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Conversion to Knee Arthroplasty Following Intra-Articular Injection of Microfragmented Adipose Tissue in Patients with Knee Osteoarthritis

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SUMMARY

Background. Few studies have investigated the need for additional treatment after use of intra-articular injection of microfragmented adipose tissue (MFAT) in treatment of knee osteoarthritis. We assessed the rate of conversion to knee arthroplasty and 1-year clinical outcomes after intra-articular injection of MFAT for knee osteoarthritis.
Methods. We retrospectively reviewed data from consecutive patients who underwent a single intra-articular MFAT injection for the treatment of symptomatic knee osteoarthritis with average 1-year follow-up.
Results. Of 56 knees (39 patients), three knees (two patients) had follow-up only to 13 and 28 weeks. All other knees were followed to a minimum of 1 year or through conversion to knee arthroplasty. The 1-year rate of conversion to knee arthroplasty was 17.9%, with an increase to 32.1% within the second year of follow-up. There was a significant improvement in mean Knee Injury and Osteoarthritis Outcome Score for Joint Replacement (KOOS JR) scores at each post-procedure time point ($p < 0.05$) and in mean Short Form 12 physical function scores at 6 weeks and 1 year postoperatively ($p < 0.05$). Conversion to knee arthroplasty was associated with significantly lower KOOS JR score at 1 year (mean difference, 10.1 ± 4.9, $p = 0.04$).
Conclusions. Use of a single intra-articular injection of MFAT was associated with a high rate of conversion to knee arthroplasty despite a significant improvement in knee pain, stiffness, and function at an average of 1-year follow-up. MFAT may be more appropriately considered as a temporizing agent rather than a means to avoid knee arthroplasty.

KEY WORDS

Microfragmented adipose-derived stem cells; osteoarthritis; knee arthroplasty; knee; pain.

INTRODUCTION

Osteoarthritis is characterized by irreversible degeneration of articular cartilage accompanied by subchondral sclerosis and synovial inflammation. Most nonoperative treatments serve to postpone further treatment, such as surgery, but do not prevent or repair cartilage damage.

Recent interest has focused on the use of adipose-derived human mesenchymal stem cells (ADSC) as an alternative treatment for knee osteoarthritis. ADSCs display chondrogenic and anti-inflammatory properties that could theoretically stop disease progression and repair cartilage, avoiding the need for further treatment (1-4). Three ways of delivering ADSC have been investigated in cultured ADSC, in stromal vascular fraction (SVF), and in micro-fragmented adipose tissue (MFAT) (5), with most research focusing on cultured ADSC or ADSC in SVF. Regardless of the delivery method, treatment of knee osteoarthritis with an intra-articular injection of ADSC is associated with a low risk of serious side effects and can decrease pain and improve func-

tion based on significant improvement in patient-reported outcome scores (6-18). Several studies on cultured ADSC have found that clinical scores peak as early as 3 (17) to 6 months after treatment with outcomes starting to decline after reaching maximum benefit (10, 11, 16, 18). In a study of 9 patients with osteoarthritis, all patients showed significant improvement in pain and clinical scores at 6 months that were maintained up to 18 months post-procedure along with cartilage improvements noted on MRI (17). However, these studies suggest that ADSC may only provide temporary relief of symptoms despite the treatment's recognized regenerative properties. Additionally, a systematic review of studies evaluating the use of MFAT for musculoskeletal conditions corroborated the effect of MFAT in improving pain, function, and cartilage degeneration; however, these results were mostly limited to low quality studies and other limitations such as inconsistencies in processing techniques and quality of MFAT (19). Only one small case series has reported on the need for additional treatment following an intra-articular injection of MFAT, documenting a 15% conversion rate to total knee arthroplasty within 1 year (9). Currently, the understanding of the clinical effect of MFAT is incomplete, particularly with respect to the need of additional treatment following an intra-articular injection of MFAT.

