Microfragmented adipose tissue injection reduced pain compared to a saline control among patients with symptomatic knee osteoarthritis during one-year follow-up: a randomized, cont…

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Microfragmented Adipose Tissue Injection Reduced Pain Compared With a Saline Control Among Patients With Symptomatic Osteoarthritis of the Knee During 1-Year Follow-Up: A Randomized Controlled Trial

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Purpose: To evaluate the effectiveness of microfragmented adipose tissue (MFAT) for pain relief and improved joint functionality in osteoarthritis (OA) of the knee in a randomized controlled clinical trial with 1-year follow-up. **Methods:** Seventy-five patients were stratified by baseline pain level and randomized to 1 of 3 treatment groups: MFAT, corticosteroid (CS), or saline control (C) injection. Patients 18 years of age or older, diagnosed with symptomatic OA of the knee, with radiographic evidence of OA of the knee and a visual analog pain scale score of 3 of 10 or greater were included. Patients were excluded if they had any previous intra-articular knee injection, current knee ligamentous instability, or an allergy to lidocaine/corticosteroid. The visual analog pain scale, Western Ontario and McMaster Universities Osteoarthritis Index, and the Knee Injury and Osteoarthritis Outcome score (KOOS) were recorded preprocedure and at 2 weeks, 6 weeks, 3 and 6 months, and 1-year follow-up. **Results:** MFAT demonstrated consistent and statistically significant improvements across all primary outcome measures for joint pain and functionality compared with C. For MFAT, there was a significant improvement over baseline at each follow-up, with median (95% confidence interval) KOOS Pain score changes of 18.1 (11.1-26.4) at week 2 to 27.8 (19.4-37.5) at 1 year. For CS, the median KOOS pain score reached a maximum of 22.2 (15.3-30.6) at week 2, only to level off to 13.9 (−2.8 to 29.2), a level not statistically different from baseline, at 1 year. The median changes for C hovered around 6 to 11 points, with statistically significant improvements over baseline indicating a placebo effect. Similar trends were seen for the Western Ontario and McMaster Universities Osteoarthritis Index Pain score and VAS Pain score. **Conclusions:** In this study, MFAT demonstrated a clinically significant improvement in primary outcome scores compared with the C group, whereas the CS group only showed statistically significant improvement compared with the C group at 2 and 6 weeks. This finding indicates that MFAT may be a viable alternative treatment for patients with OA of the knee who fall into the orthopaedic treatment gap. **Level of Evidence:** Level II, partially blinded, randomized controlled clinical trial.

In 2019, osteoarthritis (OA) of the knee affected ~364 million people worldwide.[1] Globally, the knee is the leading site of arthritis, accounting for approximately 60.6% of the total prevalent cases in 2019. The United States has the third highest prevalence of OA in the world, with 51.87 million people experiencing arthritis, an 80% increase from 1990 to 2019.[2] The lifetime risk of symptomatic OA of the knee is estimated

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to be 13.8%, and an even greater risk is identified for people with obesity (19.7%) and female patients (16.3%).[3] Thus, the burden of OA is widespread and is the most common cause of disability in the United States. OA is estimated to cost the United States $128 billion annually in direct and indirect costs, resulting in a huge economic burden on society.[4-6]

Current therapies for OA are limited to symptom management and are not curative or capable of stopping progression of the disease. Furthermore, considering the United States' aging population and high rate of obesity, the management and treatment of OA will remain an important health concern. Current treatment options include weight loss, activity modification, bracing, topical preparations, nonsteroidal anti-inflammatory drugs (NSAIDs), intra-articular injections, alternative therapies such as acupuncture, and, in severe cases, total knee arthroplasty.

Recently, the American Academy of Orthopaedic Surgeons advised that intra-articular corticosteroids may provide short term pain relief in treatment of OA.[7] In addition, the American Academy of Orthopaedic Surgeons has recommended against the routine use of alternative intra-articular treatments with hyaluronic acid and has provided a limited recommendation for the use of platelet rich-plasma to reduce pain and improve function in patients with symptomatic osteoarthritis of the knee.[8] Review of recent recommendations shows limitations to all available treatments, leading to a large group of patients who do not receive relief from conservative therapies and are not appropriate surgical candidates leading to an "orthopaedic treatment gap."

Treatment limitations have generated interest in alternative options to restore function and alleviate joint pain. It is well known that articular cartilage is avascular and lacks innervation, which limits its intrinsic healing and repair capabilities. Chondrocytes, derived from mesenchymal stem cells (MSCs), have limited potential to replicate, which also limits the intrinsic healing and repair capabilities of articular cartilage.[7-9] Within autologous adipose tissue, the stromal vascular fraction, which contains adipose-derived MSCs, has historically been isolated via enzymatic processes.[10] There has been preliminary support in the literature for reduced pain and improved functional performance in patients who received MSCs as part of treatment for OA.[11-20] In addition, the effects of these treatments appear to be long lasting, with a recent case series indicating a sustained effect up to 3 years after injection.[15] However, previous approaches to isolate MSCs are costly, time consuming, require extensive laboratory equipment, and are currently limited by complex regulatory issues.[21,22]

Thus, interest in an alternative isolation method led to the development and use of a novel therapeutic technique to harvest, process, and inject microfragmented autologous adipose tissue (MFAT). This mechanical process retains the extracellular matrix, vascular microarchitecture, mature pericytes, and MSCs for autologous injection.[23] Mechanically processed adipose tissue allows for the maintenance of the structural and morphologic unit, thought to improve efficacy through increasing resiliency to the harsh inflammatory conditions, such as those found in OA.[24] In addition, mechanically processed tissue shows an increased release of bioactive molecules via exosomes and a sustained release of regenerative factors through preserving the stromal vascular niche.[21-25]

As new therapies become available for the treatment of OA, it is important that we carefully characterize the time course and magnitude of therapeutic benefit over existing options, such as intra-articular corticosteroids (CS). To date, the authors have been unable to identify other randomized, saline controlled (C) clinical trials to evaluate the effectiveness of intra-articular MFAT injections for the treatment of OA. The goal of this study is to characterize the possible benefits of reduced joint pain and increased joint function in patients with OA of the knee after the injection of MFAT. In this study, pain relief, improvement of joint functionality, and duration of benefit of MFAT were compared with intra-articular CS and a C control. The purpose of this study was to evaluate the effectiveness of MFAT for pain relief and improved joint functionality in OA of the knee in a randomized controlled clinical trial over 1-year follow-up. The study hypothesis was that patients with OA of the knee undergoing injection of MFAT would have reduced joint pain and increased joint function compared with patients in the CS and C groups.

