Regenerative Medici

Clinical Use of Autologous Micro-Fragmented Fat Progressively Restores Pain and Function in Shoulder Osteoarthritis

Journal:	*Regenerative Medicine*
Manuscript ID	FM-RME-2020-0069
Manuscript Type:	Preliminary Communication
Keywords:	Adipose-derived stem cells, Bone & cartilage, Cell Therapy, Mesenchymal stem cells, shoulder, osteoarthritis, adipose tissue, orthopedics

Clinical Use of Autologous Micro-Fragmented Fat Progressively Restores Pain and Function in Shoulder Osteoarthritis

ABSTRACT

Non-digested micro-fragmented adipose tissue (MFat™, Lipogems®) was utilized to treat shoulder joint pain and inflammation associated dysfunction in 25 patients with mild (n=12) to moderate (n=13) shoulder osteoarthritis (OA) who have completed follow-ups at 6, 18, and 52 week intervals. All study participants received an injection of autologous MFat™ therapy to affected shoulders. Quantitative analysis of pain and function modalities was performed using the Visual Analog Scale (VAS) and the Disabilities of the Arm, Shoulder, and Hand (DASH) Western Ontario and McMaster Universities Arthritis Index (WOMAC) respectively. Study results demonstrate progressive improvement in pain as well as restoration of function in the shoulder joint in mild to moderate cases of OA for at least one year following Lipogems® MFat™ therapy.

Key words: micro-fragmented, adipose tissue, shoulder, osteoarthritis, degenerative joint disease, regenerative medicine

INTRODUCTION

Osteoarthritis (OA) is one of the most common chronic and debilitating conditions seen in the orthopedic setting. This disease results in damage to the articular cartilage and inflammation and successive damage of the joint itself. Shoulder OA can be debilitating with loss of shoulder function leading to depression, anxiety, activity limitations, and job-performance problems. Cartilage degradation in shoulder OA can cause subchondral bone remodeling, and ultimate loss in sphericity and congruity of the joint.[1] The joint capsule can thicken, leading to further loss of shoulder rotation.[2, 3]

Successful treatment of OA remains a challenge particularly due to a lack of blood supply and limited capacity of self-repair in articular cartilage.[4, 5] Traditional treatment is aimed at symptom management to control pain and restore function but nothing reparative in nature to alter the progression of disease. The initial approach to OA treatment begins with activity modification, rest, heat and ice. Physical therapy, strength training, and aerobic exercise can help alleviate symptoms. Bracing, topical creams, over the counter anti-inflammatory medications, prescription medications, and steroid injections are also traditional first line treatment options.[6] Although steroid injections are commonly given to provide pain relief by decreasing joint inflammation, often patients require numerous injections, which has been shown to accelerate OA progression and result in bone loss over time.[7] More advanced cases of OA can develop resistance or are unresponsive to traditional pharmacological methods warranting surgical intervention. Surgical treatment is challenging, requires prolonged rehabilitation, and is burdened by serious risks of complications (infection, instability, deep vein

thrombosis, etc.) and often leads to patients seeking out other less invasive options.

Recent advancements in regenerative medicine have allowed for a more holistic reparative approach to treatment of such conditions. The use of mesenchymal stem cells (MSCs) derived from adipose tissue are currently under investigation in multiple research studies.[8-11] The therapeutic use of MSCs and other reparative cells is traditionally related to both their anti-inflammatory activity and multilineage differentiation, including their chondrogenic potential.[12-14] Recent studies emphasize the paracrine effects of implanted cells, i.e., the MSCs secretion of cytokines, growth factors and extracellular vesicles capable of inducing tissue repair and modulating inflammation.[14, 15] Adipose tissue, has emerged as an easily accessible rich source of reparative cells and can serve as an excellent option in regenerative medicine because of the minimally invasive harvesting procedure.[16, 17] Reparative adipose derived cells also have an immunoregulatory effect on the joint due to the paracrine factors that are secreted into the joint. Components of adipose tissue include the stromal vascular niche, extracellular matrix and numerous cell types including pericytes, pre-adipocytes, adipocytes and adipose derived stem cells as well as progenitor and hematopoietic cells.[15] A vital component in regenerative medicine is the pericyte, which exists in the stromal vascular niche of adipose tissue and plays an important role in cell signaling and healing.[18]