Therefore, the primary aim of this study was to report the 1-year rate of conversion to knee arthroplasty after a single intra-articular injection of autologous MFAT in patients with symptomatic knee osteoarthritis. The secondary objective was to evaluate the 1-year clinical outcomes of this treatment. Results from this study will inform whether MFAT may be considered as a mainstay treatment for knee osteoarthritis.

METHODS

Study procedure

This retrospective study was approved by the Institutional Review Board through Medstar Health Research Institute (approval number: MOD00000165, approved on 1/25/2019). The study included all patients who received a single intra-articular autologous MFAT injection using a commercially available processing system (Lipogems International Spa, Milan, Italy) between October 2016 and February 2018 from a single joint fellowship-trained orthopaedic surgeon's practice. All patients were diagnosed with symptomatic knee osteoarthritis in one or more compartments as determined by radiographs with varying Kellgren Lawrence grades before undergoing treatment. Additionally, most patients had undergone a course of nonoperative treatment, including corticosteroid injections, home exercises or formal physical therapy, nonsteroidal anti-inflammatory drugs (NSAIDs), or use of ambulatory devices. Patients who had not tried non-operative treatments were included for the study if they had chronic knee pain with radiographic evidence of osteoarthritis. All patients were looking to avoid or delay surgical intervention. No patient had a contraindication for knee arthroplasty.

Retrospective data were obtained from a prospective IRB-approved, web-based clinical data orthopaedic registry of patient reported outcomes data, including Knee Injury and Osteoarthritis Outcome Score for Joint Replacement (KOOS JR) and 12-Item Short Form Survey (SF-12) for mental health and physical function pre-procedure and at the following time points post-procedure: 6 weeks, 12 weeks, 6 months, and 1 year. All patients had pre-procedure scores. The patient-reported outcome forms were sent electronically via participants' email addresses, collected during office visits, or conducted by phone per office protocol. Medical records were reviewed to 1) collect demographic data, including age, sex, body mass index (BMI), and laterality; 2) collect clinical data: volume of lipoaspirate injected at time of index procedure, serious adverse events including infection, deep venous thrombosis, pulmonary embolism, and death; and 3) identify any patient who underwent knee arthroplasty or received an additional corticosteroid injections or viscoelastic supplementation. Severity of osteoarthritis was graded based on the Kellgren Lawrence classification of osteoarthritis by reviewing patients' preoperative standard weight-bearing knee radiographs in two planes, where grade 0 = no radiographic features of knee OA; grade 1 = doubtful joint space narrowing with possible osteophyte formation; grade 2 = possible joint space narrowing with definite osteophyte formation; grade 3 = definite joint space narrowing, moderate osteophyte formation, sclerosis, possible bony deformity; and grade 4 = severe joint space narrowing, large osteophyte formation, marked sclerosis, and definitive bony deformity (20)

Adipose tissue harvest and processing

The surgical procedure took place in the office during regularly scheduled clinic visits under local anesthesia. The abdomen or flank was chosen as the harvest site, depending on which had more abundant adipose tissue. The harvest site was anesthetized with 1% lidocaine and then infiltrated with a solution comprised of lidocaine, epinephrine, and saline. Adipose tissue was aspirated with use of a vacuum syringe connected to a lipo-aspiration cannula (**figure 1**). Collected lipoaspirate was processed per the manufacturer's guidelines (**figure 2**). The processed lipoaspirate was

then injected into the diseased knee compartment(s), using a lateral suprapatellar, medial, and/or lateral approach under sterile technique (**figure 3**). The volume of lipoaspirate injected varied based on the amount of adipose tissue available and collected from the harvest site.

