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INVITED PAPERS

Two-year clinical outcomes of autologous microfragmented adipose tissue in elderly patients with knee osteoarthritis: a multi-centric, international study

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Abstract

Purpose The aim of this study is to evaluate the outcomes of autologous microfragmented adipose tissue (MFAT) injection in elderly patients with knee osteoarthritis (OA). We hypothesized that MFAT knee infiltration for the treatment of knee OA would yield good clinical results out to two years follow-up.

Methods Multi-centric, international, open-label study conducted by orthopedic surgery, and/or regenerative medicine facilities utilizing patient registries. Subjects recruited for eligibility. The primary outcome measure was Knee Injury and Osteoarthritis Outcome Score (KOOS). Outcomes and patient factors were compared to baseline, at six, 12, and 24 months. Statistical models were used to assess KOOS subscores and probability of exceeding the Minimally Clinically Important Difference (MCID) or Patient Acceptable Symptom State (PASS), and to assess the effect of the treatment variables on KOOS - Pain.

Results Seventy-five patients, 120 primary treatments, mean age 69.6 years, (95%CI 68.3–70.9), BMI 28.4 (95%CI 27.3–29.6), with KL grade 2 to 4 knee OA treated with a single MFAT injection. KL grades 2 (15.1%), 3 (56.3%), and 4 (28.6%), with 20.8% of knees having previously undergone surgery. Patients with KL grade 2 disease had the best results in KOOS - Pain ($P = 0.001$), at six, 12, and 24 months. Including advanced KL grade 3 and 4 osteoarthritis patients, significant functional and quality of life success was seen in 106/120 treatments (88.3%, 66 patients) at all follow-up time points. Fourteen treatments (11.7%, 9 patients) failed prior to the study endpoint.

Conclusion This study shows that a single-dose MFAT injection leads to clinical, functional, and quality of life improvement at two years in elderly patients, in KL grades 2 to 4 of knee osteoarthritis. These findings provide evidence that this treatment modality could be a safe and effective option to other commonly available treatments in carefully selected patients.

Keywords Adipose-derived cell therapy · Autologous microfragmented adipose tissue · Knee osteoarthritis · MFAT · OA · Bio-orthopaedics · Orthobiologics

Introduction

Knee osteoarthritis (OA) is the most common joint disease worldwide, causing pain and significant disability in the elderly population. In a recent study, it was estimated that more than 14 million people in the USA have symptomatic knee OA [1]. According to the latest Framingham study where the prevalence of knee OA was examined based on magnetic resonance imaging (MRI), they found evidence of knee OA in 86% of the population who are in their sixth decade and the incidence rose to 91% in people who are in their seventh decade, which suggest aging as a strong risk factor of OA [2]. The relationship between osteoarthritis of the knee and aging is due to oxidative damage and decline in basic tissue

Level of Evidence: Level 4

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homeostasis leading to inadequate response to stress, joint injury, and thinning of the cartilage [3]. Despite the fact that there are various conservative therapies (NSAIDs, topical anti-inflammatory gels, corticosteroids, physical therapy) for the management of early knee OA, these treatments provide short-term effects side effects, systemic, or local [4]. One of the primary foci of research in the last decade has been the regenerative cellular therapy (primarily mesenchymal stem cells and growth factors). Several studies propose these therapies not only to provide symptomatic relief but also to create an environment to repair the joint [5, 6].

The role of autologous microfragmented adipose tissue (MFAT) in the treatment of cartilage defects and osteoarthritis has been studied by several authors in various preclinical and clinical animal studies. These experimental animal studies have established the ability of these cells to stimulate cartilage regeneration and improve the symptoms in degenerative cartilage diseases [7, 8]. Following these translation studies, several clinical in vivo human studies have been performed, which have shown promising results in the treatment of osteoarthritis. Knowledge in this field is rapidly advancing, and various forms of MFAT therapy are attracting significant attention as an innovative and promising therapeutic modality.

The purpose of this study is to evaluate the clinical outcomes of a single dose of MFAT injection. It was hypothesized that one MFAT knee infiltration for the treatment of knee OA leads to good clinical results compared with the pre-treatment state and could maintain at two year follow-up and could be an alternative treatment for elderly patients 60 years or older.

Materials and methods

Study design and treatment

The study was a multi-centric, retrospective, open-label study in elderly patients with symptomatic knee osteoarthritis (OA) to assess the efficacy and safety of injected MFAT who met inclusion and exclusion criteria, Table 1. The study was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization Guidance for Good Clinical Practice. The clinical use and the study of autologous MFAT utilizes an approved device for specific use knee OA and was approved by individual registry IRBs at the respective participating centers (ESM 1). All patients provided written informed consent in accordance with local requirements.

Patients

One-hundred thirty-one consecutive patients from five international orthopaedic surgery and/or regenerative medicine treatment centers were recruited and screened for eligibility from September 2014–April 2018. Patients with minimum three months of knee pain and/or swelling and confirmed radiographic or MRI diagnosis of knee osteoarthritis Kellgren-Lawrence grades 2 to 4 as determined by independent musculoskeletal radiologists that met all inclusion and exclusion criteria were included in this study (Table 1) [9]. Standard radiographic evaluation included a standing anteroposterior long-leg radiograph (including hips and ankles), standing anteroposterior and lateral views of the knees, skyline patellofemoral and standing 45° flexion knee views, and/or magnetic resonance imaging (MRI) in all patients. Forty-four patients underwent simultaneous bilateral injections based on clinical symptomatology, see patient flow diagram (Fig. 1).

