Microfragmented Adipose Tissue Versus Platelet-Rich Plasma for the Treatment of Knee Osteoarthritis

A Prospective Randomized Controlled Trial at 2-Year Follow-up

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Background: Intra-articular microfragmented adipose tissue (MF-AT) injections have been proposed for the treatment of knee osteoarthritis (OA).

Purpose: To compare a single injection of MF-AT or platelet-rich plasma (PRP) in terms of clinical outcomes and OA progression.

Study Design: Randomized controlled trial; Level of evidence, 1.

Methods: A total of 118 patients with symptomatic knee OA were randomized to receive a single intra-articular injection of MF-AT or PRP. Patients were evaluated before the injection and at 1, 3, 6, 12, and 24 months with the International Knee Documentation Committee (IKDC) subjective score, Knee injury and Osteoarthritis Outcome Score (KOOS) subscales, EuroQol visual analogue scale (EQ-VAS), EuroQol 5 dimensions (EQ-5D), and visual analogue scale (VAS) for pain. Primary outcomes were the IKDC subjective score and the KOOS pain subscore at 6 months. Knees were evaluated at baseline and at 6, 12, and 24 months with radiography and high-resolution magnetic resonance imaging (MRI) using the Whole-Organ Magnetic Resonance Imaging Score (WORMS).

Results: Both MF-AT and PRP provided a statistically and clinically significant improvement up to 24 months. The improvement in the IKDC subjective score from baseline to 6 months was similar in both MF-AT (41.1 ± 16.3 to 57.3 ± 18.8) and PRP (44.8 ± 17.3 to 58.4 ± 18.1) groups (P < .0005). The improvement in the KOOS pain subscore from baseline to 6 months was similar in both the MF-AT (58.4 ± 15.9 to 75.8 ± 17.4) and PRP (63.5 ± 17.8 to 75.5 ± 16.1) groups (P < .0005). Overall, no differences were found between the MF-AT and PRP groups in terms of clinical outcomes, adverse events (18.9% and 10.9%, respectively), and failures (15.1% and 25.5%, respectively). Radiographic and MRI findings did not show changes after the injection. As a secondary outcome, more patients in the MF-AT group with moderate/severe OA reached the minimal clinically important difference for the IKDC score at 6 months compared with the PRP group (75.0% vs 34.6%, respectively; P = .005).

Conclusion: A single intra-articular injection of MF-AT was not superior to PRP, with comparable low numbers of failures and adverse events and without disease progression. No differences were found in clinical and imaging results between the 2 biological approaches.

Keywords: microfragmented adipose tissue (MF-AT); adipose tissue; mesenchymal stromal cell (MSC); platelet-rich plasma (PRP); knee; osteoarthritis

Knee osteoarthritis (OA) represents one of the most common disabling diseases, with a considerable effect on the ability to perform activities of daily living (ADL). Its burden is becoming even more prevalent over time because of the combined effects of aging, increasing obesity, and sports-related knee injuries in the global population. The growing awareness of this significant public health issue has not been followed by the development of optimal treatment solutions. Available nonoperative treatment methods, including physical therapy, oral medications, and intra-articular injections of steroids, hyaluronic acid, and platelet-rich plasma (PRP), are able to provide only limited clinical benefits, with an effect often not completely

The American Journal of Sports Medicine
1–12
DOI: 10.1177/03635465221115821
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Adipose-derived mesenchymal stromal cells (MSCs) have been recently proposed as a promising alternative for the treatment of knee OA, owing to their immunomodulatory, anti-inflammatory, and paracrine effects. Among the different sources of MSCs, adipose tissue is quickly becoming the preferred option because of the high number of cells and pericytes (MSC precursors) that can be obtained compared with other sources. Because of the strict regulations and high costs of isolated and cultured adipose-derived MSCs, minimally manipulated approaches are gaining interest, with the additional advantages of the ease of collection and handling and the minimally invasive procedure required. Among the available choices, microfragmented adipose tissue (MF-AT) has the advantage of providing a high number of cells and growth factors without expansion or enzymatic treatment, thus preserving the integrity of cells and tissue microarchitecture. Preclinical and clinical studies have supported the use of intra-articular MF-AT injections to address knee OA, suggesting their safety and clinical benefits. However, no high-level studies have investigated the potential of MF-AT with respect to other biological products such as PRP, which is increasingly recognized as a suitable OA treatment option, showing in some studies better results than placebo and other traditional injection approaches including corticosteroids and viscosupplementation. The aim of this randomized controlled trial (RCT) was to compare a single injection of MF-AT with PRP in terms of clinical outcomes and disease progression in patients with symptomatic knee OA.

