Biologic Orthopedic Journal

Original Article
DOI: 10.22374/boj.v3i1.13

A 12-MONTH COHORT STUDY TO INVESTIGATE CHANGES IN PATIENT-REPORTED OUTCOMES AFTER INTRA-ARTICULAR INJECTION OF MICRO-FRAGMENTED ADIPOSE TISSUE FOR KNEE OSTEOARTHRITIS

Nathan S Hogaboom, PhD[1,2]
Ella D'Amico, MD[2]
Ken Mautner, MD[3]
Christopher J Rogers, MD[4]
Gerard A Malanga, MD[2,5]

[1]Derfner-Lieberman Regenerative Rehabilitation Laboratory, Kessler Foundation, West Orange, New Jersey, USA

[2]Rutgers New Jersey Medical School, Newark, New Jersey, USA

[3]Emory University School of Medicine, Atlanta, Georgia, USA

[4]San Diego Orthobiologics Medical Group, Inc., Carlsbad, California, USA

[5]New Jersey Regenerative Institute, LLC, Cedar Knolls, New Jersey, USA

Corresponding author: Gerard Malanga, MD: gmalangamd@hotmail.com

ABSTRACT

Background
To evaluate changes in pain, function, and quality of life after treatment with injected micro-fragmented adipose tissue (MFAT) for knee osteoarthritis in a large cohort of individuals treated at multiple centers.

Methods
One hundred ten individuals were recruited from three private outpatient clinics. Participants had to be diagnosed with symptomatic knee OA (defined by persistent knee pain associated with clinical symptoms of OA and/ or classic imaging findings) and who had not received prior knee surgery or treatment with platelet-rich plasma, cortisone, or hyaluronic acid within the previous 6 weeks. Data from 120 knees were included in the analysis. Outcome measures included Knee Injury and Osteoarthritis Outcome Score (KOOS) subscales (pain, symptoms, activities of daily living [ADL], sports and recreation, quality of life [QOL]) and an 11-point Numerical Rating Scale (NRS) for average knee pain over the past week. Outcomes were collected at baseline and 3, 6, and 12 months.

Results
Significant increases and decreases in KOOS subscale and NRS scores were observed, respectively, in the cohort as a whole ($< .05$). Lower BMI was associated with more significant improvements in pain, sports/ recreation, and ADL KOOS subscale scores ($< .05$). Greater age was associated with more significant improvements in symptoms and QOL subscale scores ($< .05$).

Conclusions
A single injection of MFAT improved pain, function, and QOL outcome measures up to 12 months in this cohort for more than half of the participants. Greater BMI and lower age negatively influenced outcomes. It is not known whether improvements continue after this timeframe or why many participants reported little-to-no improvement.

Bio Ortho J Vol 2(1):e19–e28; June 2, 2021.

INTRODUCTION

Osteoarthritis (OA) is a degenerative disease characterized by chondrocytes, cartilage destruction, and inflammation that typically affects weight-bearing joints such as the knee. Due to the ongoing obesity epidemic and growing elderly population in the USA, the prevalence of OA has expanded.[1,2] Advancements in imaging and diagnostic tools have likely also contributed to increased diagnosis rates. Over the next 20 years, the expected number of US adults with OA is expected to reach 78.4 million, translating approximately to 1 in every 4 adults.[3]

Pain secondary to knee OA has a significant impact on quality of life and can ultimately limit independence in activities of daily living. The number of adults with activity limitation secondary to OA is projected to reach 34.6 million (11.4% of all adults) over the next two decades.[3] The US population with symptomatic knee OA, one of the most commonly affected joints, has jumped from 6.9% to 7.3% between the years 2007-2008 to 2001-2012.[4] Risk factors for knee OA development in adults include older age, obesity, and female gender.[5]

Though knee arthritis is one of the leading orthopedic conditions, management remains a challenge due to limited effective treatment options.[6] Treatment for mild to moderate knee OA includes conservative measures (weight reduction, exercise, orthotics, bracing), pharmacological treatment (anti-inflammatories and/or analgesics), intra-articular injections (hyaluronic acid, steroids, platelet-rich-plasma), and arthroscopic lavage and debridement.[7,8] Treatment is challenging for those not responding to these measures, many of which have poor long-term efficacy.[8] Total knee arthroplasty has classically been used to treat patients with moderate to severe pain.[7,8] Arthroplasty is costly and a majority of patients are either nonsurgical candidates or decline surgical intervention, leaving a wide gap in treatment options.[9,10] Non-operative interventions offered by the field of regenerative medicine are a promising new alternative for these patients.

