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5 Therapeutic

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Preliminary Report

"SAVE"—Shock-Assisted Viable Extraction: A Minimally Manipulative Method of Processing Regenerative Cells for Clinical Use

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Abstract

Background: Extraction of adipose-derived stem cells (ASCs) from the stromal vascular fraction (SVF) has gained significant attention lately in the realm of regenerative medicine. However, finding highly efficient methods of extraction that also comply with the US regulations has prevented widespread clinical use.

Objectives: The objective of this study was to evaluate a novel ASC extraction device to quantify viable ASC extraction and processing efficiency.

Methods: SVF extracted from abdominal fat samples and processed using a novel shock-assisted viable extraction (SAVE) device was tested for stem-cell count and viability. Additionally, time required for processing was recorded.

Results: Twelve adipose samples were utilized for this study. After a mean time of 3 min, cell count yield ranged of 47,400 to 189,400 of viable regenerative cells per cc, with an average of 122,464 viable regenerative cells per cc.

Conclusions: SAVE is a novel fat-processing technique with high stem-cell extraction that shows promise from a regulatory, yield, time efficiency, and cost perspective.

Level of Evidence: 5 (Therapeutic)

Over the past 20 years, the promise of stem-cell application in plastic surgery, particularly in the supplementation of large-volume fat transplantation, has continued. However, quantifying the amount of clinical benefit has yet to be proven. Shortly after the start of the millennium, publications predicting the procurement of adipose-derived stem cells (ASCs) from lipoaspirate as an alternative to autologous bone marrow procurement[1] opened the potential for "supercharged" fat transplantation. Supplementing with ASCs was thought to increase the yield of fat viability. This stimulated clinicians to investigate stem cell–assisted fat grafting on a relatively large scale.

Despite numerous publications, there is no definitive clinical proof based on quantitative data that ASC, or regenerative cell supplementation of fat grafts, improves fat survival or volume maintenance. When stem cells are used in smaller volume recipient sites such as scar tissue and inflammatory environments, there appears to be a more demonstrable and predictable response.[2] It has been shown that stem-cell supplementation of fat grafts exhibits improved retention/survival in an animal model.[3] However, the dosages of stem cells

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required to achieve such an effect may be impractical in the large volume fat transfer clinical setting (ie, gluteal or breast augmentation).

Additionally, regulatory restrictions by the FDA regarding the use of collagenase and other enzymatic digestion processes to procure ASCs, coupled with their increasingly firm position on restricting commercialization of "manipulated" regenerative products,[4] have prevented widespread clinical implementation of stem cells in the United States. The overwhelming majority of the research on this topic comes from outside of the United States due to less stringent regulatory control. Nevertheless, the quest for "minimally manipulative" methods to process fat in order to isolate stromal vascular fraction (SVF), the layer that contains the ASCs, represents a "workaround" strategy that has been underway for the past several years.

The critical attributes necessary for a successful adipocyte extraction technique that processes fat to yield regenerative growth factors and ASCs, are as follows:

- must be time efficient (intraoperative);
- must process large volumes of fat;
- must process viable cells; and
- must have satisfactory cell yields.

The purpose of the present study is to describe and evaluate a novel process of extracting regenerative cells (SVF) using shock-assisted fat extraction.

METHODS

Twelve patients presenting for cosmetic liposuction consented for the use of their disposed fat in accordance with the Declaration of Helsinki. Patients were made aware that their fat, which would otherwise be disposed of, would be examined using a fat-processing technique.

Fat was extracted using the standard liposuction technique. After tumescent infiltration, manual lipoaspiration was performed using a combination of 3 and 4 mm multihole MicroAire (Charlottesville, VA). Samples obtained from each patient measured 50 cc. Fat was processed using shock-assisted viable extraction (SAVE; Synova Life Sciences, Inc., Los Angeles, CA). The 50 cc samples of fat were placed into a sterile cartridge bag, which was then placed into the SAVE device for processing (Figure 1).

The SAVE device works using proprietary shockwave impulses, providing a minimally manipulated separation of regenerative cells from native adipocyte lobules and stroma. The resulting 2 to 3 cc pellet of concentrated regenerative cells is generated within minutes of processing. Following processing, the samples were examined for residual adipocyte viability, SVF cell count, and SVF viability. The average time to process was also recorded.

