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# Microfragmented adipose tissue versus platelet-rich plasma in the treatment of knee osteoarthritis: a systematic review and meta-analysis

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**This meta-analysis focuses on the controversial efficacy and safety of microfragmented adipose tissue (MFAT) as compared with platelet-rich plasma (PRP) in the clinical treatment of knee osteoarthritis (KOA). We have attempted to provide an evidence-based medicine protocol for the conservative treatment of KOA. Researchers collected and compared randomized controlled trials (RCTs) that used microfragmented adipose tissue and platelet-rich plasma to treat knee osteoarthritis. We searched CNKI, Wanfang Database, CMJD, PubMed, Sinomed, Cochrane Library, and Embase for studies published up to May 31, 2023. Two investigators independently screened literature, extracted data, and assessed bias risk using the Cochrane bias risk tool. The researchers then performed a meta-analysis using Revman 5.4 statistics software provided by the Cochrane Library. A total of 4 randomized controlled trials involving 266 patients (326 knees) were included. There were 161 knees in the MFAT group and 165 knees in the PRP group. Meta-analysis showed a statistically significant difference in VAS scores between the MFAT group and the PRP group at 12 months after treatment [MD=0.99, 95% CI (0.31, 1.67), P=0.004]. This result showed that VAS scores were lower in the PRP group than in the MFAT group, and that PRP injection reduced pain more effectively than MFAT injection. At 6 months after treatment, Tegner activity scale scores in the MFAT group were higher than that in the PRP group [MD=0.65, 95% CI (0.11, 1.19), P=0.02], and the difference was statistically significant. There were no significant differences in the remaining indicators between the two groups. Based on this meta-analysis, PRP appears to be more effective than MFAT in treating KOA in terms of long-term pain relief. However, MFAT was superior to PRP in improving short-term activity function. Overall, there was no significant difference between MFAT and PRP in the treatment of KOA. In addition, MFAT does not increase the risk of adverse events compared to PRP. However, at present, there are few clinical studies on MFAT and PRP, which need to be verified by more rigorously designed clinical trials.**

**Keywords** knee osteoarthritis, microfragmented adipose tissue, platelet-rich plasma, meta-analysis.

## INTRODUCTION

Knee osteoarthritis is a common musculoskeletal progressive condition in middle-aged and elderly people[1]. Its primary symptoms include continuous knee swelling and dysfunction. Knee osteoarthritis is characterized by degenerative changes in articular cartilage and cystic changes in subchondral bone, osteosclerosis, including structural changes in fat pads, synovium, liga-ments, and muscles, and hyperplasia of the articular margins[2-6].

Clinicians typically employ a range of treatments to slow down disease progression. At present, non-surgical interventions for KOA concentrate on relieving symptoms and improving function, including both drug and non-drug therapies[7]. The primary non-drug treatment for KOA involves regulating diet and exercise, but compliance with this approach can be problematic[8]. Medications for KOA include oral glucosamine, NSAIDs, and injections of hyaluronic acid (HA) and platelet-rich plasma directly into the joint[5,9]. It is worth noting, however, that the use

of NSAIDs and opioids can often result in undesirable side effects[10]. KOA disease progresses to the terminal stage, and total knee arthroplasty (TKA) is often needed. There are many contraindications in total knee arthroplasty, and there is a risk of infection occurring during the procedure which can lead to failure[11-13]. Moreover, the replacement artificial joint has a certain service life, and there is the possibility of revision in the later stage[14]

PRP is created by harvesting autologous whole blood and centrifuging it to concentrate the platelets. This method can obtain a concentrate of autologous-derived growth factors and other bioactive molecules capable of stimulating tissue healing and regeneration, as well as anti-inflammatory and anti-catabolic Molecules[15]. PRP has been shown to induce cartilage protection and is a good choice for injection therapy in treating KOA[16].

MFAT is liposuction in the operating room. This product is obtained through simple, minimal mechanical manipulation with a progressive reduction in the size of adipose tissue clusters and the elimination of oil and blood residue[17]. In this way, the structural properties and integrity of the microarchitecture of the original tissue are preserved. MFAT is composed of a heterogeneous cell population including fibroblasts, macro-phages, adipocytes, and mesenchymal stem cells[18-19]. Experimental animal studies have shown that MFAT can stimulate cartilage regeneration and improve the symptoms of degenerative cartilage diseases[20]. MFAT is gaining popularity for its potential in adipose tissue biology.

MFAT, as a new treatment method, has not been evaluated on its efficacy and safety. The purpose of this study was to systematically evaluate the efficacy and safety of MFAT and PRP in the treatment of KOA and to provide evidence-based medicine options for clinical non-surgical treatment of KOA.

## MATERIALS AND METHODS

Randomized controlled trials on the treatment of KOA with MFAT and PRP were collected by using the CNKI, Wanfang Database, CMJD, PubMed, Sinomed, Cochrane Library, and Embase. The search strategy was made for the use of Medical Subject Headings (MeSH) terms and correspondence keywords, and the main search term was "Osteoarthritis, Knee" "Knee Osteoarthritides" "Knee Osteoarthritis" "Osteoarthritis of Knee" "Microfragmented adipose tissue" "adipose tissue" "Platelet-Rich Plasma", etc., and the relevant journals and their references were searched manually. The time limit for retrieval is from their inception to May 31, 2023. Literature retrieval was conducted independently by two investigators, and differences were resolved through negotiation or submitted to the third investigator to assist in adjudication.

