10.5005/jp-journals-10017-1079

CASE REPORT

Adipose-derived Mesenchymal Stem Cells and Arthroscopic Surgery

[1]Kwadwo A Owusu-Akyaw MD, [2]Jonathan Godin MD, [3]Stefano Pecchia MD, [4]Alexander Oldweiler BS, [5]Claude T Moorman MD

ABSTRACT

Mesenchymal stem cells (MSCs) are multipotent cells with potential reparative properties for connective tissues, such as articular cartilage. The Lipogems adipose graft harvest system is a relatively novel technique for harvesting adipose-derived MSCs and may be utilized in conjunction with various orthopaedic sports medicine procedures.

Keywords: Arthroscopy, Orthopaedic surgery, Stem cell.

Owusu-Akyaw KA, Godin J, Pecchia S, Oldweiler A, Moorman CT. Adipose-derived Mesenchymal Stem Cells and Arthroscopic Surgery. The Duke Orthop J 2017;7(1):34-38.

Source of support: Nil

Conflict of interest: None

LIPOGENIC-DERIVED PLURIPOTENT CELL BACKGROUND

Mesenchymal stem cells (MSCs) are multipotent cells with the capacity to differentiate into several different types of connective tissue, including cartilage, muscle, tendon/ligament, and fat.[1] The process by which these cells differentiate from progenitor MSCs into mature cells of each respective lineage is referred to as mesogenesis. There is evidence to suggest that these cells play a crucial role in the injury response pathway. Under physiologic conditions, MSCs are believed to generate replacement cells for those that are damaged or injured.[1] Moreover, recent investigations have suggested that secretions produced by MSCs may play a key role in tissue repair. This process is believed to be facilitated by extracellular membrane vesicles called exosomes. Exosomes may serve to transfer nucleic acids and proteins between cells to initiate a desired tissue response.[2] Exosomes secreted by MSCs help to modulate the inflammatory response in damaged tissue. Specifically, in cartilage, MSC-derived exosomes may have a protective effect on cartilage glycosaminoglycan content in the presence of the inflammatory cytokine interleukin-1 beta.[3]

CLINICAL APPLICATION

Given the reparative properties associated with MSCs, several investigators have studied the potential benefit and application for the treatment of orthopaedic conditions. It should be noted that the US Food and Drug Administration has detailed guidelines on the clinical use of human cells for implantation into a human recipient. These guidelines specify that implanted cells should undergo minimal manipulation. Moreover, it is required that implanted cells be autologous (unless derived from first- or second-degree relative). Finally, the guidelines specify that the relevant biologic characteristics of the cells not be altered.[4]

There have been multiple studies investigating the efficacy of stem cells in the treatment of both isolated cartilage lesions and osteoarthritis.[5] Pertinent to sports medicine, Koh et al[6] compared patients receiving microfracture surgery for cartilage defects of the knee with and without augmentation with adipose-derived stem cells. In a relatively small series, they demonstrated improved radiologic and subjective pain scores in the group receiving stem cell augmentation, although there was no difference in activity or quality of life. Similarly, Kim and Koh[7] compared groups receiving microfracture for osteochondral lesions of the talus alone with patients receiving this treatment with stem cell augmentation. In this series, patients receiving MSC injections had statistically improved clinical and radiographic outcomes compared with the group receiving microfracture alone.

Human MSCs may be harvested from several sources, most commonly from bone marrow aspirate and lipoaspirate. There is evidence suggesting that there may be a higher percentage of multipotent stem cells from lipogenic sources compared with bone marrow aspirate.[8,9] The process by which adipose-derived stem cells are harvested has been a subject of study. The process of isolating cells from adipose tissue has previously been performed through enzymatic methods. The Lipogems harvest system separates the stem cells from the lipoaspirate using a mechanical fragmentation process, which may produce a higher quality of multipotent cells because the structural matrix of the tissue remains relatively intact.[10]