The processing technique used in this study involves micro-fragmenting and washing the adipose tissue to ensure that all inflammatory oils and blood cells are removed and allows for optimal absorption after reinjection. The closed, full-immersion system increases tissue

viability while maintaining the structural microarchitecture of the tissue.[19] Maintaining tissue microarchitecture enables the stromal vascular niche to remain intact, which is critical to the action of the tissue.[20] Pericytes, line the exterior of the capillaries within the stromal vascular niche therefore, keeping this intact not only enhances their viability, but also extends the longevity of their immunomodulatory signals.[14] In this prospective non-randomized clinical study of 25 patients with mild to moderate OA of the shoulder, we quantified the clinical effectiveness of the use of non-digested micro-fragmented adipose tissue (MFat™, Lipogems®) to treat shoulder joint pain and inflammation associated dysfunction as an alternative to surgical intervention.

MATERIALS AND METHODS

Participants: The current study includes 25 patients with a clinical diagnosis of mild (n=12) to moderate (n=13) shoulder OA with no other clinically complicating factors who have completed follow-ups at 6, 18, and 52 week intervals. All participants were submitted to an initial screening visit with a physical examination and shoulder radiography. Inclusion criteria were males and females over the age of 40 with a diagnosis of OA of the shoulder and confirmatory radiographs (Kellgren–Lawrence (KL) grade 2–3). Exclusion criteria were history of immunodeficiency, chronic use of oral corticosteroid or immunosuppressive therapies, history or presence of malignant disorders and/or use of chemotherapy within the last 5 years, except for cutaneous basal cell or squamous cell cancer resolved by excision, signs and symptoms of significant cardiac disease, diagnosis of transient ischemic attack within the last 6 months.

Lipoaspiration: According to the policies approved by the Institutional Review Boards for the Institute of Regenerative and Cellular Medicine ((xx-xx-xxx), adipose tissue was harvested from 25 patients with mild to moderate shoulder OA. Written informed consent was obtained from all study participants. Under aseptic sterile conditions, stab incisions were made for cannula entry in the abdominal area and infiltrated with tumescent anesthesia fluid with 500ml of saline, 50ml of 2% lidocaine plus 1ml of (1:1000) epinephrine. Approximately 15 minutes following infiltration, 50-70cc of adipose tissue was aspirated via cannula connected to a VacLock® (Merit Medical, South Jordan, UT, USA) syringe.

Lipoaspirate Processing: The MFat™ was prepared by connecting the lipoaspirate syringe to the Lipogems® device (Lipogems® International, Milan, Italy) and processed as previously described by Bianchi et al until desired volumes of Lipogems® MFat™ was achieved.[19]

Intra-articular Injections: Under aseptic conditions, 10cc of 1% lidocaine was injected into the shoulder(s) under ultrasound guidance. 15-21 cc of the MFat™ was then injected into the shoulder joint under ultrasound guidance.

Post-operative and post-injection care: Patients were discharged when stable with post procedure instructions. Prophylactic antibiotics were administered, and patients were monitored for fever and abnormal pain and swelling. Adjunct therapies of supplements and oral cytokines (GUNA® Biotherapeutics, Milan, Italy) were administered to the patient to enhance recovery and healing for a minimum of 6 weeks post injection. Patients were followed for a minimum of 1 year post Lipogems® therapy and specifically at 6, 18, and 52 weeks post therapy.

Patient Reported Outcome Measurements: A clinical and functional assessment was performed at each follow up interval. Patient reported outcomes of pain and function were measured using the Visual Analog Scale (VAS) and the Disabilities of the Arm, Shoulder, and Hand (DASH) Western Ontario and McMaster Universities Arthritis Index (WOMAC)

respectively.[21, 22] Deviations from baseline conditions were calculated and percentage improvements and/or decline were determined and quantitatively compared for each follow up time point.