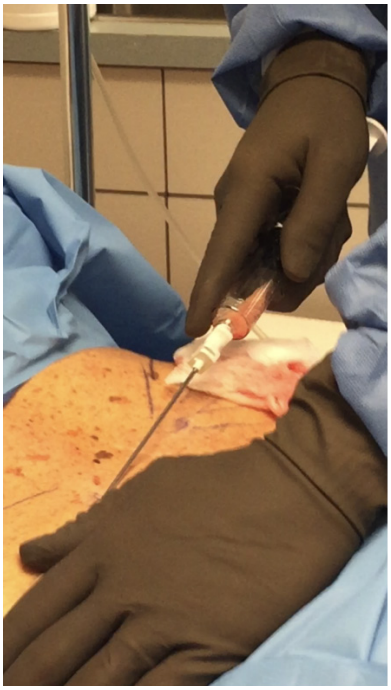

Figure 1. Aspiration of adipose tissue using a vacuum syringe connected to a lipo-aspiration cannula.

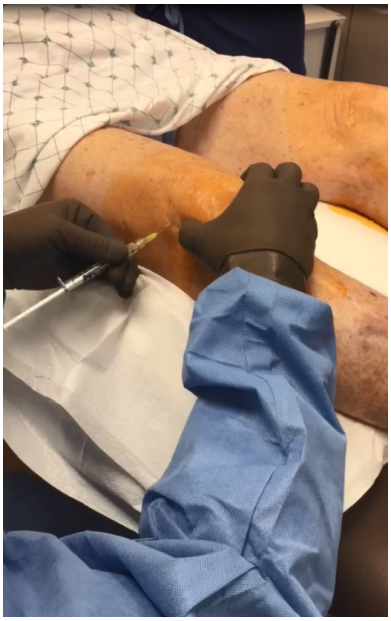

Figure 2. Processing of collected lipoaspirate.

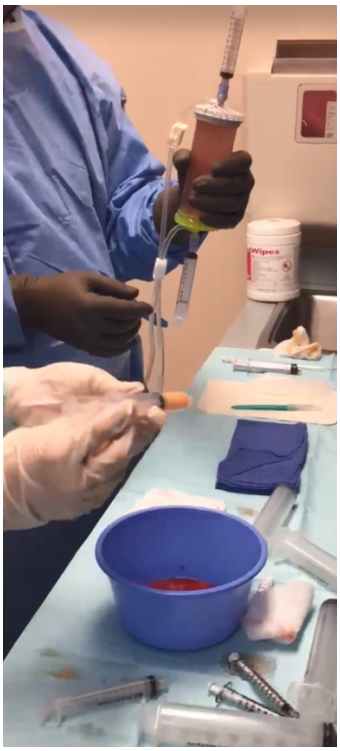

Figure 3. Injection of processed lipoaspirate using a lateral suprapatellar approach under sterile technique.

Post-procedure protocol

The injection and harvest sites were covered with a dry dressing, and an elastic bandage was applied as a compressive wrap to minimize drainage. Patients were instructed to apply an icepack locally as needed. A short course of narcotic (hydrocodone/acetaminophen 5 mg/325 mg tab, 1-2 tabs every 6 hours for 3 days) was used postoperatively for procedure-related pain. Patients were encouraged to avoid use of NSAIDs for the first 4 weeks after the procedure because NSAIDs may potentially impact anti-infla - matory properties of the MFAT. Patients were informed that they could return to pre-procedure medications such as NSAIDs and pain relievers after 4 weeks. There was no formal rehabilitation protocol post-procedure. Patients were encouraged to walk and resume other activities as tolerated but to avoid heavy exercise such as heavy lifting or running for at least 4 weeks. Patients were instructed to refrain from participating in formal physical therapy for approximately 6 weeks after the procedure.

Some patients elected to have a steroid injection or viscoelastic supplementation despite undergoing the MFAT procedure. However, patients were not allowed to have an injection within 3 months after the procedure. Patients were discouraged, though not prohibited, from receiving

an intra-articular injection within 6 months after the MFAT procedure. The indication for post-procedure injection was chronic knee pain despite the MFAT procedure and patient's request.
Some patients decided to proceed with surgical treatment such as partial or total knee replacement. The criteria for conversion to knee arthroplasty was chronic knee pain, radiographic evidence of osteoarthritis, and no resolution despite MFAT or other non-operative treatment.

