteoarthritis (OA). Because OA is the most common disease in many countries, significant efforts have long been made to develop effective treatments. Current therapies for OA include hyaluronic acid, platelet-rich plasma, bone marrow aspirate concentrates, the stromal vascular fraction from adipose tissue, bone marrow-derived mesenchymal stem cells, and adipose tissue-derived mesenchymal stem cells. Clinical trials testing these agents for OA treatment have been performed for over 10 years. In this review, we summarize and compare the effects of these agents for treating knee OA based on recent meta-analyses.

Key words: Bone marrow aspirate concentrate, Mesenchymal stem cells, Osteoarthritis, Platelet rich plasma, Stromal vascular fraction

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INTRODUCTION

Osteoarthritis (OA), especially knee OA, is the most common form of arthritis. As of 2019, it affected more than 32.5 million people in the U.S. and more than 528 million people worldwide[1]. It is a significant contributor to years lived with disability and is more prevalent in people older than 55 years. Moreover, 60% of people living with OA are women. OA is characterized by symptoms including pain, swelling, stiffness, and difficulty moving. Among the types of OA, knee OA is most common among older people. It can cause a significant decrease in quality of life, as due to pain and difficulty in moving, patients cannot participate in home, work, or social activities. This can negatively impact mental health, sleep, and relationships.

A recent study showed an association between joint inflammation signs, especially inflammation in the synovial membrane, and pain in patients with OA[2]. Therefore, almost all OA cases are treated with anti-inflammatory agents.

Current treatments for OA include noncellular agents, such as hyaluronic acid (HA) and platelet-rich plasma (PRP), and cellular agents, such as stem cells from bone marrow and adipose tissue (**Figure 1**). To summarize and compare their treatment efficacies, this review summarizes several meta-analyses on OA treatment using noncellular and cellular therapies.

CURRENT APPROACHES FOR TREATING KNEE OSTEOARTHRITIS

Hyaluronic acid

HA is used to treat OA in the form of 6000 to 7000 kDa protein at concentrations of 2–4 mg/mL[3]. HA positively affects the knee by working as a lubricant at low shear rates and providing shock absorption during movement. It also has anti-inflammatory effects and contributes to proteoglycan synthesis[4].

To investigate the therapeutic effects of HA in knee OA, Vincent *et al.* (2020) performed a meta-analysis of the effects of HA on knee OA in 1177 patients. The authors reported significant improvements in the Western Ontario and McMaster University index function subscores[5]. However, recently, Mao *et al.* (2023) systematically analyzed 15 studies involving 951 knees injected with HA after arthroscopic knee surgery. Although the meta-analysis showed that HA injection was safe, this therapy did not support pain relief or functional recovery[6].

In 2020, Zheng *et al.* performed a meta-analysis of 10 randomized controlled trials involving 998 patients to compare the effects of HA injection alone with those of combination therapy comprising acupuncture and HA injection. The analysis revealed that the combination of acupuncture and HA injection significantly reduced pain, as measured by the visual analog scale (VAS), and improved knee function, as measured by the Lysholm knee scoring scale (LKSS)[7].