One of the most promising new approaches for symptomatic OA is the use of biologics; for example, micro-fragmented adipose tissue (MFAT). MFAT promotes immunomodulatory, trophic, and anti-apoptotic actions within the affected joint, which are effects attributed to high concentrations of mesenchymal stromal cells and pericytes native to adipose tissue.[11–15] Its regenerative properties were first noted with cosmetic fat grafting, which revealed improvements in the quality of aging, scarred, and damaged skin.[16] The methods of harvesting, refinement, and placement of MFAT were subsequently refined and used as a therapeutic option for various orthopedic conditions, including meniscal tears[17] and osteochrondral talar defects.[18] Harvested tissue for these procedures is micro-fragmented and washed of pro-inflammatory oil and blood residues using mild mechanical forces.[19] The process is relatively simple and does not require any enzymes, additives, or separate centrifugation, which is imperative given the complex regulation of these therapies.[20–22]

Recent studies on MFAT for knee OA are limited but support its safety and potential efficacy.[15,23,24] There is inadequate research defining the impact of MFAT on the burden of osteoarthritis and the patient demographics for which this intervention may be most effective.[25] This study aims to bridge these gaps in the literature with a multi-center, retrospective analysis of intra-articular MFAT injections for symptomatic knee OA. It was hypothesized that a single, ultrasound-guided injection of MFAT into the knee joint would improve knee pain and function 12 months post-injection. Changes in pain and function were measured using a pain numerical rating scale (NRS) for pain and Knee Injury and Osteoarthritis Outcome Score (KOOS) subscales.

METHODS

Study Population

Data were collected from participants at three private outpatient clinic sites located in Carlsbad, California, Atlanta, Georgia, and Cedar Knolls, New Jersey, between October 2014 and October 2019.[26] Participants included in the study were at least 25 years old, had received a diagnosis of symptomatic knee OA as defined by persistent knee pain associated with clinical symptoms of OA (crepitus on active motion, restricted movement, bony tenderness or enlargement, morning stiffness, no palpable warmth of synovium) or classic imaging findings (joint-space narrowing, osteophytes). Exclusion criteria included

contraindications to liposuction; prior knee surgery; pathology requiring surgical management (e.g., end-stage OA requiring total knee arthroplasty); treatment with platelet-rich plasma, cortisone (oral or injected), or hyaluronic acid injection within the past 6 weeks; malignancy within 5 years; or any disease or condition that may hinder treatment. Diseases or medical conditions that could hinder treatment included signs of infection, unstable medical conditions such as hypertension or diabetes, bleeding disorders, or severe anatomic malalignments (Varus/Valgus).

Individuals who opted for the procedure, met the study criteria, and agreed to participate were consented and enrolled. Participants completed a survey that included demographic information (age, sex, BMI) and baseline KOOS and NRS scores after giving informed consent. They then received an intra-articular injection of MFAT in the affected knee(s). Follow-up KOOS and NRS scores were collected at 3, 6, and 12 months.

The KOOS is a valid, reliable, and responsive outcomes index widely used in research and clinical practice for short-term and long-term follow up of several types of knee injuries, and conditions including OA.[27–30] It is self-administered and assesses five outcomes: pain, other symptoms, function in daily living (ADL), function in sport and recreation, and knee-related quality of life (QOL).[30] The KOOS is cost-effective, has a high reproducibility rate, and captures symptoms that are important to the patient.[31,32] The minimal clinically significant difference (MCID) for the KOOS subscales is approximately 8–10.[29]

The NRS is also commonly used in research and clinical practice to quantify the pain intensity. Patients are asked to indicate using an 11-point scale their average pain level. The scale ranged from 0 to 10 with 0 indicating "no pain" and 10 indicating "worst possible pain."[33] The NRS is highly reliable, easy to use, and effective at detecting changes in pain.[33,34] It has an MCID of 2 for patients with pain secondary to knee OA.[34] One site asked participants to list their "best" and "worst" pain; these values were averaged together.