Radiologic Joint Space Measurements: X-rays were taken at each follow up and radiologic changes in glenohumeral joint spacing were measured as a correlate to articular cartilage growth. The external true anteroposterior projection was used with the standard positioning of the patient supine, slightly turned (20°) to imaged side (a support under the other shoulder) and the arm in the external rotation, palm facing upwards as previously published.[23] Subjects with radiographs that did not allow for a clear visualization of the glenohumeral joint space were excluded from the analysis leaving data from 18 subjects with (n=8) for mild OA and (n=10) for moderate OA shoulder cases.

In this position the projection of the joint surface of the humeral head forms a half-circle, the diameter of which is the line joining the two terminal points of the joint surface projection. The mid-point of this line was determined and with a ruler aimed at this point, a 90° angle measurement was established perpendicular to the joint surface of the head of the humerus. The glenohumeral joint space at this site was measured with a ruler from this 90° projection at each time point as indicated in **Figure 1**. Deviations from baseline conditions were calculated as normalized changes from pre-procedure measurements.

Statistical Analysis: Statistical analysis was performed using GraphPad Prism 8 (GraphPad Prism, LLC, San Diego, CA, USA). The level of significance for all hypothesis tests (*p*) was set at 0.05. Continuous variables were presented as mean and standard error. Comparisons of shoulder VAS and DASH WOMAC scores and joint space measurements were independently made with the Kruskall–Wallis test for each data set. Once the Kruskal-Wallis test showed statistical significance among all normalized timepoints, post-hoc analysis was performed using the Wilcoxon signed-rank test to delineate the improvement of measurements between each endpoint with 95% confidence intervals (CI). Patient reported outcome measurements of DASH WOMAC scores measured during each follow-up endpoint for mild and moderate OA shoulder cases were also quantitatively compared utilizing the Mann-Whitney test to reveal differences among KL severity.

Ethical Approval: This study was reviewed and approved for human studies by the International Review Board for Cellular Medicine. All patients signed a detailed informed consent, which was also reviewed and approved by the IRB. There was no funding provided to the investigator, and no patient compensation for participation.

RESULTS

Patient Reported Outcomes: At the 6 week follow up, all 25 study participants reported significant improvement from baseline with 51.92 ± 4.52% (mean ± SE) improvement in VAS and 58.78 ± 6.61% improvement in WOMAC in mild OA cases, and 49.67 ± 9.36% improvement in VAS and 38.39 ± 6.31% improvement in WOMAC in moderate OA cases. These early results continued to progress in the mild OA group through 18 weeks with 76.56 ± 4.26% improvement in VAS and 76.90 ± 6.30% in WOMAC and at the yearly follow-up 87.51 ± 4.01% improvement in VAS and 89.31 ± 2.72% improvement in WOMAC. The patients with moderate OA demonstrated significant functional improvements at the 18 week follow-up with 82.58 ± 6.02% improvement in VAS and 62.61 ± 8.65% improvement in WOMAC that were maintained at the 1 yr follow-up with 84.37 ± 5.97% improvement in VAS and 58.98 ± 7.55% improvement in WOMAC as illustrated in **Figure 2**. Results of Kruskal-Wallis tests of VAS and WOMAC results revealed statistically significant differences among all time points measured ($p<0.001$***) for both mild and moderate OA shoulder cases. Post-hoc analysis was performed with the Wilcoxon signed-rank test and showed statistically significant improvement ($p<0.01$**) of VAS and DASH WOMAC scores progressively over time for mild OA shoulder cases as indicated in plots **A** and **B** of **Figure 2**. Post-hoc analysis of data from moderate OA shoulder cases shown in plots **C** and **D** of **Figure 2** revealed statistical improvement over time through 18 weeks ($p<0.01$**), with no significant change after 18 weeks, but rather revealed a maintenance of results from 18 weeks to a year post therapy.

Outcome correlates among groups (mild and moderate OA) were made of the patient reported outcome measurements of DASH WOMAC scores for each time point measured and were quantitatively compared utilizing the Mann-Whitney test. Results of this analysis shown in **Figure 3** showed statistically significant differences in year WOMAC measurements between mild and moderate OA shoulder cases, with significantly more improvement in function at 1 year post Lipogems® therapy in mild shoulder OA when compared to moderate shoulder OA cases ($p<0.05$*).