Methods

Before we enrolled patients, we obtained study approval from our institutional review board (17-146) and registered it at ClinicalTrials.gov (NCT03379168) as an active clinical trial. This study was conducted as a randomized controlled clinical trial with 3 treatment groups. Physicians and patients were blinded with respect to C and CS only because blinding for MFAT was not feasible. Patients evaluated for OA of the knee in the Sports Medicine Clinic were screened and recruited for enrollment between April 2018 and July 2021. Inclusion and exclusion criteria are found in Table 1. No patients were included in the study who had previous knee surgery for advanced cartilage wear, including a partial or total knee arthroplasty, osteotomy, or cartilage transplantation. Patients were included if they had previous surgery for patella instability, meniscus repair or meniscectomy, chondroplasty, or microfracture. No minors younger than the age of 18 years were included in this study, as degenerative or post-traumatic arthritis is a rare presentation in this age

Table 1. Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• Patient age of 18 or older	• History of treatment with any intra-articular knee injection
• Diagnosed symptomatic knee osteoarthritis	• Current ligament instability demonstrated by a positive Lachman test, anterior or posterior drawer test, or positive valgus or varus stress test
• Minimum pain level of 3 of 10 on the visual analog scale	• Patients with an allergy to lidocaine or corticosteroid
• Radiographic evidence of knee osteoarthritis	

group. The trial was completed after all 75 patients underwent a 1-year follow-up period in July 2022.

Radiographic evidence of OA of the knee was defined as any 1 or more of the following on a posteroanterior weight-bearing radiograph (Rosenberg view): osteophytes, joint space narrowing, loss of articular cartilage thickness, subchondral sclerosis, or cysts. All patients were assigned a Kellgren-Lawrence (K-L) grade for severity of arthritis. Patients with K-L grades 1 to 4 were included, as previous studies have shown no correlation between radiographic severity of OA of the knee and patient symptomatology.[26]

Randomization

After providing informed consent, eligible patients were randomized by the Hospital Investigational Pharmacy to receive an intra-articular knee injection of either MFAT, CS, or a C injection of saline. Consenting patients were first stratified into medium, or high-pain stratum according to baseline severity of pain to ensure a balanced distribution of baseline pain across the 3 treatment groups. Within each stratum, patients were further divided into 3 subgroups with the serial label of {1, 4, …3k+1, …}, {2, 5, 3K+2, …}, and {3, 6, 3K+3 …}, respectively, in the order they were recruited. We then randomly assign MFAT, CS, and C to the 3 subgroups. This scheme of stratified systematic assignment (sampling) reduces sampling variation compared with simple random assignment. Both the treating physician and the patients were blinded for patients receiving CS or P; however, a sham lipoaspiration procedure was not performed on patients in these groups. After randomization, patients were scheduled for an in-office injection procedure by a sports medicine fellowship-trained orthopaedic surgeon (D.L.R.) and completion of joint pain and functionality measurements, as described to follow.

Lipoaspiration

For patients randomized to the MFAT group, both an orthopaedic surgeon (D.L.R.) and a plastic surgeon (A.K.S.) performed lipoaspiration in an outpatient clinical setting following a published technique.[23-27] The adipose tissue was then sterilely processed using the Lipogems system (Norcross, GA) on the back table. The Lipogems system involves 2 cluster reductions, a bead microfragmentation, and a saline wash to microfragment the adipose tissue and separate inflammatory oils and blood from the final injected material.[23] The tissue was processed per manufacturer guidelines (Lipogems).

Injection Technique

For all study groups, 7 mL of fluid was sterilely injected into the affected knee using a landmark-guided, superolateral parapatellar approach by a single sports medicine fellowship-trained orthopaedic surgeon (D.L.R.). Participants randomized to the CS group received an injection of 2 mL (80 mg) of Kenalog-40 (triamcinalone acetonide injectable suspension, USP) mixed with 5 mL of 1% plain lidocaine for a total of 7 mL of fluid injected. Participants randomized to the control group received an injection of 7 mL of normal saline. Participants randomized to the MFAT group received an injection of 7 mL of MFAT processed with the Lipogems system. For all participants, the knee was ranged after the injection and the patient was discharged from clinic with no activity restrictions.

Primary and Secondary Outcomes

Our primary outcome measure was pain level using Knee Injury and Osteoarthritis Outcome score (KOOS) Pain score, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain score, and VAS Pain score. The WOMAC and KOOS scales have been validated for use in OA of the knee and target our variables of interest.[28-34] Greater KOOS Pain scores indicate less pain. For both WOMAC Pain score and VAS Pain score, greater values were associated with increased pain. Our secondary outcomes included 5 subscales: KOOS subscales of Activities of Daily Living (ADL), Quality of Life (QOL), the mean score of all KOOS subscales, WOMAC Function subscale, and the mean score of all WOMAC subscales.

Data Collection

All participants completed baseline in-person pain and joint function surveys before randomization. The participants then returned for in-person follow-up and surveys at 2 weeks and 6 months after injection. The participants also completed the same questionnaires online at 6 weeks, 3 months, and 1 year after injection for a total of 5 repeated measurements of knee pain and functionality. All results were entered directly into REDCap (database hosted at UNMHSC).[35]

Statistical Analysis

To determine an adequate sample size for our study, we conducted a simplified analysis on the basis of

published literature. Specifically, we assumed average change in VAS pain score over the follow-up to be 15, and standard deviation to be 20 on a 100-point scale. To have 80% power with 5% error, 22 subjects per group would be needed as suggested by a 2-way analysis of variance group comparison. We target 25 subjects within the recruitment time window for a total of 75 research participants. The actual study power is greater if the longitudinal data are used for analysis of continued improvements in the follow-up. The familial power for detecting an improvement in one or more outcomes would also be greater than in VAS pain score alone.

