Short Communication

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Regenerative Medicine

An observational study evaluating the efficacy of microfragmented adipose tissue in the treatment of osteoarthritis

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Aim: Osteoarthritis (OA) prevalence is increased in ageing and obese populations. This prospective single-arm cohort study aimed to investigate the efficacy of autologous microfragmented adipose tissue treatment of severe knee or shoulder OA. **Materials & methods:** Participants received an intra-articular microfragmented adipose tissue injection to the affected joint(s). Multiple patient reported outcome measures (PROMS) were recorded from 0 to 52 weeks for 63 consecutive joints. **Results:** Compared with baseline, there were significant improvements in all PROMS from 2 to 12 weeks and maintained at 52 weeks. Regression analysis revealed an inverse correlation with BMI and change in PROMS for knee joints. **Conclusion:** Our observed findings suggest this approach represents a safe, effective treatment for moderate-to-severe knee and shoulder OA, although efficacy may be reduced with increasing obesity.

Plain language summary: Swelling and pain in the joints is common and found more often in older and overweight people. Osteoarthritis causes swelling and pain in joints because of a loss of tough, flexible tissue called cartilage. This study looks to see if injection of fat tissue into knee or shoulder joints can improve symptoms. The fat tissue used was called microfragmented adipose tissue (MFAT). This uses a technique to break down the fat tissue before injection. These cells were from the patient's own body.

All patients had an injection of MFAT into their painful joints. In total, 59 patients took part. Reports were directly collected from the patient of how well they were doing. This was done before and after the injection at weeks 2, 6, 12, 24 and 52. There were three different types of report collected for knee joints and three for shoulder joints. Scores were then compared from these reports to see if there was a difference.

An improvement was found in all three of the combined reports for both knees and shoulders. This stayed until 52 weeks. BMI is a measure of body weight in relation to height. Patients with a higher BMI were found to have had a smaller improvement in their scores.

This study shows MFAT injections are safe and effective in treating painful joints.

Tweetable abstract: A microfragmented adipose tissue injection to the shoulder or knee of osteoarthritis patients offers a safe and effective treatment in moderate-to-severe disease, with reduced efficacy at increased BMIs.

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Keywords: adipose-derived stem cells • adipose tissue • Lipogems • mesenchymal stem cells • osteoarthritis

Osteoarthritis (OA) is a prevalent disease characterized by progressive loss of articular cartilage, as well as pathophysiological changes to the subchondral bone [1]. OA is increasingly prevalent with age, and presents a significant burden on worldwide healthcare services, with one in ten adults having symptomatic OA in the UK [2]. The

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pathogenesis of OA is not simply one of 'wear and tear'. While physical forces are involved in the initial cartilage disruption, the ongoing loss of cartilage reflects a loss of balance between the repair mechanisms, resulting in a dysregulated, proinflammatory state, leading to abnormal bony remodeling and further cartilage erosion [3]. Clinically, this presents with pain worsened by exertion, stiffness, joint deformation and over time, significant impingements on functional status [3].

Current treatment options include simple analgesia such as NSAIDs, physiotherapy, intra-articular corticosteroids and various surgical interventions as a last resort. All these treatment options have limitations. For example, surgery is highly invasive and has mixed functional outcomes in patients with some studies reporting ongoing pain following joint replacement [3–5]. Furthermore, there are several patient factors which make surgery increasingly less appropriate such as the possible need for joint revision in younger patients [6]. Thus, there is an increasing call for alternative effective treatment options.

The use of orthobiologic treatments such as platelet-rich plasma have emerged as viable and effective treatment options. For example, meta-analysis suggests greater benefit of platelet-rich plasma on pain relief and functional improvement in patients with symptomatic knee OA compared with hyaluronic acid [7]. Another alternative promising treatment is intra-articular injection of mesenchymal stem cells (MSCs). While the exact mechanism of action for MSCs remains unclear, MSCs appear to enhance regenerative pathways in OA [8–11]. Nevertheless, the broad mechanisms of MSCs may be considered as paracrine secretion of antiscarring, anti-apoptotic, angiogenic and trophic cytokines, thereby creating regenerative extracellular matrices; modulation of immune cell function through cell-to-cell contact, as well as possible chondrocyte differentiation [8–11]. Bearing this in mind, and coupled with their minimal differentiation, some have advocated for MSCs to be re-named 'medicinal signaling cells' [12–14]. Overall, the prevailing mechanism of action for MSCs in OA appears to relate to the promotion of immunomodulatory pathways and restoring joint homeostasis [8,9,11].