METHODS

Study Design and Patient Selection

This single-blind RCT was approved by the Hospital Ethics Committee and Internal Review Board of the IRCCS Istituto Ortopedico Rizzoli (Bologna, Italy). The trial was registered at clinicaltrials.gov (registration No. NCT03117608), and informed consent for study participation was obtained from each patient before enrollment. Screening for participants was performed in the outpatient clinic of a highly specialized referral center for orthopedics. Treatment was performed from May 2017 to March 2019. Patients were evaluated for eligibility for study inclusion according to the following criteria: male or female patients aged between 18 and 75 years with symptomatic knee OA (Kellgren-Lawrence grade 1-4), failure of nonoperative treatment for at least 3 months, and patient agreement to actively participate in the follow-up program. The exclusion criteria were patients incapable of understanding or unwilling to follow the study protocol, participation in previous or concurrent trials (ongoing or completed within 3 months), surgical treatment for the same disease within 1 year, malignancy or metabolic or thyroid disorders, alcohol or drug (medication) abuse, pigmented villonodular synovitis, varus or valgus misalignment >15°, body mass index (BMI) >40, a recent (6 months) traumatic event of the lower limb, and injection procedure within 6 months.

A total of 118 patients with symptomatic knee OA met the inclusion criteria and were included in the study (CONSORT [Consolidated Standards of Reporting Trials] flow diagram in Figure 1). Patients were randomly assigned to 2 treatment groups through a computer-generated simple randomization system in a 1:1 ratio: group 1 (investigation arm) received a single intra-articular MF-AT injection, and group 2 (control arm) received a single intra-articular PRP injection. Patients were informed of treatment allocation after obtaining informed consent and baseline clinical and imaging evaluations. In fact, it was not possible to blind the patient to treatment, as the 2 treatment methods required different procedures: the MF-AT procedure was performed in the operating room, while the PRP procedure was performed in the outpatient clinic. On the other hand, the clinicians and radiologist who evaluated the patients at follow-ups were blinded to the treatment performed to ensure single blinding of the trial.

There were 10 patients who did not receive the allocated intervention after being enrolled; thus, the final study...
population comprised 108 patients: 53 patients in the MF-AT group and 55 in the PRP group. Baseline characteristics, including patient sex, age, BMI, affected side, symptom duration, previous knee surgery, OA grade according to the Kellgren-Lawrence classification, and OA severity (mild OA: Kellgren-Lawrence grade 1-2; moderate/severe OA: Kellgren-Lawrence grade 3-4), as well as clinical characteristics of the included patients are reported in Table 1. No intergroup differences were found, except for BMI, which was higher in the PRP group ($P = .031$).

### MF-AT Procedure

The procedure was performed in a single surgical step in the operating room. Adipose tissue was harvested from subcutaneous abdominal fat (lower or lateral abdomen). Before harvesting the fat, the site was injected with adrenaline and lidocaine at very high dilutions in 500 mL of saline solution by using a disposable 17-gauge blunt cannula connected to a 60-mL Luerlock syringe. Adipose tissue was then collected using a 13-gauge blunt cannula, for fast and atraumatic suction, connected to a 20-mL Vaclock syringe. The harvested fat was immediately processed using the Lipogems system (Lipogems International Spa, Milan, Italy) as previously described. The entire process was performed in complete immersion in a physiological solution minimizing cell trauma. The size of adipose tissue clusters was progressively reduced with a mild mechanical action to microspheres, in accordance with the manufacturer’s instructions. Oily substances, cell debris, and blood residue were eliminated. Finally, the resulting MF-AT (5 mL) was collected in a 10-mL syringe to be injected into the patient.

The injection was performed through a classic lateral parapatellar approach using an 18-gauge needle, with the patient in the supine position and the knee in extension. At the end of the injection, the patient was encouraged to bend and extend the knee a few times to allow the product to spread throughout the joint. After the

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Figure 1. CONSORT (Consolidated Standards of Reporting Trials) flow diagram used in the design of the trial. BMI, body mass index; MFAT, microfragmented adipose tissue; PRP, platelet-rich plasma.
procedure, all patients were sent home with an elastic compression band on the harvesting site, which was to be used for 2 to 3 weeks. The postoperative protocol included rest and abstention from high-impact sports activities and strenuous work for at least 2 weeks, with the aid of crutches and a progressive increase in weightbearing in the immediate period after the procedure. Mild exertion in activities such as exercise bicycles or aquatic therapy was recommended, with a progressive return to sports activities as tolerated.