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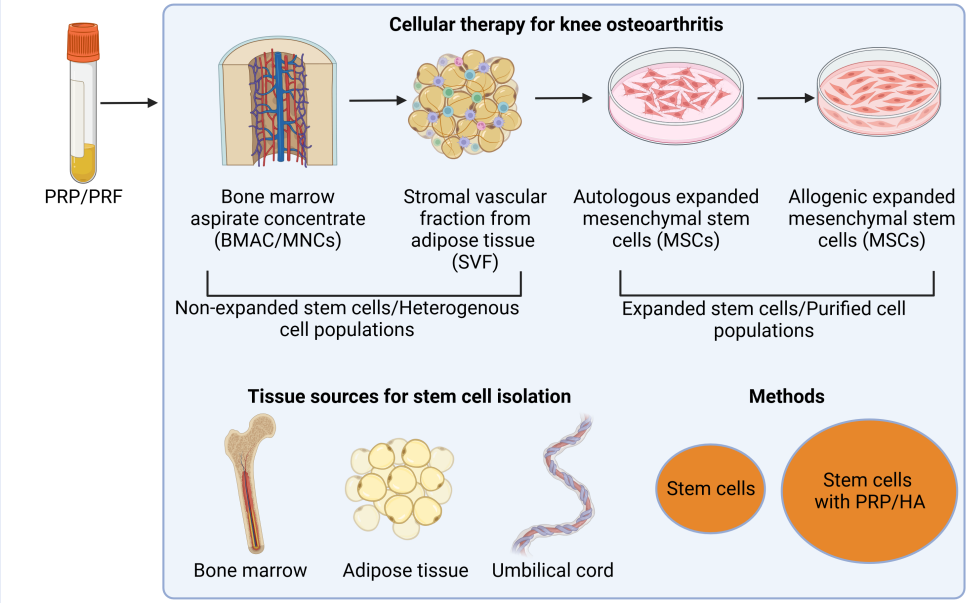

Figure 1: **Some current strategies for knee osteoarthritis treatment**. PRP/PRF is the most popular strategy used for knee osteoarthritis with promising results. Other effects are usages of bone marrow aspirate concentrate or stromal vascular fraction from adipose tissue. Recent years, expanded mesenchymal stem cells from autologous and alloegnic sources are used to treat knee osteoarthritis. **Abbreviations**: **BMAC**: Bone marrow aspirate concentrate, **MNCs**: Mononuclear cells, **MSCs**: Mesenchymal stem cells, **PRP**: Platelet rich plasma, **PRF**: Platelet rich fibril, **SVF**: Stromal vascular fraction

Platelet-rich plasma

The use of PRP is a new strategy for improving knee OA. PRP is plasma enriched with platelets. Currently, there are three types of PRP, including pure PRP, which lacks leukocytes; leukocyte-poor PRP, which contains a few leukocytes; and leukocyte-rich plasma, which contains leukocytes. Because of its high concentration of platelets, PRP is considered to contain a pool of growth factors and anti-inflammatory agents. Therefore, it has been widely used in treating knee OA for many years. However, to date, the use of PRP as a therapy for knee OA has not been recommended by societies or committees. The first consensus regarding the use of PRP for treating knee OA came from French-speaking experts in 2020[8]. Their publications included 25 recommendations related to the use of PRP for knee OA and agreed that PRP treatment was appropriate for treating knee OA. These authors also suggested that leukocyte-poor PRP is preferred for patients with knee OA[8].

However, in a study published in JAMA 2021, Bennell *et al.* (2021) showed that compared with a placebo, PRP injection did not significantly alter symptoms or joint structures at 12 months. These findings did not support PRP use for knee OA management[9]. We think that several factors caused the failure of PRP injection in this study. The most important factor may be the dose of platelets used. The authors reported a PRP dose of 5 mL, $325.10^3/mm^3$. In another study by Bansal *et al.* (2021), 10 billion platelets (a dose more than fivefold higher than that used by Bennell *et al.*) were confirmed to have long-term effects on moderate knee OA[10].

Several different publications about the efficacy of treatment for knee OA show that efficacy depends on the dose of platelets used. Therefore, identifying the best techniques to prepare PRP is essential to ensure good treatment efficacy. Patients' platelet counts are checked before their blood is collected to prepare PRP. To our knowledge, there are currently four platelet dose types, namely, low (< 1 billion), average (1–3 billion), high (3–5 billion), and very high (> 5 billion). Depending on the clinical response, a suitable dose should be recommended by medical doctors.