Historically, bone marrow stem cells were the preferred source for harvesting MSCs. An alternative source of MSCs is adipose tissue. Beyond MSCs, other adipose tissue components may promote repair. First, it is a reservoir for stromal progenitors such as pericytes, endothelial and immunoregulatory cells which may contribute to regenerative and repair processes [15,16]. Second, its extracellular matrix may act as a scaffold for regeneration [15,16]. Understanding this and given the higher MSC yield, faster cell proliferation, and relative ease of harvesting, adipose tissue has become the preferred source for MSCs [17]. There are several methods to obtain adipose-derived MSCs. Given the key regulatory and economic issues of cell culture techniques, other techniques have been developed [15,16]. One such technique is microfragmented adipose tissue (MFAT). Principally, the method avoids the use of enzymes, additives or centrifugation, instead utilizing mechanical forces to isolate and break down the adipose tissue [18]. MFAT therefore maintains the micro-architecture of adipose tissue; thereby, maximizing MSC capacity but also crucially preserving these additionally mentioned adipose tissue components that may mediate the cartilage tissue repair response [18,19]. For example, use of MFAT has been shown to secrete more growth factors and cytokines relative to cultured stromal vascular fraction and the preserved pericytes were implicated [19]. The technique has garnered widespread utilization in a plethora of medical specialties including general surgery, orthopedic surgery, plastic reconstructive and aesthetic surgery, as well as oral-maxillofacial surgery [10]. Within orthopedic surgery, there is an increasing interest for its use in degenerative conditions, such as OA, where it has been shown to be efficacious [8]. For example, in several prospective studies safely utilizing MFAT in OA patients, there has been positive patient outcomes, with decreases in size of cartilage defects, improved joint function and reduction in pain all reported [20–23]. The primary aim of this observational study was to evaluate the efficacy of a singular MFAT injection in OA joints affecting the knee and shoulder. The secondary aim was to explore whether efficacy was affected by age, sex or BMI.

Materials & methods

This clinical study was conducted in accordance with the principles of Good Clinical Practice (NIHR), the Declaration of Helsinki, and the General Medical Council (GMC) guidelines on research. All participants gave informed consent to participate in this research and for future publication of the findings. This study received approval from the institutional review board by the MSK research ethics committee (MSK002101).

A total of 59 consecutive patients from a private clinic in the UK were treated between October 2018 and January 2020. All patients had moderate-to severe OA affecting either the shoulder or knee (staged radiologically as Kellgren and Lawrence (KL) stage 3 or 4) (Table 1 & 2).

Table 1. Baseline characteristics of participants and knee joints.

	Male	Female	Combined
Patients (n)	28	18	46
Age (yrs)	67.1 ± 1.5 (44 / 82)	66.7 ± 1.1 (57 / 78)	66.9 ± 1.0 (44 / 82)
BMI (kg/m^2)	30.0 ± 1.1 (20 / 40)	34.8 ± 1.6 (23 / 48)†	32.0 ± 1.0 (20 / 48)
Joints (n)	29	21	50
Right (n)	10	8	18
Left (n)	19	13	32
Bilateral	1	3	4
KL stage 3	3	0	3
KL stage 4	26	21	47

†p = 0.0115 female vs male BMI (unpaired t test).
Age and BMI are presented as mean ± SEM with minimum/maximum in parentheses.
KL: Kellgren and Lawrence.

Table 2. Baseline characteristics of participants and shoulder joints.