**PRP Procedure**

In a sterile manner, a single 150-mL unit of peripheral venous blood was harvested in a bag with citrate-phosphate-dextrose-adrenaline from each patient at the transfusion unit. Then, 2 centrifugations were performed: the first centrifugation was at 1480 rpm for 6 minutes to separate erythrocytes, and the second centrifugation was at 3400 rpm for 15 minutes to concentrate platelets. Immediately after the second centrifugation, platelet-poor plasma was manually removed, thus obtaining 5 mL of PRP. The goal was to concentrate platelets at $10^3/\mu L \pm 20\%$. The obtained PRP was stored at $-30^\circ C$ to be used later for treatment after being thawed in a dry thermostat at $37^\circ C$ for 30 minutes. Frozen PRP was thawed 15 minutes before the injection. After thawing, the PRP sample was transferred directly from the transfusion unit to the outpatient clinic, located in the same hospital, using a thermal bag and avoiding exposure to light. PRP characteristics were evaluated, showing a platelet concentration of 5.0 times higher than baseline whole blood values. Leukocytes were present with a mean concentration of 1.5 times than the whole blood value.

All patients were treated by orthopaedic surgeons at the outpatient clinic. The injection was performed 1 week after the blood harvest. Before the injection, PRP was activated by adding 1 mL of calcium gluconate. The skin was sterilely dressed, and the injection was performed through a classic lateral parapatellar approach using a 22-gauge needle, with the patient in the supine position and the knee in extension. At the end of the procedure, the patient was encouraged to bend and extend the knee a few times to allow PRP to spread throughout the joint. After the injection, all patients were sent home with instructions to use cold therapy or analgesics for pain control, and full weight-bearing was allowed immediately. High-impact sports activities and strenuous work were not recommended for at least 2 weeks, while mild exertion in activities such as exercise bicycles or aquatic therapy was approved, with a progressive return to sports activities as tolerated.

**Clinical Evaluation**

All patients were clinically evaluated before the injection procedure and at follow-up visits at 1, 3, 6, 12, and 24 months by clinicians blinded to treatment allocation. To examine treatment safety, all complications and adverse
events were assessed and reported at every follow-up visit for both groups. Mild adverse events were defined as the presence of significant pain or swelling of the treated knee for >5 days as reported by patients, and severe adverse events were defined as any event that resulted in death, or were life-threatening and required hospitalization or an intervention to prevent permanent impairment or damage. The primary clinical outcome was the change in the International Knee Documentation Committee (IKDC) subjective score and the Knee injury and Osteoarthritis Outcome Score (KOOS) pain subscore at 6 months after the injection. Moreover, further measures were used for the clinical evaluation, including the other KOOS subscales for subjective functional improvement, the EuroQol visual analogue scale (EQ-VAS) and EuroQol 5 dimensions (EQ-5D) for patient generic health status, and the visual analogue scale (VAS) for pain. At the 1-month follow-up, only the VAS score and adverse events were determined, while a complete assessment of clinical scores was performed at 3, 6, 12, and 24 months.

The treated knees were evaluated with radiography (anteroposterior and lateral views) at baseline and at 6, 12, and 24 months after the procedure. Moreover, high-resolution (1.5 T) magnetic resonance imaging (MRI) was performed at baseline and at 6, 12, and 24 months of follow-up. The imaging evaluation was performed by an independent investigator, an experienced musculoskeletal radiologist, who blindly assessed and reviewed the images (M.B.). OA severity was assessed by evaluating radiographs with Kellgren-Lawrence grading. The Whole-Organ Magnetic Resonance Imaging Score (WORMS) was used to assess 7 features of the treated knees on MRI: articular cartilage morphology, bone marrow edema, subchondral cysts, articular profile, marginal osteophytes, meniscal integrity, and synovitis.

Treatment was deemed to have failed if the patient needed a new surgical or injection procedure because of the persistence or worsening of knee symptoms. For patients with failure, the worst clinical evaluation between baseline and available follow-ups was considered for the following assessments. Kaplan-Meier survival analysis was performed to examine the survival from failure up to 24 months. A further evaluation of the clinical effectiveness of the treatment methods was performed to assess the number of patients who achieved the minimal clinically important difference (MCID) for the primary outcomes (IKDC subjective score and KOOS pain subscore) at 6 and 12 months of follow-up.

An external independent agency (PHARM srl, Lodi, Italy) was involved to ensure data correctness and objectiveness of the study results. In particular, an investigation was conducted to ensure the protection of the rights and integrity of the participants, adequate and correct performance of all study procedures, data collection, documentation, and data verification.