Joint Space Measurements: Glenohumeral joint space measurements were recorded for each subject at each time point. Normalized deviations from baseline were calculated and quantitatively compared for each follow-up time point as shown in **Figure 4** for mild OA shoulder cases (**A**) and moderate OA shoulder cases (**B**). At the 6 week follow-up, all included study participants (n=18) reported significant increases in glenohumeral joint spacing from baseline with 22.19 ± 4.83% (mean ± SE) increase in mild OA cases, and 21.75 ± 10.64% increase in moderate OA cases. Continued joint space increase was revealed at 18 weeks with 25.86 ± 7.04% increase in mild OA cases and 30.39 ± 10.94% increase in moderate OA cases. Yearly follow-ups revealed 37.55 ± 7.19% increase in joint space in mild OA shoulder cases with 36.34 ± 10.61% increase in joint space in moderate OA shoulder cases. Significantly, post hoc analysis of normalized data sets with the Wilcoxon signed rank tests showed significant increases in glenohumeral joint spacing following MFat™ therapy up to one year post treatment ($p<0.05$**)

for both mild and moderate OA shoulder cases with a mean increase in joint spacing of 1.133 ± 0.138 mm in mild OA shoulder cases and 0.9 ± 0.186 mm in moderate OA shoulder cases as illustrated in **Figure 4.** No significant difference was found among groups but could be due to smaller sample size and greater variation in results among moderate OA subjects.

DISCUSSION

Data from mild OA shoulder cases revealed continued progressive improvement over time in both pain and functional scales up to a year post Lipogems® MFat™ therapy. Results of analysis of VAS and WOMAC data from moderate OA shoulder cases revealed statistical improvement over time through 18 weeks, with a maintenance of those results at a year post therapy, implicating limitations in improvements of such measurements with increased severity of OA. Additionally, the improvement in WOMAC scores in moderate shoulder OA cases at a year post therapy was statistically less than the improvement in mild OA shoulder cases at a year post, suggesting a correlation between the degree of functional restoration to KL severity. Analysis of joint space measurements reveal statistically significant increases in glenohumeral joint spacing following MFat™ therapy up to one year post treatment. These results suggest cartilage modification as a result of Lipogems® MFat™ therapy to both mild and moderate OA shoulders, further elucidating the reparative capacity of MFat™ therapy. Our results are in line with Striano et al who analyzed the role of MFat™ injection for shoulder pain and arthritis in 20 patients in which they demonstrated significant improvements in pain, function and quality of life as measured by patient reported outcomes up to a year post.[24] Additionally, our results prove more effective and longer lasting than previous studies by Zhang et al examining the use of hyaluronic acid (HA) and corticosteroid injections in glenohumeral OA patients, where they showed that neither HA nor corticosteroid injections were significantly better than any other conservative treatment options for shoulder OA.[25] Currently, longer-term progress with larger data sets and the application of such methods in the presence of complicating shoulder pathologies including rotator cuff injury and tendinopathies in the absence and presence of OA

are being explored. Preliminary data and anecdotal clinical findings are positive and align with data sets for OA shoulder cases. Implementation in other joints is also being explored and evaluated, but this innovative research is promising for the field of orthopedic regenerative medicine and should be a considered a valuable alternative for the treatment of pain and inflammation associated dysfunction in mild-moderate OA in shoulders.

CONCLUSION

The use of Lipogems® MFat™ therapy in mild to moderate OA shoulder cases results in clinically significant improvement in both pain and functional scales, signifying Lipogems® as a novel regenerative orthopedic modality for the treatment of degenerative shoulder OA. Our results show that the improvements are not only significant, but also progressive in nature, with optimal results being achieved at up to 1 year post therapy. Future studies will focus on larger randomized control trials to further investigate the clinical efficacy of micro-fragmented adipose tissue.