A literature search was also conducted to obtain peer-reviewed published data on regenerative cell yields obtained using a variety of collagenase digestion methods as well as mechanical separation methods. An extensive PubMed search using the keywords "Adipose Stem Cells" AND "Processing" OR "Extraction" was performed. Papers that reported objective data that included cell counts, ASC concentrations, and/or processing times were included. The data were intended to be used in comparison with the current method being examined.

RESULTS

All 12 patients that volunteered to donate their lipoaspiration to this study were females with an average age of 26 years (range, 25-45 years). The raw data in Table 1 summarize the number of "adipocyte-derived regenerative cells" (ADRCs) using the "SAVE" platform. The third-party examination (UCLA flow Cytometry Core Facility, Department of Medicine, Division of Hematology-Oncology, David Geffen School of Medicine, CA) of samples derived from the SAVE device revealed a viable regenerative cell count of 182,800 cells/cc. This is in line with the 44 sample data sets summarized in Table 1.

Figure 1. Wave device (Synova Life Sciences, Inc, Los Angeles, CA) used for shock-assisted viable extraction.

SAVE processed 50 cc of fat in 3 min for an average processing time of 8.3 cc of fat per minute. This is in comparison with other techniques that require longer processing times. Examination of fat viability, using SAVE revealed a residual fat viability of 85%.

Examining regenerative cell yields, SAVE yielded a range of 47,400 to 189,400 viable regenerative cells per cc, with an average of 122,464 viable regenerative cells per cc of fat extracted. Table 2 compares the viable regenerative cell yields using various collagenous digestive methods, as well as several mechanical ("minimally manipulative") methods reported in the literature.[5] Examining time efficiency, SAVE yielded 47,400 viable regenerative cells per cc per minute, in comparison with other mechanical and enzymatic digestion techniques in the literature, which averaged 5000 regenerative cells per cc per minute.

DISCUSSION

ASCs and regenerative cells have shown clinical promise for nearly 2 decades. When used in large-volume fat transplantation, its advantages and beneficial effects are muted by inadequate dosing. Although efficacy in fat transplantation is indisputable, the dose–response curve, which is concentration dependent, has yet to be elucidated.

Zhu et al.[3] animal study demonstrated a successful doubling in fat graft retention, by supplementing 60 mg of donor mouse fat with 5 million cultured ASCs derived from homologous mice. This amounts to a concentration of 83 million stem cells per cc of fat grafted. Based on a yield assumption of 200,000 stem cells per cc of fat using adipocytes and collagenase digestion methods (which is not

Table 1. Raw Data on Regenerative Cell Yield, Cell, Viability, and Processing Time for 44 Runs of Shock-Assisted Fat Extraction

Regenerative cells, total	Cell viability, %	Total live cells	Regenerative cell yield/cc
5,680,000	83	4,720,000	94,400
7,280,000	77	5,580,000	111,600
7,980,000	82	6,580,000	131,600
7,420,000	85	6,280,000	125,600
5,500,000	85	4,660,000	93,200
7,000,000	86	6,010,000	120,200
10,500,000	90	9,470,000	189,400
10,500,000	89	9,360,000	187,200
6,290,000	94	5,890,000	117,800
6,480,000	94	6,090,000	121,800
6,670,000	93	6,190,000	123,800
7,280,000	91	6,620,000	132,400
7,280,000	92	6,690,000	133,800
4,820,000	95	4,570,000	91,400
3,110,000	93	2,900,000	58,000
3,620,000	96	3,480,000	69,600
4,550,000	89	4,040,000	80,800
4,700,000	91	4,290,000	85,800
4,840,000	85	4,120,000	82,400
8,680,000	76	6,620,000	132,400
7,910,000	76	6,020,000	120,400
9,380,000	80	7,530,000	150,600
8,960,000	81	7,210,000	144,200
9,730,000	78	7,580,000	151,600
6,850,000	76	5,190,000	103,800
7,560,000	81	6,090,000	121,800
2,470,000	96	2,370,000	47,400
2,470,000	96	2,370,000	47,400
9,100,000	87	7,910,000	158,200
7,630,000	92	7,030,000	140,600
9,310,000	83	7,700,000	154,000
8,330,000	85	7,060,000	141,200
8,750,000	80	6,980,000	139,600
9,310,000	83	7,700,000	154,000
8,330,000	85	7,060,000	141,200
8,750,000	80	6,980,000	139,600
6,830,000	95	6,470,000	129,400
8,960,000	77	6,890,000	137,800
7,490,000	72	5,420,000	108,400
7,210,000	86	6,210,000	124,200
7,420,000	83	6,160,000	123,200
8,120,000	83	6,750,000	135,000
8,890,000	83	7,370,000	147,400
8,960,000	81	7,210,000	144,200
7,247,727	85	Average	122,464
		Regen cells/min	40,821