Bone marrow aspirate concentrates

Bone marrow aspirate concentrates (BMACs) are mononuclear cells (MNCs) derived from bone marrow aspirates. Bone marrow is known as a source of stem cells. It contains various types of stem cells, including hematopoietic stem cells, mesenchymal stem cells, and endothelial progenitor cells[11]. BMACs are prepared by centrifuging bone marrow in gel or Ficoll to eliminate red blood cells and some mature leukocytes. Traditionally, BMACs are prepared by centrifuging 60–90 mL of bone marrow at 2400 rpm for 10 minutes to obtain platelet-poor plasma and a buffy coat layer for a second centrifugation at a higher speed (approximately 3400 rpm for 6 minutes). The resulting cell pellet is collected and resuspended in platelet-poor plasma[12]. Therefore, compared with whole bone marrow, bone marrow concentrates contain MNCs with a greater percentage of stem cells. The quality of BMACs depends on the harvest site and the patient's age[13]. Cavallo *et al.* (2022) showed that younger patients had three times more MNCs than older patients did, and the number of MNCs was four times greater in BMACs from the iliac crest than in those from the tibia[13]. Muthu *et al.* (2023) also confirmed this finding. Thus, age affects the number of MNCs. The MNC count is also significantly reduced in patient populations with comorbidities[14].

Keeling *et al.* (2022) analyzed eight studies with 299 knees treated with BMACs. The results showed that BMAC injection effectively improved pain in knee OA patients with short- to mid-term follow-up[15]. A recent study by Rascovic *et al.* (2023) involving 111 patients also showed that BMAC therapy is effective, especially for younger patients with milder OA[16]. The combination of intra-articular and subchondral BMAC injection can provide clinical and imaging benefits for up to 24 months in patients with knee OA[17].

Stromal vascular fraction from adipose tissue

The stromal vascular fraction (SVF) from adipose tissue is a new candidate for treating knee OA. Like MNCs or BMACs, SVFs are freshly isolated from adipose tissue; therefore, they contain a variety of cells enriched with stromal stem cells. Although several types of stem cells are found in SVFs, mesenchymal stem cells (MSCs) are the most important types of stem cells that benefit knee OA patients. SVFs can be easily prepared by digesting adipose tissue with collagenase to disrupt fat cells and release nucleated cells. The MSCs inside SVFs are considered the main component that can help to reduce pain and stimulate cartilage regeneration. The biological functions of MSCs have been described in many publications[18–20].

In 2019, Hong *et al.* performed a double-blinded clinical trial in which SVF was used to treat knee OA. The study included 60 patients with K-L grades II to III divided into two groups. Group 1 included mice with SVF injected into one side of the knee joint, and group 2 included mice with HA injected on the other side. The results revealed that SVF-treated knees exhibited improved mean VAS and WOMAC scores, while the scores in the control group worsened[21]. A recent publication by Goncharov *et al.* (2023) analyzed 22 clinical studies using SVFs for knee OA; most of those studies showed the therapeutic benefits of SVF injection for knee OA[22].

The effects of SVFs on knee OA depend on the dose of SVF cells. A high dose of SVF cells (50.10^6 SVF cells) showed better results than did low-dose SVF cells (25.10^6 SVF cells)[23]; however, at a dose of 25.10^6 SVF cells, the WOMAC score and VAS and KOOS improved[24]. In a recent publication, Kim *et al.* (2023) confirmed that the cartilage lesion size and number of SVF cells strongly influence the clinical outcome of knee OA treatment[25]. The therapeutic effects of SVF can persist for the first 2 years in patients with knee OA grades 2–3, and the positive effects of the injection disappear in the third year[26].

Expanded mesenchymal stem cells

Expanded MSCs constitute the next generation of cellular therapy for knee OA. In contrast to SVFs or BMACs, in which the percentage of MSCs inside the space is low, expanded MSCs comprise pure MSCs expanded from the SVF, BMAC, or umbilical cord blood (UCB)/tissue. MSCs can be isolated and expanded for several applications. MSCs used to treat knee OA have various sources, such as bone marrow, adipose tissue, umbilical cord tissue, and UCB. In several early studies, autologous MSCs were injected into joints, and most current applications use allogeneic MSCs for this purpose. In fact, MSCs exhibit low immunogenicity and act as immune modulators and anti-inflammatory agents. For this reason, MSCs have rapidly become excellent candidates for treating knee OA[18–20].