REFERENCES

1. Ansok, C.B. and S.J. Muh, *Optimal management of glenohumeral osteoarthritis.* Orthop Res Rev, 2018. **10**: p. 9-18.
2. Kerr, R., et al., *Osteoarthritis of the glenohumeral joint: a radiologic-pathologic study.* AJR Am J Roentgenol, 1985. **144**(5): p. 967-72.
3. Petersson, C.J., *Degeneration of the Gleno-Humeral Joint: An Anatomical Study.* Acta Orthopaedica Scandinavica, 1983. **54**(2): p. 277-283.
4. Diekman, B.O. and F. Guilak, *Stem cell-based therapies for osteoarthritis: challenges and opportunities.* Curr Opin Rheumatol, 2013. **25**(1): p. 119-26.
5. Berenbaum, F. and C. Walker, *Osteoarthritis and inflammation: a serious disease with overlapping phenotypic patterns.* Postgrad Med, 2020: p. 1-8.
6. Brouwer, R.W., et al., *Braces and orthoses for treating osteoarthritis of the knee.* Cochrane Database Syst Rev, 2005(1): p. CD004020.
7. Papacrhistou, G., S. Anagnostou, and T. Katsorhis, *The effect of intraarticular hydrocortisone injection on the articular cartilage of rabbits.* Acta Orthop Scand Suppl, 1997. **275**: p. 132-4.
8. Wolfstadt, J.I., et al., *Current concepts: the role of mesenchymal stem cells in the management of knee osteoarthritis.* Sports Health, 2015. **7**(1): p. 38-44.
9. Shin, Y.S., et al., *Intra-Articular Injection of Bone Marrow-Derived Mesenchymal Stem Cells Leading to Better Clinical Outcomes without Difference in MRI Outcomes from Baseline in Patients with Knee Osteoarthritis.* Knee Surg Relat Res, 2018. **30**(3): p. 206-214.

10. Jo, C.H., et al., *Intra-articular injection of mesenchymal stem cells for the treatment of osteoarthritis of the knee: a proof-of-concept clinical trial.* Stem Cells, 2014. **32**(5): p. 1254-66.

11. Emadedin, M., et al., *Long-Term Follow-up of Intra-articular Injection of Autologous Mesenchymal Stem Cells in Patients with Knee, Ankle, or Hip Osteoarthritis.* Arch Iran Med, 2015. **18**(6): p. 336-44.

12. Nava, S., et al., *Long-Lasting Anti-Inflammatory Activity of Human Microfragmented Adipose Tissue.* Stem Cells Int, 2019. **2019**: p. 5901479.

13. Paolella, F., et al., *Effect of microfragmented adipose tissue on osteoarthritic synovial macrophage factors.* J Cell Physiol, 2019. **234**(4): p. 5044-5055.

14. Vezzani, B., et al., *Higher Pericyte Content and Secretory Activity of Microfragmented Human Adipose Tissue Compared to Enzymatically Derived Stromal Vascular Fraction.* Stem Cells Transl Med, 2018. **7**(12): p. 876-886.

15. Carelli, S., et al., *Characteristics and Properties of Mesenchymal Stem Cells Derived From Microfragmented Adipose Tissue.* Cell Transplant, 2015. **24**(7): p. 1233-52.

16. Russo, A., et al., *Autologous micro-fragmented adipose tissue for the treatment of diffuse degenerative knee osteoarthritis: an update at 3 year follow-up.* J Exp Orthop, 2018. **5**(1): p. 52.

17. Minteer, D., K.G. Marra, and J.P. Rubin, *Adipose-derived mesenchymal stem cells: biology and potential applications.* Adv Biochem Eng Biotechnol, 2013. **129**: p. 59-71.

18. Ceserani, V., et al., *Angiogenic and anti-inflammatory properties of micro-fragmented fat tissue and its derived mesenchymal stromal cells.* Vasc Cell, 2016. **8**: p. 3.

19. Bianchi, F., 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 Transplant, 2013. **22**(11): p. 2063-77.

20. Tremolada, C., V. Colombo, and C. Ventura, *Adipose Tissue and Mesenchymal Stem Cells: State of the Art and Lipogems(R) Technology Development.* Curr Stem Cell Rep, 2016. **2**: p. 304-312.

21. McConnell, S., P. Kolopack, and A.M. Davis, *The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC): a review of its utility and measurement properties.* Arthritis Rheum, 2001. **45**(5): p. 453-61.

22. Bellamy, N., et al., *Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee.* J Rheumatol, 1988. **15**(12): p. 1833-40.

23. Lehtinen, J.T., et al., *Radiographic joint space in rheumatoid glenohumeral joints. A 15-year prospective follow-up study in 74 patients.* Rheumatology (Oxford), 2000. **39**(3): p. 288-92.