Table 1 Inclusion and exclusion criteria

	Inclusion criteria	Exclusion criteria
Study design	• Consecutive patients treated with intra-articular AMAT • Patients recruited • Minimum 24-month follow-up	• Patients surgically treated concomitantly with some other treatment platform or a part of another study • Had knee surgery other than debridement • Excluded surgical procedures included: • Chondroplasty • High tibial osteotomy • Marrow stimulation procedure • Other cellular therapy • Collagen implantation therapy • Implanted simultaneously with scaffold device
Participants	• Human subjects aged ≥ 60 years. • Chronic knee pain or symptoms for at least 3 months • Radiographic and/or MRI confirmation of Kellgren-Lawrence grades 2–4 osteoarthritis of knee joint	• Active infection • Pregnancy • Gout, hyperlipidemia • Inflammatory arthritis • Pathologies of the lower limb which would interfere with the evaluation of osteoarthritis of the knee joint Patients were also excluded if they received in the 6 weeks prior to treatment: • Any intra-articular injections • Had taken any symptomatic slow-acting drugs in osteoarthritis (SYSADOA): oral or topical steroids and/or non-steroidal anti--inflammatories (NSAIDs)

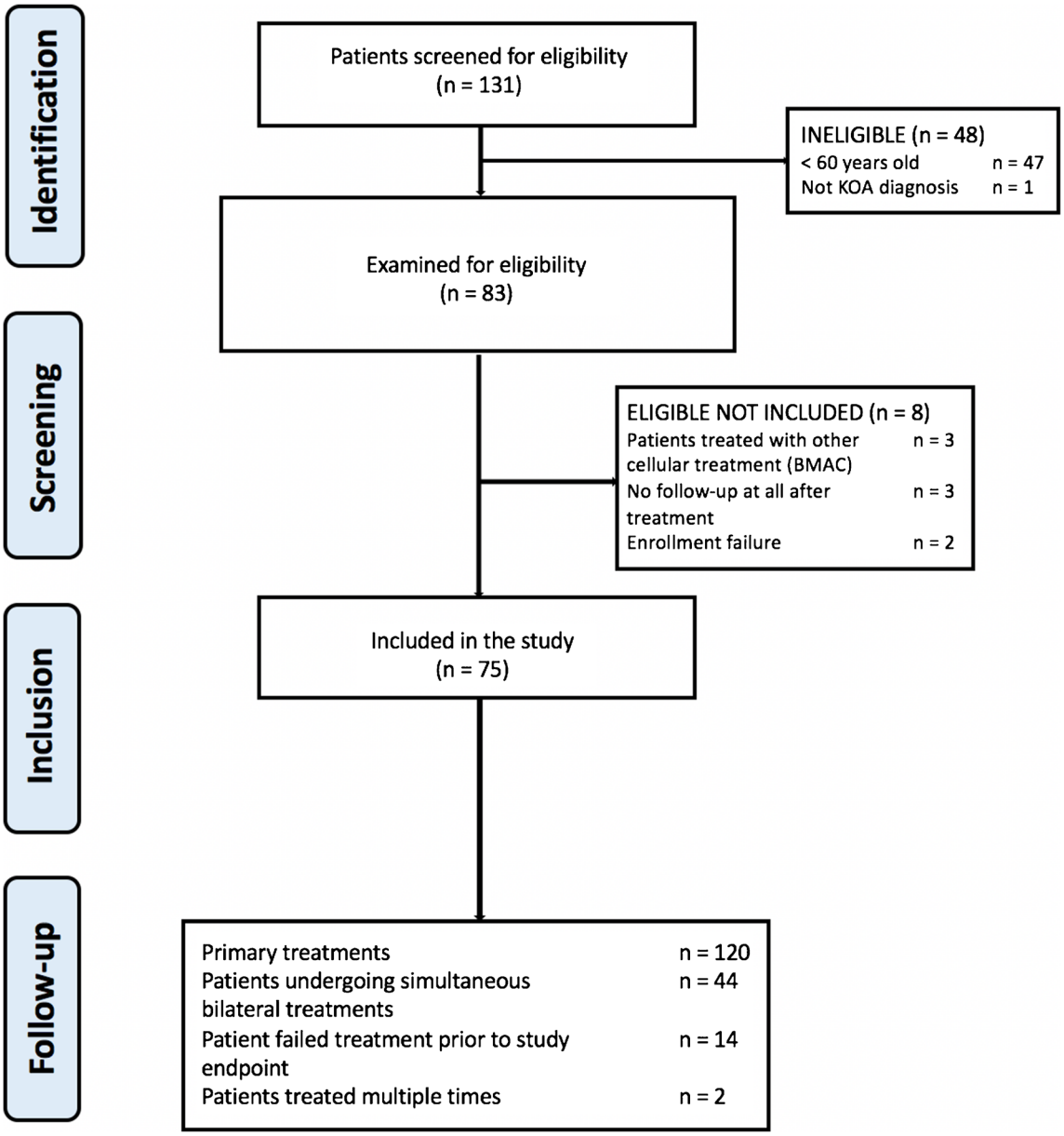

Fig. 1 Flow diagram of a patient undergoing autologous MFAT injection therapy

Autologous microfragmented adipose tissue therapy

MFAT was prepared for all patients, using a kit (Lipogems, Italy). Using aseptic precautions, under local anaesthesia or general anaesthesia, adipose tissue was harvested in either (1) a supine position using an abdominal or (2) prone position using a supra-gluteal lipoharvest procedure. In either approach, the subcutaneous fat was infiltrated with up to 300 ml of tumescent fluid (comprised of 30 ml of 2% lidocaine, 1 ml of 1:1000 adrenaline, and 1 ml of 8.4% bicarbonate suspended in a normal saline solution for a total of 1000 ml). Following this, 60–120 cc of adipose tissue and tumescent fluid was aspirated through a 4 mm lipoaspirate cannula and collected within a sterile medical grade single use Shippert Tissu-Trans Collection filter (Shippert Medical, CO, USA) [10]. The lipoaspirate was transferred directly to a Lipogems device, a closed, full-immersion, low-pressure cylindrical system, to obtain fluid with a concentrated population of pericytes and MSCs [10]. The final product created by this process is quite consistent, characterization of the MFAT injectate has been described elsewhere [10].