Our objective was to assess the treatment effects (MFAT and CS) relative to C over the follow-up period. Treatment efficacy/placebo effect was assessed using post, versus preprocedure changes of an outcome measure at each follow-up. Outcome measurements were VAS, KOOS, and WOMAC subscales. Treatment effectiveness relative to C was assessed using the difference in (median) pain score changes between MFAT and C or CS and C. This was effectively a difference-in-difference (DnD) approach. Score changes and DnD were analyzed using the nonparametric Kruskal-Wallis test to account for a skewed distribution in the outcomes. Because of loss to follow-up as well as missed postprocedure evaluations, we modified our intention-to-treat approach by including only patients with at least 1 postprocedure evaluation. At each postprocedure follow-up, only patients who had complete data at baseline and the follow-up were included. We also conducted a longitudinal analysis of the KOOS pain score to take advantage of the multiple follow-ups and to better quantify the time-trend of the treatment effects. Finally, we conducted an analysis of minimal clinically important difference (MCID) for the 3 pain scores at 3-month and 6-month follow-up. In the MCID analysis, we used half standard deviation as the benchmark. We derived standard deviation from the baseline score pooled from three intervention groups. All analyses were performed independently by a seasoned biostatistician (Y.Z.) using software R (version 4.3.2; R Foundation for Statistical Computing).[36]

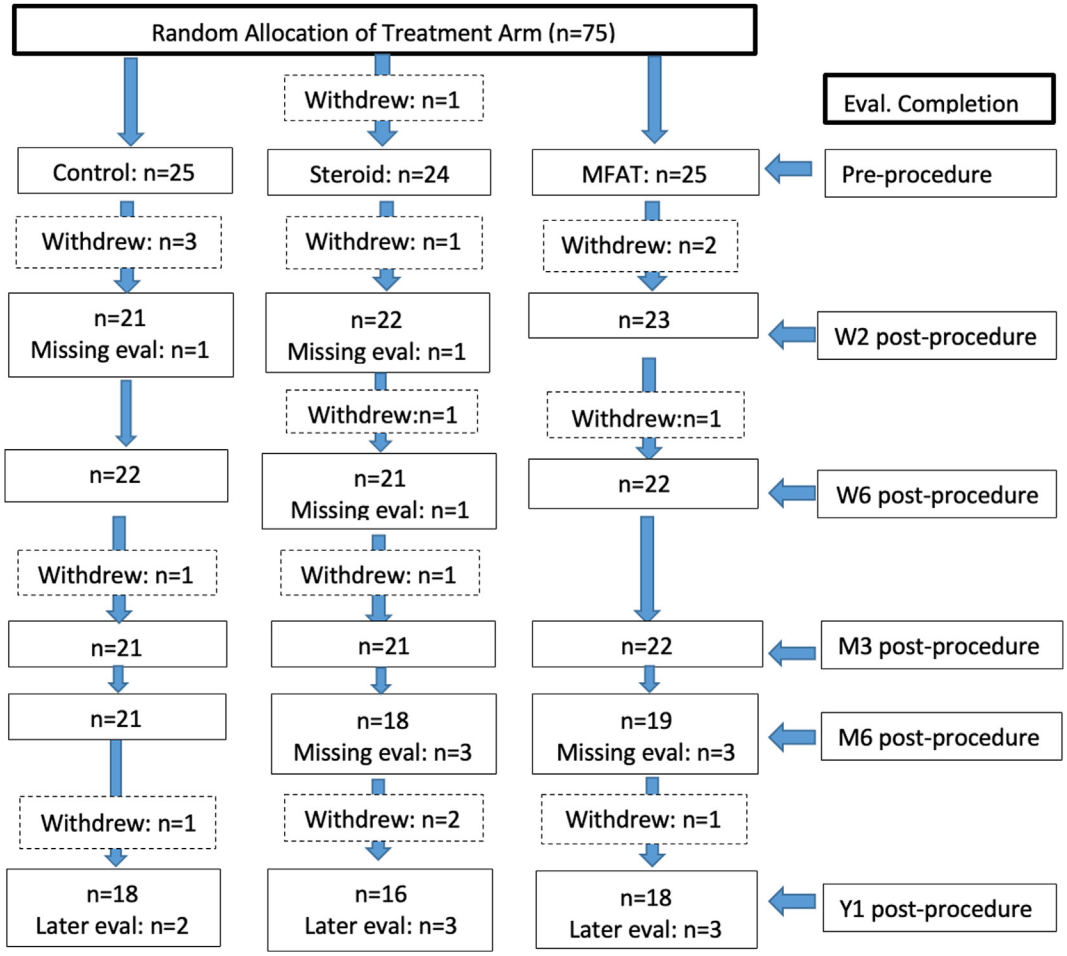

Fig 1. Consort diagram with pre and postprocedure evaluations.

Table 2. Patient Characteristics (Patients Withdrew Before Week 2 Evaluation Were Excluded)

	Pooled	Control (n = 22)	Steroid (n = 23)	MFAT (n = 23)	*P* Value (Group Difference)
Female sex, n (%)	37 (54.4)	15 (68.2)	14 (60.9)	8 (34.8)	.07
Age, yr, mean (SD)	60.0 (10.5)	61.2 (10.8)	56.3 (11.5)	62.6 (8.4)	.25
Other race, n (%)*	22 (32.4)	5 (22.7)	6 (26.1)	11 (47.8)	.18
Left laterality, n (%)	33 (48.5)	10 (45.5)	13 (56.5)	10 (43.5)	.68
BMI, mean (SD)†	31.6 (8.3)	31.7 (8.0)	32.9 (11.0)	30.0 (4.8)	.91
High pain level, n (%)	16 (24.2)	6 (27.3)	6 (26.1)	6 (26.1)	1.00
Diabetes: yes, n (%)§	11 (16.2)	2 (9.1)	3 (13.0)	6 (26.1)	.35
Hypertension: yes, n (%)	27 (39.7)	8 (36.4)	6 (26.1)	13 (56.5)	.40
HLD: yes, n (%)	19 (27.9)	7 (31.8)	4 (17.4)	8 (34.8)	.44
K-L grade 1, n (%)	10 (14.7)	2 (9.1)	4 (17.4)	4 (17.4)	.24
K-L grade 2, n (%)	25 (36.8)	7 (31.8)	12 (52.2)	6 (26.1)	
K-L grade 3, n (%)	27 (39.7)	9 (40.9)	7 (30.4)	11 (47.8)	
K-L grade 4, n (%)	6 (8.8)	4 (18.2)	0 (0.0)	2 (8.7)	
NSAID: yes, n (%)	44 (64.7)	11 (50.0)	17 (73.9)	16 (69.6)	.22
Tylenol: yes, n (%)	12 (17.6)	4 (18.2)	4 (17.4)	4 (17.4)	1.00
Narcotic: yes, n (%)	3 (4.4)	0 (0.0)	2 (8.7)	1 (4.3)	.77
Nicotine: yes, n (%)‡	15 (22.1)	7 (31.8)	3 (13.0)	5 (21.7)	.31
Alcohol, n (%)	38 (55.9)	16 (72.7)	12 (52.2)	10 (43.5)	.14
Baseline outcome score					
KOOS Pain Score	50.82 (15.46)	53.16 (14.83)	48.43 (16.54)	50.97 (15.27)	.73
VAS Pain Score	5.32 (1.97)	5.23 (2.25)	5.65 (1.82)	5.09 (1.88)	.59
WOMAC Pain Score	8.81 (3.60)	8.55 (3.78)	9.22 (3.48)	8.65 (3.66)	.88
KOOS ADL Score	55.88 (18.03)	59.22 (17.71)	52.30 (18.70)	56.27 (17.77)	.43
WOMAC Fun Score	29.88 (12.39)	27.64 (12.36)	32.00 (12.70)	29.91 (12.27)	.62
KOOS QOL Score	30.15 (17/91)	32.67 (18.89)	26.09 (15.95)	31.79 (18.83)	.36

