TITLE: Adipose Derived Stromal Cell Transplantation as an Adjunct to Arthroscopy in Treatment of Effusion Synovitis of the Early Degenerative Knee

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Abstract:

This is a prospective study that will evaluate the early clinical outcomes of adipose-derived stromal cell injection plus arthroscopic debridement in the management of symptomatic effusion synovitis in patients with meniscal tears and knee osteoarthritis. There has been increasing focus on the use of mesenchymal stromal cells (MSCs) in the management of knee joint pathology including early knee OA. Specifically, MSCs obtained from fat tissue is called autologous adipose stromal cells (ADSCs) and is garnering attention as a treatment of the painful degenerative knee joint. Part of the enthusiasm behind use of ADSCs as a treatment is the potential abundance of cells that can be harvested from the lipoaspiration (harvested fat cells), the high concentration of MSCs within the fat harvest and the low morbidity associated with fat harvesting and subsequent injection. Lipogems is an innovative suction lipoplasty system that involves the harvesting, processing and injection of 'microfragmented, minimally manipulated' fat that is composed of MSCs. Lipogems has been clinically available since 2013 and was FDA approved for orthopedic surgery in 2016.

At this institution, the senior authors (RJW; AP) have been performing ADSCs using Lipogems as an addition to knee arthroscopy since 2016. Since its FDA approval, the Lipogems suction lipoplasty technique has been proposed as a treatment option in the management of mild to moderate osteoarthritis. While initial ADSC studies with Lipogems for management of osteoarthritis have demonstrated promising results, the clinical outcomes (functional, patient reported and radiographic) of ADSC as an adjunct to knee arthroscopy in the management of symptomatic knee effusion in the setting of osteoarthritis with meniscal tear is unclear.

The first aim of this study is to report the patient-reported outcomes (pain, function and quality of life) after ADSC + arthroscopy for the management of symptomatic knee swelling and inflammation (effusion synovitis) in patients with mild to moderate knee OA with or without meniscal tear. We will do this by comparing the characteristics among patients above and below a minimal important clinical change (MIC) threshold of 8 points on the KOOS pain scale to determine any clinical predictors for failure among this patient population.

The second aim is to report the clinical outcomes of ADSC and arthroscopy in this patient population. Clinical outcomes will include presence and severity of knee effusion as well as measured knee range of motion at 2 weeks, 6 weeks, 12 weeks, 6 months and 1 year. Clinical outcomes will also include adverse events related to ADSC + arthroscopy within 90 days of treatment.

The third aim of the study is to report the radiographic outcomes of ADSC and arthroscopy in this patient population. To achieve this, baseline preoperative non-contrast MRI will be compared to repeat MRI at 6 months by a board-certified radiologist.

The final aim will be to retain discarded lipoaspirate from all patients in order to create a repository of lipoaspirate specimens for future study.

Patients who present to the senior authors (RJW, AP) clinic with clinical and radiographic findings consistent with early symptomatic degenerative knee OA with effusion synovitis who have failed conservative treatment and who would have otherwise been indicated for knee arthroscopy with ADSC based on the clinical judgement of the senior authors, are screened, and approached by research staff based on the inclusion and exclusion criteria outlined in the study protocol.

Patients who meet criteria for the study will under knee arthroscopy with adjunct ADSC injection as routinely performed by the senior authors. Following the procedure, they will be followed at clinical intervals of 2 weeks, 6 weeks, 12 weeks, 6 months and 1 year to report clinical and radiographic outcomes of the procedure. Ultimately, 50 patients will be enrolled in this prospective observational study

Hypotheses:

- Hypothesis 1:
    - (a) We hypothesize that the majority of patients undergoing ADSC+ knee arthroscopy will meet the MIC of 8 points on the KOOS pain scale from baseline to 6 months.
    - (b) Patients undergoing ADSC + arthroscopy will also demonstrate improvements on the other 4 KOOS subscales: KOOS Symptoms, Function in daily living (KOOS ADL), Function in Sport and Recreation (KOOS Sport/Rec), and knee-related Quality of Life (KOOS QOL).
    - (c) Patients undergoing ADSC + arthroscopy achieving the MIC on the KOOS pain scale will also demonstrate improvements on the IKDC score and the NRS pain subscale.
    - (d) Patients undergoing ADSC + arthroscopy achieving the MIC on the KOOS pain subscale will maintain it at 12 months.
- Hypothesis 2:
    - Patients undergoing ADSC + arthroscopy will have clinical improvement of at least one effusion grade and no change in knee range of motion at all measured time points out to 1 year.
- Hypothesis 3:
    - Repeat MRI will demonstrate measurable improvement in effusion/synovitis features from baseline.

