

Preliminary Report

Adipose Derived Stromal Cell (ADSC) Injections for Pain Management of Osteoarthritis in the Human Knee Joint

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Abstract

Background: This safety and feasibility study used autologous adipose-derived stromal vascular cells (the stromal vascular fraction [SVF] of adipose tissue), to treat 8 osteoarthritic knees in 6 patients of grade I to III (K-L scale) with initial pain of 4 or greater on a 10-point Visual Analog Scale (VAS).

Objectives: The primary objective of the study was evaluation of the safety of intra-articular injection of SVF. The secondary objective was to assess initial feasibility for reduction of pain in osteoarthritic knees.

Methods: Adipose-derived SVF cells were obtained through enzymatic disaggregation of lipoaspirate, resuspension in 3 mL of Lactated Ringer's Solution, and injection directly into the intra-articular space of the knee, with a mean of 14.1 million viable, nucleated SVF cells per knee. Metrics included monitoring of adverse events and preoperative to postoperative changes in the Western Ontario and McMaster Universities Arthritis Index (WOMAC), the VAS pain scale, range of motion (ROM), timed up-and-go (TUG), and MRI.

Results: No infections, acute pain flares, or other adverse events were reported. At 3-months postoperative, there was a statistically significant improvement in WOMAC and VAS scores ($P < .02$ and $P < .001$, respectively), which was maintained at 1 year. Physical therapy measurements for ROM and TUG both improved from preoperative to 3-months postoperative. Standard MRI assessment from preoperative to 3-months postoperative showed no detectable structural differences. All patients attained full activity with decreased knee pain.

Conclusions: Autologous SVF was shown to be safe and to present a new potential therapy for reduction of pain for osteoarthritis of the knee.

Level of Evidence: 4



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Osteoarthritis (OA) of the knee results from degeneration of the cartilage in the knee and is the most common musculoskeletal disorder (> 10% of Americans).¹ Risk factors for OA include age, heredity, injury, excessive exercise, obesity, and disease, and occurrence is expected to increase exponentially as the world population ages and obesity increases.² Currently, treatments for OA include medication to control pain, injection of corticosteroids to reduce inflammation, or injection of viscosupplements based on hyaluronic acid. None of these treatment types reverse or repair the degenerative nature of the disease.³ Regenerative cell therapy uses the anti-inflammatory and healing properties of a patient's own cells to treat inflamed and painful tissues.

Recent studies on animals and humans have shown the efficacy of adipose-derived stem and stromal vascular

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fraction (SVF) cells to decrease inflammation and pain and to increase range of motion (ROM) in joints.⁴⁻¹¹

Regenerative cells that may be derived from adipose tissue include the SVF cells, which are a heterogeneous reparative cell population.¹²⁻¹⁸ The adipose-derived SVF cells are readily obtained from human lipoaspirate samples using enzymatic digestion to separate the SVF cells from the extracellular matrix and the adipocytes. The SVF obtained from adipose tissue has been characterized by flow cytometry and contains a mesenchymal stem cell compartment (6.7%), an endothelial precursor cell compartment (2%), and a monocyte/macrophage compartment (10%).¹⁹⁻²¹ Differences in cytometric assessment result from different isolation techniques, different cell surface markers, and/or different gating strategies for the flow cytometer. The SVF does not include any mature adipocytes (floating cells). Only non-floating mono-nucleated cells are counted in the SVF, and the counting method used to assay the SVF needs to be capable of accurately excluding red blood cells (RBCs), other nonviable small debris fragments, and oil droplets.

In this article, we describe autologous adipose-derived SVF to treat OA in 8 knees of 6 patients (2 patients with bilateral OA and 4 patients with unilateral disease) with initial pain evaluated at 4 or greater on a 10-point Visual Analog Scale (VAS), a validated pain scale instrument. Our primary objective with this pilot study was to evaluate the safety of SVF injection for OA of the knee and potential clinical changes in knee pain resulting from SVF injection.

METHODS

Study participants voluntarily provided written informed consent to participate in the study and signed the Health Insurance Portability and Accountability Act (HIPAA) authorization before any study procedures were performed. This clinical study received institutional review board review and approval (IntegReview, Austin, TX) and was conducted in accordance with the guidelines set forth in the International Conference on Harmonisation and Declaration of Helsinki. The study is listed on the clinical trials.gov website (number NCT02357485).