[1-5]Reader

[1,4,5]Department of Orthopaedic Surgery, Duke University Durham, North Carolina, USA

[2] Department of Sports Medicine, Steadman Phillipon Research Institute, Vail, Colorado, USA

[3]Department of Orthopaedic Surgery, University of Rome Tor Vergata, Italy

Corresponding Author: Kwadwo A Owusu-Akyaw, Reader Department of Orthopaedic Surgery, Duke University, Durham North Carolina, USA e-mail: kwadwo.owusuakyaw@duke.edu

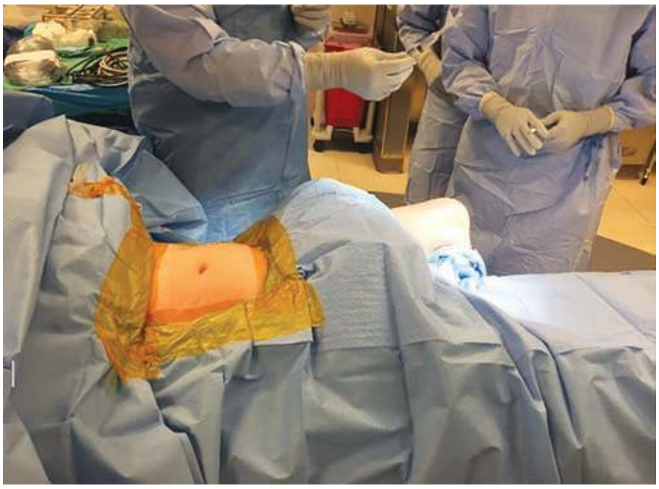


Fig. 1: Patient positioned supine for left knee arthroscopy and Lipogems harvest with cell implantation. The left knee is positioned and draped in standard fashion for planned procedure. Additionally, the abdomen is draped in preparation for fat graft harvest

Figs 2A and B: Sixty mL of tumescent solution is prepared for injection into the fat graft harvest site; (A) The solution is injected superior and inferior to the umbilicus via a small stab incision; and (B) The adipose tissue is allowed to emulsify from approximately 10 minutes. The fat graft is then aspirated

SURGICAL TECHNIQUE

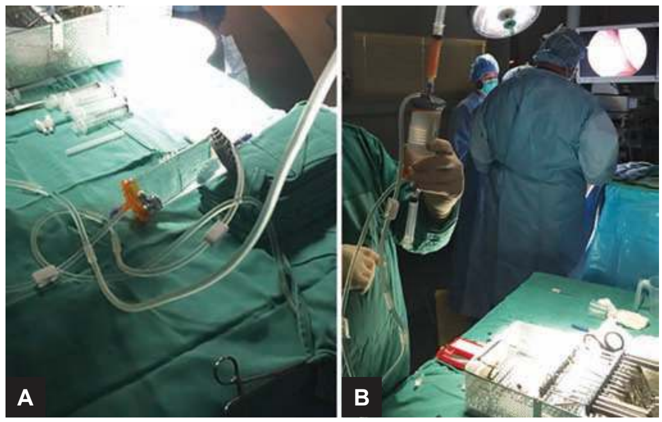
The operative extremity is prepared for arthroscopic or open procedure as indicated by the surgical plan. The abdomen is also prepared for sterile fat graft harvest (Fig. 1).

Graft Harvest

A small stab incision is made in the patient's flank, typically on the same side as the operative extremity. Sixty milliliters of tumescent solution (Galenica Senese S.r.l., Monteroni D'Arbia, Italy; 2 µg/mL final concentration) is infiltrated above the umbilicus into the subcutaneous tissue using a specialized blunt-tipped cannula. Another 60cc of solution is injected below the umbilicus. Ten minutes is allowed to pass for emulsification of the fat. To aspirate the fat graft, a 19 cm blunt cannula attached to a 10-cc Luer-Lock syringe is inserted into the infiltration site (Becton Dickinson). Using this aspiration system, liposuction is performed with gentle back and forth stroking motion with the blunt cannula while aspirating with the syringe. Ideally, a minimum of 40 to 100 mL of fat aspirate is obtained by this method (Fig. 2).