Trial Design:

- Participants are screened and approached by research staff based on the inclusion and exclusion criteria outlined below. If patients are not found to meet the inclusion criteria for the intervention at the time of their diagnostic arthroscopy, they will not undergo suction lipectomy graft harvesting. Only patients who are eligible based on inclusion criteria will undergo the graft harvest.
- <u>Diagnostic Arthroscopy and Harvesting</u>

- A diagnostic arthroscopic examination of the knee is performed in all eligible patients using standard anterolateral and anteromedial portals and a 4-mm arthroscope. The treating surgeon will exam the medial, lateral, and patellofemoral joint compartments and grade the intra-articular pathologic changes. If the patient is confirmed to be eligible, then the surgeon will proceed with adipose graft harvesting from the abdomen using liposuction per standard protocol (see adipose harvest protocol below). After the Adipose Tissue Emulsification and Harvest portion of the protocol is completed, the surgeon proceeds with the remainder of the knee arthroscopy.
- **Any reactive synovitis is debrided. The knee is inspected for meniscal tears, loose bodies, chondral flaps, synovial plica and fat pad adhesions, which can be addressed surgically without excluding the patient from the study.** Concomitant procedures that are allowed will include: chondroplasty, partial meniscectomy, plica excision, arthroscopic debridement including synovial debridement All therapeutic procedures are carefully documented and no invasive procedures beyond debridement of chondral flaps, meniscus or other soft tissue is allowed (such as microfracture, meniscal repair, ligament repair or reconstruction, osteotomy or other realignment procedures) .

- <u>Patient Positioning:</u>
  - The patient is positioned supine. Prophylactic antibiotics are given intravenously prior to skin incision. The abdominal area and lower extremity are draped and then prepped using ChloraPrep. The entire abdomen from the xiphoid process to the pubiSterile 1015 U-drapes (Steri-Drape; 3M, St. Paul, MN) are placed just distal to the tourniquet and around the prepped area of the flanks and abdomen. Sterile split drapes are then used to drape the abdominal area free followed by an extremity drape. A rectangular area is cut in the extremity drape to expose the abdominal area. Four strips of 3M Ioban 2 Antimicrobial Drapes are used to seal the operative field along the perimeter of the cut-out section in the extremity drape
- <u>Adipose Tissue Emulsification and Harvesting:</u>
  - The right flank area is injected with 1% lidocaine with epinephrine to create a small skin wheal. An 11-blade scalpel is used to make a stab incision in the subcutaneous tissue. The tumescent solution contains 25 mL of 2% lidocaine and 0.5 mL epinephrine (1:1,000) in a 250-mL bag of normal saline. This solution is injected subcutaneously using a 18 gauge cannula. Sixty milliliters of solution are injected below the umbilicus and 60 mL above the umbilicus. Gentle agitation of the tissue using a hacking tapotement technique is completed followed by a 10-minute resting period to allow for adequate emulsification. The adipose tissue is then harvested with the liposuction cannula connected to a 10-mL Vaclok syringe (Lipogems International, Milan, Italy). This syringe allows the plunger to lock, creating a negative pressure vacuum. Liposuction of abdominal fat is performed using brisk broad strokes until a total of 80 to 120 mL of aspirate is obtained depending on the patient's body habitus. The adipose tissue from each of the Vaclok syringes is transferred to a single 60-mL syringe using a luer lock connector. Enough adipose tissue is collected to prepare a 15cc quantity of transplantable lipoaspirate.