BMI, body mass index; HLD, hyperlipidemia; K-L, Kellgren-Lawrence; KOOS, Knee Injury and Osteoarthritis Outcome score; MFAT, micro-fragmented adipose tissue; NSAID, nonsteroidal anti-inflammatory drug; SD, standard deviation; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

*"Other" included 5 self-identified American Indian, 2 Black, and 15 who declined to identify race.

†Two patients in "MFAT" and one in "Steroid" did not have BMI data.

‡Included 1 patient who smoked cigars.

§Included 1 patient with gestational diabetes.

Results

Participants

Seventy-five patients were recruited and randomized to the 3 groups within the strata of high versus medium level of pain. The Consolidated Standards of Reporting Trials flowchart (Fig 1) shows loss to follow-up as well as missed follow-up evaluation (those who came back for a later follow-up evaluation). Altogether, there were 5, 6, and 4 withdrawals from P, CS, and MFAT, respectively. Among those who completed 1-year evaluation, one patient skipped 2 follow-up evaluations before, 7 patients skipped 1 follow-up evaluation before. Six (3 each from CS and MFAT) did not complete 1-year evaluation but had an evaluation between 36 and 156 weeks after 1 year.

Patient Baseline Characteristics

The results indicate that the distribution of clinical conditions or risk factors (diabetes, hypertension, obesity, and lifestyle, such as use of alcohol) were evenly distributed (Table 2). Similarly, the K-L grade was evenly distributed, with most patients in grades 2 and 3. There were fewer female patients in the MFAT group (35%) compared with C and CS (68% and 69%). Importantly, the baseline outcome scores on average were comparable clinically across the 3 treatment groups. We included *P* values in Table 2 to provide a statistical reference with the understanding the *P* values were dependent on both the group difference and group size.

Primary Outcome: KOOS

MFAT transfer for OA of the knee demonstrated a consistent and statistically significant improvement across all primary outcome measures for joint pain and functionality compared with the C group. The results demonstrated significant increases in KOOS Pain score (reduced pain level) at each follow-up compared with baseline in the MFAT group (Table 3). For MFAT, the trend increased over follow-ups, with median score increases of 18.1 (95% confidence interval [CI] 11.1-26.4) at week 2 to 27.8 (95% CI 19.4-37.5) at 1 year. For CS, however, the median score change reached a maximum improvement of 22.2 (95% CI 15.3-30.6) at week 2, only to level off to 13.9 (95% CI −2.8 to 29.2)

Table 3. Median (95% CI) Score Changes From Baseline

	Control	Steroid	MFAT	
Outcome	Median (95% CI)	Median (95% CI)	Median (95% CI)	*P* Value*
KOOS Pain Score				
2 wk	11.11 (4.17-16.67)	22.22 (15.28-30.56)	18.05 (11.11-26.39)	**.010**
6 wk	6.94 (−1.39 to 12.50)	13.89 (5.56-23.61)	16.67 (12.50-26.39)	.120
3 mo	9.72 (1.39-19.44)	17.42 (9.72-27.78)	19.44 (11.11-27.78)	.214
6 mo	8.33 (1.39-15.28)	18.06 (5.56-30.56)	20.83 (13.89-29.17)	**.035**
1 yr	6.94 (1.39-12.50)	13.89 (−2.78 to 29.17)	27.78 (19.44-37.50)	**.018**
VAS Pain Score				
2 wk	−1.50 (−3.00-0.00)	−3.00 (−4.00 to −2.00)	−2.00 (−3.00 to −1.50)	**.021**
6 wk	−1.50 (−3.00-0.00)	−2.00 (−3.00 to −1.00)	−2.00 (−3.50 to −1.50)	.269
3 mo	−1.50 (−3.00-0.50)	−2.00 (−3.00 to −1.00)	−2.50 (−3.50 to −1.00)	.729
6 mo	−1.50 (−2.50-0.00)	−2.00 (−4.00-0.00)	−3.00 (−4.00 to −2.00)	.175
1 yr	−1.50 (−2.50-0.00)	−2.00 (−5.00-0.00)	−3.00 (−4.00 to −1.00)	.395
WOMAC Pain Score				
2 wk	−2.00 (−4.00-0.00)	−4.00 (−5.50 to −2.00)	−2.50 (−4.50 to −1.50)	.220
6 wk	−2.00 (−3.50-0.00)	−4.00 (−6.00 to −2.00)	−3.50 (−5.00 to −2.50)	.088
3 mo	−2.50 (−4.50-0.00)	−4.00 (−6.00 to −2.50)	−4.00 (−5.50 to −2.50)	.092
6 mo	−2.00 (−3.00 to −0.50)	−3.50 (−6.00 to −1.50)	−4.00 (−6.00 to −2.50)	**.047**
1 yr	−3.50 (−4.50 to −1.50)	−3.50 (−6.50 to 0.00)	−5.00 (−7.00 to −3.50)	**.034**
KOOS ADL Score				
2 wk	8.82 (−1.47-17.65)	24.26 (16.18-30.88)	15.44 (10.29-21.32)	**.019**
6 wk	9.56 (−0.00-18.38)	18.66 (8.82-27.21)	18.38 (11.76-26.47)	.222
3 mo	10.29 (0.74-20.59)	18.38 (10.29-30.15)	19.12 (12.50-28.68)	.220
6 mo	6.62 (−0.74-14.71)	15.44 (5.88-39.41)	22.06 (13.97-29.41)	**.039**
1 yr	10.29 (2.94-19.85)	15.07 (1.47-26.47)	26.47 (19.12-35.29)	**.027**
WOMAC Function Score				
2 wk	−6.15 (−12.50-0.50)	−14.50 (−20.00 to −8.00)	−8.50 (−13.50 to −4.00)	**.048**
6 wk	−5.50 (−11.50-0.50)	−11.70 (−20.00 to −5.00)	−12.00 (−18.00 to −5.50)	.393
3 mo	−7.50 (−14.00 to −1.50)	−11.00 (−18.50 to −3.50)	−13.00 (−19.00 to −7.00)	.303
6 mo	−5.00 (−11.50-1.00)	−13.00 (−21.00 to −4.50)	−14.50 (−20.50 to −9.00)	**.036**
1 yr	−6.00 (−12.00 to −1.50)	−11.50 (−20.50 to −2.50)	−18.00 (−24.00 to −12.00)	**.027**
KOOS QOL Score				
2 wk	9.37 (0.00-15.63)	18.75 (9.38-25.00)	15.62 (6.25-28.13)	.127
6 wk	9.70 (6.25-15.63)	14.11 (6.25-21.88)	21.87 (9.38-31.25)	.400
3 mo	12.50 (3.12-21.88)	12.50 (6.25-21.88)	21.88 (15.62-34.37)	.098
6 mo	9.38 (3.12-15.63)	18.75 (6.25-28.12)	25.00 (12.50-34.37)	.110
1 yr	15.62 (6.25-21.88)	21.88 (9.37-31.25)	28.13 (12.50-40.63)	.218
KOOS Mean Score				
2 wk	7.87 (2.38-13.91)	20.71 (14.09-27.00)	11.35 (6.72-16.93)	**.011**
6 wk	9.26 (2.83-15.19)	14.45 (7.58-25.41)	14.72 (8.69-22.44)	.326
3 mo	10.20 (2.25-18.94)	16.60 (8.78-24.23)	14.50 (10.52-25.29)	.302
6 mo	6.53 (0.90-13.78)	18.79 (7.44-28.60)	19.98 (12.15-28.08)	**.021**
1 yr	10.45 (4.56-16.36)	12.16 (1.92-23.83)	24.99 (15.46-35.42)	**.025**
WOMAC Mean Score				
2 wk	−7.84 (−17.35-0.74)	−19.71 (−28.38 to −11.47)	−12.70 (−20.66 to −6.47)	.091
6 wk	−8.65 (−17.11 to −1.30)	−17.07 (−26.47 to −6.62)	−14.51 (−24.04 to −8.55)	.299
3 mo	−7.65 (−19.71 to −1.25)	−15.49 (−24.53 to −7.55)	−19.56 (−27.45 to −10.78)	.197
6 mo	−7.35 (−13.97 to −0.69)	−15.34 (−26.76 to −3.55)	−22.02 (−29.17 to −14.31)	**.035**
1 yr	−10.47 (−17.79 to −3.68)	−11.85 (−25.15 to −1.08)	−26.84 (−35.05 to −18.28)	**.018**