Surgical Procedure

The Lipogems® processing kit was used to harvest MFAT for this study. This disposable kit can be used to aspirate, process, and re-injection autologous MFAT without expansion or enzymatic treatment.[11] Patients were placed supine on the procedure table, and an area for fat harvesting, typically the abdomen, was marked in an oval with a surgical marker. In patients with limited abdominal adipose the lateral lower spine area or postero-lateral thigh was used to aspirate adipose tissue. Tumescent anesthesia was prepared by combining 50 cc 1% lidocaine with 1 cc of 1:1000 epinephrine and 500 cc of normal saline. Chloroprep was used to disinfect skin, and the area was bordered with sterile drapes. The lidocaine mixture was injected using an 18-gauge needle for local anesthesia. A #11 blade was used to make a small incision, and a 17-gauge blunt cannula was then inserted at the same entry point and used to diffuse 60–120cc of tumescent subcutaneously below Scarpa's fascia at the harvest site. While wait-ing 20 minutes for the anesthetic to take effect, the Lipogems® kit was assembled and prepared. A bag of 1000 cc of sterile saline and a waste bag was attached at either end. The saline was used for flushing the compartments and creating an airless, closed system.

The procedure was continued and a 13-gauge blunt end cannula was used to obtain 30 to 80 mL of lipoaspirate. The lipoaspirate was then injected into the device while passing through a reduction filter, which helped relieve blood and oil residue. Once in the central compartment, the device was shaken for thirty second intervals. Stainless steel ball bearings within the central compartment created mechanical forces that further fragmented and washed the lipoaspirate. The residue was flushed into the waste bag, and the resulting MFAT was drawn into 3-cc syringes for injection.

The joint line and areas of degeneration secondary to OA were visualized using a high-frequency linear ultrasound transducer. If a large effusion was identified, it was aspirated before MFAT injection. Joint space was assessed for the most suitable injection approach given the presence of joint space narrowing and osteophyte pathology typical of OA. MFAT was then injected under direct ultrasound guidance into the joint using a 1.5 inch -22g or 3 inch-18 g needle.

Participants were educated on post-injection guidelines. These included weight-bearing restrictions and avoidance of non-steroidal anti-inflammatory drugs for

the first few weeks, with a progression to unrestricted activity (as tolerated) by 6–8 weeks. There was no specific post-treatment rehabilitation protocol that was instituted after the treatment.

Statistical Analysis

All statistical analyses were conducted using SPSS version 21 (IBM, Inc., Armonk, New York, USA). Statistical significance was determined as $p<.05$ for all analyses. Participants with missing data at baseline were excluded, as were those with data only at baseline and no other time point. Standard descriptives were calculated, including means and standard deviations for continuous variables and frequencies for categorical variables. Missing data were determined not to be missing at random and thus were imputed using the Multivariate Imputation by Chained Equations (MICE) package in R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).[35] The data were analyzed using mixed-effects models because of the repeated measurements and non-uniform time points at which the data were collected. Time was considered a fixed effect, and BMI, age, and gender were included as covariates in these models. Random intercepts were included in all models to account for variance in subject baseline scores. Post hoc analyses were conducted with Bonferonni corrections to determine significant differences in outcomes at each time point compared to baseline.

Secondary analyses were conducted to evaluate characteristics of those deemed "responders" and "non-responders." Responders were participants who improved beyond the MDIC for each respective outcome measure (10 for each KOOS subscale and 2 for the NRS), while non-responders were those who did not. Logistic regression models were built to determine whether participant age, BMI, and gender impacted the odds of being a responder or non-responder for each outcome measure. Baseline KOOS subscale and NRS scores were included in the respective regression models to control for disease state.

RESULTS

A total of 110 individuals were included in the study, and 120 knees were injected. Participants were