**Statistical Analysis**

All continuous data were expressed in terms of the mean and standard deviation, and the categorical data were expressed as the frequency and percentage. The Shapiro-Wilk test was performed to examine the normality of continuous variables. The Levene test was performed to assess the homogeneity of variances. A repeated-measures general linear model with the Sidak test for multiple comparisons was used to assess the differences at different follow-up times. The Friedman nonparametric test, followed by the Wilcoxon post hoc pairwise test corrected by the Bonferroni method for multiple comparisons, was used to examine the differences in not normally distributed scores at different follow-up times. Analysis of variance was performed to assess the between-group differences in continuous, normally distributed, and homoscedastic data; the Mann-Whitney test was used otherwise. Analysis of variance, followed by the Scheffé post hoc pairwise test, was also used to assess the among-group differences in continuous, normally distributed, and homoscedastic data; the Kruskal-Wallis test, followed by the Mann-Whitney test with the Bonferroni correction for multiple comparisons, was used otherwise. The Pearson chi-square test was performed to investigate relationships between grouping variables; the Fisher exact test was performed to investigate relationships between dichotomous variables. The Spearman rank correlation was used to assess the correlation between continuous data, and the Kendall tau correlation was used to assess the correlation between ordinal data. The repeated-measures general linear model with treatment groups as fixed effects and the Sidak test for multiple comparisons were used to assess the influence of the treatment groups on the time evolution of the scores. Kaplan-Meier survival analysis was performed to examine the survival from failure, and the log-rank test was used to assess the influence of treatment groups on survival. For all tests, \( P < .05 \) was considered significant. All statistical analyses were performed using SPSS Version 19.0 (IBM). The sample size was determined by considering the IKDC score at 6 months. From a previous pilot study, the standard deviation of the IKDC score at 6 months was 18.2 points; considering an alpha of 0.05 and a minimum power of at least 0.8, the minimum sample size was 106 patients (53 for each treatment group). Considering a 10% dropout rate, the resulting sample size was 118 patients (59 for each treatment group).

**RESULTS**

**MF-AT Group**

The MF-AT group showed a statistically significant improvement in all clinical scores, except for the EQ-VAS. The IKDC subjective score improved from 41.1 ± 16.3 to 57.3 ± 18.8 at 6 months (\( P < .0005 \)) and the KOOS pain subscore from 58.4 ± 15.9 to 75.8 ± 17.4 at 6 months (\( P < .0005 \)) (Figures 2 and 3). Changes in other clinical scores up to 24 months of follow-up are reported in detail in Table 2. The MCID for the IKDC subjective score was achieved in 73.5% of the patients at 6 months and in 60.4% at 12 months, while the MCID for the KOOS pain subscore was achieved in 63.3% of the patients at 6 months and in 56.3% at 12 months.
<table>
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<th>12 mo</th>
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aData are reported as mean ± SD. No significant intergroup differences were observed in all scores at all follow-ups. EQ-5D, EuroQol 5 dimensions; EQ-VAS, EuroQol visual analogue scale; IKDC, International Knee Documentation Committee; KOOS, Knee injury and Osteoarthritis Outcome Score; MF-AT, microfragmented adipose tissue; PRP, platelet-rich plasma; VAS, visual analogue scale.

bStatistically significant improvement (P < .05) from baseline to the follow-up.

**Figure 2.** International Knee Documentation Committee (IKDC) subjective score in the microfragmented adipose tissue (MF-AT) and platelet-rich plasma (PRP) groups at baseline and at 3, 6, 12, and 24 months of follow-up. Box-and-whisker plots showing median values and interquartile ranges.
No differences were documented based on OA severity in terms of clinical outcome and MCID achievement at all follow-ups. Younger patients showed a greater improvement in the KOOS pain subscore at 24 months compared with older patients ($\rho = -0.317; P = .026$). The IKDC subjective score and VAS score, as well as KOOS pain, symptoms, and ADL subscores, at 12 months of follow-up were significantly correlated to the baseline WORMS values, with better values in patients with less bone marrow edema and synovitis (all $P < .05$). The KOOS pain and ADL subscores at 12 months were also significantly correlated to the baseline WORMS-1 value, with better results in patients with superior articular cartilage morphology ($P = .008$ and $P = .027$, respectively). Sex, BMI, symptom duration, and previous surgery did not significantly influence the clinical and imaging outcomes.

PRP Group

The PRP group showed a statistically significant improvement in all clinical scores, except for the EQ-VAS. The IKDC subjective score improved from $44.8 \pm 17.3$ to $58.4 \pm 18.1$ at 6 months ($P < .0005$) and the KOOS pain subscore from $63.5 \pm 17.8$ to $75.5 \pm 16.1$ at 6 months ($P < .0005$) (Figures 2 and 3). Changes in other clinical scores up to 24 months of follow-up are reported in detail in Table 2. The MCID for the IKDC subjective score was achieved in 55.1% of the patients at 6 months and in 56.0% at 12 months, while the MCID for the KOOS pain subscore was achieved in 44.9% of the patients at 6 months and in 50.0% at 12 months.