Graft Processing

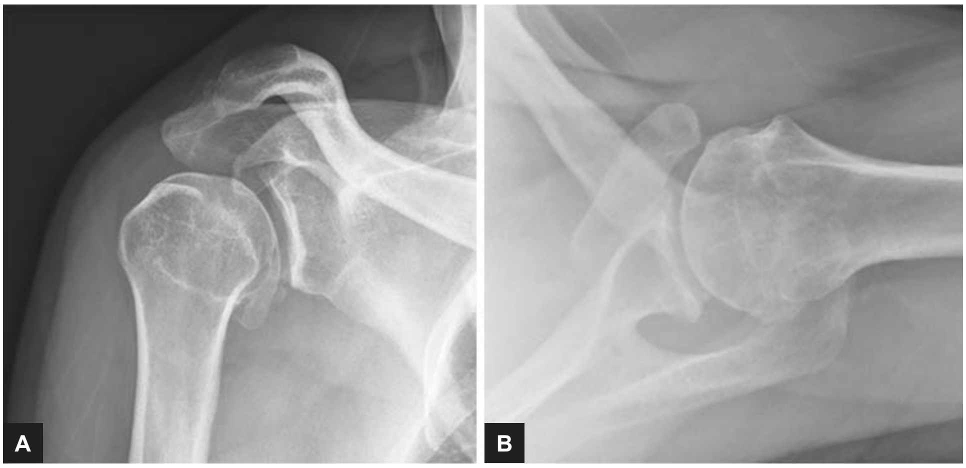
The harvested fat graft is then passed to the back table. The aspirate is injected directly into the Lipogems processing device through a large filter. Within the processing apparatus, the aspirate is emulsified with gentle mechanical force. A gravity counterflow of saline solution is used to separate adipose tissue from contaminating blood components. The adipose tissue is then passed through a series of filters to isolate clusters of human adipose-derived stem cells (hASCs). The processed lipoaspirate is injected into the affected joint, typically following completion of the surgical procedure (Fig. 3).



Figs 3A and B: (A) The adipose tissue aspirate is then injected into the Lipogems filtration system on the back table; and (B) The filtration system emulsifies the aspirate with gentle mechanical force via a set ball-bearings. The adipose stem cells are then separate using a series of filters

Case 1 – Glenohumeral Osteoarthritis

A 42-year-old male patient with progressive history of chronic bilateral shoulder pain is studied. The patient is status post bilateral shoulder labrum repairs. Patient previously participated in weight lifting and golf but had discontinued these activities due to pain. Patient examination demonstrated pain with full forward flexion and abduction with clinical signs of subacromial impingement. Radiographs of the bilateral shoulders demonstrated severe arthritic changes and acromioclavicular joint arthropathy (Fig. 4). Following discussion of potential treatment options, the patient elected to proceed with right shoulder arthroscopic biceps tenodesis, debridement