Literature screening was conducted independently by two investigators according to the established inclusion and exclusion criteria. Two investigators extracted and cross-checked the data according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement[21]. Divergences of opinion between the two investigators were resolved by consulting a third investigator. The literature was chosen by reviewing abstracts and reading full texts after preliminary screening. All analyses were conducted using previously published research, therefore ethical approval and patient consent are not necessary.

*The inclusion criteria were as follows*

1. Study content: All published RCTs of MFAT and PRP in the treatment of KOA are included, with no language or blind method restrictions;
2. Subjects: Patients diagnosed with KOA according to symptoms, signs, and radiographs fulfill the diagnostic criteria of the American College of Rheumatology/Arthritis Foundation Guideline[7];
3. Interventions: The group undergoing experimentation received MFAT treatment, while the control group was given PRP;
4. Citing studies involving at least one of the following indicators: visual analog scale (VAS), Tegner activity scale, Knee injury and Osteoarthritis Outcome Score (KOOS), and adverse events.

*The exclusion criteria were as follows*

1. Included animals as research objects;
2. Non-randomized controlled trial;
3. There are no specific diagnostic criteria, inclusion criteria, and exclusion criteria;
4. Full-text literature is not available.

Data extraction and quality evaluation of the included literature were carried out independently by two investigators. In case of disagreement, it was resolved through negotiation or submitted to the third investigator to assist in adjudication. The extracted data included article identification (first author, year of publication), general information of subjects (number of cases in experimental group and control group), treatment course, intervention measures, and outcome indicators of subjects, etc. The quality of included studies was evaluated strictly according to the Cochrane bias risk assessment tool.

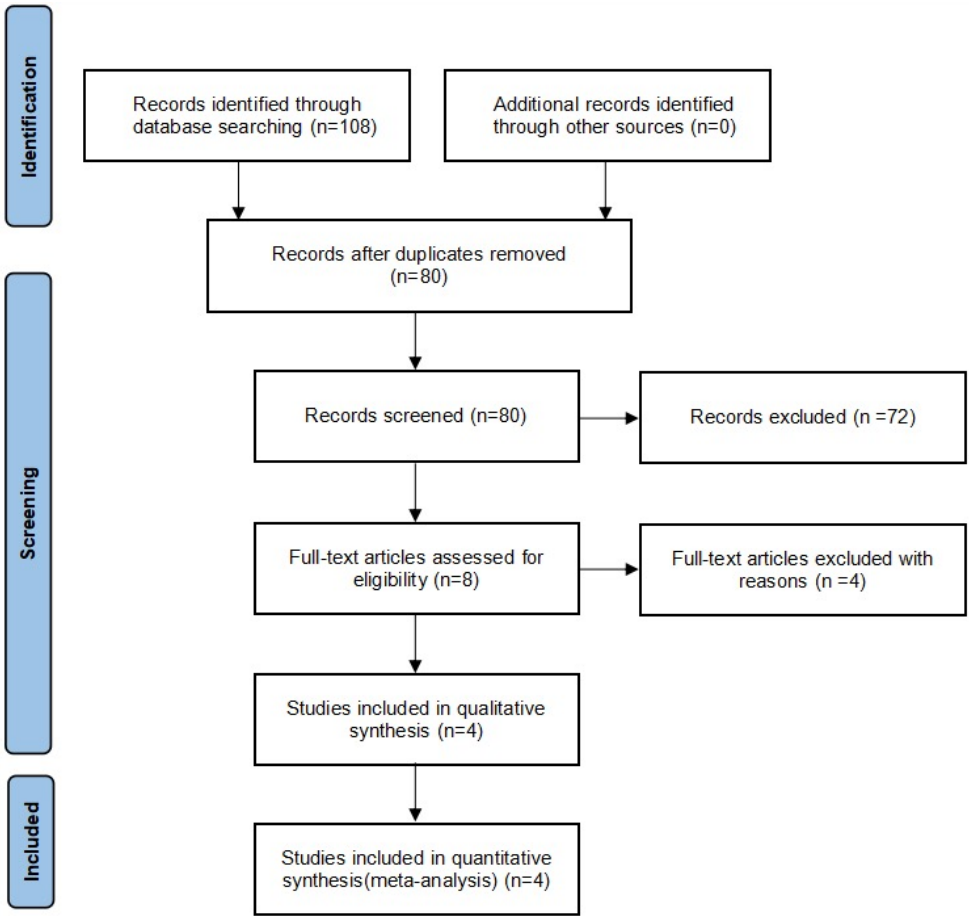


*Figure 1 — Flowchart of the study search and inclusion criteria.*

Statistical software was used for meta-analysis using Review Manager (Revman) 5.4 software. The main indicators in this study are continuous variables, which are expressed as mean difference (MD) or standardized mean difference (SMD). A heterogeneity test was performed using P values and $I^2$ statistics. When heterogeneity was statistically significant ($P \leq 0.05$, $I^2 > 50\%$), a random-effects model was selected for meta-analysis; when heterogeneity was not statistically significant ($P > 0.05$, $I^2 \leq 50\%$), a fixed-effects model was selected for meta-analysis.