	Male	Female	Combined
Patients (n)	4	9	13
Age (yrs)	61.3 ± 5.8 (44 / 68)	65.4 ± 2.4 (52 / 72)	64.2 ± 2.4 (44 / 72)
BMI (kg/m^2)	33.3 ± 2.3 (30 / 40)	28.7 ± 2.1 (22 / 43)	30.1 ± 1.7 (22 / 43)
Right (n)	1	3	4
Left (n)	3	6	9
KL stage 3	2	2	4
KL stage 4	2	7	9

Age and BMI are presented as mean ± SEM with minimum/maximum in parentheses.
KL: Kellgren and Lawrence.

Following normal clinical procedures and an informed consenting process, patients were treated with a singular intra-articular autologous MFAT injection to either the knee or shoulder. 63 joints were injected in total with 50 knee joints and 13 shoulder joints injected. In four patients, injections to the knee were bilateral. The surgical method and MFAT injections were standardized as detailed below.

Obtaining the lipoaspirate

The Lipogems® procedure was performed according to the manufacturer's guidance using the prepacked Lipogems orthokit [24]. First, 5 ml of 1% lidocaine was injected to the subcutaneous tissue below the umbilicus with the patient in a supine position after preparing the surgical field in an aseptic manner. Then, a small incision was made with a size 15 blade, while a 17G blunt cannula connected to a Luer Lock 60 ml syringe was used to introduce a premixed solution (containing 1000 ml Hartmann's solution, 20 ml lidocaine 2%, 20 ml Marcaine 0.5% and 1 ml adrenaline 1:1000) into the subcutaneous fat. Approximately, 200 ml of this solution was injected in 50 ml aliquots into the lower abdominal area. Fat was then harvested manually via a 13G blunt cannula connected to a vaclock 20 ml syringe from the Lipogems kit. The fat was then transferred to a 50 ml syringe and any excess solutions were drained. Following this, the abdominal wound was closed with a steri-strip and tissue glue and a dressing was applied.

Processing & injecting the lipoaspirate

The lipoaspirate was processed using the closed Lipogems system. In brief, the lipoaspirate was injected into a transparent cylindrical container containing stainless steel ball bearings prefilled with Hartman solution through a stainless-steel wire mesh. The lipoaspirate was then subjected to mechanical agitation through a manual up and down motion to progressively reduce the size of the adipose tissue fragments. The container was then flushed with Hartman solution and the resulting product filtered through a 500 micron filter steel mesh. 50 ml of lipoaspirate typically produces 6–8 ml of MFAT/Lipogems. About 6–8 ml of the final MFAT product was then directly injected as per the manufacturer's guidelines into the affected joint under ultrasound guidance using aseptic technique.

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Participant reported outcome measures

Participant reported outcome measures (PROMS) were collected for all patients at baseline, weeks 2, 6, 12, 24 and 52. Patients who received MFAT injection to the knee, completed the visual analogue score (VAS), Oxford Knee Score and the Tegner Lysholm Knee Scoring Scale. For patients who received MFAT injection to the shoulder, the VAS, The Disabilities of the Arm, Shoulder and Hand Score (QuickDash), and the Oxford Shoulder Score were recorded. 57 patients completed their own scores during routine, nurse led follow-up at clinic. Two patients were unable to attend clinic for follow-up. Their scores were completed via telephone call by a clinic nurse who was blinded to the results of the original PROMS.

Statistical analysis

Statistical analysis was performed using GraphPad PRISM (version 9.2). All datasets were tested for normality using the Anderson–Darling test which revealed all were non-normally distributed (i.e., alpha <0.05). Mixed effects analysis followed by Tukey's multiple comparisons test was used for knee joints. A last observation carried forward approach was employed for Figure 1 where total knee reconstruction was performed on six joints (total knee reconstruction was made freely available to the patients through the NHS during the study period). Analysis for shoulder joints was performed using Friedman test followed by Dunn's multiple comparisons test.

Results

Knee joint outcomes

At the outset of the study 50 knee joints from 46 patients (28 male, 18 female, four bilateral treatments) were included. The BMI of females was significantly higher than that of males (Table 1).