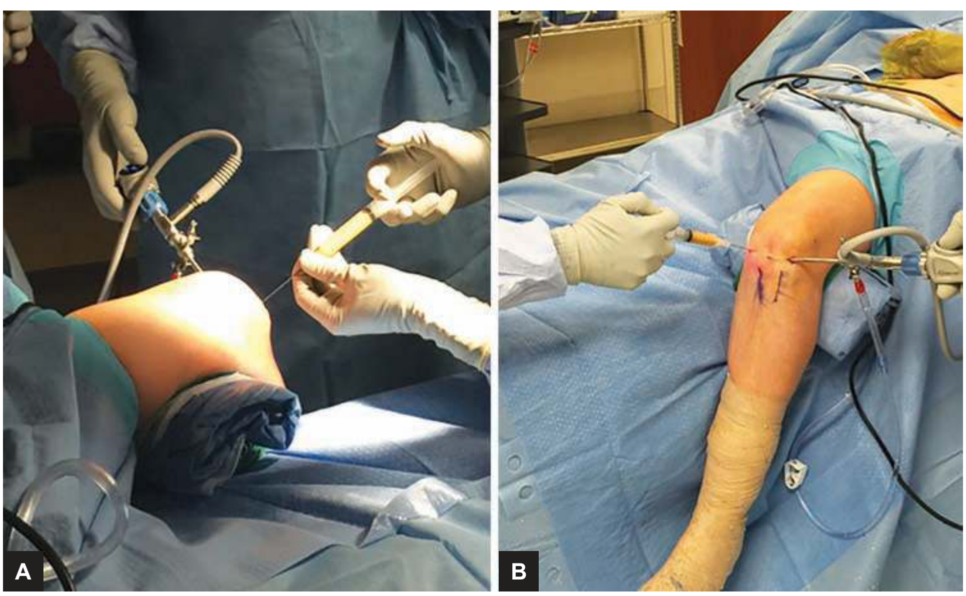


Figs 4A and B: Grashey (A) and axillary lateral (B) radiographs of the shoulder. Patient demonstrated decreased glenohumeral articular space and inferior osteophyte formation consistent with shoulder osteoarthritis. There are additional moderate degenerative changes of the acromioclavicular joint

of the glenohumeral arthritis, and subacromial decompression with adipose-derived stem cell augmentation using the Lipogems system. Liposuction was performed at the time of surgery using the abdominal fat as described earlier. The procedure was completed without complication. Postoperatively, the patient was enrolled in a physical therapy program to focus on shoulder passive range of motion (ROM) and strengthening. He was seen in clinic 1 month postoperatively with improved right shoulder pain. By his 2-month visit, the patient reported near resolution of his preoperative symptoms, as well as improved ROM compared with his preoperative condition. At that time, he elected to proceed with arthroscopic glenohumeral debridement of the left shoulder with biceps tenodesis and adipose-derived stem cell autograft (Fig. 5). The second surgery was scheduled approximately 4 months after the first. This procedure was performed without complication and a similar postoperative physical therapy regimen was initiated. One month postoperatively, the patient noted that his pain relief was not as significant as the contralateral side. At 2 months follow-up, he was prescribed a steroid taper for ongoing pain and stiffness in the left shoulder. He continued physical therapy and had dry needling therapy performed on the left shoulder. At his 4-month postoperative visit, the patient reported steady improvement of his left shoulder symptoms.

Case 2 – Multiligamentous Knee Injury

The patient is a 23-year-old male referred to our clinic following open reduction internal fixation of a left medial tibial plateau fracture sustained in a rock climbing