## RESULTS

Initially, we retrieved 108 articles through a literature search. After removing duplicates, we scanned the

**Table I.** — General characteristics of the included studies

| Author | Number (MFAT vs PRP) | Age(years, MFAT vs PRP) | BMI (kg/m$^2$, MFAT vs PRP) | Sex (male,female MFAT vs PRP) | Kellgren-Lawrence grade(MFAT vs PRP) | | | | Outcomes | Follow-up-(months) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 1 | 2 | 3 | 4 | | |
| Baria 2022[22] | 28/30 | 56.1±1.7/ 51.9±2.4 | 31.0±0.9/ 31.0±0.8 | 8,20/20,10 | 2/6 | 5/8 | 11/12 | 10/4 | KOOS, VAS-ADL, Tegner | 6 |
| Dallo 2021[23] | 25(40 knees)/ 25(40 knees) | 61.5±9.5/ 62.5±11.3 | 25.8±5.1/ 26.3±3.6 | 9,16/14,11 | 18/15 | 22/25 | 0/0 | 0/0 | VAS, Marx, KOOS, Tegner | 12 |
| Gobbi 2022[24] | 40 knees/40 knees | 62.75±12.99/ 62.00±10.82 | NS | 17,23/22,18 | 18/15 | 22/25 | 0/0 | 0/0 | Tegner, Marx, IKDC, KOOS, VAS | 24 |
| Zaffagnini 2022[25] | 53/55 | 54.5±12.1/ 54.1±10.6 | 25.9±4.3/ 28.0±5.5 | 28,25/36,19 | 8/9 | 20/16 | 13/18 | 12/12 | IKDC, KOOS, VAS, EQ-VAS, EQ-5D | 24 |

Abbreviations: MFAT, microfragmented adipose tissue; PRP, platelet-rich plasma; BMI, body mass index; NS, not stated; KOOS, Knee injury and Osteoarthritis Outcome Score; VAS, visual analog scale; ADL, Activities of Daily Living; QoL, Quality of Life; Sport/Rec, Sport and Recreation; IKDC, International Knee Documentation Committee; EQ-VAS, EuroQol visual analogue scale; EQ-5D, EuroQol 5 dimensions.

**Table II.** — Detail treatment protocols of MFAT and PRP injections

| Author | MFAT | | | PRP | | | |
|---|---|---|---|---|---|---|---|
| | Injection dose (ml) | Times | Intervals | Injection dose (ml) | Times | Intervals | Type |
| Baria 2022[22] | up to 8 ml | 1 | NS | up to a maximum volume of 8 ml | 1 | NS | NS |
| Dallo 2021[23] | NS | 1 | NS | 4 | 3 | 1 month | LP-PRP combined with HA |
| Gobbi 2022[24] | NS | 1 | NS | NS | 3 | 1 month | LP-PRP combined with HA |
| Zaffagnini 2022[25] | 5 | 1 | NS | 5 | 1 | NS | NS |

Abbreviations: MFAT, microfragmented adipose tissue; PRP, platelet-rich plasma; NS, not stated; LP-PRP, Leucocyte-Poor platelet-rich plasma; HA, Hyaluronic Acid