24. Striano RD, M.G., Bilbool N, Azatullah K, *Refractory Shoulder Pain with Osteoarthritis, and Rotator Cuff Tear, Treated with Micro-Fragmented Adipose Tissue.* Journal of Orthopaedics Spine and Sports Medicine, 2018. **2**(1).

25. Zhang, B., et al., *Outcomes of hyaluronic acid injections for glenohumeral osteoarthritis: a systematic review and meta-analysis.* J Shoulder Elbow Surg, 2019. **28**(3): p. 596-606.

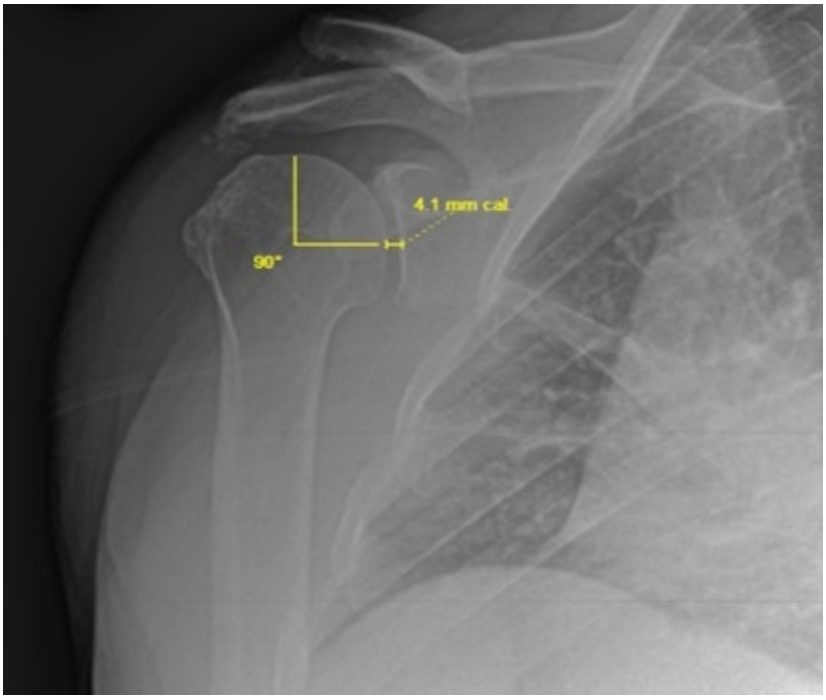
FIGURE CAPTIONS

Figure 1: External true anteroposterior view radiograph showing an OA shoulder with glenohumeral space measurement technique overlaid in yellow.

Figure 2: Graphs of normalized mean deviations from baseline (mean±SE) of VAS (A & C) and DASH WOMAC (B & D) scores for mild OA (blue) and moderate OA (red) measured during each follow-up endpoint. Quantitative comparative analysis was performed utilizing the Kruskall–Wallis test, revealing statistically significant changes from baseline value among all data sets for both mild and moderate shoulder OA ($p<0.001$***). Approximate mean percent changes from baseline values are overlaid on plots for clarity. Post-hoc analysis was performed with the Wilcoxon signed-rank test and shows statistically significant improvement ($p<0.01$**) of VAS and DASH WOMAC scores progressively over time measured with 95% confidence intervals (CI) for mild OA as indicated in plots **A** and **B**. Post-hoc analysis of data from moderate OA shoulder cases in plots **C** and **D** reveal statistical improvement over time through 18 weeks ($p<0.01$**), with no significant change after 18 weeks, but rather reveal a maintenance of results from 18 weeks to a year post Lipogems® therapy.