Study Inclusion/Exclusion Criteria

Inclusion criteria were men and women, aged 20 to 70 years, Kellgren-Lawrence Scale (K-L, a 1 to 4 scale with 1 indicating beginning signs of osteoarthritis and 4 indicates end stage osteoarthritis) grades I to III radiologically documented OA of 1 or both knees, American Society of Anesthesiologists class I to II, body mass index (BMI) less than 35 kg/m², knee pain graded as greater than 4 out of 10 on screening questionnaire, having previously tried a regimen of anti-inflammatory systemic medicines and/or physical

therapy and/or injections (corticosteroids or viscosupplements), and the ability to speak, read, and understand English. Exclusion criteria were any patient parameters falling outside of the inclusion criteria parameters, any current oral or parenteral steroid or blood thinner use, any hyaluronic acid-based injection to the affected knee joint within the previous 6 months, or any corticosteroid injection to the affected knee joint within the previous 3 months. End stage (Grade IV) OA was excluded. The patient screening questionnaire assessed the participant's ability to avoid steroids or strong pain medications during the study.

Adipose Harvest

Because some of the patients enrolled in the study presented with low BMI and limited donor tissue that necessitated harvest from multiple sites, it was elected, for standardization of the approach, to utilize laryngeal mask airway general anesthetic for all patients. Adipose tissue was harvested from the abdomen, flanks, and or lateral thighs. The SuperWet technique was used with approximately 1 cc of infusate for each cc of estimated aspirate. Wetting solution (1 L Lactated Ringer's [LR], 50 mg 1% lidocaine, and 1 cc of 1:1000 epinephrine) was administered to donor subcutaneous fat through infiltration prior to suction. Fat was harvested with the standard Suctioned-Assisted Lipoplasty (SAL) method with a 3.7 mm blunt Mercedes cannula. A target volume of approximately 150 to 250 cc of lipoaspirate was harvested directly into a sterile tissue-processing container (GID SVF-1, Louisville, CO). The harvested adipose tissue was processed completely within the tissue-processing container to produce the SVF. The SVF dose was a direct result of the SVF generated from the adipose harvest. For the 2 patients with bilateral OA, the SVF was divided between the 2 knees.

Just before the patient emerged from general anesthetic, the affected knee(s) was injected subcutaneously at the planned intra-articular injection site with 1% Marcaine (bupivacaine HCl; Hospira Inc., Boulder, CO). The injection of the local anesthetic was superficial with extreme care taken not to enter the intra-articular space.

Adipose-Processing Method

The entire harvest and tissue processing for the SVF was accomplished within the SVF-1 sterile disposable device, which contains the washing mechanism, the mesh filter, and the centrifuge capability. After harvest, the lipoaspirate was washed 3 times with 37°C LR solution and the fluid portion was removed using the mesh filter system, leaving washed adipose tissue inside the canister. The washed adipose was disaggregated using Type I collagenase (Worthington, Lakewood, NJ) at a concentration of 200 CDU/mL of total catalytic volume in which total catalytic volume is the volume of the adipose tissue plus an equal volume of 37°C LR solution. The collagenase

was injected into the canister through a sterile 0.22- μm sterilizing filter (Millex-MP, Millipore, Cork, Ireland). The device with adipose, LR solution, and collagenase was then placed into an incubated shaker for 40 minutes at 38°C at 150 revolutions per minute. After disaggregation, human albumin solution was added to achieve a concentration of 2.5% and to reduce further collagenase activity. The device was then centrifuged at 800g for 10 minutes (Sorvall ST-40, ThermoScientific, Asheville, NC) to concentrate the cell pellet (Figure 1). The supernatant, including all floating cells and debris and the aqueous phase, was removed using a port on the top of the device and discarded. The SVF pellet at the bottom was resuspended in 3 mL (single knee) or 6 mL (bilateral knees) of sterile LR solution accessed via the central port on the device using a 14 gauge 5.5-in spinal needle (Abbotath-T, Hospira, Sligo, Ireland). A 0.5 mL sample of the resuspension was collected in a 1.5 mL Eppendorf tube to be used for cell counting and assay. The 6 mL of resuspended SVF cells was divided between two 3 mL syringes for patients with bilateral OA.