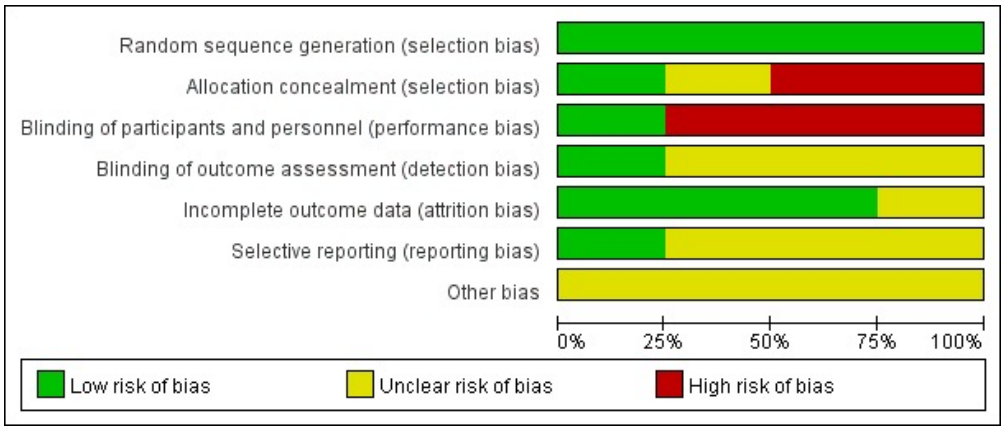


*Figure 2 — Risk of bias graph of included studies.*

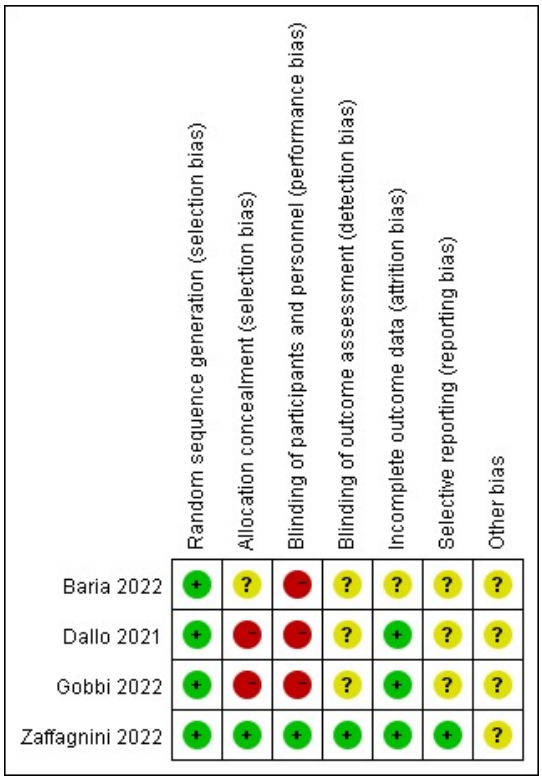


*Figure 3 — Risk of bias assessment graph of included studies.*

titles and read the abstracts, resulting in 8 full-text articles that were assessed for eligibility. Upon reading the full text of these 8 articles, we included 4 in the data extraction and meta-analysis[22-25]. Details of the literature search are shown in Fig. 1.

General information regarding the 4 included studies is summarized in Table I. A total of 266 patients (326 knees), comprising the MFAT group (n=161 knees) and the PRP group (n=165 knees) were included. All the included studies were in English, and all the included studies were randomized controlled trials. 3 studies[22,24,25] used the computer-generated randomization scheme, and 1 study[23] used the simple randomization method of a coin flip. Because of differences in harvest between the 2 groups, no blind method was used in 3 studies[22-24] and a single-blind method was used in 1 study[25]. On the other hand, 3 studies[22,23,25] mentioned the loss of follow-up. The administrated timing and dosage of MFAT and PRP injections are shown in Table II, which varied among these studies.

Included RCTs were analyzed using Cochrane bias risk tools for their random sequence generation (selection bias), allocation concealment (selection bias), and blinding of participants and personnel

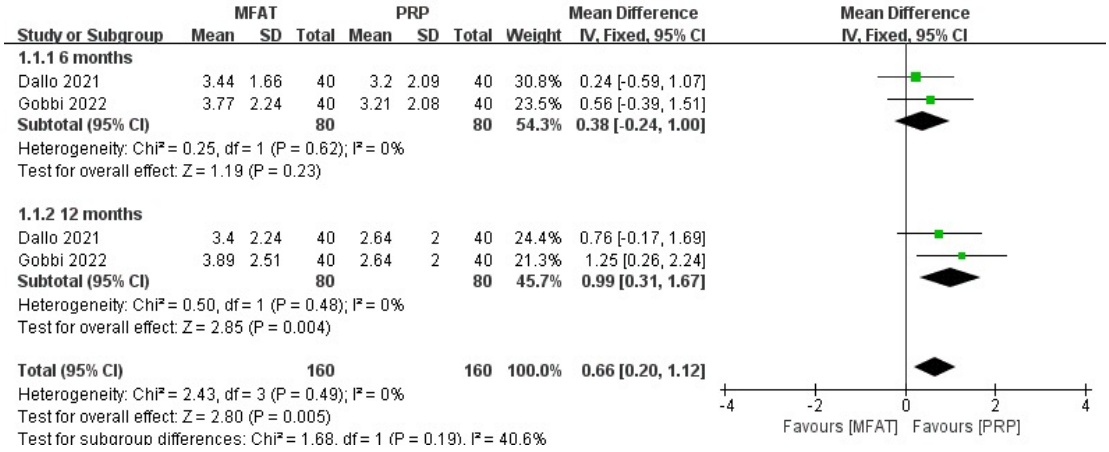


*Figure 4 — Forest plot for VAS scores between MFAT and PRP groups.*

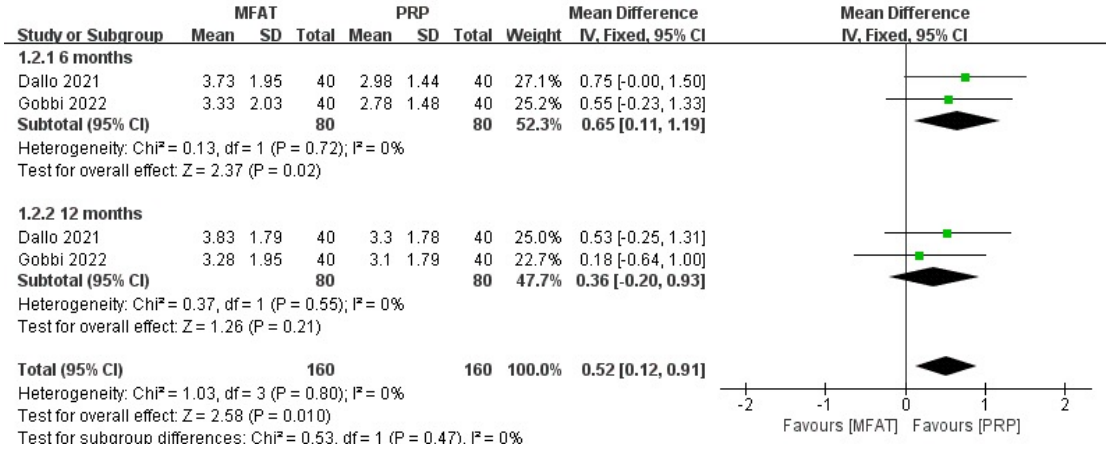


*Figure 5 — Forest plot for Tegner activity scale scores between MFAT and PRP groups.*

(performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) for evaluation. The results of the bias risk assessment are shown in Fig. 2 and 3.