Statistical analysis

Descriptive statistics were presented using mean, median, ranges and standard error for continuous variables and frequencies and percentages for categorical variables. Associations between conversion to knee arthroplasty and baseline characteristics were analyzed using a logistic regression model with mixed effect to account for within-patient correlation for patients who underwent bilateral knee injections in the cohort. Wilcoxon rank sum test was used to evaluate the association between conversion to arthroplasty and volume of lipoaspirate injected. Pearson correlation coefficient was used to describe the correlation between demographic information and severity of osteoarthritis, with r value greater than 0.7 representing strong correlation, greater than 0.5 to less than 0.7 representing moderate correlation, greater than 0.3 to less than 0.5 representing weak correlation, and any value less than 0.3 representing a negligible relationship. A mixed effect regression model was used to analyze the change in KOOS JR and SF-12 physical function and mental health scores from baseline and to evaluate the association of patient-reported outcome scores with baseline characteristics and conversion to arthroplasty. A P-value of < 0.05 was considered statistically significant. The median minimal clinically important difference (MCID) of 15.1 was used (21) to determine significan findings for KOOS JR scores. For subjects with bilateral involvement, both knees were independently included in the analysis. Patient-reported outcome scores collected after conversion to knee arthroplasty or after receiving an additional intra-articular injection were excluded from the analysis.

RESULTS

A total of 56 knees from 39 consecutive patients (20 females, 19 males) were included in the study. The average follow-up was 52 (range 7-96) weeks. Three knees (two patients) had follow-up only through 13 weeks and 28 weeks. All other knees, excluding those that converted to knee arthroplasty within 1 year, had a minimum of 1-year clinical follow-up. The mean age at time of index procedure was 71.1 (range 47.0-94.9) years. The mean BMI was 28.4 (range 19-37) kg/m^2. The following are the number of knees based on the Kellgren Lawrence classification of knee osteoarthritis: grade 1 (n = 8); grade 2 (n = 9); grade 3 (n = 29); grade 4 (n = 4). Preoperative radiographs of six knees were unavailable for the study. Post-procedure radiographs for these patients were also not available because they were not a part of the post-procedural protocol. Age was moderately correlated (r = 0.55, p = 0.0006), and BMI was weakly correlated (r = 0.32, p = 0.06) with Kellgren Lawrence grade. The mean lipoaspirate volume injected was 19.75 (range 3.5-36) mL. No serious adverse events were reported.
A total of 10 knees (17.9%) converted to a knee arthroplasty within 1 year of the index procedure. An additional eight knees converted to a knee arthroplasty within the second year of follow-up, resulting in a total of 18 knees (32.1%) converting to a knee arthroplasty. Thirteen knees underwent total knee arthroplasty, and 5 knees underwent unicompartmental knee arthroplasty.
The average time to conversion to knee arthroplasty was 17 (median 43.5; range 7-96) weeks. Two were classifie as Kellgren Lawrence grade 1, 13 as grade 3, 1 as grade 4 and 2 unclassified due to missing radiographs. Among all patients with Kellgren Lawrence grade 3 and 4 OA (33 total knees), 8 knees (24.2%) converted to knee arthroplasty within 1 year, increasing to a total of 14 knees (42.4%) within the second year of follow up. Conversion to arthroplasty was not associated with sex (OR = 1.68, 95% CI: 0.47-6.00, p = 0.42), age (OR = 0.10, 95% CI: 0.93-1.07, p = 0.91), BMI (OR = 1.03, 95% CI: 0.90-1.17, p = 0.71), Kellgren Lawrence grade (OR = 1.36, 95% CI: 0.60-3.02, p = 0.46), or lipoaspirate volume (p = 0.19). Knees converting to arthroplasty had a significantly lower KOOS JR score at 1-year compared to those that did not convert with a mean difference of 10.1 ± 4.9 points (p = 0.04) (**table I**).
A total of three knees (5.4%) received an additional intra-articular knee injection, including cortisone or viscoelastic supplementation, within 1 year of the index procedure. Four additional knees received an intra-articular knee injection within the second year of follow-up, resulting in seven knees (12.5%) receiving an additional injection. The average time to additional injection was 44 (range, 19-63) weeks. One knee underwent an intra-articular injection prior to converting to a total knee arthroplasty.
KOOS JR scores increased significantly compared to preoperative scores at 6 weeks ($p < 0.0001$), 12 weeks (p = 0.0007), 6 months ($p < 0.0001$), and 1 year ($p < 0.0001$) (**table II**). The largest mean increase in KOOS JR scores occurred at 6 weeks and 1 year, with an increase of 11.6 and 12.5 points, respectively. The mean 1-year increase in