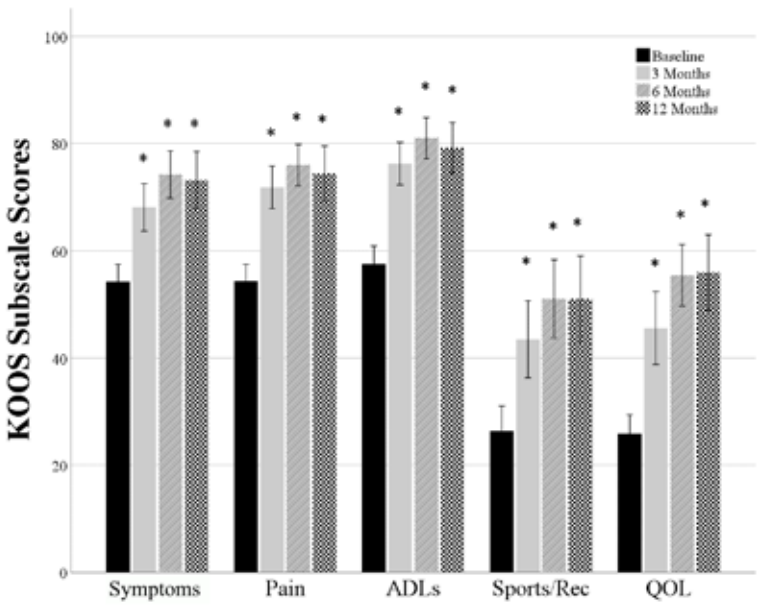

Figure 1. Changes in KOOS subscales (symptoms, pain, function in activities of daily living [ADLs], function in sports/recreation, and quality of life [QOL]) between baseline, 3 months, 6 months, and 12 months post-injection. Error bars indicate 95% confidence intervals. *** Significant** difference with respect to baseline, $p< .05$

on average 64.3±10.3 years of age (range, 31–83 years) with an average BMI of 30.0±4.7 kg/m^2 (range, 20.2 – 46.2 kg/m^2) and consisted of 55.3% females. Significant improvements in all KOOS subscale and NRS scores were noted after baseline (p<.001). With respect to baseline, KOOS subscale and NRS scores showed significant improvement at 3, 6, and 12 months post-treatment (p<.001, Figure 1). Descriptive statistics and percentages of participants with clinically meaningful 12-month improvements in KOOS subscales and NRS scores are presented in Tables 1 and 2, respectively.

Lower BMI was associated with greater improvements in pain (*B* = -0.47, *SE B* = 0.22, *B* 95%CI= -0.92 – -0.03, p<.05), sports/recreation (*B* = -1.0, *SE B* = 0.38, *B* 95%CI = -1.8 – -0.29, p<.01), and ADL (*B* = -0.64, *SE B* = 0.21, *B* 95%CI = -1.1 – -0.22, p<.01) KOOS subscale scores. Greater age was associated with greater improvements in symptoms (*B* = 0.27, *SE B* = 0.11, *B* 95%CI = 0.04 – -0.49, p<.05) and QOL (*B* = 0.33, *SE B* = 0.15, *B* 95%CI = 0.04 – 0.62, p<.05) subscales. No other covariates were associated with NRS scores.

Results of the secondary analysis suggested females were more than four times more likely to be responders for the pain (OR: 4.1, OR 95%CI: 1.6-10.5, p<.01) KOOS subscale. Participants who were older were 5% and 8% less likely to be responders for sports/recreation (OR: 0.95, OR 95%CI: 0.91-1.0, p<.05) and QOL (OR: 0.92, OR 95%CI: 0.87-0.97, p<.001) subscales, respectively. Participants with higher BMIs were 12% and 9% less likely to be responders for ADL (OR: 0.88, OR 95%CI: 0.78-0.98, p<.05) and sports/recreation (OR: 0.91, OR 95%CI: 0.82-1.0, p<.05) subscales, respectively. No factors were associated with NRS response. Percentage changes between baseline and 12 months post-treatment in non-responders and responders are presented in Table 3.

DISCUSSION

Conservative measures and surgery have classically defined treatment of symptomatic knee OA.[7,8] These options are often ineffective or unsuitable for a large subset of patients, particularly those who have failed conservative therapy yet are not surgical candidates, creating a significant gap in treatment options.[10] Recent advancements in regenerative medicine have provided promising results for these patients. This retrospective, multi-center, longitudinal study examined the application of ultrasound-guided intra-articular MFAT therapy as a potential option for symptomatic knee

Table 1. Descriptive Statistics of Knee Injuries and Osteoarthritis Outcome Scale Subscales and Numerical Rating Scale Scores Up to Twelve Months Post-Treatment

	Baseline	Month 3	Month 6	Month 12
Symptoms[a]	54.0 (18.3)	69.8 (16.9)	75.1 (17.1)	71.4 (18.8)
Pain[b]	54.5 (17.8)	69.9 (15.0)	75.9 (14.8)	71.3 (17.7)
ADL[c]	58.0 (18.8)	76.3 (16.3)	80.4 (16.4)	78.8 (18.3)
Sports/Recreation[d]	27.5 (26.7)	46.7 (30.8)	51.2 (28.5)	45.3 (29.6)
QOL[e]	26.4 (19.9)	45.6 (24.1)	51.5 (23.9)	52.6 (24.3)
NRS[f]	5.4 (2.2)	4.4 (2.9)	3.2 (2.6)	3.4 (2.4)

Notes. Means and standard deviations are presented for each scale, as well as linear mixed model statistics for the main effect of time on the respective outcome variable. ADLs = Activities of daily living subscale. QOL = quality of life subscale. NRS = numerical pain rating scale.