Seventy-five patients received one dose of MFAT (Lipogems, Italy) via an ultrasound-guided supra-patellar approach or during surgical procedure under direct arthroscopic control at the discretion of the operating surgeon or multiple injections intra-/extra-articularly [11]. Prior to any procedure, routine blood analysis was carried out before treatment, including complete blood count, coagulation profile, and test

for transmittable diseases at four of five centres. Patients were advised to use ice pack/cold therapy for any knee pain at home and to avoid prolonged walking and standing for 24 hours after injection. Patients were also instructed to use only paracetamol or acetaminophen (1 g up to four times per day) for post-injection pain and to strictly avoid NSAIDs. Post-injection rehabilitation, patients were asked to avoid strenuous exercise and were allowed only non-impact exercises such as walking, cycling, and pool exercises; subsequently, gradual resumption of normal sports or recreational activities was allowed. Supervised physiotherapy and/or knee brace/support was not required.

Assessments

The outcome of treatment was assessed through the following patient-reported outcome measure scores (PROMS): Knee Injury and Osteoarthritis Outcome Score (KOOS), which consists of five subscales: pain, other symptoms, function in activities of daily living (ADL), function in sport and recreation (Sport/Rec), and knee-related quality of life (QOL); and visual analog scale (0 = no pain to 10 = worst possible pain) [12]. All scores were tabulated through questionnaires completed by the patients prior to the commencement of treatment and at six month, 12-month, and 24-month follow-up. Data entry and collection were performed by independent investigators at IRB-approved registries and attendant data collection systems unique to the individual participating centres (ESM 1).

Treatment outcomes

Defined treatment failure is defined as any re-treatment using injection with subsequent MFAT injection or conversion to knee arthroplasty within the two year follow-up period. To further elucidate the effects of treatment and impact of the associated patient condition(s), we calculated minimal clinically important difference (MCID) status for KOOS Pain, symptoms, ADLs, and VAS as reported by Lyman et al. [13] and included in systematic review/meta-analysis by Celik et al. [14].

Cost: outcome considerations to commonly available treatments

A survey among participating facilities was carried out, and the average cost per individual knee treatment with MFAT was calculated. The average cost of knee arthroplasty including rehabilitation was obtained from published references [15, 16].

Analysis

Patient-level data (age, sex, body mass index (BMI), smoking status) was summarized using mean and 95% confidence intervals for continuous variables and counts for categorical variables. Treatment-level data (bilateral status, dosage, previous surgery status, KOOS subscales, time point (pre-treatment 6 months, 12 months, 24 months) was summarized with a similar method. Dosage was recoded to remove outlier treatments (21 cc).

Treatment failure was recoded from notes and defined as any knee undergoing subsequent re-injection or definitive surgical intervention. A binary logistic model (logit link function) was weighted based on the ratio of failure events (1:7) to assess the relationship between KOOS baseline pain, symptoms and quality of life, bilateral status, dosage, previous surgery, age, sex, and BMI with the probability of failure prior to the study endpoint. A mixed-effects model with *PatientID* as a random factor was used to assess the effect of the treatment variables above (with the addition of *time point*) on KOOS - Pain. Post hoc comparisons were performed using Dunnett tests with control.

Responders were defined as those treatments that reported a difference in pre-treatment and 24-month follow-up KOOS scores that exceeded the minimal clinically important difference (> MCID) for the respective subscore as defined by Lyman et al. for patients undergoing total knee arthroplasty [13]. The 24-month follow-up data for KOOS - Pain was also dichotomized to those above or below the patient acceptable symptom state (PASS) defined by Connelly et al., for patients three years after total knee arthroplasty [17]. Binary logistic models (logit link function) were used for both dichotomous outcomes to assess the relationship between baseline KOOS subscores (symptoms, ADL, quality of life) on the probability of exceeding MCID or PASS for KOOS - Pain.

Incremental cost-effective ratios (ICER) were calculated in terms of cost per KOOS - Pain point improvement. The ICER is a summary measure representing an economic value of an intervention compared with an alternative. It is calculated by dividing the difference in total costs (incremental costs) by the difference in outcome measure (incremental effect) to provide a ratio of extra cost per extra unit of health effect for the more expensive treatment versus the alternative [18, 19]. An ICER, unadjusted for covariates, was calculated on *patient direct* costs comparing the MFAT injection to arthroplasty treatment (total or unicompartmental replacement surgery). The cost of treatments was estimated from an average of treatment charges for primary episodes offered by the participating sites in the study.

The effectiveness of the MFAT treatment was determined by the change in the KOOS - Pain subscale established in the present cohort, while previously published results were used to estimate the effectiveness of arthroplasty [13]. The ICER

was performed using a before/after a design that attributed all changes in KOOS - Pain to the intervention (injection or arthroplasty). A sensitivity analysis was not performed. The cost of rehabilitation was also added to the calculations for total knee arthroplasty, but not for injection, as it is not formally recommended as a part of the treatment at any of the participating centres. An average cost of US$10,000 was estimated, to summarize costs associated with varying combinations of inpatient or outpatient rehabilitation delivery as recommended at each participating site [20]. This cost was added in full to the revision procedure cost, but for primary procedures, a take-up rate of 70% was used, as not all patients participate in post-operative rehabilitation programs.