Patients with mild OA showed a significantly greater improvement in the IKDC subjective score from baseline to 6 months compared with patients with moderate/severe OA ($19.2 \pm 15.0$ vs $8.6 \pm 14.2$, respectively; $P = .014$) and had a higher rate of achieving the MCID for the IKDC subjective score at 6 months of follow-up (78.3% vs 34.6%, respectively; $P = .002$). Younger patients obtained better clinical results in terms of IKDC ($P = .048$), KOOS pain ($P = .047$), KOOS ADL ($P = .033$), and EQ-5D ($P = .039$) scores at 12 months of follow-up. A longer symptom duration before treatment was correlated to worse results in terms of KOOS pain ($P = .035$), VAS ($P = .023$), and EQ-VAS ($P = .040$) scores at 12 months of follow-up. Compared with men, women showed a greater improvement in IKDC ($P = .023$), KOOS ADL ($P = .005$), and EQ-5D ($P = .005$) scores at 24 months of follow-up. The IKDC subjective score at 6 and 12 months ($P = .017$ and $P = .005$, respectively) and KOOS pain subscore at 6 and 12 months ($P = .008$ and $P = .005$, respectively), as well as KOOS symptoms, ADL, and sport/recreation subscores at all follow-ups (all $P < .05$), were significantly correlated to the baseline WORMS-1 value, with better clinical results in patients presenting superior articular cartilage morphology. Lower baseline WORMS values for articular profile ($P = .017$), marginal osteophytes ($P = .028$), and meniscal integrity ($P = .008$) were also correlated to a better clinical improvement in the IKDC subjective score at 12 months of follow-up. BMI, symptom duration, and previous surgery did not significantly influence the clinical and imaging outcomes.

MF-AT vs PRP: Safety

No statistically significant differences were reported between the MF-AT and PRP groups in terms of adverse events (18.9% vs 10.9%, respectively; not significant). In detail, the MF-AT group presented a total of 10 mild adverse events after the procedure, including mild or moderate knee pain, joint swelling and/or effusion, and injection site pain. All of these adverse events were
treatment-related and self-limiting, lasted for only a few days, and none required a specific procedure or hospitalization. Regarding severe adverse events, 1 patient in the MF-AT group reported pain and edema in the treated leg, requiring hospitalization for 1 day and the use of oral analgesics, with resolution of symptoms in a few days. The cause of edema was related to the unrecommended use by the patient of a compression band at the thigh level. Another patient reported a vertebral fracture after trauma not related to the treatment. Moreover, 1 patient died 24 months after treatment: the death was caused by a pulmonary embolism after prostatectomy for prostate cancer not related to the injection procedure.

No severe adverse events were described in the PRP group, while a total of 6 mild adverse events were reported after the procedure (knee pain, joint swelling and/or effusion, and injection site pain). All of these adverse events were treatment-related and self-limiting for a few days, and none required a specific procedure or hospitalization.

**MF-AT vs PRP: Clinical Outcomes**

Comparative analysis of the primary outcomes (change in the IKDC subjective score and KOOS pain subscore at 6 months) did not show statistically significant differences between the MF-AT and PRP groups (Figures 2 and 3). Moreover, no statistically significant differences were observed between the 2 groups in terms of improvement in other clinical scores or achieving the MCID at any time point, including the VAS pain score at 1-month follow-up (improvement of 2.3 ± 2.8 for MF-AT group and 3.0 ± 3.0 for PRP group; not significant) (all other detailed results are shown in Table 2).

No statistically significant differences were reported between the MF-AT and PRP groups in terms of failures (15.1% vs 25.5%, respectively; not significant), with comparable treatment survival over time (Figure 4). In detail, 8 patients were considered treatment failures in the MF-AT group: 3 patients were treated with an intra-articular injection, 3 patients were treated with TKA, and 2 patients were treated with unicompartmental knee replacement. There were 14 patients who had failed treatment in the PRP group between the 3- and 24-month follow-ups: 9 patients were treated with a new injection procedure, while 5 patients were treated with TKA.

**MF-AT vs PRP: Subgroup Analyses**

Patients with mild OA did not show any statistically significant differences between the 2 treatment groups. On the other hand, patients with moderate/severe OA treated with MF-AT showed a significantly greater improvement in the IKDC subjective score at 6 months compared with those treated with PRP (15.7 ± 19.0 vs 8.6 ± 14.2, respectively; \( P = .041 \)), while this difference was not confirmed at 12 months (10.0 ± 21.7 vs 10.1 ± 18.6, respectively; not significant) and at 24 months (9.3 ± 17.4 vs 5.6 ± 19.1, respectively; not significant) (Figure 5). Similarly, more patients with moderate/severe OA treated with MF-AT achieved the MCID for the IKDC subjective score at 6 months compared with the PRP group (75.0% vs 34.6%, respectively; \( P = .005 \)), while no differences were found for the IKDC subjective score at 12 months (52.2% vs 46.4%, respectively; not significant) or for the KOOS pain subscore at both follow-up time points (58.3% vs 42.3%, respectively, at 6 months [not significant] and 43.5% vs 46.4%, respectively, at 12 months [not significant]).