Two of the included literature[23-24] reported VAS scores at 6 months after treatment, involving a total of 160 knees, including 80 in the MFAT group and 80 in the PRP group. Heterogeneity test results showed (P=0.62, $I^2$=0%), suggesting low heterogeneity, so the fixed-effect model was used for meta-analysis, combined effect size [MD=0.38, 95% CI (-0.24, 1.00), P=0.23)], and the difference was not statistically significant (Fig. 4).

Two of the included literature[23-24] reported VAS scores at 12 months after treatment, involving a total of 160 knees, including 80 in the MFAT group and 80 in the PRP group. Heterogeneity test results showed (P=0.48, $I^2$=0%), suggesting low heterogeneity, so the fixed-effect model was used for meta-analysis, combined effect size [MD=0.99, 95% CI (0.31, 1.67), P=0.004], and the difference was statistically significant (Fig.4).

Two of the included literature[23-24] reported Tegner activity scale scores at 6 months after treatment, involving a total of 160 knees, including 80 in the MFAT group and 80 in the PRP group. Heterogeneity test results showed (P=0.72, $I^2$=0%), suggesting low heterogeneity, so the fixed-effect model was used for meta-analysis, combined effect size [MD=0.65, 95% CI (0.11, 1.19), P=0.02], and the difference was statistically significant (Fig. 5).

Two of the included literature[23-24] reported Tegner activity scale scores at 12 months after treatment, involving a total of 160 knees, including 80 in the MFAT group and 80 in the PRP group. Heterogeneity test results showed (P=0.55, $I^2$=0%), suggesting low heterogeneity, so the fixed-effect model was used for meta-analysis, combined effect size [MD=0.36, 95% CI (-0.20, 0.93), P=0.21], and the difference was not statistically significant (Fig. 5).

**Table. III.** — Meta-analysis results of KOOS between MFAT and PRP groups

| Outcomes | 3 months | | | 6 months | | | 12 months | | | 24 months | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | mean difference (95%CI) | $I^2$ (%) | P | mean difference (95%CI) | $I^2$ (%) | P | mean difference (95%CI) | $I^2$ (%) | P | mean difference (95%CI) | $I^2$ (%) | P |
| KOOS–Pain | -0.47[-8.61,7.68] | 56 | 0.91 | 0.90[-3.02,4.82] | 0 | 0.65 | 3.95[-2.11,10.01] | 0 | 0.20 | -3.31[-9.02,2.41] | 0 | 0.26 |
| KOOS–Symptoms | -1.39[-6.68,3.91] | 0 | 0.61 | 2.03[-1.54,5.60] | 0 | 0.27 | -0.67[-5.61,4.27] | 0 | 0.79 | -0.37[-5.12,4.38] | 0 | 0.88 |
| KOOS–ADL | -0.61[-10.37,9.14] | 73 | 0.90 | 0.91[-2.59,4.40] | 48 | 0.61 | 3.79[-1.71,9.28] | 0 | 0.18 | 5.36[-11.02,21.74] | 85 | 0.52 |
| KOOS–Sport/Rec | -1.18[-9.17,6.81] | 0 | 0.77 | 4.14[-2.02,10.30] | 0 | 0.19 | 3.61[-5.74,12.96] | 0 | 0.45 | -9.00[-26.49,8.49] | 73 | 0.31 |
| KOOS–QoL | -0.33[-6.42,5.76] | 45 | 0.92 | 1.20[-3.48,5.89] | 0 | 0.61 | 2.25[-4.64,9.14] | 4 | 0.52 | -1.49[-8.88,5.91] | 0 | 0.69 |

Abbreviations:CI, confidence interval; KOOS, Knee injury and Osteoarthritis Outcome Score; ADL, Activities of Daily Living; QoL, Quality of Life; Sport/Rec, Sport and Recreation

Two of the included literature[22,25] reported KOOS–Pain at 3 months after treatment, involving a total of 155 knees, including 77 in the MFAT group and 78 in the PRP group. Heterogeneity test results showed (P=0.13, $I^2$=56%) suggesting high heterogeneity, so the random-effect model was used for meta-analysis, combined effect size [MD=-0.47, 95% CI (-8.61, 7.68), P=0.91], and the difference was not statistically significant (Table III).

Four of the included literature[22-25] reported KOOS–Pain at 6 months after treatment, involving a total of 316 knees, including 157 in the MFAT group and 159 in the PRP group. Heterogeneity test results showed (P=0.76, $I^2$=0%), suggesting low heterogeneity, so the fixed-effect model was used for meta-analysis, combined effect size [MD=0.90, 95% CI (-3.02, 4.82), P=0.65], and the difference was not statistically significant (Table III).