Statistical methods

Statistical analysis (Minitab v18, Minitab Inc., USA), with alpha set a priori at 5% significance and was performed by an independent statistician.

A post hoc power analysis was performed to assess the sample size required to detect an effect equivalent to a Cohen's *d* of 0.4 or a change of 8 points in the KOOS - Pain subscale defined by Lyman et al. [13], with respect to the observed standard deviation of 20. A mixed-effects (repeated measures ANOVA, within-between interaction) model design was entered into GPower (v3.1.1, University of Dusseldorf) with an estimated power of 0.8 and alpha of 0.05 and number of measurements four (pre, 6 m, 12 m, 24 m), correlation between measurements of 0.7 and sphericity correction of 0.9. Given the number of groups of 30, a total of 60 patients was required to detect this change. Therefore, the available records for 75 patients were adequate for purposes of statistical analysis.

Results

Patients

The cohort included 75 patients, predominantly female (65.3%) and non-smoking (80%) with an average age at the treatment of 69.6 years (95%CI 68.3–70.9) and overweight on average (BMI 28.4, 95%CI 27.3–29.6).

A total of 120 primary treatments were assessed with 44 patients undergoing simultaneous bilateral treatments with no differences observed between unilateral versus bilateral patients at baseline or at any follow-up time point (supplementary data). Patients presented with KL grades of 2 (15.1%), 3 (56.3%), and 4 (28.6%), with 20.8% of knees having undergone surgery of some type previously (arthroscopy, meniscus repair, ACL reconstruction, or combination). Baseline KOOS on average were below PASS for pain (52.4, 95%CI 49–55.8), symptoms (54.1, 50.8–57.5), ADL (54.6, 51.1–58.2), sports and recreation (26.7, 22–31.3), and quality of life (29.6, 25.9–33.3). The total score average was 48.4 points (45.3–51.6). Single treatment dosage was distributed between 5 cc (30.8%), 6 cc (18.3%), 7 cc (30%), and 9 cc (17.5%). A small number of treatments comprised 21 cc (3.3%).

Adverse events

The most common adverse event was adipose tissue donor site pain that required non-narcotic analgesic for a mean time of three days in 37 patients (49%) and donor site swelling/bruising that occurred in 21 patients (28%) for a mean time of seven days. The next most common adverse event was prolonged swelling in the knee joint, a mean time of six days, that occurred in ten patients (13%). There were no severe adverse events were not observed in this study.

Treatment failure

A total of 14 treatments (11.7%, 9 patients) failed prior to the study endpoint (24-month follow-up). This subgroup was predominantly male (64.3%), with a mean age of 70.7 years (67–74.5), with a more severe joint disease (KL grades 4–57.1%, 3–35.7%, 2–7.1%) and classed as obese on average with BMI 33.2 (29.7–36.6). Weighted binary logistic regression (ESM 2) revealed that previous surgery, advanced age, increased BMI, and male sex were significant risk factors for treatment failure (Table 2).

Effect of treatment on KOOS - Pain

The dataset was analyzed with failed treatments removed. Follow-up for successful treatments ranged from 24 to 39 months. Patient response rates were 84%, 82.1%, and 92.5% at six, 12, and 24 months respectively. A mixed-effects model explained 61.5% of the variance (adjusted) in KOOS - Pain score, which increased significantly from pre-treatment to six months and remained stable to 24-month follow-up (Fig. 2a) and was significantly affected by KL grade (Fig. 2b) and previous surgery (Fig. 2c). A proportion of the variance in KOOS - Pain overall was explained by *Patient* (40.7%).

Table 2 Model summary for treatment failure prior to study endpoint

	Beta (SE)	Odds ratio (95%CI)	*P* value
Age	0.6 (0.24)	1.1 (1.0–1.2)	0.01
Male	2.8 (0.59)	16.8 (5.3–53.6)	< 0.001
BMI	1.4 (0.27)	1.3 (1.2–1.4)	<0.001
Previous surgery	1.4 (0.55)	4.2 (1.4–12.2)	0.009