**MF-AT vs PRP: Imaging Outcomes**

The radiographic evaluation with the Kellgren-Lawrence classification did not show any deterioration in OA severity at 6, 12, and 24 months of follow-up for both treatment groups, and no statistically significant intergroup differences were observed. The MRI findings, analyzed with the WORMS, did not show any significant changes after the injection, neither an improvement nor signs of disease progression, for both groups at all follow-ups (6, 12, and 24...
DISCUSSION

The main finding of this RCT is that a single intra-articular injection of both MF-AT and PRP provided a significant and similar clinical improvement up to 24 months of follow-up in patients with symptomatic knee OA. Both treatment groups reported a low number of failures and adverse events, without signs of disease progression. Compared with PRP, MF-AT provided a greater clinical improvement and more patients achieved the MCID for the IKDC score at 6 months in cases of moderate/severe OA.

The MF-AT approach is becoming a popular strategy to exploit the biological potential of adipose tissue directly as a 1-step treatment. This product is obtained through TABLE 3

<table>
<thead>
<tr>
<th>Feature</th>
<th>Baseline</th>
<th>6 mo</th>
<th>12 mo</th>
<th>24 mo</th>
<th>P Value</th>
</tr>
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<tbody>
<tr>
<td>Articular cartilage morphology</td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>MF-AT group</td>
<td>4.1 ± 2.1</td>
<td>4.2 ± 2.0</td>
<td>4.1 ± 2.0</td>
<td>4.5 ± 1.9</td>
<td>NS</td>
</tr>
<tr>
<td>PRP group</td>
<td>4.1 ± 1.7</td>
<td>4.0 ± 1.7</td>
<td>4.0 ± 1.8</td>
<td>3.9 ± 1.5</td>
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</tr>
<tr>
<td>Subchondral cysts</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>MF-AT group</td>
<td>1.8 ± 1.3</td>
<td>1.9 ± 1.3</td>
<td>2.0 ± 1.3</td>
<td>1.8 ± 1.4</td>
<td>NS</td>
</tr>
<tr>
<td>PRP group</td>
<td>1.9 ± 1.2</td>
<td>2.0 ± 1.2</td>
<td>1.9 ± 1.3</td>
<td>1.4 ± 1.5</td>
<td></td>
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<tr>
<td>Bone marrow edema</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MF-AT group</td>
<td>1.3 ± 1.3</td>
<td>1.4 ± 1.4</td>
<td>1.3 ± 1.4</td>
<td>1.4 ± 1.3</td>
<td>NS</td>
</tr>
<tr>
<td>PRP group</td>
<td>1.2 ± 1.3</td>
<td>1.0 ± 1.2</td>
<td>1.0 ± 1.2</td>
<td>1.0 ± 1.2</td>
<td></td>
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<tr>
<td>Articular profile</td>
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<tr>
<td>MF-AT group</td>
<td>1.4 ± 1.1</td>
<td>1.4 ± 1.1</td>
<td>1.4 ± 1.1</td>
<td>1.7 ± 1.2</td>
<td>NS</td>
</tr>
<tr>
<td>PRP group</td>
<td>1.3 ± 1.0</td>
<td>1.3 ± 1.1</td>
<td>1.4 ± 1.0</td>
<td>1.2 ± 1.0</td>
<td></td>
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<tr>
<td>Marginal osteophytes</td>
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<tr>
<td>MF-AT group</td>
<td>2.8 ± 1.7</td>
<td>2.9 ± 1.8</td>
<td>2.9 ± 1.9</td>
<td>3.1 ± 1.6</td>
<td>NS</td>
</tr>
<tr>
<td>PRP group</td>
<td>3.1 ± 1.7</td>
<td>3.1 ± 1.7</td>
<td>3.3 ± 1.6</td>
<td>3.0 ± 1.5</td>
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<tr>
<td>Meniscal integrity</td>
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</tr>
<tr>
<td>MF-AT group</td>
<td>2.1 ± 1.5</td>
<td>2.2 ± 1.5</td>
<td>2.0 ± 1.5</td>
<td>2.4 ± 1.4</td>
<td>NS</td>
</tr>
<tr>
<td>PRP group</td>
<td>2.4 ± 1.4</td>
<td>2.3 ± 1.5</td>
<td>2.5 ± 1.3</td>
<td>2.3 ± 1.4</td>
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</tr>
<tr>
<td>Synovitis</td>
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</tr>
<tr>
<td>MF-AT group</td>
<td>1.2 ± 0.8</td>
<td>1.0 ± 0.8</td>
<td>1.0 ± 0.8</td>
<td>1.2 ± 0.8</td>
<td>NS</td>
</tr>
<tr>
<td>PRP group</td>
<td>1.0 ± 0.8</td>
<td>1.0 ± 0.7</td>
<td>0.8 ± 0.7</td>
<td>1.1 ± 0.9</td>
<td></td>
</tr>
</tbody>
</table>