The average viable regenerative cell yield was 122,464 cells/cc of fat. Adjusted for time, the SAVE platform yielded 40,800 viable regenerative cells per minute.

approved in the United States for clinical use), such a supplementation in Hedrick's study would require 25 cc of fat to process stem cells for every 60 mg of fat transferred, which is 0.06 g or 0.06 cc. If such concentrations are applied to a human clinical case, the dose becomes unobtainable. Using the above concentrations derived from Hedrick's publication, grafting 50 cc of donor fat (breast or buttock, for example) would require 21 L of fat to obtain a sufficient number of stem cells to be in line with the published dose.

The graph in Figure 2 depicts the volume of fat needed to process in order to "supercharge" various reasonable volumes of donor fat staying in line with Hedrick's published concentrations. Because ASC cannot be obtained from a regulatory perspective by enzymatic digestion or expanded using cell culturing techniques in the United States and in many other western countries,[4] the focus for many clinicians has been to move toward obtaining regenerative cells, using "minimal manipulation" for therapeutic intervention.

Although emerging technologies and new business models offer off-site cellular processing and culturing of ASCs, internationally shipping the cultured cells back to clinicians for clinical use[5] such strategies are even more manipulative and are unlikely to be adopted in western countries in the near term.

The quantitative regenerative outputs on a per cc of donor fat basis from this SAVE device compare favorably to the nonpermissible enzymatic digestion techniques, as well as the nonpermissible mechanical techniques, being on the same order of magnitude in terms of gross yield. When factoring in the practical constraints of time efficiency, the SAVE platform demonstrates superiority in the metric of regenerative cells per cc per minute. Once time efficiency is factored into regenerative cell processing, the power of shock-assisted fat extraction emerges and appears as the clear leader in minimally manipulative regenerative cell processing.

Table 2. Summary Data on Regenerative Cell Yields Using a Variety of Manipulative and Minimally Manipulative Methods