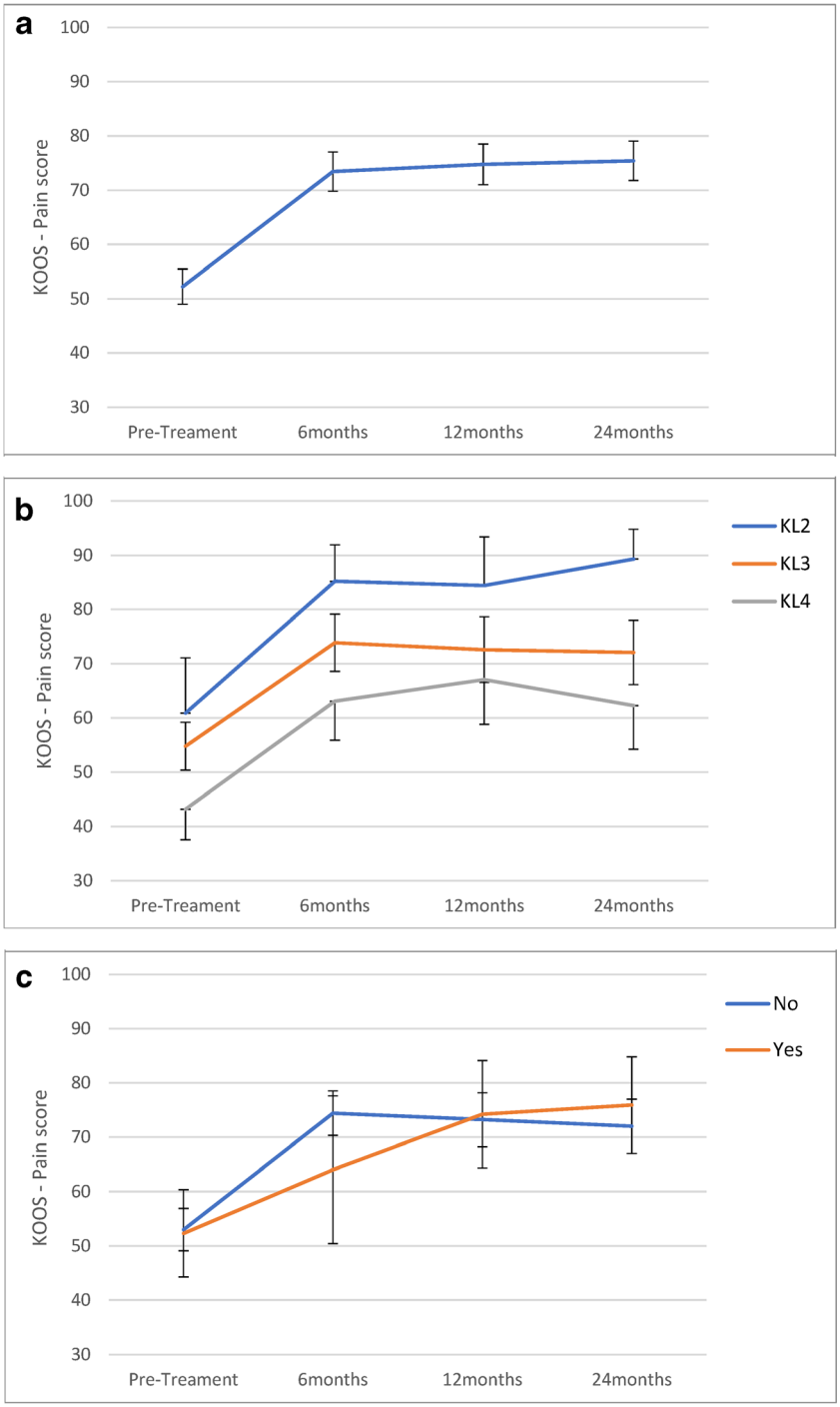

Fig. 2 **a**–**c** KOOS - Pain (mean with 95%CI) by time point for all successful treatments combined (**a**), separated by KL grade (**b**), and by previous surgery status (**c**)

Effect of treatment—responder analysis

In the dataset presented, the incidence of responders (from successful treatments) was noted for pain (65.7%), symptoms (64.8%), ADL (72.4%), and quality of life (74.3.7%). Factors associated with < MCID for KOOS - Pain were identified with binary logistic regression (ESM 2) and included baseline KOOS - ADL and dosage (Table 3). Activities of daily living

Table 3 Model summary for KOOS - Pain < MCID prior to study endpoint

	Beta (SE)	Odds ratio (95%CI)	*P* value
Baseline KOOS-ADL (T0)	0.71 (0.3)	1.04 (1.01–1.07)	0.014
Dosage 9 cc vs 7 cc	− 0.11 (0.96)	0.11 (0.02–0.59)	< 0.001

in particular demonstrated a curvilinear relationship with the probability of < MCID for KOOS - Pain (Fig. 3).

Factors associated with > PASS for KOOS - Pain were identified with binary logistic regression and included baseline KOOS - Pain (OR 1.05, 95%CI 1.02–1.07, $P = 0.001$) and KL grade (OR 4 vs 2 0.22, 0.06–0.86, $P = 0.037$). KL grade in particular demonstrated a curvilinear relationship with the probability of > PASS for KOOS - Pain (Fig. 4).

Cost-effectiveness analysis

The average cost for the MFAT procedures from the five different international centers was $6000. The published average cost for knee arthroplasty averaged for the respective countries is $25,000. The ICER for arthroplasty to achieve an additional point improvement in KOOS - Pain at the two year follow-up was $1825 over MFAT injection; this takes into consideration possible revision injection, surgical revision, and rehabilitation costs within two years of treatment that increases the relative cost of the MFAT procedure to $16,300 and knee arthroplasty to $50,000. The two year post-treatment risk for revision to arthroplasty or repeat injection with MFAT is 12 in 100 patients, whereas the risk for revision total knee arthroplasty is three in 100 patients. Of the twelve patients who failed treatment with MFAT, 5.5 patients (45%) were successfully re-treated with MFAT, and 6.5 patients (55%) were treated with knee arthroplasty. The results are summarized in Supplementary Data 1. The ICER accounted for the risk and additional associated costs of treatment revision and post-TKR rehabilitation with a take-up rate of 70% as not all patients participate in post-operative rehabilitation programs and is summarized in Supplementary Table 1. The incremental cost per patient for revision treatments was added to the base costs for primary treatment.