aData are reported as mean ± SD. MF-AT, microfragmented adipose tissue; NS, not significant; PRP, platelet-rich plasma.

Figure 5. Improvement in the International Knee Documentation Committee (IKDC) subjective score for both treatment groups based on Kellgren-Lawrence (KL) grading. A statistically significant difference was found between patients with moderate/severe osteoarthritis (OA) treated with microfragmented adipose tissue (MF-AT) and patients with moderate/severe OA treated with platelet-rich plasma (PRP) at 6 months of follow-up (P = .041).

months), with no intergroup difference. Further details are reported in Table 3.
simple, minimal mechanical manipulation with a progressive reduction in the size of adipose tissue clusters and the elimination of oil and blood residue, without gross physical destruction of tissue components or the use of enzymes.50 In this way, the structural properties and integrity of the microarchitecture of the original tissue are preserved.10 MF-AT can ensure the preservation of the adipose “niche,” which represents the main structural and morphological adipose unit, and can help to preserve the MSC microenvironment and function.53 Moreover, MF-AT can aid biomechanical functions through viscosupplementation activity, reducing friction between cartilage surfaces, improving the lubrication of the articular compartment, and in the end cushioning loads on the cartilage surface.53,54

The advantage of preserving the native environment of adipose tissue with MF-AT was confirmed by an in vitro analysis: compared with an enzymatically processed liposapirate, MF-AT secreted a higher amount of growth factors and cytokines involved in tissue repair.52,53 Another in vitro study demonstrated that MF-AT contains a significantly higher concentration of exosomes secreted by MSCs compared with the enzymatic method.23 Exosomes have important paracrine effects that may affect the therapeutic potential of cellular products.15 Thus, their higher concentration with nonenzymatic methods may better preserve the paracrine cell potential of liposapirate-based products. MF-AT is also rich in microvessels with a high positivity for CD146 and NG2, 2 pericyte markers, suggesting a higher amount of MSC precursors.12,49 These potential advantages of MF-AT with respect to enzymatic methods were recently confirmed in this study. On the other hand, MF-AT injections demonstrated a safe and feasible procedure, without local or systemic major adverse effects, providing a gradual improvement in clinical outcomes.54

These promising preclinical results were accompanied by clinical studies focused on patients with knee OA. In an observational study of 110 OA knees treated with a single ultrasound-guided intra-articular injection of MF-AT, Heidari et al26 reported a very low number of adverse events and complications and a significant improvement in pain, function, and quality of life, regardless of OA severity. Boric et al7 evaluated the effect of an intra-articular MF-AT injection in 17 patients with knee OA using a functional MRI assessment to analyze the glycosaminoglycan content in hyaline cartilage, which is known to decrease during the natural course of knee OA. At 12 and 24 months after the MF-AT injection, the authors observed a significant increase in the glycosaminoglycan content, suggesting that the positive effects of MF-AT applied intra-articularly were likely because of positive biochemical changes in articular cartilage.31 Several authors investigated the role of intra-articular MF-AT injections as postoperative augmentation to arthroscopic debridement in patients with knee OA, reporting the safety and effectiveness of this application at up to 3 years of follow-up.11,45,47,48 In a recent retrospective study, Mautner et al38 compared the clinical results obtained in 35 patients treated with an MF-AT injection versus 41 patients treated with a bone marrow aspirate concentrate injection for symptomatic knee OA. After a minimum follow-up of 6 months, both groups had a significant similar improvement in clinical outcomes. Despite the growing number of clinical reports focusing on intra-articular MF-AT injections for knee OA, high-level evidence is needed to understand the potential of MF-AT injections compared with other injectable products.