Semi-quantitative data, showing the individual PROMS for each joint from baseline and weeks 2, 6, 12, 24 and 52 are presented in Figure 1A, C & D. More quantitative data, showing median scores and statistical analysis, are presented in Figure 1B, D & F. There was a significant reduction in VAS and a significant increase in the Lysholm score at 2 weeks (both $p < .005$) while a significant increase in the Oxford Knee score was not observed until 6 weeks ($p < .0001$). Improvements across all three PROMS peaked at 12–24 weeks and was maintained at 52 weeks with VAS decreased by 4 points (44%), the Lysholm Score increased by 24 points (63%), and the Oxford Knee score increased by 10 points (33%) at this time (all $p < .0001$). Improvement in the VAS, and to a lesser extent the Lysholm score, regressed from 24 to 52 weeks although these changes failed to reach significance. While there was no relationship between any of the PROMS and gender, age or KL stage the improvement in VAS and Lysholm scores correlated inversely with BMI at 52 weeks (both $p < 0.05$).

Shoulder joint outcomes

There were 13 shoulder joints from 13 patients included in the study (four male and nine female [Table 2]).

Individual and combined PROMS are presented in Figure 2. Significant improvements were observed in combined PROMS with changes in VAS becoming significant from 6 weeks ($p < 0.05$) and DASH and Oxford Shoulder Scores from 12 weeks (both $p < 0.0005$). Improvements typically peaked at 24 weeks and were maintained at 52 weeks for the DASH and Oxford Shoulder Scores, with the former decreased by 31 points (39%) and the latter increased by 21 points (150%) compared with baseline (both $p < 0.0001$). At 52 weeks the VAS was reduced by 3 points (38%) compared with baseline ($p < 0.0001$) and showed a nonsignificant regression in improvement from 24 to 52 weeks, similar to that observed for VAS in knees.

Discussion

OA represents an increasing burden within healthcare and orthopedics reflecting the rising rates of obesity and aging of populations. Cell-based therapies, using MSCs, have emerged as treatments with proven efficacy in OA [25]. For example, two recent RCTs in patients with mild-to-moderate knee OA (KL grade 1–3) demonstrated significant benefits, including improvements in pain, quality of life (SF-36) and cartilage regeneration (MRI), following injection of adipose derived MSCs [25,26].

The current study shows a significant improvement in all measured PROMs following a single intra-articular MFAT injection to knee or shoulder joints with moderate-to-severe OA (KL grade 3 or 4) out to 52 weeks. This contributes to the growing body of evidence supporting the use of MFAT in the treatment of OA [18,20–23,27,28]. A recent study, employing a single-dose MFAT injection (also using Lipogems) in relatively elderly patients (average 69.6 years) with mild-to-severe knee OA (KL grade 2–4) reported significant improvements in all measures out to