Two of the included literature[23-24] reported KOOS–Pain at 12 months after treatment, involving a total of 160 knees, including 80 in the MFAT group and 80 in the PRP group. Heterogeneity test results showed (P=0.77, $I^2$=0%), suggesting low heterogeneity, so the fixed-effect model was used for meta-analysis, combined effect size [MD=3.95, 95% CI (-2.11, 10.01), P=0.20], and the difference was not statistically significant (Table III).

Two of the included literature[24-25] reported KOOS–Pain at 24 months after treatment, involving a total of 179 knees, including 89 in the MFAT group and 90 in the PRP group. Heterogeneity test results showed (P=0.86, $I^2$=0%), suggesting low heterogeneity, so the fixed-effect model was used for meta-analysis, combined effect size [MD=-3.31, 95% CI (-9.02, 2.41), P=0.26], and the difference was not statistically significant (Table III).

Two of the included literature[22,25] reported KOOS–Symptoms at 3 months after treatment, involving a total of 155 knees, including 77 in the MFAT group and 78 in the PRP group. Heterogeneity test results showed (P=0.84, $I^2$=0%), suggesting low heterogeneity, so the fixed-effect model was used for meta-analysis, combined effect size [MD=-1.39, 95% CI (-6.68, 3.91), P=0.61], and the difference was not statistically significant (Table III).

Four of the included literature[22-25] reported KOOS–Symptoms at 6 months after treatment, involving a total of 316 knees, including 157 in the MFAT group and 159 in the PRP group. Heterogeneity test results showed (P=0.53, $I^2$=0%), suggesting low heterogeneity, so the fixed-effect model was used for meta-analysis, combined effect size [MD=2.03, 95% CI (-1.54, 5.60), P=0.27], and the difference was not statistically significant (Table III).

Two of the included literatures[23-24] reported KOOS–Symptoms at 12 months after treatment, involving a total of 160 knees, including 80 in the MFAT group and 80 in the PRP group. Heterogeneity test results showed (P=0.60, $I^2$=0%), suggesting low heterogeneity, so the fixed-effect model was used for meta-analysis, combined effect size [MD=-0.67, 95% CI (-5.61, 4.27), P=0.79], and the difference was not statistically significant (Table III).

Two of the included literature[24-25] reported KOOS–Symptoms at 24 months after treatment, involving a total of 179 knees, including 89 in the MFAT group and 90 in the PRP group. Heterogeneity test results showed (P=0.38, $I^2$=0%), suggesting low heterogeneity, so the fixed-effect model was used for meta-analysis, combined effect size [MD=-0.37, 95% CI (-5.12, 4.38), P=0.88], and the difference was not statistically significant (Table III).

Two of the included literature[22,25] reported KOOS–ADL at 3 months after treatment, involving a total of 155 knees, including 77 in the MFAT group and 78 in the PRP group. Heterogeneity test results showed (P=0.05,$I^2$=73%), suggesting high heterogeneity, so the random-effect model was used for meta-analysis, combined effect size [MD=-0.61, 95% CI (-10.37, 9.14), P=0.90], and the difference was not statistically significant (Table III).

Four of the included literature[1-22-25] reported KOOS–ADL at 6 months after treatment, involving a total of 316 knees, including 157 in the MFAT group and 159 in the PRP group. Heterogeneity test results showed (P=0.13, $I^2$=48%), suggesting low heterogeneity, so the fixed-effect model was used for meta-analysis, combined effect size [MD=0.91, 95% CI (-2.59, 4.40), P=0.61], and the difference was not statistically significant.(Table III)

Two of the included literature[23-24] reported KOOS–ADL at 12 months after treatment, involving a total of 160 knees, including 80 in the MFAT group and 80 in the PRP group. Heterogeneity test results showed (P=0.87, $I^2$=0%), suggesting low heterogeneity, so the fixed-effect model was used for meta-analysis, combined effect size [MD=3.79, 95% CI (-1.71, 9.28), P=0.18], and the difference was not statistically significant (Table III).

Two of the included literature[24-25] reported KOOS–ADL at 24 months after treatment, involving a total of 179 knees, including 89 in the MFAT group and 90 in the PRP group. Heterogeneity test results showed (P=0.010, $I^2$=85%), suggesting high heterogeneity, so the random-effects model was used for meta-analysis, and the combined effect size [MD=5.36, 95% CI (-11.02, 21.74), P=0.52], and the difference was not statistically significant (Table III).

Two of the included literature[22,25] reported KOOS–Sport/Recreation at 3 months after treatment, involving a total of 155 knees, including 77 in the MFAT group and 78 in the PRP group. Heterogeneity test results showed (P=0.87, $I^2$=0%), suggesting low heterogeneity, so the fixed-effect model was used for meta-analysis, combined effect size [MD=-1.18, 95% CI (-9.17, 6.81), P=0.77], and the difference was not statistically significant (Table III) .

Four of the included literature[22-25] reported KOOS–Sport/Recreation at 6 months after treatment, involving a total of 316 knees, including 157 in the MFAT group and 159 in the PRP group. Heterogeneity test results showed (P=0.71, $I^2$=0%), suggesting low heterogeneity, so the fixed-effect model was used for meta-analysis, combined effect size [MD=4.14, 95% CI (-2.02, 10.30), P=0.19], and the difference was not statistically significant (Table III).