NOTE. Values in bold were statistically significant with a *P*-value <.05.

ADL, activities of daily living; CI, confidence interval; KOOS, Knee Injury and Osteoarthritis Outcome score; MFAT, microfragmented adipose tissue; QoL, quality of life; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

by 1 year, a level not statistically different from baseline. The median changes in the C group hovered around 6 to 11 points, with significant improvements over baseline indicating a placebo effect. Overall group differences in the KOOS Pain score changes were significant at week 2, month 6, and year 1 ($P < .05$) but not at week 6 and month 3.

Efficacy: Changes in Secondary Outcomes From Pre to Postprocedure

With KOOS ADL score, MFAT showed significant improvements in outcome at each time point, 18.4 (95% CI 11.76-26.47) at week 2 to 26.5 (95% CI 19.1-35.3) at year 1, suggesting a sustained long-term effect over the follow-up period. CS showed maximal

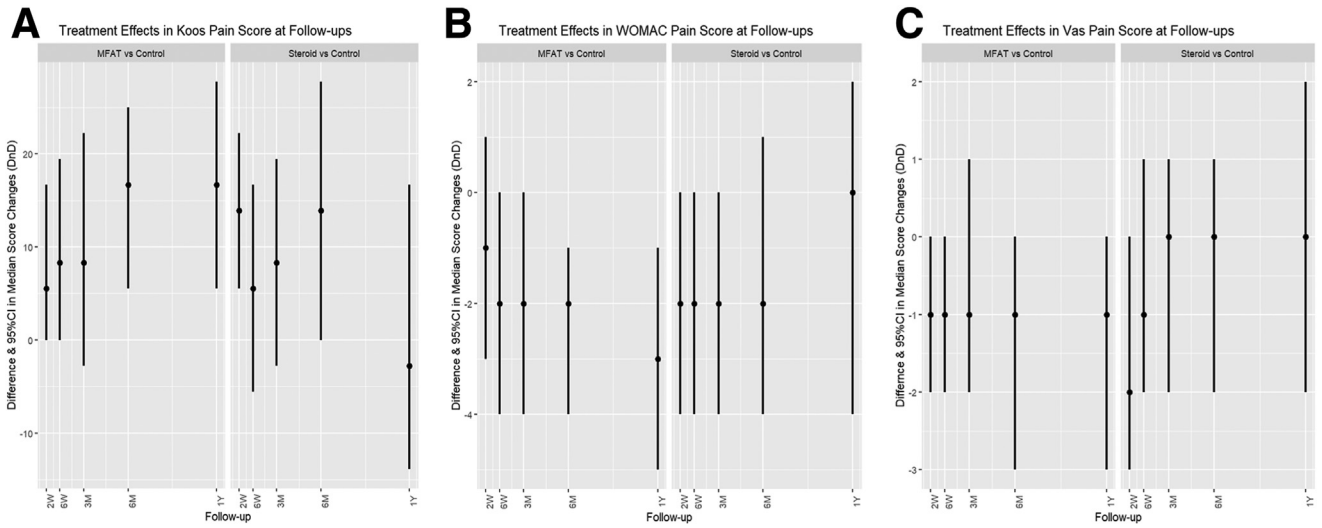

Fig 2. (a-c) display the estimated effectiveness of a treatment (MFAT or steroid) compared with the control in primary outcomes. The estimated effect at each follow-up (dot) is the difference in median score changes from the baseline between MFAT or steroid and control (DnD). The vertical bar is the 95% confidence interval for the estimated effect. (CI, confidence interval; DnD, difference-in-difference; KOOS, Knee Injury and Osteoarthritis Outcome score; MFAT, microfragmented adipose tissue; VAS, visual analog scale.)

improvement of 24.3 (95% CI 16.2-30.9) at week 2, followed by a steady decrease to 15.1 (95% CI 1.5-26.5) at year 1. There was a small saline placebo effect seen with a maximum change of 9.72 (95% CI 1.39-19.44) at 3 months. We observed similar patterns for WOMAC Function score, KOOS QOL, KOOS Mean score and WOMAC Mean score.