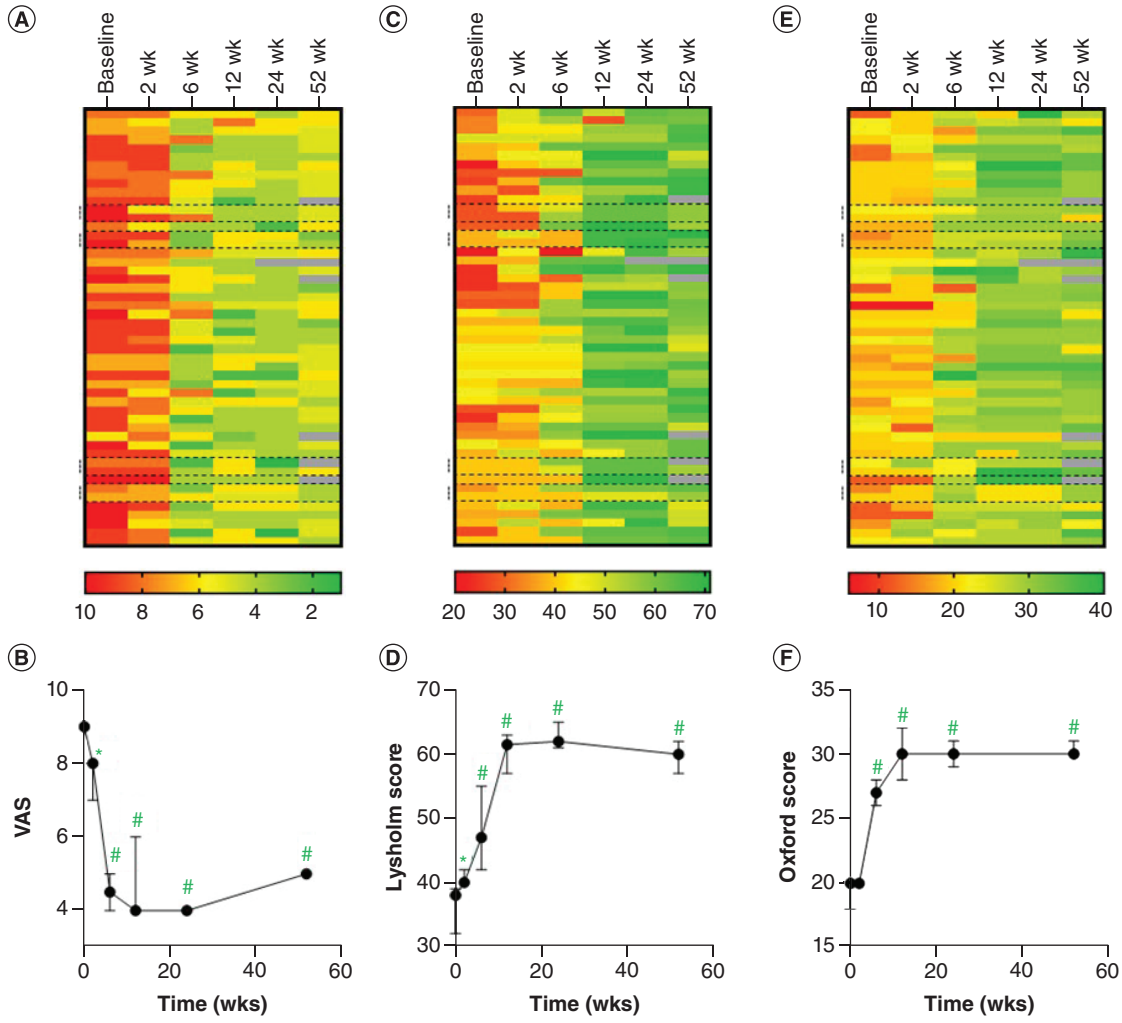

Figure 1. Individual and group changes following microfragmented adipose tissue treatment of osteoarthritis knees. (A, C & E) Show heat maps of individual participant VAS, Lysholm and Oxford Scores at the indicated times. Individual participant responses are presented from lowest to highest BMI (22–48 respectively), from top to bottom. Scale bars are shown below and define the range observed across each score. The response of four participants who each underwent bilateral treatment are highlighted within the dotted lines. Participants who underwent total knee reconstruction during the follow-up-period are indicated in grey. **(B, D & F)** Depict median ± 95% CIs. Statistical analysis was performed using Repeated Measures One way ANOVA followed by Tukey's multiple comparisons test. *$p < 0.005$, #$p < 0.0001$ compared with week 0 ($n = 50$).
VAS: Visual analogue score.

2 years [22]. It is noteworthy that the temporal profiles of changes in pain scores (KOOS-Pain) were similar across KL grades 2–4 at both 6 and 12 months but diverged at 24 months, with scores improving for KL2 but regressing for KL4 [22].

In the present study, where 47 (94%) of the knee joints treated had severe OA (KL grade 4), we observed a significant inverse correlation between BMI and changes in VAS and Lysholm scores from 24 to 52 weeks. Diverging data at 24 weeks supports previous findings that repeated stem cell injections may provide better long-term effects in OA [23]. While the underlying mechanism(s) for these observations is currently unknown. There are several possible explanations. For example, it may reflect the more demanding physical challenges given patients with higher BMI place increased biomechanical stress on their joints and higher BMI predicts OA progression and perceived OA severity in some joints [29–31]; it may also be indicative of a more hostile, proinflammatory environment in patients with higher BMI; it may also represent fundamental differences in the capacity of the MFAT from patients with higher BMI to mediate the beneficial changes necessary to afford such mid-to-long term improvements. Indeed,