Discussion

Microfragmented adipose tissue has gained recent popularity as a treatment for orthopaedic conditions. Compared to peripheral blood, adipose tissue has 25,000 times more reparative cells [21]. In the bone marrow, MSCs represent a small fraction (0.001–0.01%) of nonhaematopoietic, multipotent cells [22]. Adipose tissue has been reported to have larger quantities of progenitor cells [23]. The clinical results at 12-month follow-up in the group of MFAT in our study are comparable to the studies in the recent literature. Koh et al. published a therapeutic case-control study of 50 patients with knee OA treated with one dose of 1.89×10^6 adipose-derived cells harvested from the infrapatellar fat pad after arthroscopic debridement and three doses of PRP, compared with 25 patients with three doses of PRP alone. They showed significant improvement in Lysholm, Tegner, and VAS scores in both groups with no significant difference at one year [24]. More recently, Koh et al. analyzed the group of adipose-derived cells at two years and reported that the whole-organ MRI score had significantly improved from 60.0 points to 48.3 points ($P < .001$) particularly in the cartilage which improved from 28.3 points to 21.7 points [25]. In another study of 30 patients with knee OA, Adriani et al. demonstrated significant improvements in pain, quality of life, and function at 12 months after ultrasound-guided injection of autologous microfragmented adipose tissue. Twelve males and 18 females with a mean age of 63.3 years, mean body mass index of 25.1, and without prior treatment over the last 12 months were included in the study. The patients were evaluated at baseline and one, three, six and 12 months after treatment using the visual analog scale (VAS) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).

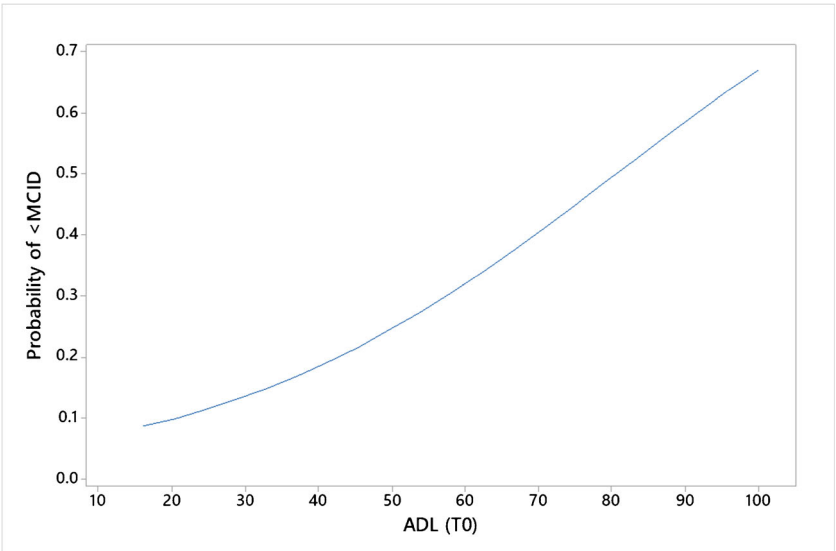

Fig. 3 Main effects of baseline KOOS - ADL on the probability of KOOS - Pain < MCID

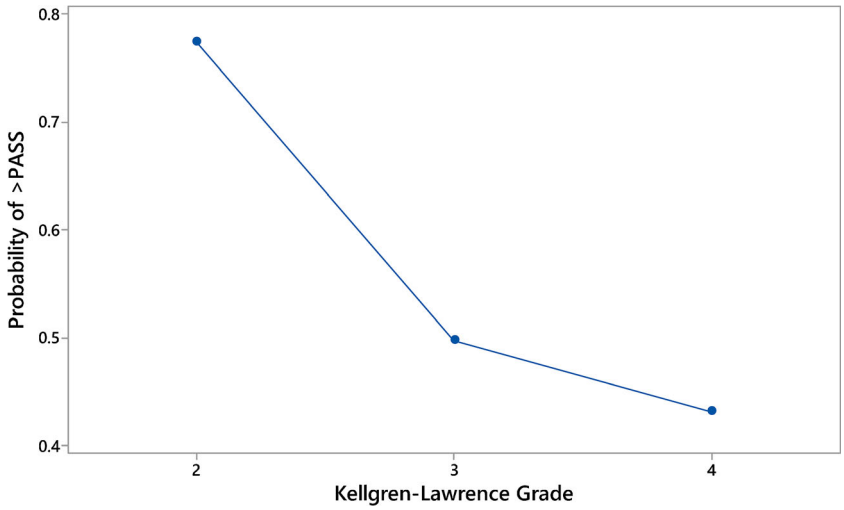

Fig. 4 KL grade compared to the probability of > PASS for KOOS - Pain

The average VAS was 7.7 at baseline and improved to 4.3 at a three month follow-up. However, a slight deterioration (VAS = 5.0) was noted at one year. Total WOMAC score was 89.9 at baseline, 68.6 at three month, and 73.2 at 12-month follow-up [26]. Recently, Russo et al. showed that clinical improvement using autologous microfragmented adipose tissue for the treatment of diffuse degenerative knee osteoarthritis was maintained at three years of follow-up [27]. Finally, this year, Garza et al. published a double-blinded prospective randomized controlled clinical trial of thirty-nine patients with symptomatic knee OA who were treated with a stromal vascular fraction (SVF). They reported significantly decreased knee OA symptoms and pain at six months and one year [28].

In our study, with the average age of subjects being almost 70 years old, our hypothesis is supported by the data that this treatment can be an option for KL grade 2 to 4 knee OA in carefully selected patients, which is consistent with previously published data [29]. A significant improvement in KOOS - Pain was observed between pre-treatment and six months, and this improvement plateaued for up to 24 months thereafter in all grades of knee OA. However, the responder analysis suggested that about one in three patients failed to respond such that those with higher baseline KOOS - ADL were less likely to reach MCID for KOOS - Pain. In other words, patients with higher functional demands may be at increased risk for non-response to therapy. Yet, this bar is set high as the comparator is knee arthroplasty. In addition, the high rate of patients at 24-month follow-up reporting KOOS - Pain scores below PASS, especially in KL grades 3 and 4, suggest that the results observed may not be robust far beyond the endpoint of the study. With PASS as a threshold, it is recommended that further follow-up be conducted at five years to establish the rate of treatment failure (i.e., re-treatment or conversion to knee arthroplasty). That being said, the cost-effectiveness data still suggests that MFAT revision treatment within the five year window may be more cost-effective than total knee arthroplasty within the same time period per point increase in KOOS - Pain.