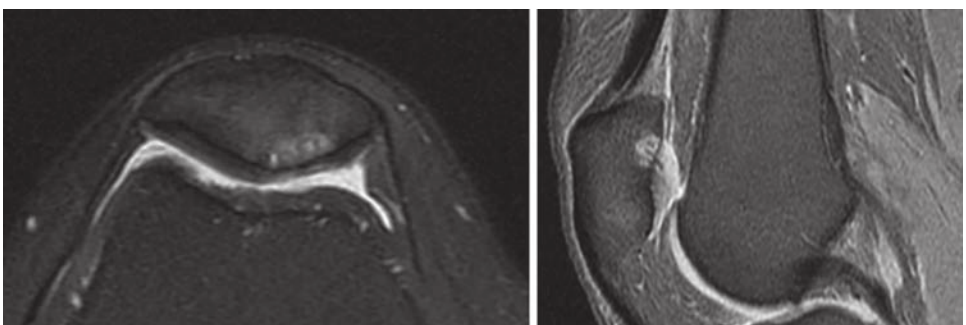
Figs 5A and B: Following completion of the arthroscopic procedure, the concentrated adipose stem cell graft is injected into the knee accident. Patient complained of ongoing subjective instability with clinical and radiographic evidence of posterior cruciate ligament (PCL), medial collateral ligament (MCL), and posterolateral corner (PLC) injuries. He initially underwent a trial of nonoperative treatment with a custom knee orthosis and physical therapy. Approximately 5 months following initial evaluation, the patient complained of ongoing knee laxity. He was determined to have failed nonoperative therapy and elected to proceed with surgical treatment, which consisted of arthroscopic-assisted reconstruction of the PCL with Achilles tendon allograft, PLC reconstruction with hamstring autograft, and open MCL repair. Adipose-derived stem cell autograft was harvested from the abdomen as described earlier, and the graft was injected into the PCL docking sites and the PLC fixation sites (Fig. 5). Patient was discharged home with instructions for non-weight-bearing on the operative extremity except for transfers (Fig. 6). He was referred to outpatient physical therapy for passive ROM exercises, strengthening, and flexibility. Patient was seen in clinic 4 weeks postoperatively, at which time he demonstrated a firm endpoint on posterior drawer testing, mild varus instability, minimal knee effusion, and quadriceps atrophy. By 3 months postoperatively, the patient continued to demonstrate excellent anterior–posterior stability and knee ROM. He was discharged from physical therapy approximately 3 months postoperatively, reporting minimal pain and instability.

Case 3 – Patellar Articular Cartilage Defect

A 49-year-old female was seen in clinic with over 1 year of anterior right knee pain. She reported that pain began after an injury sustained while exercising. She had undergone 3 months of physical therapy without improvement of symptoms. Pain was exacerbated with stair use. On examination, she demonstrated tenderness to palpation over the quadriceps tendon and mild effusion with pain at maximal extension. Magnetic resonance imaging of the right knee demonstrated full-thickness articular cartilage fissuring of the medial patellar facet. Given her long-standing symptoms and lack of improvement with conservative measures, she elected to proceed with arthroscopic chondroplasty of the patellar chondral defect with injection of adipose-derived stem cells. In the operating room, a grade IV chondral lesion was noted on the medial patellar facet. The edges were stabilized and loose fragments were removed. The Lipogems harvest was prepared as described earlier and injected into the joint. Postoperatively, the patient was referred to physical therapy for general stretching and strengthening of the right knee. When seen in clinic 4 weeks postoperatively, she was reported to be progressing appropriately with physical therapy. At her 8-week visit, she reported increased activity levels with only occasional knee soreness and improved ability to ambulate on stairs. Patient was discharged from care at that time with plan to follow-up as needed.

Short-term Results

We have collected telephone survey data for nine subjects who have undergone the Lipogems fat graft harvest and injection system in association with knee or shoulder surgery. These nine subjects had a variety of procedures performed in coordination with their Lipogems injection. Concomitant procedures



Figs 6A and B: Axial T2-weighted (A) and sagittal proton density (B) of the knee. Patient demonstrated partial thickness articular cartilage defect of the medial patellar facet with diffuse trochlear cartilage delamination included the following: Arthroscopy of the knee with synovectomy and meniscal debridement, arthroscopic chondroplasty and microfracture of the patellofemoral joint, ligamentous knee reconstruction, arthroscopic shoulder debridement, and arthroscopic rotator cuff repair with acromioplasty and distal clavicle excision. Phone surveys were conducted to evaluate patients for perioperative complications. There were no cases of excessive blood loss, hypothermia, visceral perforation, fat embolism syndrome, thromboembolic event, or pulmonary edema. With regard to donor site pain, three subjects reported mild to moderate pain within the first week of the procedure. No subject reported donor site pain 1 month postoperatively. Two subjects reported ecchymosis at the donor site lasting 1 week.