Cell Counting

The SVF cell count and viability was assessed using a ChemoMetec NC-200 image cytometry system (ChemoMetec, Allerød, Denmark). The NC-200 uses acridine orange and DAPI staining to count viable and nonviable nucleated cells. A 100 μL aliquot of the assay sample was diluted with a 1:5 ratio (1 part sample to 5 parts sterile LR solution) to adjust the sample within the operating limits of the NC-200. The total volume of the resuspension in the syringe was multiplied by the concentration to give the total number of resuspended mononucleated cells (no adipose cells, no RBCs, and no fragments included in the counting process).

Injection

Once the patient emerged from general anesthetic, the patient was transferred from the operating table on to a

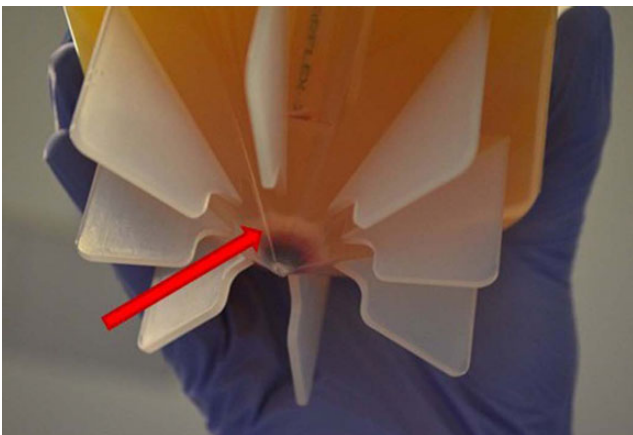


Figure 1. GID SVF-1 device (Louisville, CO) with concentrated cell pellet.

gurney and kept in the supine position. The knee joint was evaluated for the presence of effusion using diagnostic ultrasonography (Sonosite, Bothell, WA).

Next, the knee joint(s) were circumferentially re-prepped with Technicare solution (Aplicare Inc., Meridian, CT) and draped in the usual sterile fashion. If an effusion was found at the ultrasonography, up to 5 mL of fluid in the knee joint was aspirated using an 18 gauge 1.5-in needle. All of the 3 cc of SVF suspension was then slowly injected into the intra-articular space through the same 18 gauge/1.5-inch needle. The needle was then removed and direct pressure applied over the injection site for approximately 10 seconds. Hemostasis after injection was confirmed and the injection site was cleaned with an alcohol wipe and covered with a sterile bandage.

Postoperative Instructions

The patient was given crutches and instructed to be non-weight bearing on the injected knee for 2 days. The patient was allowed to bend and flex the knee as long as nonweight bearing was observed.

Pain and Mobility Assessment

Knee pain and daily function was assessed using the Western Ontario and McMaster Universities Arthritis Index (WOMAC) patient questionnaire, a validated pain and function scale developed for assessment of OA (a blank copy of the WOMAC questionnaire is available as Supplementary Material at www.aestheticsurgeryjournal.com). The WOMAC questionnaire consists of 24 questions: 5 for pain (20 total points), 2 for stiffness (8 total points), and 17 for daily activities (68 total points). Patient responses were converted to numeric values in a validated scale with a range from 0 (minimum) to 96 (maximum). Additionally, each patient was administered a VAS 10-point validated pain scale questionnaire with 0 indicating no pain and 10 indicating worst possible pain (a blank copy of the VAS scale questionnaire is available as Supplementary Material at www.aestheticsurgeryjournal.com). Both instruments were administered preoperatively and postoperatively at 3 months and 1 year.

Orthopedic Evaluation

The patient's orthopedic status was evaluated by one of the investigators (S. P., a doctor of physical therapy) prior to injection and again at 3 months post-SVF injection. ROM and timed up-and-go (TUG) measurements, as described by Podsiadlo and Richardson,²² were recorded. The TUG evaluation assessed the patient's ability to rapidly rise from a chair, move rapidly 2 m from the chair, turn, and return and sit in the chair.

Statistical Analysis

A *t* test for paired data (2-tailed) was used to determine statistical significance.

Radiologic Evaluation

Magnetic Resonance Imaging (MRI) of the patient's knee (s) preoperatively and postoperatively at 3 months was completed using a Philips Achieva 1.5 Tesla MRI device (Andover, MA), with sequencing as follows: coronal T1, STIR; axial T2 fat sat; sagittal T1, PD, fat sat. MRI was only conducted preoperatively and postoperatively at 3 months; no additional images were obtained. The study's protocol did not call for further MRIs. A comparative assessment of the preoperative and 3-month postoperative images was completed by a single, independent, experienced orthopedic radiologist.