Difference-in-Difference Evaluation of Treatment Effectiveness

We reported, as estimated treatment effects, shifts in median score changes (DnD median) between MFAT and P and between CS and C along with a 95% CI at each follow-up. Note that the nonparametric statistical method yields DnD median estimate that is not necessarily the same as the arithmetic difference between the two medians. With KOOS Pain score, MFAT had an estimated DnD median of 5.6 points (95% CI 0.0-16.67) over control at week 2 (Fig 2a). This effectiveness improved overtime, reaching a DnD median of 16.7 (95% CI 5.56-27.78) at 1 year (Fig 2a). In contrast, CS reached a peak DnD median of 13.9 at week 2 and eventually decreased to −2.8 at year 1, with no statistical difference from the placebo effect (Fig 2a). Similar trends were seen with the WOMAC Pain score (Fig 2b). For VAS Pain score (Fig 2c), MFAT demonstrated a DnD median of −1.0 throughout the study period and gained more statistical significance toward year 1. CS in comparison had a significant DnD median of −2.0 at week 2, which faded away completely by month 3 and beyond.

For KOOS ADL score, MFAT steadily increased with a median DnD of 5.9 at week 2, reaching 13.2 and 16.2 at 6 months and 1 year, respectively (Fig 3a). CS had a decreasing trend, reaching a median DnD of 14.7 at week 2, decreasing to 2.9 at final follow-up, which did not significantly differ from the C.

For WOMAC Function score, MFAT showed a decreasing trend (increasing trend of improvement) over the study period. It started with a median DnD of −2.0 points at week 2, not significantly different from P, and eventually reached −10.0 and −12.0 at 6 months and 1-year follow-up, respectively (Fig 3b), both significant effects compared with C. CS showed a reverse trend, starting with a significantly lower median DnD of −10.0 at week 2, and dropping to a nonsignificant DnD of −4.0 at 1 year.

With WOMAC QOL score, MFAT also sustained improvements over C (Fig 3c). Specifically, the median DnD of MFAT started at 0.0 at week 2, then became significantly improved compared to P, reaching a median DnD of 12.5 after month 3. CS had a median DnD of 6.4 at week 2, which fluctuated afterwards, with no consistent improvements above the C effects.

With KOOS Mean score, MFAT was increasingly more effective compared with C, starting at a median DnD of 3.7, sustaining a 13.0-point improvement above C after 6 months (Fig 3d). CS reached its peak effect at week 2 with a median DnD of 12.3, and dropped over time to a low median DnD of 1.2 at 1 year. With WOMAC Mean score, we saw a similar pattern of short-term effect in CS and longer-term effect in MFAT (Fig 3e).

Longitudinal Effects of Treatments

To better quantify the treatment effects over time, we analyzed changes in KOOS Pain Score from baseline at

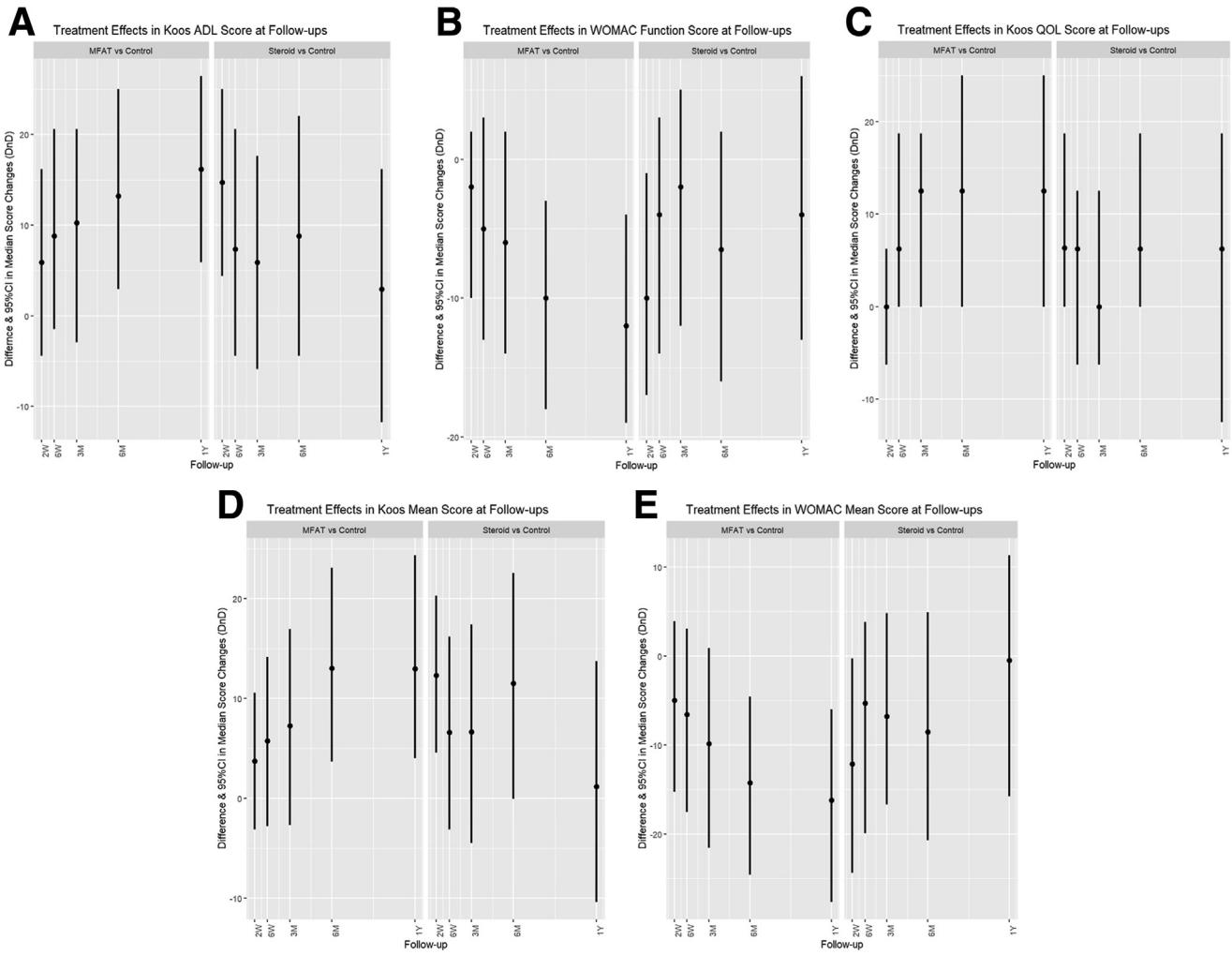

Fig 3. (a-e) display the estimated effects of a treatment (MFAT or steroid) compared with the control in secondary outcomes. The estimated effect at each follow-up (dot) is the difference in median score changes from the baseline between MFAT or steroid and control (DnD). The vertical bar is the 95% confidence interval for the estimated effect. (ADL, activities of daily living; CI, confidence interval; DnD, difference-in-difference; KOOS, Knee Injury and Osteoarthritis Outcome score; MFAT, microfragmented adipose tissue; QoL, quality of life; VAS, visual analog scale.)