An intriguing explanation for these results may come from the new vision of Medicinal Signaling Cells (MSC) recently proposed by Caplan. According to this concept, MSCs, rather than participating in tissue formation, work as site-regulated "drugstores" in vivo by releasing trophic and immunomodulatory factors and are activated by local injury [30, 31]. Although promising, these studies have been insufficient to support the efficacy of MFAT therapy to be able to adopt it into standard practices. It is recommended that the use of minimally manipulated cell products and tissue-derived cells be referred to as cell therapy, and the nature of these treatments be clearly understood. Clinicians should consider utilizing the DOSES tool and consider using the Minimum Information for Studies Evaluating Biologics in Orthopaedics to standardize the description of cell therapies so that researchers, regulators, and industry professionals can improve transparency and to allow clinicians and patients to understand the true potential of current and future cellular treatment interventions [32, 33]. It is recommended that physicians and institutions offering biologic therapies establish patient registries for surveillance, cost, and quality assessments [34, 35].

This study has several limitations; the obvious is that the study is retrospective and has no control group, and only presents short-term clinical results. Additional data on treatment failures such as medical comorbidity and more precise timing of failures is recommended for it can provide for long-term survivorship analyses of treatment. More specifically, there is an opportunity to frame the success of the treatment with respect to survival curves up to a minimum of two to five years will assist in framing it as an alternative

procedure to delay knee arthroplasty in appropriate patient and disease category groups.

Additional work is required to compare the performance of the survival curve of the MFAT treatment to *gold standard* nonoperative therapy such as structured physiotherapy programs. In addition, comparison to a control group for patient-reported outcomes and clinical definitions of treatment failure (e.g., MCID, PASS) will help to protect the results against biases such as *regression to the mean*.

Although the follow-up was adequate for the purposes of the present analysis, techniques to deal with missing data, such as imputation, paired with sensitivity analysis should be considered in future analyses. These approaches will assist in protecting against reporting and selection bias with respect to patient follow-up and compliance with patient-reported outcome measures.

Additionally, some patients were treated in both knees at the same time, so the symptoms of one knee could affect the outcome of the analysis of the other knee. More extensive controlled trials with long-term follow-up and biological outcomes are of great interest for future studies.

Conclusion

This study shows that a single-dose MFAT injection leads to clinical, functional, and quality of life improvement at two years in elderly patients, in KL grades 2 to 4 of knee osteoarthritis. These findings provide evidence that this treatment modality could be a safe and effective option to other commonly available treatments in carefully selected patients.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00264-021-04947-0.

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Authors' contributions All authors analyzed and/or interpreted data. All authors collaborated in the drafting and critical revision of the manuscript. All authors approved the final version of the manuscript and vouch for the accuracy of the analysis and the fidelity of the study to the protocol.

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Availability of data and material statement Underlying data from this manuscript may be requested by qualified researchers upon request. Investigators may request access to deidentified patient data and redacted study documents which may include raw datasets, analysis-ready data sets, blank data forms. Prior to the use of data, proposals need to be approved by an independent review panel at www.clinicalstudyrequest.com and a signed data-sharing agreement will need to be executed. Some documents are available in Italian, and others in English.

Declarations

Consent to participate All patients were approved for treatment by written informed consent.

Consent for publication Written informed consent was obtained from all patients.

Competing interests C.R.: Consultant, Lipogems, Inc.; Medical Director and shareholder, Personalized Stem Cells, Inc.; Co-Founder and shareholder, DataBiologics, Inc.

References

1. Deshpande BR, Katz JR, Solomon DH et al (2016) Number of persons with symptomatic knee osteoarthritis in the US: impact of race and ethnicity, age, sex, and obesity. Arthritis Care Res 68: 1743–1750
2. Guermazi A, Niu J, Hayashi D et al (2012) Prevalence of abnormalities in knees detected by MRI in adults without knee osteoarthritis: population based observational study (Framingham osteoarthritis study). BMJ 345:e5339
3. Litwic A, Edwards MH, Dennison EM et al (2013) Epidemiology and burden of osteoarthritis. Br Med Bull 105:185–199
4. Jevsevar DS (2013) Treatment of osteoarthritis of the knee: evidence-based guideline, 2nd edition. J Am Acad Orthop Surg 21:571–576
5. Cerza F, Carnì S, Carcangiu A et al (2012) Comparison between hyaluronic acid and platelet-rich plasma, intra-articular infiltration in the treatment of gonarthrosis. Am J Sports Med 40:2822–2827
6. Gobbi A, Karnatzikos G, Mahajan V et al (2014) Platelet-rich plasma treatment in symptomatic patients with knee osteoarthritis: preliminary results in a group of active patients. Sports Health 4:162–172
7. Ude CC, Sulaiman SB, Min-Hwei N et al (2014) Cartilage regeneration by chondrogenic induced adult stem cells in osteoarthritic sheep model. PLoS One 9:e98770
8. Guercio A, Di Marco P, Casella S et al (2012) Production of canine mesenchymal stem cells from adipose tissue and their application in dogs with chronic osteoarthritis of the humeroradial joints. Cell Biol Int 36:189–194
9. Kellgren JH, Lawrence JS (1957) Radiological assessment of osteoarthrosis. Ann Rheum Dis 16:494–502
10. Tremolada C, Ricordi C, Caplan AI et al (2016) Mesenchymal stem cells in Lipogems, a reverse story: from clinical practice to basic science. Methods Mol Biol 1416:109–122
11. Ulasli AM, Ozcakar L, Murrell WD (2019) Ultrasound imaging and guidance in the management of knee osteoarthritis in regenerative medicine field. J Clin Orthop Trauma 10:24–31
12. Roos EM, Lohmander LS (2003) The Knee Injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. Health Qual Life Outcomes 1:64
13. Lyman S, Lee YY, McLawhorn AS et al (2018) What are the minimal and substantial improvements in the HOOS and KOOS and JR versions after total joint replacement? Clin Orthop Relat Res 476:2432–2441
14. Çelik D, Coban Ö, Kiliçoğlu O (2019) Minimally clinically important difference of commonly used hip-, knee-, foot-, and ankle-specific questionnaires: a systematic review. J Clin Epidemiol 113:44–57
15. Statista from 2018 survey for TKR. Assessed 11.7.2020; https://www.statista.com/statistics/189975/cost-of-a-knee-replacement-in-various-countries/