Table I. Mixed effect model estimate mean KOOS JR scores and change from baseline in those that converted to TKA and those that did not convert to TKA at baseline, 6 weeks, 12 weeks, 6 months, and 1 year.

Time Point	Mixed Effect Model Estimate KOOS Jr TKA Mean (SE)	Change from Baseline TKA Mean (SE)	Mixed Effect Model Estimate KOOS Jr Non-TKA Mean (SE)	Change from Baseline Non-TKA Mean (SE)	Mixed Effect Model Estimate TKA *vs* Non-TKA P value	Change from Baseline TKA *vs* Non-TKA P value
Baseline	52.52 (3.48)	-	53.52 (2.68)	-	0.7931	-
6 weeks	66.52 (3.96)	14.01 (3.84)	64.12 (2.86)	10.60 (2.60)	0.2690	0.4623
12 weeks	59.54 (3.71)	7.02 (3.65)	60.79 (2.75)	7.27 (2.49)	0.8828	0.9558
6 months	56.81 (3.96)	4.29 (3.96)	63.49 (2.75)	9.97 (2.49)	0.1329	0.2260
1 year	57.68 (4.62)	5.16 (4.55)	67.94 (2.83)	14.41 (2.52)	0.0402	0.0766

KOOS JR: Knee Injury and Osteoarthritis Outcome Score for Joint Replacement; TKA: Total Knee Replacement; SE: standard error.

KOOS JR scores was below the median MCID. KOOS JR scores were not associated with age (p = 0.05), BMI (p = 0.75), Kellgren Lawrence grade (p = 0.79), or sex (p = 0.73). There was a significant increase in mean SF-12 physical function scores compared to preoperative scores at 6 weeks (p = 0.02) and 1 year (p = 0.003) (**table II**). SF-12 physical function scores were not associated with age (p = 0.06), BMI (p = 0.95), Kellgren Lawrence grade (p = 0.75), or sex (p = 0.21). There was no significant change in SF-12 mental health scores at any timepoint compared to preoperative scores (**table II**). There was no significant association with age (p = 0.67), BMI (p = 0.25), Kellgren Lawrence grade (p = 0.85), or sex (p = 0.10).

DISCUSSION

We found a high rate of conversion to knee arthroplasty after treatment with MFAT, while also observing a statistically significant improvement in knee pain, stiffness, and

Table II. Mixed effect model mean KOOS JR, SF-Physical Function, and SF-Mental Health scores and mixed effect model estimate increase at baseline, 6 weeks, 12 weeks, 6 months and 1 year.