RESULTS

All 6 patients were followed for 1 year (April 2014 to May 2015), with no loss to follow-up. Five patients were female and 1 was a male, with an age range of 51 to 69 years (mean, 59 years). Patient demographics and procedural data are shown in Table 1.

Adverse Events

Donor site postoperative course was uneventful other than minimal discomfort, edema, and ecchymosis characteristic

for small-volume lipoplasty. The patients did not experience any deformity related to adipose harvest and were uniformly content with the aesthetic quality of the outcomes. There were no adverse events (including pain and infection) related to the knee injection.

SVF Processing

Average lipoaspirate harvest was 173.5 mL, with an average viable SVF cell count of 14.1 million (Table 1). Tissue processing time from the end of harvest to delivery of the SVF in a syringe for injection into the knee was 60 to 70 minutes. The completion of the liposuction procedure and preparation of the patient for the knee injection was completed during this processing time.

WOMAC and VAS Scores

A decreasing WOMAC score and/or a decreasing VAS score represents decreasing pain (ie, an improving outcome).

The WOMAC score decreased from a preoperative mean of 32.9 to a postoperative mean of 10.8 at 3 months and 9.4 at 1 year, respectively (Table 2 and Figure 2). Results were statistically significant at $\alpha = 0.05$ for both the 3-month and 1-year postoperative time points using the *t* test for paired data (2-tailed) (Table 2).

The VAS score decreased from a preoperative mean of 5.9 to a postoperative mean of 1.8 at 3 months and 2.1 at 1 year, respectively (Table 2 and Figure 3). Results were statistically significant at $\alpha = 0.05$ for both the 3-month and

Table 1. Patient and Procedural Data

Patient	Knee No.	Side	K-L Score	Age (years)	Gender	Viable SVF Cells Injected (millions)	Total Lipoaspirate Harvest (mL)
1	1	Left	II	63	Female	41.0	215
2	2	Right	II	51	Female	7.0	160
	3	Left	III			7.0	
3	4	Left	III	51	Female	17.1	150
4	5	Left	I	64	Female	17.6	146
5	6	Right	I	58	Female	7.6	247
	7	Left	III			7.6	
6	8	Right	III	69	Male	7.9	123
Mean		NA	NA	59	NA	14.1	173.5
STD DEV		NA	NA	7.3	NA	11.8	47.3
SEM		NA	NA	2.6	NA	4.2	16.7
95% Conf. Int.		NA	NA	5.1	NA	8.2	32.7

NA, not applicable.

Table 2. Preoperative, 3-Month Postoperative, and 1-Year Postoperative WOMAC and VAS Scores

Knee	WOMAC Preoperative	WOMAC 3 Months	WOMAC 1 Year	VAS Preoperative	VAS 3 Months	VAS 1 Year
1	29	0	0	6	0	0
2	37	0	4	5	0	1
3	43	4	15	7	1	3
4	18	10	5	6	2	5
5	9	22	7	5	1	3
6	31	5	6	4	1	0
7	41	38	32	8	8	3
8	55	7	6	6	1	1
Mean	32.9	10.8	9.4	5.9	1.8	2.0
STD DEV	14.6	13.1	10.1	1.2	2.6	1.8
SEM	5.1	4.6	3.6	0.4	0.9	0.6
95% CI	10.1	9.0	7.0	0.9	1.8	1.2
<i>T</i> test (<i>p</i>) from preoperative		.020	.003	NA	.001	.0003

NA, not applicable; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Arthritis Index.

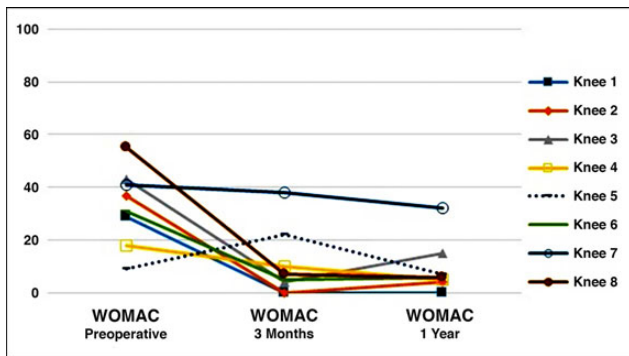


Figure 2. Preoperative, 3-month postoperative, and 1-year postoperative WOMAC Scores.