Two of the included literature[23-24] reported KOOS–Sport/Recreation at 12 months after treatment, involving a total of 160 knees, including 80 in the MFAT group and 80 in the PRP group. Heterogeneity test results showed (P=0.35, $I^2$=0%), suggesting low heterogeneity, so the fixed-effect model was used for meta-analysis, combined effect size [MD=3.61, 95% CI (-5.74, 12.96), P=0.45], and the difference was not statistically significant (Table III).

Two of the included literature[24-25] reported KOOS–Sport/Recreation at 24 months after treatment, involving a total of 179 knees, including 89 in the MFAT group and 90 in the PRP group. Heterogeneity test results showed (P=0.06, $I^2$=73%), suggesting high heterogeneity, so the random-effects model was used for meta-analysis, combined effect size [MD=-9.00, 95% CI (-26.49, 8.49), P=0.31], and the difference was not statistically significant (Table III).

[1]Two of the included literature[22,25] reported KOOS–QoL at 3 months after treatment, involving a total of 155 knees, including 77 in the MFAT group and 78 in the PRP group. Heterogeneity test results showed (P=0.18, $I^2$=45%), suggesting low heterogeneity, so the fixed-effect model was used for meta-analysis, combined effect size [MD=-0.33, 95% CI (-6.42, 5.76), P=0.92], and the difference was not statistically significant (Table III).

Four of the included literature[22-25] reported KOOS–QoL at 6 months after treatment, involving a total of 316 knees, including 157 in the MFAT group and 159 in the PRP group. Heterogeneity test results showed (P=0.61, $I^2$=0%), suggesting low heterogeneity, so the fixed-effect model was used for meta-analysis, combined effect size [MD=1.20, 95% CI (-3.48, 5.89), P=0.61], and the difference was not statistically significant (Table III)

Two of the included literature[23-24] reported KOOS–QoL at 12 months after treatment, involving a total of 160 knees, including 80 in the MFAT group and 80 in the PRP group. Heterogeneity test results showed (P=0.31, $I^2$=4%), suggesting low heterogeneity, so the fixed-effect model was used for meta-analysis, combined effect size [MD=2.25, 95% CI (-4.64, 9.14), P=0.52], and the difference was not statistically significant (Table III).

Two of the included literature[24-25] reported KOOS–QoL at 24 months after treatment, involving a total of 179 knees, including 89 in the MFAT group and 90 in the PRP group. Heterogeneity test results showed (P=0.89, $I^2$=0%), suggesting low heterogeneity, so the fixed-effects model was used for meta-analysis, combined effect size [MD=-1.49, 95% CI (-8.88, 5.91), P=0.69], and the difference was not statistically significant (Table III).

Adverse events were reported in 3 studies[23-25], but no serious complications were recorded. All adverse reactions tend to be non-serious, mild, and self-healing, none were critical and required additional medical attention. During the follow-up period of the studies that were included, there were no reported cases of joint infections.

## DISCUSSION

In this study, we analyzed the efficacy and safety of MFAT and PRP in the clinical treatment of KOA, compared the therapeutic effects of MFAT and PRP in different time periods, and provided evidence-based medicine options for the non-surgical treatment of KOA. The MFAT group was superior to the PRP group in terms of Tegner activity scale scores at 6 months. The VAS scores of the PRP group were better than that of the MFAT group at 12 months. There were no statistical differences in the other indicators.

Microfragmented adipose tissue, also known as adipose stromal vascular fraction therapy, is widely used as a new therapeutic method. Relevant research reports that adipose tissue contains a greater number of reparative cells compared to peripheral blood[26]. In addition to that, adipose tissue contains a large number of Mesenchymal stem cells[27], therefore, many scholars are full of expectations for MFAT in the treatment of KOA. However, there is no clinical meta-analysis on the efficacy comparison between MFAT and PRP. This study conducted a meta-analysis on several recently published high-level randomized controlled trials to provide some evidence-based medical evidence for clinical treatment.

Pain relief is the most intuitive manifestation in the treatment of KOA, and the VAS score is an important therapeutic index. This meta-analysis showed that VAS scores at 12 months after treatment were significantly lower in the PRP group than in the MFAT group, but VAS scores at 6 months and KOOS-pain scores at different time periods were not statistically significant in the two groups. The aforementioned results are mainly due to the different mechanisms of MFAT and PRP. The existence of pertinent literature has been reported that PRP can inhibit inflammatory factors such as tumor necrosis factor α and interleukin and reduce the inflammatory response in KOA[28-33]. In addition, Asfaha et al.[34] found that protease-activated receptor-4 in PRP has endogenous analgesic effects and alleviates inflammation-related pain. As for MFAT, there are many growth factors and cytokines present in it that play a significant role in repairing tissues[35]. Adipose-derived mesenchymal stromal cells (MSCs) possess immunomodulatory and paracrine properties. They have the ability to rebuild and repair cartilage.