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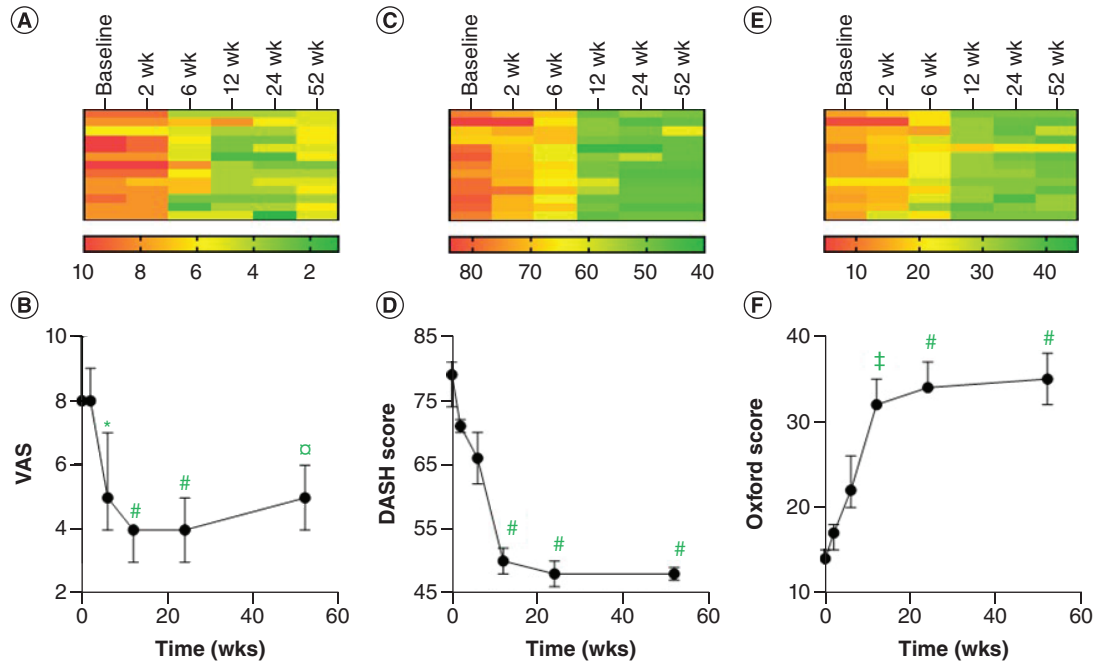

Figure 2. Individual and group changes following microfragmented adipose tissue treatment of osteoarthritis shoulders. (A, C & E) Show heat maps of individual participant VAS, DASH and Oxford Scores at the indicated times. Individual participant responses are presented from lowest to highest BMI (22–43, respectively) from top to bottom. Scale bars are shown below and define the range observed across each score. **(B, D & F)** Depict median ± 95% CIs. Statistical analysis was performed using Friedman test followed by Dunn's multiple comparisons test.
*$p < 0.05$, $p < 0.005$, ‡$p < 0.0005$, #$p < 0.0001$ compared with week 0 (n = 13).
VAS: Visual analogue score.

evidence indicates that stem cell content, immunomodulation, function and differentiation capacity are altered by factors including age, sex and obesity/BMI [32–34]. Further, more detailed investigations are required to define the cellular and molecular characteristics of the MFAT samples stratified by BMI, which were beyond the scope of this observational study.

While a relatively small study, our findings showing efficacy of MFAT to treat moderate-to-severe shoulder OA (KL grade 3 and 4) extend published reports demonstrating that MFAT is efficacious in patients with mild-to-moderate shoulder OA (KL grade 2 and 3) [35].

Safety concerns will naturally be present for new techniques and procedures. There are some theoretical risks such as infection or bleeding similar to those for other intramuscular (IM) injections [36]. In Pas *et al.*'s review of stem cell injections for knee OA in randomized and non randomized trials, adverse events were reported in four studies with no serious adverse events reported in follow-up to 24 months [37]. Furthermore, a recent systematic review concluded that MSC therapy exhibits a favorable safety profile [38].