To provide an overview of this therapy, Long *et al.* (2022) summarized and analyzed the results of 28 RCTs using MSCs for knee OA (27) with 1494 participants. They concluded that MSC injection is effective for treating knee OA, and the curative effect should

be maintained for no less than 12 months, during which the WOMAC pain score, VAS score, WOMAC stiffness score, and WOMAC physical function improve[27]. In another review, 12 articles comprising 539 patients and 576 knees treated with a single intra-articular injection of MSCs for knee OA were analyzed by Kyriakidis *et al.* (2023)[28], who reported that MSC injection is a safe and effective treatment for K-L grade I-III knee OA. Interestingly, a triple-blinded, placebo-controlled, randomized trial compared the treatment efficacy of allogeneic MSCs (from adipose tissue) to that of normal saline (control group) and confirmed that allogeneic MSC injection is safe and significantly improves treatment efficacy[29].

The efficacy of this therapy depends on various factors, including the dose of cells, the kind of MSCs, and the grade of knee OA. The efficacy of MSC injection also depends on the cell dose. Huang *et al.* (2023) reported three popular doses of adipose-derived stem cells used to treat knee OA, including a low dose (0–25.10^6 cells), an elevated dose (25–50.10^6 cells), and a high dose (> 50.10^6 cells), based on 16 studies. The authors suggested that a high dose had the best treatment effects; however, adverse effects also increased with increasing doses[30].

Wei *et al.* (2021), based on eight studies with 203 knee OA patients, evaluated the differences in the efficacy of several types of MSCs used to treat this disease. The authors concluded that MSCs from adipose tissue are the most effective at improving function[31].

Some allogeneic MSCs have been successfully developed into "off-the-shelf" MSC products for knee OA and have been approved in some countries as stem cell drugs. A system that contains allogeneic UCB-derived MSCs was first approved by the Korean FDA for knee OA treatment. Multiple RCTs investigating the use of Cartistem (a combination of UCB-MSCs with HA) for large, full-thickness cartilage defects in older patients showed that Cartistem improved the cartilage defect grade, as well as pain and function, for up to 5 years compared to microfracture[32]. Another product, an off-the-shelf MSC product for knee OA named StemOne, has been approved in India[33]. This approval is based on the results of a multicenter, double-blinded, randomized, placebo-controlled study published by Gupta *et al.* (2023)[34]. StemOne comprises vials containing 25.10^6 pooled allogeneic bone marrow-derived MSCs in 1 mL of CryoStor CS5 plus 1 mL of PlasmaLyte-A. In the abovementioned phase 3 RCT, a total of 65 patients received one dose of StemOne (treatment group) and 2 mL of 20 mg HA (placebo group). The results showed that StemOne injection is safe and effective for the treatment of Grades II and III OA. This therapy relieves pain and stiffness, improves physical function, and prevents the worsening of cartilage quality for more than 12 months[34]. Another allogeneic MSC-based treatment from adipose tissue that is being developed as an off-the-shelf therapy for knee OA is Cartilatist. This is a product consisting of adipose tissue-derived MSCs resuspended in MSCCryosave OTS (Regenmedlab, HCMC, Vietnam) developed by the Stem Cell Institute (University of Science, Vietnam National University, Ho Chi Minh City, Vietnam). This product is currently undergoing clinical trials. Like Cartilatist, ElixCyte, which was developed by UnicoCell (Taiwan), also contains allogeneic AT-MSCs[35]. This product is also undergoing clinical trials[35].

COMPARISONS OF THE THERAPEUTIC EFFECTS OF KNEE OSTEOARTHRITIS THERAPIES

A comparison between hyaluronic acid and platelet-rich-plasma

Although both HA and PRP are shown to be beneficial for treating knee OA, which treatment is the best is a common question for most clinical doctors. Due to differences in their mechanisms of action, PRP exhibited better clinical effects than HA in most clinical studies.