Time Point	Mean Score (± SE)	Increase in Score (± SE)	P-value
KOOS Jr			
Baseline	53.29 (2.38)	-	-
6 weeks	64.87 (2.55)	11.59 (2.17)	< 0.0001
12 weeks	60.45 (2.48)	7.16 (2.07)	0.0007
6 months	61.85 (252)	8.57 (2.11)	< 0.0001
1 year	65.81 (2.63)	12.53 (2.21)	< 0.0001
SF-Physical Function			
Baseline	34.40 (1.67)	-	-
6 weeks	39.83 (1.91)	5.43 (2.30)	0.02
12 weeks	38.09 (1.82)	3.69 (2.11)	0.08
6 months	35.92 (1.82)	1.53 (1.92)	0.43
1 year	39.47 (1.87)	5.07 (1.66)	0.003
SF-Mental Health			
Baseline	53.14 (1.63)	-	-
6 weeks	54.71 (1.89)	1.56 (2.44)	0.52
12 weeks	52.73 (1.80)	- 0.41 (2.30)	0.86
6 months	54.75 (1.82)	1.60 (2.18)	0.46
1 year	52.77 (1.92)	- 0.37 (1.99)	0.85

KOOS JR: Knee Injury and Osteoarthritis Outcome Score for Joint Replacement; SF: Short Form; TKA: Total Knee Replacement; SE: standard error.

function at 6 weeks, 12 weeks, 6 months and 1 year. These findings suggest that MFAT injection may be more appropriately considered as a temporizing procedure, like other nonoperative treatments rather than a treatment to circumvent the need for a knee replacement.

MFAT is used as a treatment of symptomatic knee osteoarthritis with the expectation that patients can avoid or delay additional treatment. Moreover, the regenerative properties of ADSC may lead to preconceived notions that treatment with ADSC could theoretically circumvent the need for surgical intervention. The application of MFAT has been noted in animal (22) and human studies (6, 9, 13, 23). A study of eight race horses with osteoarthritis were treated with a combination of plasma-rich protein and micro-fat demonstrated improvement in function and gait in horses (22). Similar findings were found in humans. Several small case series have found a statistically significant improvement in patient-reported outcomes after isolated MFAT injection (6, 9, 13). In a case series of 15 patients with shoulder osteoarthritis and rotator cuff injuries, most patients noted significant improvement in pain and function for 6 months, and up to 10 months in almost half the patients (23). Additionally, a retrospective-prospective study comparing the effect of MFAT *versus* bone marrow aspirate concentrate (BMAC) injection for patients with knee osteoarthritis demonstrated similar improvement in pain, function, and quality of life in both groups (13). A recent systematic review of MFAT application in patients with knee osteoarthritis showed improvement not only in clinical improvements, but also regeneration of cartilage in diagnostic imaging (24). Unfortunately, though a systematic review of studies evaluating the use of MFAT for musculoskeletal conditions noted improvement in pain, function, and even cartilage regeneration in imaging studies, the evidence was limited by low quality studies and heterogeneity in MFAT processing techniques and quality (19).

There has only been one study that has investigated the need for additional treatment for osteoarthritis. Hudetz *et al.* found a significant improvement in KOOS and WOMAC scores at 1-year follow-up with an associated 15% conversion rate to total knee arthroplasty in 20 patients with Kellgren Lawrence grade 3 or 4 OA treated with a single MFAT injection without concomitant procedures (9). The current study found a slightly higher 1-year conversion rate of 24.2% among those with Kellgren Lawrence grades 3 and 4. The discrepancy in conversion rates between these studies for patients with more severe OA may be explained by the moderate to poor inter-observer reliability of the Kellgren-Lawrence classification (25). Furthermore, patients in this study were typically offered MFAT injection after exhausting other non-operative treatment, potentially increasing the conversion rate to knee arthroplasty compared to that found by Hudetz *et al.* (9).

In the current study, no baseline characteristics provided insight into which patients may benefit most from MFAT. The rate of conversion to knee arthroplasty was independent of age, BMI, sex, Kellgren Lawrence grade, pre-operative KOOS JR scores, and lipoaspirate volume. However, patients who converted tended to have more severe OA with approximately 75% classified as Kellgren Lawrence grade 3 or 4. Those who converted to knee arthroplasty had a significantly lower KOOS JR score at 1 year but no significant difference at any other time point. This suggests that patients who converted to a knee arthroplasty within the second year of follow-up might have experienced a plateau or drop in clinical outcomes at 1 year. A previous study by Jo *et al.* found that peak clinical outcomes tended to decline as early as 1 year after an intra-articular injection of cultured ADSC (10). Longer term studies are warranted to further evaluate this trend with MFAT.