16. Medical Tourism - 5 Spots for affordable high quality knee replacement.. Assessed 11.7.2020; https://internationalliving.com/medical-tourism-5-spots-for-an-affordable-high-quality-knee-replacement/ cost in Italy $22,729. 2018 newsletter
17. Connelly JW, Galea VP, Rojanasopondist P et al (2019) Patient acceptable symptom state at 1 and 3 years after total knee arthroplasty: thresholds for the Knee Injury and Osteoarthritis Outcome Score (KOOS). J Bone Joint Surg Am 101:995–1003
18. York Health Economics Consortium (2016) Incremental cost-effectiveness ratio (ICER). Assessed 22.7.2020; https://yhec.co.uk/glossary/incremental-cost-effectiveness-ratio-icer/
19. Skou ST, Roos E, Laursen M et al (2020) Cost-effectiveness of total knee replacement in addition to non-surgical treatment: a 2-year outcome from a randomised trial in secondary care in Denmark. BMJ Open 10:e033495
20. Nassar I, Fahey J, Mitchell D (2020) Rapid recovery following hip and knee arthroplasty using local infiltration analgesia: length of stay, rehabilitation protocol and cost savings. ANZ J Surg 90: 355–359
21. Russo A, Screpis D, Di Donato SL et al (2017) Autologous and micro-fragmented adipose tissue for the treatment of diffuse degenerative knee osteoarthritis. J Exp Orthop 4:33
22. Murphy MB, Moncivais M, Caplan AI (2013) Mesenchymal stem cells: environmentally responsive therapeutics for regenerative medicine. Exp Mol Med 45:e54
23. Lopa S, Colombini A, Moretti M et al (2019) Injective mesenchymal stem cell-based treatments for knee osteoarthritis: from mechanisms of action to current clinical evidences. Knee Surg Sports Traumatol Arthrosc 27:2003–2020
24. Koh YG, Choi YJ (2012) Infrapatellar fat pad-derived mesenchymal stem cell therapy for knee osteoarthritis. Knee 19:902–907
25. Koh YG, Jo SB, Kwon OR et al (2013) Mesenchymal stem cell injections improve symptoms of knee osteoarthritis. Arthroscopy 29:748–755
26. Adriani E, Moio M, Di Paola B et al (2017) Percutaneous fat transfer to treat knee osteoarthritis symptoms: preliminary results. Joints 5:89–92
27. Russo A, Screpis D, Di Donato SL et al (2018) Autologous micro-fragmented adipose tissue for the treatment of diffuse degenerative knee osteoarthritis: an update at 3 year follow-up. J Exp Orthop 5: 52
28. Garza JR, Campbell RE, Tjoumakaris FP et al (2020) Clinical efficacy of intra-articular mesenchymal stromal cells for the treatment of knee osteoarthritis: a double-blinded prospective randomized controlled clinical trial. Am J Sports Med 48:588–598
29. Pancha J, Malanga G, Sheinkop M (2018) Safety and efficacy of percutaneous injection of lipogems micro-fractured adipose tissue for osteoarthritic knees. Am J Orthop (Belle Mead NJ) 47. https://doi.org/10.12788/ajo.2018.0098
30. Caplan AI, Correa D (2010) The MSC: an injury drugstore. Cell Stem Cell 9:11–15
31. Caplan AI (2017) Mesenchymal stem cells: time to change the name! Stem Cells Transl Med 6:1445–1451
32. Murray IR, Chahla J, Safran MR et al (2019) International expert consensus on a cell therapy communication tool: DOSES. J Bone Joint Surg Am 101:904–911
33. Murray IR, Geeslin AG, Goudie EB et al (2017) Minimum information for studies evaluating biologics in Orthopaedics (MIBO): platelet-rich plasma and mesenchymal stem cells. J Bone Joint Surg Am 99:809–819
34. Chu CR, Rodeo S, Bhutani N (2019) Optimizing clinical use of biologics in orthopaedic surgery: consensus recommendations from the 2018 AAOS/NIH U-13 conference. J Am Acad Orthop Surg 27: e50–e63
35. Marenah M, Li J, Kumar A et al (2019) Quality assurance and adverse event management in regenerative medicine for knee osteoarthritis: current concepts. J Clin Orthop Trauma 10:53–58