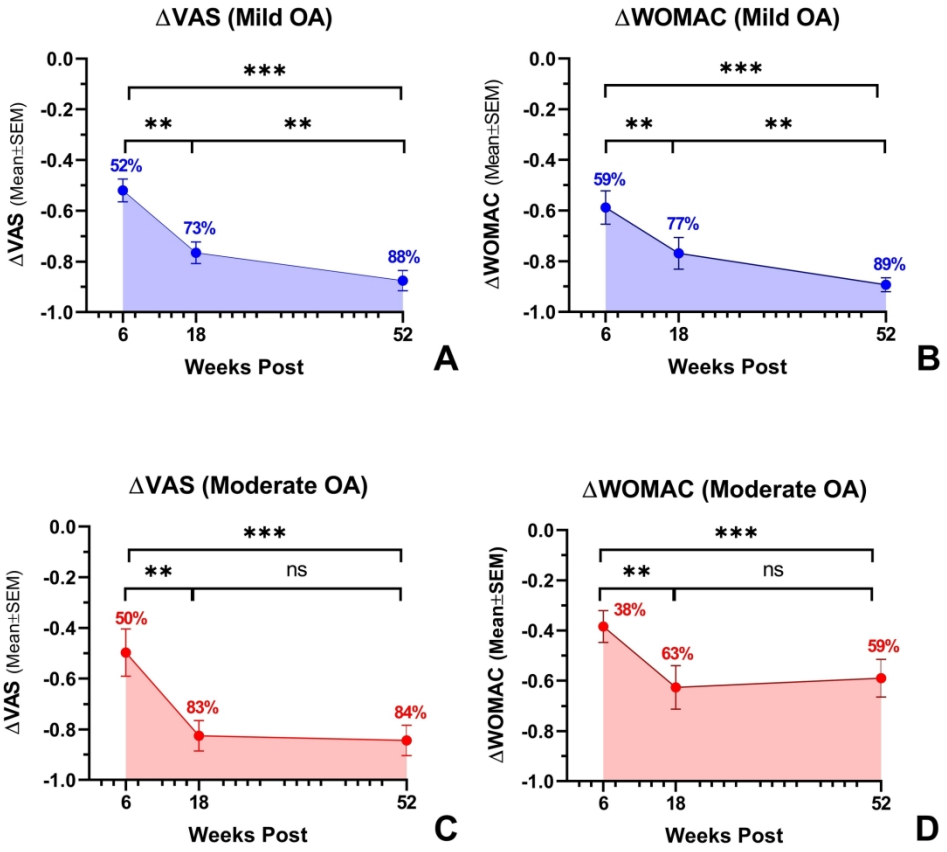
Figure 3: Graph of normalized mean deviations from baseline (mean±SE) of WOMAC scores for mild shoulder OA (blue) and moderate shoulder OA (red) for each follow up time point. Results of Mann-Whitney comparisons test among groups at each time point reveals statistically significant differences in WOMAC scores at the yearly follow up ($p<0.05$*), with marked improvement in WOMAC scores at a year post Lipogems® therapy for mild OA shoulder cases when compared to that of moderate OA shoulder cases.

Figure 4: Plot of glenohumeral joint space measurements recorded as normalized changes from baseline values for mild (**A**) and moderate (**B**) OA shoulder cases. Approximate mean percent increases in joint space are overlaid for clarity as well as mean joint space increases (mean±SE mm) for the 52 week follow up. Statistically significant (*p<0.05******) increases in glenohumeral joint spacing following MFat™ therapy up to 1 year post therapy are indicated in both graphs.



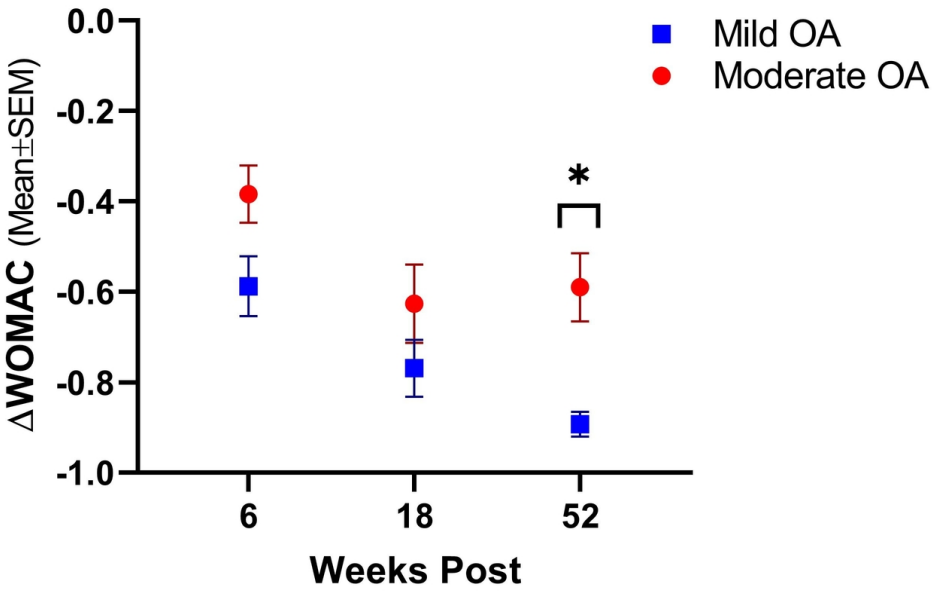
External true anteroposterior view radiograph showing an OA shoulder with glenohumeral space measurement technique overlaid in yellow.