Functional improvement is the ultimate goal of KOA treatment. To comprehensively evaluate the improvement of the knee joint, we adopted the Tegner activity scale scores and KOOS scores. Tegner activity scale scores were higher in the MFAT group than in the PRP group at 6 months. Tegner activity scale scores at 12 months and KOOS (Symptoms, Activities of Daily Living, Quality of Life, Sport and Recreation) scores at each period were not statistically significant in the two groups. In the original study of the included literature, both the MFAT and PRP groups showed clinically and statistically significant improvements in all outcome measures for KOA compared with baseline. At present, most scholars recognize the efficacy of PRP in treating KOA. There was no difference between the two treatments, which also indirectly demonstrated the efficacy of MFAT in treating KOA.

In addition to clinical outcomes and scores of the knee joint, clinicians and patients inevitably need to consider each therapy's convenience, comfort, and cost. When compared to MFAT, preparing PRP is simpler and it can be repeated easily whenever required. Therefore, for patients with KOA, PRP is a more convenient and cost-effective option. Adipose tissue harvesting was a more invasive and painful procedure, needing local anesthesia and being performed within a surgery center compared to simple blood aspiration in an outpatient facility. However, it seems that adipose tissue is less "precious" than blood. For some anemic patients, drawing blood may not seem "friendly".

The literature included in the study did not provide a subgroup analysis of KOA severity due to the limited number of randomized controlled trials related to MFAT. A previous study by Chang KV et al.[36] have already demonstrated the lower results with PRP in patients with high OA severity. Kon E et al.[37] and Filardo G et al.[38] showed the same results. Accordingly, previous literature suggests that PRP may be a viable treatment for mild KOA in younger patients, but may not be as effective for older patients with advanced KOA. However, Hudetz et al.[39] confirmed that MFAT may be beneficial for delaying or avoiding TKA. To sum up, MFAT and PRP seem to have different indications. MFAT may be preferable in patients with a high degree of KOA, and the satisfactory clinical results demonstrated by PRP in those with mild KOA. This requires further targeted clinical studies to confirm differences between MFAT and PRP in treating KOA of varying severity.

The adverse events reported in the MFAT and PRP groups were nonspecific, mild, and self-limiting. No serious complications were documented. In other words, both MFAT and PRP treatments demonstrated a favorable safety profile without any additional side effects.

## LIMITATIONS

First of all, this study is limited by the differences in the original RCT protocols and insufficient representation

of some of the outcome indicators. Meanwhile, only 4 literature were included in this study, so more high-quality large-scale randomized controlled trials are needed for verification. Another concern is that there is no uniform standard for the preparation and injection of MFAT and PRP. In this study, HA was used in combination with PRP in two original literatures. There are individual differences in the preparation components of MFAT and PRP, and there is no uniform standard for scale scoring, which may cause certain heterogeneity in each study. Thirdly, due to the different environmental requirements for the preparation of MFAT and PRP, the preparation of MFAT is required to be carried out in the operating room, while PRP only needs to draw blood, which makes it impossible to adopt the double-blind method. Therefore, we suggest that a single-blind design could be used in future studies. We recommend that both clinicians and radiologists who evaluate patients at follow-ups are blinded to the assigned treatments to avoid any detection bias. Finally, only subjective questionnaires were used in this study to assess treatment efficacy. However, objective results, such as magnetic resonance, are often needed in clinical efficacy assessment. The present study attempted to overcome with exhaustive clinical scores repeated over time. We hope that future studies will incorporate pre and post-injection radiological differences in the assessment of efficacy.

## CONCLUSION

This meta-analysis indicates that Intra-articular PRP injection appeared to be more efficacious than MFAT injection for the treatment of KOA in terms of long-term pain relief. But MFAT injection was superior to PRP injection in terms of short-term function improvement. Overall, there was no significant difference between MFAT and PRP in the treatment of KOA. In addition, MFAT injection did not increase the risk of adverse events when compared with PRP injection. Additional RCTs are needed to identify the optimal doses and intervals of MFAT and PRP. It is necessary to carry out large-sample, multi-center, randomized double-blind controlled trials in the design and implementation of clinical trials in the future, and make long-term follow-up visits to objectively report the loss of follow-up and adverse events, so as to ensure the accuracy of clinical results, constantly update and improve the systematic evaluation, and enhance the reliability of research conclusions.

*Abbreviations:* MFAT: microfragmented adipose tissue; PRP: Platelet-Rich Plasma; KOA: Knee Osteoarthritis; RCTs: randomized controlled trials; VAS: Visual Analogue Scale; HA: Hyaluronic Acid; TKA: total knee arthroplasty; MeSH: Medical Subject Headings; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; KOOS: Knee Injury and Osteoarthritis Outcome Score; MD: Mean difference; SMD: Standardised mean difference; BMI: body mass index; IKDC: International Knee Documentation Committee; NS: not stated; CI: confidence interval; EQ-5D: EuroQol 5 dimensions; EQ-VAS: EuroQol visual analogue scale; LP-PRP: Leucocyte-Poor platelet-rich plasma; ADL: Activities of Daily Living; QoL: Quality of Life; Sport/Rec: Sport and Recreation; MSCs: mesenchymal stromal cells.

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*Authors' contributions:* LGW, XAY, BBZ and GBS contributed to the conception and design of the study. XAY, XRL and ZS performed the statistical analysis and drafted the manuscript. XAY, XRL and ZS contributed to the literature search and study selection. BBZ and XRL contributed to the quality assessment. XRL contributed to the data extraction. GBS contributed to the revisions of the manuscript. All authors read and approved the final manuscript.

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