all 5 follow-ups using a linear mixed effects model (Table 4). Although the data showed no time trend in control (C), we were able to establish a significantly increasing trend (continued improvement) for MFAT with a rate of weekly change 0.16 ($P = .009$) starting from week 2 of the follow-up; in contrast, we saw a

Table 4. A Linear Mixed-Effects Model of Changes in KOOS Pain Score Through 1-Year Follow-Up

	Change @ Week 2 (Intercept)		Rate of Change (Slope)	
Intervention Arm	Estimate (SE)	*P* Value	Estimate (SE)	*P* Value
Reference (control)	−7.69 (6.36)	.231	0*	
CS	10.24 (4.49)	**.007**	−0.14 (0.06)	**.024**
MFAT	12.27 (4.39)	**.026**	0.16 (0.06)	**.009**
Covariate adjustments†				
(BMI −29.05)‡	0.61 (0.25)	**.017**		
Diabetes (no)	12.00 (5.43)	**.031**		
Hyperlipidemia (yes)	6.74 (4.07)	.103		

NOTE. Values in bold were statistically significant with a *P*-value <.05.

BMI, body mass index; CS, corticosteroid; KOOS, Knee Injury and Osteoarthritis Outcome score; MFAT, microfragmented adipose tissue; SE, standard error.

*Slope was set to 0, as the estimate was 0.006 ($P = .917$).

†Covariate adjustment included only patient/clinical characteristics with a $P \leq .10$.

‡BMI was truncated at 50 and centered on its sample median of 29.05 in the model.

Table 5. Percentage of Patients Achieving MCID* by Treatment Group at 3-Month and 6-Month Follow-up

Pain Score	Follow-up, mo	Control %	Steroid %	MFAT %	Fisher Test *P* Value
VAS	3	67 (14/21)	75 (15/20)	77 (17/22)	.772
	6	62 (13/21)	56 (10/18)	79 (15/19)	.294
KOOS	3	48 (10/21)	67 (14/21)	77 (17/22)	.211
	6	52 (11/21)	67 (12/18)	79 (15/19)	.138
WOMAC	3	38 (8/21)	71 (15/21)	77 (17/22)	**.046**
	6	48 (10/21)	72 (13/18)	84 (16/19)	**.020**

NOTE. Values in bold were statistically significant with a *P*-value <.05.

KOOS, Knee Injury and Osteoarthritis Outcome score; MCID, minimal clinically important difference; MFAT, microfragmented adipose tissue; SD, standard deviation; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

*MCID was defined as improvements greater than 0.5 SD from baseline. The SDs were derived from the baseline sample pooled across the 3 groups for each outcome: 1.97, 15.46, and 3.60 for VAS, KOOS, and WOMAC pain scores, respectively.

continued decreasing trend in CS with a weekly rate of −0.14 ($P = .024$). This linear model appeared to describe the data reasonably well, although we were unable to confirm potential nonlinear trends because of limited data in our study. This model further confirmed a short-term CS effect that started to dissipate after peaking at week 2 of follow-up. This was in contrast with a sustained effect of MFAT. The model also showed that BMI was positively associated with improved KOOS Pain Score, and the patients without diabetes mellitus scored greater (less pain) than those with diabetes mellitus.

Minimal Clinically Important Difference (MCID)

The MCID analysis on the VAS Pain Score, KOOS Pain Score, and WOMAC Pain Score is summarized in Table 5. For each outcome MFAT consistently resulted in the greatest percentage of patients achieving MCID, followed by the CS and C groups. Although the MCID results were consistent with the DnD results, the treatment effects were statistically significant in WOMAC Pain Score only. Dichotomization of the outcome could have reduced statistical power.

Preliminary Analysis of Lipoaspirate

All patients had a small aliquot of the final lipoaspirate collected just before injection. A preliminary analysis of all MFAT samples using an enzyme-linked immunosorbent assay to detect cytokines, chemokines, and growth factors is shown in Figure 4.

Discussion

In this study, MFAT demonstrated a clinically significant improvement in primary outcome scores compared with a C saline control group, whereas the CS group only showed statistically significant

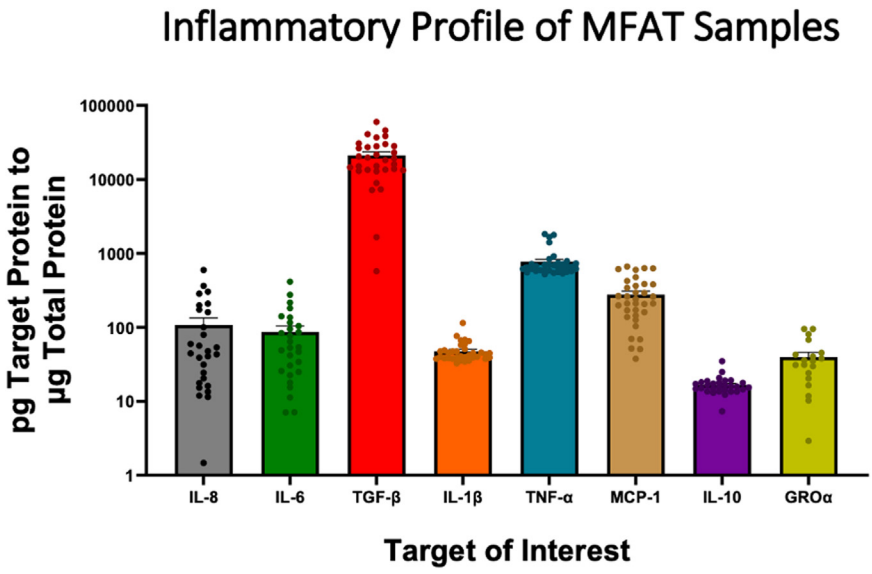

Fig 4. Preliminary enzyme-linked immunosorbent assay analysis of MFAT samples for analysis of inflammatory milieu. (MFAT, microfragmented adipose tissue.)

improvement compared with C at 2 and 6 weeks. No complications were noted except minimal, expected donor-site morbidity of mild pain and ecchymosis in the MFAT group. The results of this study are relevant because of the rigorous study design and sizable, significant, and lasting effects of MFAT in comparison with a control group.