[a]F(3,357)=57.4, p<.001

[b]F(3,357)=50.0, p<.001

[c]F(3,357)=59.5, p<.001

[d]F(3,357)=22.3, p<.001

[e]F(3,357)=49.1, p<.001

[f]F(3,357)=22.5, p<.001

Table 2. Percentages of Participants with Clinically-Meaningful Improvements in Each Outcome Measure

	≥25%	≥50%	≥75%
Symptoms	56.7	35.0	25.8
Pain	56.7	36.7	25.0
ADLs	56.7	35.8	30.8
Sports/Recreation	55.4	48.9	43.5
QOL	68.0	56.0	49.0
NRS	62.7	42.4	19.5

Notes. N=120. Data are presented as percentages of participants with greater than or equal to a 25%, 50%, or 75% improvement at 12 months with respect to baseline in each of the Knee Osteoarthritis and Injuries Outcome Score (KOOS) subscales and Numerical Rating Scale (NRS) scores. Percentages of participants with changes greater than established Minimal Clinically Important Differences (MCID) are also presented. KOOS subscales include symptoms, pain, function during activities of daily living (ADL) and sports and recreation, and knee-related quality of life (QOL).

OA. Overall, participants reported positive outcomes compared to baseline, verifying the application of MFAT for knee OA.

Participants reported less knee pain, improved function, and greater QOL at six and twelve months post-treatment according to the KOOS subscale and NRS scores. More than half reported greater than 25% improvement in all subscales, with nearly 70% reporting this level of improvement in knee-related QOL. Moreover, between 63% and 72% of individuals reported improvements in each KOOS subscale more significant than the established MCID of 10 points. Improvements more significant than the MCID across all subscales clinically suggest that patients can expect to see improvements in pain and their function and ability to participate in activities that may have been limited before treatment. Discrepancies were noted between changes in KOOS subscale and NRS scores, which were not as impressive despite the fact that both scales measure similar constructs. This may be due to different collection methods between sites. For example, one site collected least and worst pain for both knees, which then had to be averaged for a final "average" NRS score. Another site collected a single KOOS subscale and NRS data point regardless of whether one knee was injected or both. The final site collected NRS scores for either one or both knees depending on whether one or both knees were injected, while collecting a single KOOS score for each subscale. Future multi-center outcomes data collection efforts should strongly consider standardizing collection methods between locations to improve accuracy and interpretation of statistical findings.

Participants with lower BMI had more significant improvements in pain, function, and QOL, and were less likely to respond to the treatment with respect to function. These results are not surprising given the association of BMI and OA in adults[5] and the reported differences in outcomes post-arthroplasty between obese and non-obese individuals.[36,37] There are several potential explanations for this association; for example,

Table 3. Changes in Outcome Measures At 12 Months between Responders and Non-Responders to Treatment

	% Participant Responders	Outcome Changes at 12 Months (%, % SD):	
		Non-Responders	Responders
Symptoms	63.3	-9.4 (20.4)	86.4 (90.3)
Pain	63.3	-10.6 (16.6)	127.3 (301.5)
ADLs	65.8	-11.8 (17.3)	80.1 (72.5)
Sports/Recreation	60.8	-36.0 (36.6)	316.0 (321.3)
QOL	71.7	-28.2 (35.9)	233.7 (247.2)
NRS	53.3	-22.3 (96.4)	65.8 (24.2)

Notes. N=120. Responders are those participants whose improvements were greater than or equal to the minimal clinically significant difference for each outcome measure. Frequencies of participants considered responders are described as percentages of the total number of participants. The average percentage changes (and standard deviations) in each outcome measure are also presented for "responders" and "non-responders." ADLs = Activities of daily living subscale. QOL = quality of life subscale. NRS = numerical pain rating scale.

more significant joint loading, psychosocial factors, and the heightened inflammatory state associated with pain and obesity, all of which may have attenuated positive responses to the treatment.[38] The environment local to adipose tissue in obese individuals (e.g., hypoxia, chronic low-grade inflammation) has been shown to alter adipose-derived MSCs in vitro,[39,40] which could potentially translate to worse clinical outcomes. Also, synovial fluid levels of different adipokines – proteins that are often dysregulated in obese individuals – have been found to correlate with varying severity levels of OA.[41–43] It is also possible that participants with lower BMI were generally more active before their treatment. The MFAT treatment may have improved symptoms enough for these individuals to resume or approach their normal activity levels, whereas those with higher BMIs reported more limited changes. This would explain why BMI was associated with changes in function and sports/ recreation subscales and not the symptoms or QOL subscales. Additional research is necessary to understand the mechanisms behind this relationship and additional markers that could predict positive or negative responses to treatment with MFAT.