108x91mm (96 x 96 DPI)



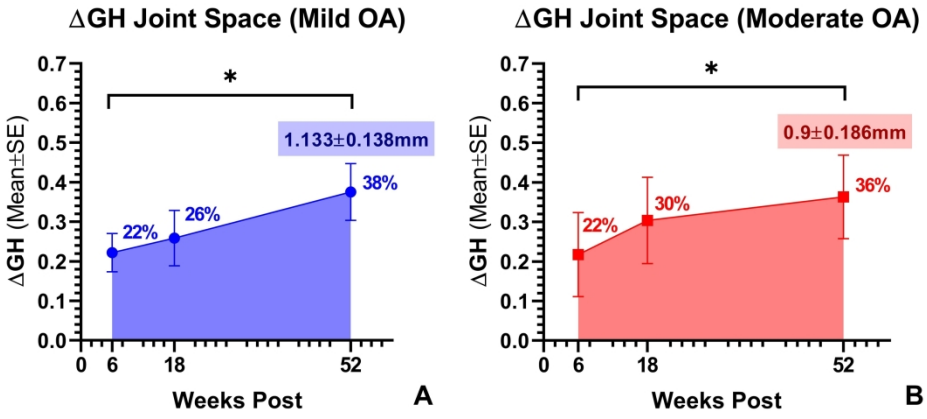
Graphs of normalized mean deviations from baseline (mean±SE) of VAS (A & C) and DASH WOMAC (B & D) scores for mild OA (blue) and moderate OA (red) measured during each follow-up endpoint. Quantitative comparative analysis was performed utilizing the Kruskall–Wallis test, revealing statistically significant changes from baseline value among all data sets for both mild and moderate shoulder OA ($p<0.001$***). Approximate mean percent changes from baseline values are overlaid on plots for clarity. Post-hoc analysis was performed with the Wilcoxon signed-rank test and shows statistically significant improvement ($p<0.01$**) of VAS and DASH WOMAC scores progressively over time measured with 95% confidence intervals (CI) for mild OA as indicated in plots A and B. Post-hoc analysis of data from moderate OA shoulder cases in plots C and D reveal statistical improvement over time through 18 weeks ($p<0.01$**), with no significant change after 18 weeks, but rather reveal a maintenance of results from 18 weeks to a year post Lipogems® therapy.

200x184mm (300 x 300 DPI)



Graph of normalized mean deviations from baseline (mean±SE) of WOMAC scores for mild shoulder OA (blue) and moderate shoulder OA (red) for each follow up time point. Results of Mann-Whitney comparisons test among groups at each time point reveals statistically significant differences in WOMAC scores at the yearly follow up ($p<0.05$*), with marked improvement in WOMAC scores at a year post Lipogems® therapy for mild OA shoulder cases when compared to that of moderate OA shoulder cases.

112x74mm (300 x 300 DPI)



Plot of glenohumeral joint space measurements recorded as normalized changes from baseline values for mild (A) and moderate (B) OA shoulder cases. Approximate mean percent increases in joint space are overlaid for clarity as well as mean joint space increases (mean±SE mm) for the 52 week follow up. Statistically significant ($p<0.05$*) increases in glenohumeral joint spacing following MFat™ therapy up to 1 year post therapy are indicated in both graphs.

260x124mm (300 x 300 DPI)