In 2016, Duymus *et al.* compared the effects of PRP, HA, and ozone for knee OA in a clinical trial. In this study, 102 patients with mild-to-moderate or moderate knee OA and a history of at least 1 year were included. In the PRP group, patients were intra-articularly injected with two doses of PRP; in the HA group, patients were injected with a single dose of HA; and in the ozone group, patients were injected with four doses of ozone. All patients in the three groups showed significant improvement after the first month of follow-up. However, at the 3-month follow-up visit, the WOMAC and VAS scores in the PRP and HA groups were significantly greater than those in the ozone group. In the sixth month, the therapeutic effects were maintained and similar in both the PRP and HA groups but disappeared in patients treated with ozone injections. In the twelfth month, the effects of PRP injections were clearly greater than those of HA[36]. These observations were checked and confirmed by Raeissadat *et al.* (2021). Raeissadat *et al.* (2021) compared the effects of the intra-articular injection of PRP, plasma rich in growth factor (PRGF), HA, and ozone therapy for knee OA. In this study, 238 patients were randomly divided into four groups: HA

(three doses weekly), PRP (two doses at a 3-week interval), PRGF (two doses at a 3-week interval), and ozone (three doses weekly). The results showed that ozone injection had rapid effects but improved short-term results after 2 months. Until the 6-month point, the effects of PRP, PRGF, and HA were superior to those of ozone. However, up to 12 months of follow-up, symptoms improved in only patients who received PRP or PRGF[37].

In a systematic review and meta-analysis published in 2022, Costa *et al.* analyzed 40 studies with 3034 participants to compare the effects of PRP therapy with those of HA, corticosteroids, and saline[38]. At the 6-month follow-up, PRP therapy was as effective as other therapies, and in some studies, it was even more effective than other therapies[38].

In a recent publication, Chen *et al.* (2023) analyzed the effects of PRP versus HA for knee OA based on 30 articles with 2733 patients. The results also confirmed that PRP injection was better than HA injection; in particular, the WOMAC and IKDC scores were better in the PRP group than in the HA group at the last follow-up timepoint[39]. Additionally, in this analysis, Chen *et al.* showed that LP-PRP appeared to be superior to LR-PRP in terms of functional recovery but not in terms of pain relief. They also showed that there were no differences between single PRP injections and triple PRP injections[39]. However, in another analysis, Peng *et al.* (2022) compared the effects of LR-PRP and HA and showed that although LR-PRP had no significant pain relief effect, LR-PRP injection demonstrated better overall outcomes than HA injection[40]. Kim *et al.* (2022) compared the effects of LP-PRP to those of HA and showed that LP-PRP injection improved pain and function in patients with knee OA for 12 months and was superior to HA regardless of the leukocyte concentration or number of injections[41]. In addition, in a previous publication, Kim *et al.* (2021) showed that LR-PRP can cause more adverse effects than LP-PRP; patients treated with LR-PRP experienced significantly greater pain than those treated with LP-PRP, and LR-PRP was associated with a significantly greater rate of swelling than was LP-PRP[42]. However, according to Abbas *et al.* (2022), LP-PRP is preferred to LR-PRP according to the SUCRA rankings; nevertheless, this preference is not important in clinical practice[43].

An RCT with 7 years of follow-up showed that PRP was also more effective than HA in terms of survival, reintervention rates, VAS score, and WOMAC score, with higher satisfaction than was observed in patients with HA, although there were no significant differences in the imaging evaluation between the PRP and HA groups[44].

Which kinds of stem cells are the best for treating knee osteoarthritis?

In general, MSCs from adipose tissue, bone marrow, SVFs from adipose tissue, and bone marrow adenocarcinoma (BMAC) are beneficial for treating knee OA. Almost all the studies reviewed here showed that these treatments improved the VAS score, KOOS, WOMAC score, and MRI results without significant adverse effects[45].

A meta-analysis of 1042 patients from 27 studies was performed to compare the therapeutic effects of PRP, HA, and BMAC. Belk *et al.* (2023) reported no difference in outcome scores between PRP and BMAC, but both the PRP and BMAC outcome scores were better than those for patients receiving HA injection[46]. A recent study showed that autologously expanded AT-MSCs are better than PRP, especially at 12- and 24-month follow-ups[47].