Female participants were more likely to respond to the treatment with respect to improvements in pain. Greater disease severity in women may create a broader range for improvement in women than men treated with MFAT; however, this pattern was still evident after including baseline disease severity in the regression models. One possible explanation for this association is the different concentrations and turnover rates of systemic and synovial fluid adipokines in males and females; such differences have been shown to promote OA progression in women, and it is likely that they also affect the efficacy of MFAT treatment.[44,45] Additional research is needed to explain these pathways and their effects on MFAT treatment. It is also possible that varying perceptions of pain between genders may have affected the response to treatment.[46] This is unfortunately, one limitation of the subjective scales utilized in this study, which is difficult to avoid in trials designed to evaluate clinical outcomes that may not be quantified objectively.

Findings in the present study are limited by the lack of blinding, randomization, and a control group, which may have introduced a placebo effect and affected participants' responses. As a result, the causality of the responses and effectiveness of the treatment cannot be definitively evaluated. Future studies aimed at determining the efficacy of MFAT for knee OA would require incorporating these elements into their designs. It is important to note that it would be ethically challenging to blind participants to the procedure considering the method of harvesting the lipoaspirate. Many participants were lost to follow up at one or more time points. Statistical methods were utilized to minimize the impact of missing data; however, the bias inherent to dropout could not be avoided and should be considered when interpreting the findings of this study. Although procedural methods were identical, the three sites collected their data independently, and thus differences were present in their collection methods, which likely introduced bias and error in the statistical outcomes. Staging of knee OA was not collected across all sites, so it is difficult to determine whether this variable influenced outcomes. One of the exclusion criteria was receiving a PRP injection within the past 6 weeks, although the benefits of PRP may appear after that timeframe. Information about prior PRP treatments was not collected in this study. Larger, randomized controlled studies with minimal loss to follow-up and more coordinated data collection methods would likely attenuate these limitations and improve study outcomes.

CONCLUSION

Research into alternative treatment options for knee OA, such as those offered by the field of regenerative medicine, is imperative to meet the demands of an aging population. Participants with knee OA in the current study self-reported improvement in pain, function, and QOL after a single, intra-articular injection of MFAT. Furthermore, lower BMI, female gender, and older age appeared to impact outcomes after the injection positively. Such findings suggest the therapy may be beneficial in ameliorating symptoms of OA, and highlight the importance of studying MFAT with adjuvant therapy and subject characteristics that may predict better outcomes. Larger, randomized, controlled studies comparing MFAT to knee OA standard-of-care therapies are needed to validate the efficacy of MFAT and clarify the clinical application of the therapy.

AUTHOR CONTRIBUTIONS:

Nathan Hogaboom: Data analysis and interpretation, manuscript writing, final approval of manuscript, assembly of data

Ella D'Amico: Data analysis and interpretation, manuscript writing, final approval of manuscript.

Ken Mautner: Conception and design, administrative support, provision of study material or patients, collection of data, manuscript writing, final approval of manuscript.

Christopher Rogers: Conception and design, administrative support, provision of study material or patients, collection of data, manuscript writing, final approval of manuscript.

Gerard Malanga: Conception and design, administrative support, provision of study material or patients, collection of data, manuscript writing, final approval of manuscript.

FUNDING

This material is the result of work supported with resources and the use of facilities at the Kessler Foundation and Kessler Institute for Rehabilitation and was funded by a fellowship grant from the Derfner Foundation. This research received funding from the Alliance for Regenerative Rehabilitation Research Training (AR3T), which is supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), National Institute of Neurological Disorders and Stroke (NINDS), and National Institute of Biomedical Imaging and Bioengineering (NIBIB) of the National Institutes of Health under Award Number P2CHD086843. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The contents of this manuscript do not necessarily represent the policy of HHS and you should not assume endorsement by the Federal Government.