There are several limitations to the present study. First, while a 1 year study allows conclusions to be drawn about the early to mid-term efficacy of MFAT treatment, a longer study would allow interpretation of the sustained outcomes following treatment with MFAT. Second, as has been highlighted in recent reviews, the absence of a control group precludes the comparison of outcomes following MFAT treatment with other alternative treatments [37,39]. Third, while recording of multiple PROMs (covering pain and function) has advantages, the lack of any measurements of biological markers, such as repeat MRI to determine cartilage repair, fails to provide independent validation and capture mechanistic details. Furthermore, the use of PROMS in a self-selected unblinded patient group who have actively sought MFAT treatment for OA exposes the study to a range of possible bias including selection bias around the patient group, as well as bias surrounding PROMs measurements that are inherently subjective. Investigations of the placebo effect have revealed particularly profound outcomes in relieving subjective symptoms including pain, with expectation of symptom improvement, psychosocial forces, and mental cueing all implicated in perceptual processes that result from the treatment procedure [40–43]. Indeed, the use of PROMs in clinical research is increasingly debated within the literature [44]. Finally, a lack of MFAT injection

analysis limits the ability to conclude stem cells and MSCs explain the positive clinical benefits as no verification of MSC content took place.

Notwithstanding, a strength of this report is the relatively large number of knee joints with severe OA (KL grade 4) included. This has enabled us to conclude that intra-articular injection of MFAT represents a safe and effective treatment for severe knee OA and identify a potential negative effect of BMI on mid-term outcomes. Further studies, potentially including reanalysis of data from studies where BMI was not originally considered in the analysis, should be performed to investigate this.

Conclusion

In conclusion, this novel study is the first to correlate patient demographics, such as BMI and gender, to clinical outcomes, following intra-articular MFAT injection. Overall, multiple validated PROMs were utilized to demonstrate efficacy of a single intra-articular MFAT injection with moderate severe OA affecting the knee or shoulder. This study builds on the growing body of evidence supporting use of MFAT in OA.

Summary points

- Present medical and surgical management of osteoarthritis (OA) have mixed outcomes for patients.
- Microfragmented adipose tissue (MFAT) is a clinic-based method that maintains adipose tissue micro-architecture allowing high yield of adipose-derived mesenchymal stem cells as well as providing other regenerative components of adipose tissue.
- This year-long study used multiple validated Patient Related Outcome Measures (PROMs) to assess the efficacy of a single intra-articular MFAT injection with moderate-to-severe OA affecting the knee or shoulder.
- The PROMs were clinically appropriate for the joint and included: the visual analogue score, Oxford Knee Score, the Tegner Lysholm Knee Scoring Scale, The disabilities of the Arm, Shoulder and Hand Score (QuickDash) and the Oxford Shoulder Score were recorded.
- There were statistically significant improvements in all PROMs from 2 to 12 weeks and maintained at 52 weeks.
- Additionally, regression analysis revealed an inverse correlation with BMI and change in PROMS for knee joints. This may suggest decreased effectiveness of mesenchymal stem cells with raised BMIs.
- Intra-articular MFAT injection represents a safe and efficacious treatment for moderate-to-severe knee and shoulder OA.

Author contributions

F Fan was responsible for production and revision of the manuscript. RA Grant contributed significantly to production and revision of the manuscript. JP Whitehead contributed to analysis and interpretation of the data. A Yewlett and PYF Lee designed and acquired the data as well as revising and approving the manuscript.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending or royalties.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval from the MSK research ethics committee (MSK002101) for all human experimental investigations. In addition, for investigations involving human subjects, verbal and written informed consent has been obtained from the participants involved.

Data sharing statement

The authors certify that this manuscript reports original clinical trial data. Deidentified, individual data that underlie the results reported in this article (text, tables, figures and appendices) are available from the corresponding author from the date of publication until May 2027. The PROMS scores, study timeline and study questionnaire are available for the purpose of meta-analyses.

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