References	Method summary	Mechanical or enzymatic	Automated, semiautomated, or manual	Time, min	Total nucleated cells/cc lipoaspirate	ASC content	Viability	Cells processed per minute
Baptista et al.[19]	Lipoaspirate incubated with RBC lysis buffer for 15 min, then centrifuged 15 min at 900 × *g*	Mechanical	Manual	30	240,000	12,000/cc of lipoaspirate (5%)	NA	8000
Shah et al.[20]	Lipoaspirate vigorously shaken for 1 to 2 min with PBS. Infranatant saved. Repeated 2 times. Infranatant centrifuged 1200 rpm for 5 min	Mechanical	Manual	11	NA	25,000/cc of lipoaspirate after culture	NA	
	Incubate adipose with 0.1% collagenase at 37 °C for 1 h. Centrifuge 1200 rpm for 10 min	Enzymatic	Manual		NA	480,000/cc of lipoaspirate after culture	NA	
Markarian et al.[21]	Lipoaspirate incubated with RBC lysis buffer for 15 min, then centrifuged for 10 min at 600 × *g*	Mechanical	Manual	25	25,000	NA	65%	1000
	Centrifuged lipoaspirate at 800 or 1280 × *g* for 15 min	Mechanical	Manual	30	10,000	NA	70%	333
	Lipoaspirate incubated with collagenase solution at 37 °C for 30 min. Centrifuge for 10 min at 600 × *g*	Enzymatic	Manual		350,000	NA	65%	
Raposio et al.[22]	Shake lipoaspirate in vibrating shaker for 6 min at 600 rpm. Centrifuge 6 min at 1600 rpm. Considered ASC to be any cell $CD31^{-}/CD34^{+}/CD45^{-}$	Mechanical	Manual	12	125,000	6250/cc of lipoaspirate (5%)	NA	10,417
Mitchell et al.[23]	Incubate lipoaspirate in 0.1% collagenase for 60 min at 37 °C	Enzymatic	Manual		308,000	NA	NA	
Aust et al.[24]	Incubate lipoaspirate in 0.1% collagenase for 45 min at 37 °C	Enzymatic	Manual		400,000	NA	93.9%	
Yoshimura et al.[25]	Incubate with 0.075% collagenase at 37 °C for 30 min with constant agitation	Enzymatic	Manual		1,310,000	NA	NA	
Suga et al.[26]	Incubate with 0.075% collagenase at 37 °C for 30 min with constant agitation	Enzymatic	Manual		100,000	NA	NA	
Conde-Green et al.[27]	High-speed centrifugation or vortexing and centrifuging	Mechanical	Manual	unknown	17,250	MSC frequency: 6%-13%	80%-90%	
	Collagenase-based digestion	Enzymatic	Manual		230,000	MSC frequency: 60%	80%-90%	
Fraser et al.[28]	Cytori Celution System	Enzymatic	Automated		360,000	1900 CFU-F/g (<1%)	84.7%	
Lin et al.[29]	Cytori Celution System	Enzymatic	Automated		295,000	CFU-F/g = 1.6%	86.6%	
Aronowitz et al.[30]	Cytori Celution System	Enzymatic	Automated		240,000	39,000 CFU-F/g (16%)	93%	
	PNC Multi-Station: 35 U collagenase/50 mL lipoaspirate. Incubate 30 min at 37 °C with constant agitation. Centrifuge at 2000 rpm for 10 min	Enzymatic	Manual		107,000	6000 CFU/g (5.6%)	57%	
	CHA Biotech CHA Station	Enzymatic	Semiautomated		5000	390 CFU-F/g 7.8%	87%	

Table 2. Continued

References	Method summary	Mechanical or enzymatic	Automated, semiautomated, or manual	Time, min	Total nucleated cells/cc lipoaspirate	ASC content	Viability	Cells processed per minute
Doi et al.[31]	Tissue Genesis Cell Isolation system	Enzymatic	Automated		702,000	NA	80.7%	
	Lipoaspirate incubated with 0.075% collagenase for 30 min at 37 °C with constant agitation, then centrifuged at 800 × *g* for 10 min	Enzymatic	Manual		701,000	NA	82.4%	
Williams et al.[32]	Tissue Genesis Cell Isolation System	Enzymatic	Automated		7,100,000	NA	78%	
Güven et al.[33]	Sepax Technology	Enzymatic	Automated		260,000	CFU-F frequency	>90%	
						14%		
	Lipoaspirate incubated with 0.15% (w/v) collagenase for 60 min at 37 °C with agitation	Enzymatic	Manual		160,000	CFU-F frequency 11%	>90%	
Vilaboa et al.[34]	GID SVF Platform	Enzymatic	Semiautomated		719,000	NA	83%	
Millan et al.[35]	StromaCell by Microaire	Mechanical	Semiautomated	unknown	140,000	NA	87.3%	
	Lipoaspirate incubated in 0.2% (w/v) collagenase for 90 min at 37 °C	Enzymatic	Manual		368,000	NA	74.5%	
Wang et al.[36]	Medi-Kan Lipokit	Enzymatic	Semiautomated		NA	41.67%	NA	
Average regenerative cell yield by mechanical processes					92,875			
STDEV					91,753			
Average regenerative cells by mechanical processed per minute								4938
STDEV								5037

From Aronowitz et al: Mechanical vs enzymatic isolation of stromal vascular fraction cells from adipose tissue. Springer (open access) Plus 4, 713 (2015). Note the viable regenerative cell yield of all the minimally manipulative techniques averages 92,800, which is in line with the SAVE platform's viable regenerative cell yield of 122,400. However, when adjusted for time efficiency, the average of the mechanical processes yielded 5000 viable regenerative cells per minute, compared with 47,400 viable regenerative cells per cc per minute using the SAVE platform. NA, not applicable; SVF, stromal vascular fraction.