REFERENCES

1. Deshpande BR, Katz JN, Solomon DH, Yelin EH, Hunter DJ, Messier SP, et al. Number of Persons With Symptomatic Knee Osteoarthritis in the US: Impact of Race and Ethnicity, Age, Sex, and Obesity. Arthritis Care Res (Hoboken). 2016;68(12):1743-50.
2. Mihalko SL, Cox P, Beavers DP, Miller GD, Nicklas BJ, Lyles M, et al. Effect of intensive diet and exercise on self-efficacy in overweight and obese adults with knee osteoarthritis: The IDEA randomized clinical trial. Translat Behav Med. 2019;9(2):227-35.
3. Hootman JM, Helmick CG, Barbour KE, Theis KA, Boring MA. Updated Projected Prevalence of Self-Reported Doctor-Diagnosed Arthritis and Arthritis-Attributable Activity Limitation Among US Adults, 2015-2040. Arthritis Rheumatol. 2016;68(7):1582-7.
4. Coggon D, Reading I, Croft P, McLaren M, Barrett D, Cooper C. Knee osteoarthritis and obesity. Int J Obes Relat Metab Disord. 2001;25(5):622-7.
5. Blagojevic M, Jinks C, Jeffery A, Jordan KP. Risk factors for onset of osteoarthritis of the knee in older adults: a systematic review and meta-analysis. Osteoarthritis Cartilage. 2010;18(1):24-33.
6. Zhang W, Ouyang H, Dass CR, Xu J. Current research on pharmacologic and regenerative therapies for osteoarthritis. Bone Res. 2016;4:15040.
7. Ringdahl E, Pandit S. Treatment of knee osteoarthritis. Am Fam Physician. 2011;83(11):1287-92.
8. Zhang W, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N, et al. OARSI recommendations for the management of hip and knee osteoarthritis, part I: critical appraisal of existing treatment guidelines and systematic review of current research evidence. Osteoarthritis Cartilage. 2007;15(9):981-1000.
9. Hawker GA, Guan J, Croxford R, Coyte PC, Glazier RH, Harvey BJ, et al. A prospective population-based study of the predictors of undergoing total joint ar-throplasty. Arthritis Rheum. 2006;54(10):3212-20.
10. London NJ, Miller LE, Block JE. Clinical and economic consequences of the treatment gap in knee osteoarthritis management. Medical Hypotheses. 2011;76(6):887-92.
11. Bianchi F, Maioli M, Leonardi E, Olivi E, Pasquinelli G, Valente S, et al. A new nonenzymatic method and device to obtain a fat tissue derivative highly enriched in pericyte-like elements by mild mechanical forces from human lipoaspirates. Cell Transplantation. 2013;22(11):2063-77.