DISCUSSION

There has been increasing investigation into the use of MSCs as a therapeutic tool for the treatment of osteoarthritis. Mesenchymal stem cells represent multipotent cells with the capacity to differentiate into progenitor cells for various connective tissues (bone, cartilage, etc.). These cells may be harvested from different sources including adipose tissue and bone marrow aspirate.[11] There is evidence to suggest that MSCs have some capacity for cartilage repair.[1] Previous investigations have demonstrated that lipogenic sources of MSCs contain a higher percentage of viable multipotent cells when compared with bone marrow aspirates.[8,9] Moreover, when compared with enzymatic processing, mechanical methods for separating MSCs from fat aspirate may produce a higher quality of multipotent cells.[10] Our described technique allows for the harvesting and administration of lipogenic pluripotent cells at the time of arthroscopic procedure. On a very limited short-term basis, we have not demonstrated any serious donor site complications. There are future plans to perform prospective clinical trials evaluating the efficacy of the Lipogems harvest system in sport medicine surgical procedures.

CONCLUSION

Nine patients undergoing lipogenic pluripotent cell harvest and aspiration at the time of arthroscopic procedure demonstrated no serious donor site complications at 7 and 30 days following the procedure. The Lipogems system represents a viable option for harvesting and administrating hASCs intraoperatively. Further long-term outcomes data are needed to fully understand the safety and outcomes profile for this system.

REFERENCES

1. Caplan AI. Review: mesenchymal stem cells: cell-based reconstructive therapy in orthopedics. Tissue Eng 2005 Jul-Aug;11(7-8):1198-1211.
2. Yáñez-Mó M, Siljander PR, Andreu Z, Zavec AB, Borràs FE, Buzas EI, Buzas K, Casal E, Cappello F, Carvalho J, et al. Biological properties of extracellular vesicles and their physiological functions. J Extracell Vesicles 2015 May;4:27066.
3. Rey-Rico A, Reinecke J, Wehling P, Cucchiarini M, Madry H. Effects of exosomes upon the metabolic activities of human osteoarthritic articular cartilage in situ. Osteoarthr Cartil 2015 Apr;23(2):A399.
4. U.S. Department of Health and Human Services. Minimal manipulation of human cells, tissues, and cellular and tissue-based products: draft guidance for industry and Food and Drug Administration staff. Silver Spring (MD): U.S. Department of Health and Human Services; 2014.
5. Koh YG, Choi YJ, Kwon OR, Kim YS. Second-look arthroscopic evaluation of cartilage lesions after mesenchymal stem cell implantation in osteoarthritic knees. Am J Sports Med 2014 Jul;42(7):1628-1637.
6. Koh YG, Kwon OR, Kim YS, Choi YJ, Tak DH. Adipose-derived mesenchymal stem cells with microfracture versus microfracture alone: 2-year follow-up of a prospective randomized trial. Arthroscopy 2016 Jan;32(1):97-109.
7. Kim YS, Koh YG. Mesenchymal stem cell injection for osteochondral lesions of the talus: response. Am J Sports Med 2014 Jun;42(2):NP35-NP36.
8. Banfi A, Bianchi G, Galotto M, Cancedda R, Quarto R. Bone marrow stromal damage after chemo/radiotherapy: occurrence, consequences and possibilities of treatment. Leuk Lymphoma 2001 Sep-Oct;42(5):863-870.
9. Strem BM, Zhu M, Alfonso Z, Daniels EJ, Schreiber R, Beygui R, MacLellan WR, Hedrick MH, Fraser JK. Expression of cardiomyocytic markers on adipose tissue-derived cells in a murine model of acute myocardial injury. Cytotherapy 2005 Feb;7(3):282-291.
10. Bianchi F, Maioli M, Leonardi E, Olivi E, Pasquinelli G, Valente S, Mendez AJ, Ricordi C, Raffaini M, Tremolada C, 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 oct;22(11):2063-2077.
11. Filardo G, Madry H, Jelic M, Roffi A, Cucchiarini M, Kon E. Mesenchymal stem cells for the treatment of cartilage lesions: from preclinical findings to clinical application in orthopaedics. Knee Surg Sports Traumatol Arthrosc 2013 Aug;21(8):1717-1729.