1-year postoperative time points using the *t* test for paired data (2-tailed) (Table 2).

Physical Therapy Measurements

The results for ROM and TUG testing preoperatively and postoperatively at 3 months are shown in Table 3. ROM increased an average of 10 degrees but was not statistically significant at $\alpha = 0.05$. The average time for the TUG test decreased by 2.6 seconds and was statistically significant at $\alpha = 0.05$.

Radiologic Evaluation

No significant observations of differences were detectable between 0 and 3 months in the MRI images as read by the same independent, experienced orthopedic radiologist.

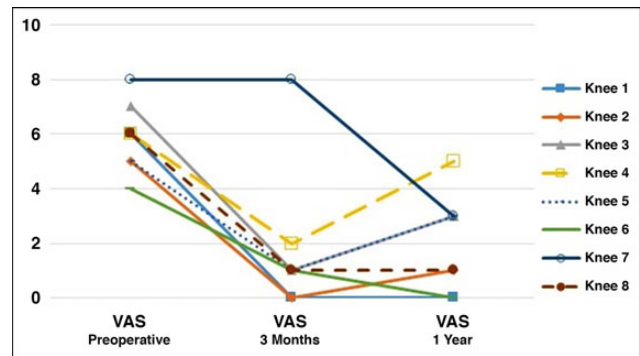


Figure 3. Preoperative, 3-month postoperative, and 1-year postoperative VAS Scores.

DISCUSSION

Similar to previous pilot studies, this study confirmed that the use of autologous adipose-derived SVF for treatment of OA pain was safe and feasible for treatment of pain.^{6,8,10,23}

This pilot study clearly confirmed that the harvest of donor adipose tissue, isolation of the SVF, and then use of the SVF for an intra-articular knee injection is a relatively simple procedure to perform by a surgeon functioning with a team limited to what he is accustomed to in the course of performing lipoplasty procedures, with the addition of approximately 60 to 70 minutes of time spent on processing and injecting 1 or 2 knees.

At 1-year postoperative, the WOMAC scores decreased (indicating improvement) in 8 of 8 knees in this study. Similarly, at 1-year postoperative the VAS scores decreased

Table 3. Preoperative and 3 Month Postoperative Knee Flexion ROM and TUG Results

Knee	ROM Preoperative (degrees)	ROM 3 Months (degrees)	TUG Preoperative (seconds)	TUG 3 Months (seconds)
1	135	156	6.0	2.5
2	135	142	6.0	2.5
3	139	144	3.0	3.0
4	138	145	3.0	3.0
5	132	145	7.0	3.0
6	130	140	7.0	3.0
7	153	145	5.0	2.5
8	131	132	6.0	3.0
Mean	136.6	143.6	5.4	2.8
Change in Mean		10.0	NA	-2.6
STD DEV	7.3	6.7	1.6	0.3
SEM	2.6	2.4	0.6	0.1
95% Conf. Int.	5.1	4.6	1.1	0.2
T test (<i>p</i>)	NA	.053	NA	.003

NA, not applicable; ROM, range of motion; TUG, timed up-and-go.

(indicating improvement) in 8 of 8 knees in this study. There was no statistically significant change in the mean WOMAC score from 3 months to 1 year. Similarly, there was no statistically significant change in the mean VAS score from 3 months to 1 year, while 2 of the knees did show an increase between 3 months and 1 year. One knee of patient 5 (knee no. 7) did not respond to the SVF injection at 3 months, with only a small change on the WOMAC score and no change in the VAS score. At 1 year this patient reported a modest improvement in the WOMAC score and a more significant improvement in the VAS score (Table 2).

The amount of SVF yield varied; however there was no dose response to the amount of SVF injected. The yield of SVF did not seem to be dependent on the amount of adipose because the highest SVF yield was not due to the greatest amount of adipose harvested (Table 1). The patient with the highest SVF yield was, however, the only patient to report no pain on the WOMAC and VAS at both 3 months and 1 year (Table 2). It is unknown why this patient had a higher SVF yield.