It is difficult to interpret the clinical importance of the improvement in patient-reported outcomes in the current data due to the lack of a well-established MCID for both KOOS JR and SF-12 physical and mental components. KOOS JR survey was used because it is a valid and reliable alternative to KOOS for patients with knee OA and reduces respondent burden (26). However, the reported MCID values for both patient-reported outcome tools are dependent on the method used (20, 25). Hung *et al.* found a wide range of MCID values for KOOS JR among patients with hip and knee pathology (21). The anchor-based approach, which relates to patient reports of change, found an MCID range between 14.51 and 18.85. Receiver operating characteristic curve analysis, which maximizes sensitivity and specificity of the instrument, identified cutoff points ranging from 2.21 to 8.16. The distribution-based method, which relates to statistical precision, resulted in an MCID range between 20.84 and 40.67. The median MCID value including data from both anchor-based and distribution-based methods was 15.1 (21). The investigators suggested that the lowest MCID value could potentially be used for screening purposes, whereas the highest values provide assurance that clinically important change has occurred. Use of the median MCID value was suggested (21). Our mean 1-year KOOS JR score was below that median MCID, suggesting that this improvement may not be clinically important.

Evaluating the efficacy of MFAT is dependent on defining the goals of treatment, whether to avoid knee arthroplasty or to provide symptomatic improvement while delaying the need for additional treatment. An overall 32.1% conversion rate likely indicates an unsuccessful treatment if the goal is to circumvent the need for arthroplasty. If the goal is to

delay surgical intervention, like other current nonoperative treatments, then an 18% 1-year conversion rate with an associated improvement in pain and function may indicate an efficacious treatment. Future studies should focus on the time to surgical intervention, as a proxy for pain reduction and disease progression, to further evaluate the efficacy of MFAT as a temporizing agent. Moreover, it is important to consider the high cost of MFAT. Future comparative studies are needed to evaluate the cost-benefit of this treatment. The main limitation of this study is its retrospective design and a lack of control group. A comparison group with placebo or standard treatment may have provided more information on the efficacy of MFAT injection in treating and managing knee OA. The study did not evaluate lipoaspirates in terms of the cell type or count but merely volume. Moreover, there was no standardization of volume or concentration of the MFAT injection. Patients might have undergone knee arthroplasty or received an additional intra-articular injection from an outside provider. However, it is likely that this information would have been noted at the patient's 1-year clinical follow-up. The study population was relatively small and heterogeneous in terms of osteoarthritis severity, with a small number of patients for each Kellgren Lawrence grade. Larger studies stratified based on Kellgren Lawrence grade are needed to assess whether there is an association between severity of OA and conversion to arthroplasty.

CONCLUSIONS

In conclusion, we found a high rate of conversion to knee arthroplasty following a single intra-articular injection of MFAT in patients with symptomatic knee osteoarthritis, while observing a statistically significant improvement in knee pain, stiffness, and function during mid-term follow-up. These results suggest that if treatment with MFAT is offered to patients with knee osteoarthritis, it should be described as a potential nonoperative treatment option with the aim of providing temporary relief of symptoms, despite the potential regenerative properties. These results can assist the treating physician in managing patient expectations from this treatment. Comparative clinical studies are needed to further assess the efficacy of MFAT against well-accepted nonoperative treatments for knee osteoarthritis.

FUNDINGS

None.

DATA AVAILABILITY

Data are available under reasonable request to the corresponding author.

CONTRIBUTIONS

MRM, JL: design of work, acquisition and interpretation of data. MRM: manuscript preparation. JL, KLM, SD, HB: manuscript revisions. KLM: acquisition of data. SD: data analysis. HB: conceptualization. SD, HB: data interpretation.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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