Bolia *et al.* (2021) compared the clinical efficacy of BMAC and SVF for knee OA[48] based on 10 studies with 472 patients (233 patients with BMAC, 239 patients with SVF). The analysis showed that SVF injection had a greater effect on pain than BMAC injection. However, more complications were associated with SVF injection than with BMAC injection (67% of patients with SVF injection vs. 50% of patients with BMAC injection)[48].

Allogenic UCB-MSCs were better than BMAC for cartilage regeneration in knee OA[49]. In a study of 176 patients with knee OA, Yang *et al.* (2022) compared the therapeutic efficacy of BMAC and UCB-MSCs and reported similar clinical outcomes between the two groups; however, UCB-MSC implantation was more effective at promoting cartilage regeneration than was BMAC implantation[50]. UCB-MSC implantation is comparable to SVF implantation in knee OA[51].

To compare treatment efficacy between BM-MSCs and AT-MSCs, Han *et al.* (2020) analyzed nine RCTs with 377 patients[52]. According to the VAS and WOMAC scores, AT-MSCs are better than BM-MSCs for treating knee OA[52]. Wei *et al.* (2021) analyzed 203 knee OA patients in eight studies using three types of MSCs: BM-MSCs, AD-MSCs, and UC-MSCs. The analysis suggested that AD-MSCs are the most effective at relieving pain, while UC-MSCs are the most effective at improving function[31]. Jeyaraman *et al.* (2021) also confirmed that MSCs from adipose tissue were better than BM-MSCs for treating knee OA[53]. Indeed, after 24 months of implantation, AD-MSCs had significantly better Lysholm scores than BM-MSCs did[53].

To compare the therapeutic effects of PRP, MSCs from adipose tissue, and MSCs from bone marrow with HA and normal saline in treating knee OA, Zhao *et al.* (2021) analyzed 43 studies involving 6 months of follow-up and concluded that MSCs from adipose tissue are the best kind of treatment for relieving pain, while leukocyte-poor PRP is the most effective for functional improvement. At the 12-month follow-up, both MSCs from adipose tissue and LP-PRP had clinical pain relief effects[54].

Which dose of stem cells is best for treating knee osteoarthritis?

Matas *et al.* (2019) reported that two doses of UC-MSCs (on day 0 and after 6 months, 20.10^6 cells per dose) were better than a single dose of 20.10^6 UC-MSCs[55]. In a recent publication, Sadri *et al.* (2023) used a high dose of 100.10^6 allogeneic AT-MSCs to treat knee OA patients. At this high dose, the authors found that intra-articular injection is safe, as indicated by significant improvements in laboratory data, MRI findings, and clinical examination at the 12-month follow-up[29]. Based on 14 studies with 564 patients, Muthu *et al.* (2021) categorized the treatments into four doses, namely < 10.10^6 MSCs, 10–50.10^6 MSCs, 50–100.10^6 MSCs, and > 100.10^6 MSCs, and recommended that a dose of 50–100.10^6 MSCs confers superior benefits[56].

Based on 16 studies, Huang *et al.* (2023) grouped the doses of stem cells used for treating knee OA into three types: low dose (0–25.10^6 cells), high dose (25–50.10^6 cells), and high dose (> 50.10^6 cells)[30]. In general, a high dose of stem cells results in a better response; however, the adverse effects also increase with increasing doses[30].

Non-expanded stem cells or expanded stem cells: which are better?

Muthu *et al.* (2021) investigated the following question: is culture expansion necessary in autologous MSC therapy to obtain superior results in treating knee OA? A meta-analysis was performed, with 17 studies including 767 patients. Based on the improvements in the VAS, WOMAC, Lysholm, and KOOS scores, the authors concluded that *in vitro* culture of autologous MSCs is unnecessary for obtaining superior results[57]. In a meta-analysis, Kim *et al.* (2023) also showed that autologous AD-MSCs and SVF injections had similar efficacy in treating knee OA[58].