ROM increased by an average of 10 degrees but was not statistically significant at $\alpha = 0.05$. TUG decreased by 2.6 seconds, which was statistically significant, a reduction of 48% from an initial value of 5.4 seconds, demonstrating increased functionality.

This study shows initial longer-term benefits compared with standard-of-care treatments. Studies have shown standard-of-care treatments such as viscosupplementation and corticosteroid injections last for a few weeks to 6 months,²⁴ whereas the procedure in our study showed results were maintained for 1 year. The decrease in WOMAC and VAS scores at 3 months and the further maintenance of these scores to 1 year is indicative of the potential for this therapy.

OA is a chronic inflammatory condition of the tissues of the knee, having both inflammation and degradation of knee tissues, resulting in pain. While not specifically investigated in this study, a proposed mechanism of action for the adipose-derived SVF on tissues of the OA knee is reduction of pain due to the anti-inflammatory properties of the SVF cells.^{4,6,10,25} The inflammation-degradation cycle is difficult to interrupt, as evidenced by the relatively short-lived results of standard-of-care treatments for OA of the knee, including use of corticosteroids and viscosupplementation. Decreasing or breaking the inflammation cycle potentially gives the knee tissues a reparative period with reduced pain and slowed degradation.

Limitations

MRI imaging using standard a MRI device, and sequencing showed no observable changes between the preoperative and 3-month evaluations. This was not surprising, especially in light of the postoperative MRIs being performed only 3 months after treatment. Another MRI evaluation at least 6-months postoperative would be desirable using a different, significantly improved MRI sequencing. We learned that the critical sequencing parameter for the MRI is the step size. For the current study, a standard orthopedic 1 mm step size was used, which is not sufficient to capture small changes on the order of 0.01 or 0.1 mm. Should future studies wish to determine these changes, imaging should be conducted with a higher Tesla magnetic field and a decreased step size with advanced image assessment software. However, such imaging will take much more time than standard MRI sequencing.

At screening, patient 4 reported moderate or greater pain with a VAS score of 5 out of a possible 10 points. At the preoperative assessment, the same patient's WOMAC questionnaire score was 9 out of a possible score of 96, thus essentially documenting a minimally symptomatic knee. At 3-months postoperative, this patient reported a VAS score of 1, demonstrating decreased and minimal pain, however the WOMAC score, at the same time period, indicated that the patient's knee was more symptomatic than before treatment. It is not known why the patient reported such divergent scores, but in the future, studies using multiple questionnaires with similar measurement parameters should be interpreted as soon as possible to investigate the reason for such a dichotomy.

Placing the SVF precisely into the intra-articular space is essential for obvious reasons. Aspiration of joint fluid prior to injection is reassuring as to the correct needle placement for SVF installation into the articular space.

At this point in time, the majority of the evidence for cellular therapies comes from small studies with low numbers of patients. This pilot study was also a small study with only 8 knees and 6 patients, was not randomized, and did not include a control arm. It was designed to primarily assess feasibility and patient safety. We recognize that a control group, as in all studies, is desirable and should be the next step in evaluation. If we have the opportunity to conduct such a study, it is possible to use a design where the patients would serve as their own control, which would require individuals with bilateral disease with a similar degree of severity. One knee could be treated with SVF injection and the other, control knee, with saline injection (placebo).

We fully realize that performing a study in knee joints affected by degenerative arthritis has no readily apparent relationship with aesthetic or reconstructive surgery. However, the results of this study provide evidence of safety for the potential use of autologous adipose-derived reparative/regenerative cells in aesthetic and reconstructive surgery. Treatment with adipose-derived SVF cells of nonhealing wounds, diabetic ulcers, radiation injury, and inflamed tendons or ligaments are just some possible reconstructive applications. For this pilot study, which focused on safety and initial evidence of efficacy for treatment of pain, degenerative arthritis of the knee joint was chosen as a clinical study model because clinical outcomes are more readily quantified across a number of patients than outcomes in aesthetic surgery involving aesthetic assessment or volume retention.

CONCLUSIONS

In this pilot study, autologous SVF was shown to be safe and to present a new potential therapy for reduction of pain for OA of the knee.

Supplementary Material

This article contains supplementary material located online at www.aestheticsurgeryjournal.com.

Disclosures

The authors declared no potential conflicts of interest with respect to the research, authorship, and publication of this article.

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