12. Ceserani V, Ferri A, Berenzi A, Benetti A, Ciusani E, Pascucci L, et al. Angiogenic and anti-inflammatory properties of micro-fragmented fat tissue and its derived mesenchymal stromal cells. Vasc Cell. 2016;8:3.
13. Koh YG, Choi YJ, Kwon SK, Kim YS, Yeo JE. Clinical results and second-look arthroscopic findings after treatment with adipose-derived stem cells for knee osteoarthritis. Knee Surg Sports Traumatol Arthrosc. 2015;23(5):1308-16.
14. Li M, Luo X, Lv X, Liu V, Zhao G, Zhang X, et al. In vivo human adipose-derived mesenchymal stem cell tracking after intra-articular delivery in a rat osteo-arthritis model. Stem Cell Res Ther. 2016;7(1):160.
15. Russo A, Condello V, Madonna V, Guerriero M, Zorzi C. Autologous and micro-fragmented adipose tissue for the treatment of diffuse degenerative knee osteoarthritis. J Exp Orthop. 2017;4(1):33.
16. Coleman SR. Structural fat grafting: more than a permanent filler. Plastic Reconstruct Surg. 2006;118(3 Suppl):108s-20s.
17. Chirichella PS, Jow S, Iacono S, Wey HE, Malanga GA. Treatment of Knee Meniscus Pathology: Rehabilitation, Surgery, and Orthobiologics. PM R. 2019;11(3):292-308.
18. D'Ambrosi R, Indino C, Maccario C, Manzi L, Usuelli FG. Autologous Microfractured and Purified Adipose Tissue for Arthroscopic Management of Osteochondral Lesions of the Talus. J Vis Exp. 2018(131).
19. Tremolada C, Colombo V, Ventura C. Adipose Tissue and Mesenchymal Stem Cells: State of the Art and Lipogems(R) Technology Development. Curr Stem Cell Rep. 2016;2:304-12.
20. Ahrlund-Richter L, De Luca M, Marshak DR, Munsie M, Veiga A, Rao M. Isolation and production of cells suitable for human therapy: challenges ahead. Cell Stem Cell. 2009;4(1):20-6.
21. Arcidiacono JA, Blair JW, Benton KA. US Food and Drug Administration international collaborations for cellular therapy product regulation. Stem Cell Res Ther. 2012;3(5):38.
22. Sensebe L, Bourin P, Tarte K. Good manufacturing practices production of mesenchymal stem/stromal cells. Hum Gene Ther. 2011;22(1):19-26.
23. Cattaneo G, De Caro A, Napoli F, Chiapale D, Trada P, Camera A. Micro-fragmented adipose tissue in-jection associated with arthroscopic procedures in patients with symptomatic knee osteoarthritis. BMC Musculoskeletal Disord. 2018;19(1):176.
24. Malanga GA, Bemanian S. Microfragmented adipose injections in the treatment of knee osteoarthritis. J Clin Orthop Trauma. 2019;10(1):46-8.
25. Roos EM, Roos HP, Lohmander LS, Ekdahl C, Beynnon BD. Knee Injury and Osteoarthritis Outcome Score (KOOS)--development of a self-administered outcome measure. J Ortho Sports Phys Ther. 1998;28(2):88-96.
26. Malanga G, Mautner K, Rogers C. Orthobiologics Database. New Jersey Regenerative Institute, LLC; 2014.
27. Alviar MJ, Olver J, Brand C, Hale T, Khan F. Do patient-reported outcome measures used in assessing outcomes in rehabilitation after hip and knee arthroplasty capture issues relevant to patients? Results of a systematic review and ICF linking process. J Rehabil Med : official journal of the UEMS European Board of Physical and Rehabilitation Medicine.2011;43(5):374-81.
28. Collins NJ, Misra D, Felson DT, Crossley KM, Roos EM. Measures of knee function: International Knee Documentation Committee (IKDC) Subjective Knee Evaluation Form, Knee Injury and Osteoarthritis Outcome Score (KOOS), Knee Injury and Osteoarthritis Outcome Score Physical Function Short Form (KOOS-PS), Knee Outcome Survey Activities of Daily Living Scale (KOS-ADL), Lysholm Knee Scoring Scale, Oxford Knee Score (OKS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Activity Rating Scale (ARS), and Tegner Activity Score (TAS). Arthritis Care Res (Hoboken). 2011;63 Suppl 11:S208-28.

40. Frazier TP, Gimble JM, Devay JW, Tucker HA, Chiu ES, Rowan BG. Body mass index affects proliferation and osteogenic differentiation of human subcutaneous adipose tissue-derived stem cells. BMC Cell Biol. 2013;14:34-.
41. Staikos C, Ververidis A, Drosos G, Manolopoulos VG, Verettas DA, Tavridou A. The association of adipokine levels in plasma and synovial fluid with the severity of knee osteoarthritis. Rheumatology. 2013;52(6):1077-83.
42. Honsawek S, Chayanupatkul M. Correlation of plasma and synovial fluid adiponectin with knee osteoarthritis severity. Arch Med Res. 2010;41(8):593-8.
43. Calvet J, Orellana C, Gratacós J, Berenguer-Llergo A, Caixàs A, Chillarón JJ, et al. Synovial fluid adipokines are associated with clinical severity in knee osteoarthritis: a cross-sectional study in female patients with joint effusion. Arthritis Res Therapy. 2016;18(1):207-.
44. Presle N, Pottie P, Dumond H, Guillaume C, Lapicque F, Pallu S, et al. Differential distribution of adipokines between serum and synovial fluid in patients with osteoarthritis. Contribution of joint tissues to their articular production. Osteoarthritis Cartilage. 2006;14(7):690-5.
45. Teichtahl AJ, Wluka AE, Proietto J, Cicuttini FM. Obesity and the female sex, risk factors for knee osteoarthritis that may be attributable to systemic or local leptin biosynthesis and its cellular effects. Med Hypotheses. 2005;65(2):312-5.
46. Keefe FJ, Lefebvre JC, Egert JR, Affleck G, Sullivan MJ, Caldwell DS. The relationship of gender to pain, pain behavior, and disability in osteoarthritis patients: the role of catastrophizing. Pain. 2000;87(3):325-34.