- Lipoaspirate Processing:
    - The processing cylinder (Lipogems) containing the 5 stainless steel marbles is connected to 2 hoses. The hose attached to the blue or orange size reduction filter is connected to a bag of normal saline. The gray size reduction filter on the opposite end of the cylinder is attached to a hose connected to a waste bag, which rests on the floor. The cylinder is then rotated so that the gray filter points upward. Both the blue/orange filter hose and waste hose are opened to allow the cylinder to fill with normal saline while holding it vertically and shaking intermittently to remove air bubbles. Both hoses are then clamped closed once the cylinder is filled completely. The 60- mL syringe containing the lipoaspirate is connected to the blue/orange filter. The adipose tissue is injected into the processing cylinder through the blue/orange filter with the clamp on the gray waste side open. With the blue/orange filter pointing up, both clamps are opened to allow for rinsing or elimination of blood and oily impurities into the waste bag. Once the fluid is transparent, the shaking process will begin. Both hoses are clamped closed, and the cylinder is shaken for 30 seconds to allow the action of the steel spheres to emulsify and microfracture the adipose tissue. This sequence is repeated, followed by a final wash. Two 10-mL luer lock syringes are connected to both sides of the chamber in order to allow removal of the stem cell product. The processing cylinder is flipped with the gray filter at the top. The blue/orange filter hose is opened. Through the syringe connected to the blue/orange filter a full 10 mL of saline is drawn. The blue/orange filter hose is closed. The cylinder is held vertically with the gray filter at eye level. Acting on the syringe connected to the blue/orange filter, the saline is pushed into the cylinder, thus forcing the stem cell product through the gray filter into the empty syringe connected on top. The top syringe containing the stem cells is removed and placed facing up to allow the cells to settle within the syringe and separate from the excess fluid. The cylinder is shaken slightly, and the process is repeated to continue retrieving the cells. This is performed until no more cells are yielded from th cylinder. The individual syringes that were left standing on the bac table are decanted, removing the excess fluid that has separate from the stem cells. The cells are then combined into one syringe using a white luer lock connector. The goal is to obtain 15 mL of final stem cell product of which, 10mL will be injected into the knee.
    - The knee is aspirated dry, and the anteromedial portal is closed. An 18-gauge needle is placed into the knee and intraarticular placement is confirmed with direct visualization. Following placement of the needle, the arthroscope is removed, and the anterolateral portal is closed. The lipoaspirate syringe is applied to the remaining needle and the contents (10mL) are injected into the knee. The knee and the abdominal donor sites are sterilely dressed in standard fashion.
    - The remaining 5 mL (of the original 15mL aliquot) will be sealed in a 5 mL syringe and given to the research assistant for storage. The stored 5mL syringe will be transported by the research assistant to the HSS core histopathology lab for storage within 1 hour of preparation.

Primary Outcome:

- Primary Outcome - Baseline, 2 weeks, 6 weeks, 12 weeks, 6 months and 12 months
    - Knee Injury and Osteoarthritis Outcome Score pain subscale
        - The minimal important clinical change (MIC) threshold on the KOOS pain scale is 8 points

Secondary Outcome:

- Secondary Outcomes - Baseline, 2 weeks, 6 weeks, 12 weeks, 6 months and 12 months
- Patient-reported outcomes
    - KOOS subscales (0 -100 points per scale)
    - KOOS Symptoms
    - KOOS ADL - Function in daily living
    - KOOS Sport/Rec - Function in sport and recreation
    - KOS QOL - knee-related quality of life
        - International Knee Documentation Committee subjective knee form (IKDC-SKF) (0 -100 points)
        - Numerical Pain Rating Scale for pain in KNEE (0-10)
        - Promis Global-10
        - Marx Activity Rating Scale
- Clinical Outcomes
    - Effusion grade based on stroke test effusion grading scale (Sturgill et al, JOSPT 2009)
    - Knee ROM measure using goniometer
- Adverse events:
    - Surgical site complications – knee effusion requiring therapeutic aspiration, surgical infection, knee stiffness requiring surgical manipulation
    - Donor site complications – persistent donor site pain, contour defects, permanent skin color changes, infection, embolism, hematomas, or seromas, persistent post-operative bleeding.
    - Re-arthroscopy or knee replacement within 1 year of intervention.

- Tertiary outcomes - Baseline, 6 months
    - The radiological efficacy of the procedure will be measured using the MRI OA Knee Score (MOAKS) criteria by a board certified radiologist to assess extent of effusion-synovitis as well cartilage damage using ICRS criteria on HSS-quality MRI scans, using fluid-sensitive sequences (such as intermediate-weighted sequences with and without fat suppression) and proton-density sequences. An MRI to assess ICRS grade will be performed at 6 months

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