Review of current recommendations shows limitations to all available treatments for OA of the knee. Oral NSAIDs provide limited relief and can be used only by patients without risk factors or contraindications. Topical NSAIDs are recommended to improve function and quality of life when not contraindicated, rather than oral NSAIDs. However, improvement in pain was evident over the first 6 weeks, but did not show any significant improvement at 13 weeks or longer.[7-37] A recent systematic review of intra-articular corticosteroids reported that intra-articular corticosteroids provided small-to-moderate relief up to 4 to 6 weeks and no evidence of effect at 13 weeks.[38] Similar to existing data on MFAT, Taylor's review of hyaluronic acid treatment is hampered by the variability of preparations and shortage of double-blind placebo-controlled studies resulting in conflicting data.[37-39] Osteoarthritis Research Society International currently recommends corticosteroid injections for short-term pain relief, as the duration of improvement is uncertain, and current results with hyaluronic acid show some improvement, however duration of improvement and amount is uncertain as the result of variability in results.[40]

The orthopaedic treatment gap is defined as patients who experience a severe musculoskeletal disorder that is unresponsive to conservative therapy; however, these patients are not yet ready for or are not appropriate candidates for major invasive surgery. Patients who fall into this treatment gap are seeking safe, effective, less-invasive, and more cost-effective treatment options for moderate-to-severe OA pathologies.[41] Given that many current therapeutic options lack long-term efficacy or provide minimal symptom relief, there has been renewed interest in alternatives to restore function and alleviate joint pain.[27,42] MFAT maintains the important reparative cells within the structural and functional unit to continue to function normally in the hostile inflammatory environment found in OA and may provide a viable alternative for patients in the orthopaedic treatment gap.[24]

Across all outcome measures, this study demonstrates that MFAT provided a sustained clinical significance at 6 and 12 months when compared with the CS and C groups. It has previously been shown that a VAS Pain of approximately 14 points is clinically important, as supported by Tashjian et al.[43] who estimated 1.4 cm as MCID on a 10-cm scale. When compared to baseline, the MFAT group demonstrated a median decrease of 3 cm at the 1-year time point. Lyman et al.[44] determined the MCID for the KOOS Pain and QOL scores to be 8-18 and 8-17 respectively. Compared with baseline, we demonstrated the median change in MFAT for the KOOS Pain and QOL scores to be 27.8 and 28.1 at 1 year, respectively. Compared with C, we demonstrated the median DnD in the MFAT group for the KOOS Pain and QOL scores to be 16.7 and 12.5 at 1 year, respectively. Kim et al. showed the MCID for the WOMAC score to be 4.2 points for the pain subscale, 1.9 points for the stiffness subscale, 10.1 points for the function subscale, and 16.1 points for the total.[45,46] Compared with baseline we demonstrated a median change in WOMAC score to be 5.1 for pain, 18.2 for function, and 26.9 for the total WOMAC score at 1 year.

MFAT also has been shown to increase proteoglycan synthesis over a 2-year period in patients with OA of the knee after a single intra-articular injection.[47] A systematic review of clinical outcomes in patients who underwent treatment with MFAT for symptoms of OA of the knee was recently published. The authors concluded that MFAT injection therapy is effective in improving pain and functional outcomes but cautioned on the overall external validity of the results, given the moderate risk of bias and quality of studies included in the review.[48]

In vitro studies have demonstrated that MFAT, compared with enzymatically processed lipoaspirate, secretes a greater amount of growth factors and cytokines involved in tissue repair.[25-49,50] The mechanism of MFAT is not fully understood; however, there are multiple proposed mechanisms of action.[51] Although speculative, we propose that the therapeutic benefit is attributable to more than differentiating adipose-derived stem cells for regenerative capacity. Rather, we postulate that adipose-derived stem cells produce and release endogenous anti-inflammatory cytokines, and it is the actions of these released factors on articular cartilage, chondrocytes, and osteocytes that complement and drive a reparative environment to improve joint structural integrity while minimizing chronic microinflammation. Future studies looking at the anti-inflammatory/proinflammatory characterization of MFAT will provide insight into additional factors that can be exploited for us in next-generation lipoaspirate formulations.

In our preliminary analysis of the MFAT samples, greater levels of transforming growth factor-β, interleukin-8, interleukin-6, and tumor necrosis factor-α were observed, indicating a possible increase in T-cell activity within the MFAT. Moreover, transforming growth factor-β is a critical factor in directing CD4+ T cells to differentiate into regulatory T cells, which are T cells with strong anti-inflammatory function and act as an immunosuppressant while mediating apoptosis in a variety of cells. Future work includes correlating cytokine and chemokine levels with patient outcomes and demographic/baseline characteristics.

Limitations

This RCT does have some limitations. One significant limitation is that the study is only partially blinded as a sham lipoaspiration procedure was not performed on C and CS. Despite active patient engagement, some patients were lost to follow-up or withdrew from the study. There were fewer female patients in the MFAT group (35%) compared with C and CS (68% and 69%), which may present a selection bias. No pre, or post-procedure advanced imaging was obtained, as we hypothesized that tissue regeneration is not the primary mechanism by which MFAT is effective in OA of the knee. There is also a lack of complete characterization of MFAT effects at this time, given funding and time constraints.

Conclusions

In this study, MFAT demonstrated a clinically significant improvement in outcome scores compared with a saline control (C) group, whereas the CS group only showed statistically significant improvement compared to the control group at 2 and 6 weeks. This finding indicates that MFAT may be a viable alternative treatment for patients with OA of the knee who fall into the orthopaedic treatment gap.

Disclosures

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: D.L.R. reports equipment, drugs, or supplies provided by Lipogems; fellowship funding support from Arthrex and Stryker; editorial board, *Video Journal of Sports Medicine*; and education Committee, American Orthopaedic Society for Sports Medicine. A.K.S. reports board membership, Mountain West Society of Plastic Surgeons. R.C.S. reports board membership, consulting or advisory, and travel reimbursement with *Journal of Bone and Joint Surgery*; educational support from Arthrex; Deputy Editor, *Journal of Bone and Joint Surgery*; and editorial board, *American Journal of Sports Medicine*. All other authors (J.L.H., L.F., S.S., Y.Z., C.P., L.W.) declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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