This RCT compared the safety and effectiveness of intra-articular MF-AT and PRP therapies in patients with knee OA. Both injection strategies showed a similar safety with a low rate of adverse events and treatment failures at 24 months. Also, no signs of OA progression were found in either group. The overall clinical improvement provided by the 2 treatment options was comparable at all follow-ups for all clinical scores, showing benefits in terms of pain and symptom relief up to 24 months. Nevertheless, the procedures demonstrated different results for specific demographic characteristics, and in particular, significant differences were observed when taking into account OA severity. In fact, the subanalysis on OA severity, with an explorative nature, demonstrated that MF-AT had better results in patients with moderate/severe OA compared with PRP. The lower results with PRP in patients with high OA severity have already been demonstrated in a previous study by Filardo et al.18 The satisfactory clinical results demonstrated by PRP in those with mild OA are supported by previous literature.1,21 Accordingly, PRP may be considered a suitable treatment option in young patients with mild OA, while lower results can be expected in older patients with more advanced OA, as confirmed in this study. On the other hand, MF-AT injections provided good results, regardless of OA severity. In light of these results and considering the relative invasiveness of the procedure and the higher cost of MF-AT compared with PRP, these treatment methods seem to have different indications. MF-AT may be preferable in patients with a high degree of knee OA, aiming at delaying or avoiding TKA, or as a second-line treatment for less degenerated cases not responding to other injectable solutions. This is in line with the results of Hudetz et al,30 which confirmed the promising clinical findings of intra-articular MF-AT injections in 20 patients with late-stage knee OA (grade 3 or 4 according to the Kellgren-Lawrence classification) who were candidates for TKA, delaying the need for knee replacement in 17 patients (85%) for 12 months. While confirming the potential in advanced OA, the current study also showed the limitations of this treatment potential in cases of moderate/severe OA, as the improvement with MF-AT decreased from 6 to 12 months and remained stable at 24 months. Further specifically targeted studies are needed to confirm the differences between the MF-AT and PRP approaches based on OA severity.

The durability of MF-AT injections should be further investigated as well as the results of a multiple-injection

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The durability of MF-AT injections should be further investigated as well as the results of a multiple-injection...
schedule. In fact, other biological treatment methods demonstrated the effectiveness of repeat treatments in terms of the durability of results. In this light, research efforts should pursue the development of procedures that preserve the adipose tissue derivative over time to offer more treatment options while avoiding repetitive surgeries.

This RCT has some limitations, with one being the single-blind design, which was unavoidable for ethical reasons because of the need for a surgical procedure for MF-AT production. Nevertheless, clinicians and radiologists who evaluated patients at follow-ups were blinded to the allocated treatment to avoid any detection bias. Another limitation was the high number of dropouts compared with the study plan, although this aspect did not affect the baseline characteristics of the 2 groups. In fact, the randomization process guaranteed the creation of 2 homogeneous groups, with only residual differences the BMI at baseline, although both groups were classified as “overweight” according to the United States Centers for Disease Control and Prevention criteria. There was a dropout rate higher than what was considered in the sample size calculation, and there were some delays in the follow-up visits because of force majeure (eg, COVID-19 pandemic), which could affect the results of this study, even though this affected both groups comparably. Finally, another limitation was the absence of a control group with placebo. The decision to select PRP for the control group is derived from recent large evidence supporting its superiority over saline, corticosteroids, and hyaluronic acid. Thus, PRP is a challenging choice for a comparison of new injection options to address knee OA, even though there might be differences because of PRP types and injection schedules, and further studies are needed to understand if there are different results with other PRP formulations.

Despite these limitations, the results of this study are relevant because of the high-level study design comparing the safety and effectiveness of MF-AT versus PRP injections and the long-term follow-up considering the injectable nature of the treatments. MF-AT showed overall safety and effectiveness comparable with PRP, with a higher clinical improvement in patients with moderate/severe OA at 6 months of follow-up. Therefore, MF-AT seems to represent a suitable strategy for knee OA, especially for more advanced cases. Further high-level studies should confirm these findings, investigating the aspects that may influence the response to MF-AT injections, ranging from baseline clinical characteristics to biomarker profiles. Moreover, a proper characterization of this promising biological approach could help us to understand the most suitable way to exploit the adipose tissue potential by comparing its efficacy with other injectable options at a longer follow-up.

CONCLUSION

A single intra-articular injection of both MF-AT and PRP provided a significant clinical improvement up to 24 months of follow-up in patients with symptomatic knee OA. Both treatment groups reported a comparable low number of failures and adverse events, without signs of disease progression. Overall, no differences could be documented in both clinical and imaging results between the 2 biological approaches at all follow-ups. Compared with PRP, MF-AT provided a higher clinical improvement and more patients achieved the MCID for the IKDC score at 6 months in cases of moderate/severe OA.

ACKNOWLEDGMENT

The authors acknowledge Eleonora Pignotti for her help with statistical analysis.

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