In a rabbit model of knee OA, Anjiki *et al.* (2023) compared the therapeutic effects of SVF (a type of nonexpanded stem cells) and AT-MSCs. The authors found that SVF had better effects on chondrocytes. The SVF group showed greater expression of collagen II and SOX9 in the cartilage, greater expression of TGF-beta and IL-10 in the synovium, lower expression of MMP-13, and a lower M1/M2 macrophage ratio than the ADSC group. These findings revealed that SVF cells were superior to ADSCs[59]. However, in terms of clinical findings, Yokota *et al.* (2019) showed that AT-MSCs were better than SVFs at treating knee OA after 6 months of follow-up[60] or 2 years of follow-up[61].

Should treatments for knee osteoarthritis be combined for greater efficacy?

Huang *et al.* (2022) compared the effects of combinations of PRP with different hyaluronans and PRP alone in 99 patients with K-L grade II OA. Although this combination is safe, the efficacy of the two regimens did not differ significantly[62]. In contrast to the findings of Huang *et al.* (2022), Sun *et al.* (2021) reported that the combination of PRP with Hyajoint Plus helped reduce pain better than PRP alone at 6 months[63]. However, in a recent analysis by Howlader *et al.* (2023), based on six studies, five of which were RCTs, the authors suggested that the combination of PRP and HA yields outcomes comparable to those of PRP therapy alone at the 12-month follow-up[64]; however, at the 24-month follow-up, the combination has the potential to yield superior outcomes compared to PRP alone[64].

Zhao *et al.* (2022) compared the effects of MSC injection alone and MSC in combination with PRP injection for the treatment of knee OA[65] in a meta-analysis of six RCTs including 493 patients. Although the results showed that the combination of MSCs and PRP had good clinical efficacy in improving pain and joint functions, there were no significant differences between the MSC plus PRP group and the MSC alone group[65].

Which grade of OA is suitable for treatment?

Bakowski *et al.* (2023) followed 59 knee OA patients treated with intra-articular injection of autologous adipose tissue. They found that patients with stage II disease and a normal BMI are most likely to benefit from this therapy, while patients with stage IV disease are not satisfied with this therapy[66]. Similarly, Kuwasawa *et al.* (2023) reported a study in which expanded AT-MSCs were used for knee OA patients with K-L grades 2, 3, and 4. The data demonstrated that intra-articular administration of AT-MSCs to knee OA pa-

tients improved KOOS at 6 months; however, the difference was more significant for K-L grade 2 or 3 knees than for K-L grade 4 knees.

CONCLUSION

Several strategies are currently used to treat knee OA, ranging from the use of accelerated therapies such as HA or PRP injection to the use of heterogeneous cell populations (BMAC or SVF) or pure cell populations (MSCs from adipose tissue, bone marrow, or the umbilical cord). Although almost all therapies show some benefits in almost all patients with knee OA according to short-term follow-up studies, their treatment efficacy differs over long-term follow-up. Based on the results of the meta-analyses presented in this review, we propose that increasing the efficacy from HA to PRP, BMAC, SVF, BM-MSCs, UC-MSCs, and AT-MSCs. Almost all the analyses showed that expanded MSCs are effective at treating knee OA, but the best candidate for reducing pain is AT-MSCs. Because these findings were based on meta-analyses, well-designed clinical trials should be performed to confirm these observations.

ABBREVIATIONS

AT: Adipose tissue, **AT-MSC**: Adipose tissue derived MSCs, **BMAC**: Bone marrow aspirate concentrate, **BM-MSC**: Bone marrow derived MSCs, **HA**: Hyaluronic acid, **MNC**: Mononuclear cells, **MSC**: Mesenchymal stem cell, **OA**: Osteoarthritis, **PRP**: Platelet rich plasma, **SVF**: Stromal vascular fraction, **UC-MSC**: Umbilical cord derived MSCs

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AUTHOR'S CONTRIBUTIONS

LTBP and VBN drafted the manuscript, PVP suggested the ideas, finalized the manuscript, and drew the figure 1. All authors read and approved the final manuscript.

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The authors declare that they have no competing interests.

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