Making Sense of the Science

The use of regenerative and ASCs in surgery and in clinical medicine represents an intimidating collection of published information. While researchers and basic scientists strive to maximize regenerative cell and ASC yields using any means necessary, practitioners measure success in the practicalities of clinical volume retention and time efficiency. This explains the "motivation misalignment" often seen when reviewing the large number of publications on this topic. The promise of stem-cell yields often places prohibitive scenarios on the clinician and confusion emerges.

One of the earliest clarifying concepts in fat transplantation was that not all fat grafting is clinically equivalent. There can be large volume vs small volume, and there can be regenerative vs nonregenerative fat transfer.[6] In each of these 4 scenarios, the clinical problems are uniquely different, requiring markedly different instrumentation and techniques (Figure 3).

Given the practicality of donor fat limitations regarding dosages as discussed above, the obvious best clinical application of regenerative cells would appear to be the small-volume regenerative category.

Small-Volume Regenerative Fat Grafting Application: Osteoarthritis of the Hip

In the United States, 32.5 million people have osteoarthritis of the hip,[7] and there are ~500,000 total hip replacements performed

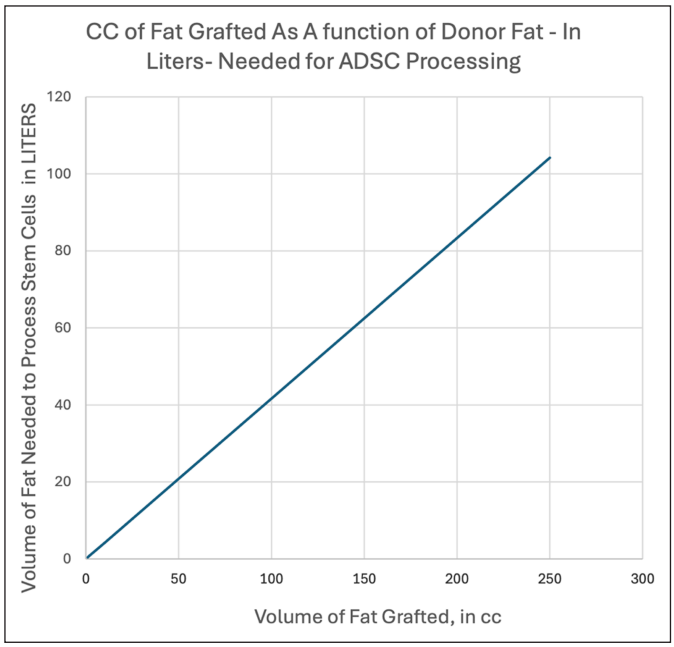

Figure 2. Volumes of fat (in liters) required to process in order to supercharge donor fat using dose concentration from Zhu et al study.[3] It is obvious that such donor fat required is impractical for high-volume fat transfer procedures.

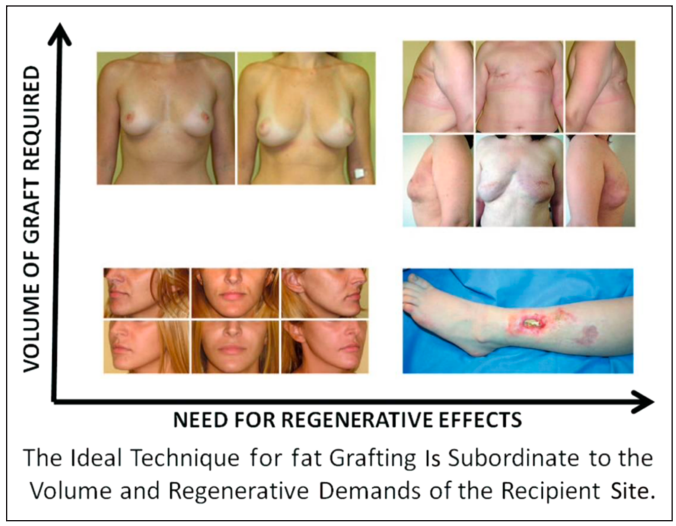

Figure 3. A matrix classification of fat grafting. The correct strategy for fat grafting must take into consideration the relative volume requirements, dosage concentrations, and the regenerative demands of the recipient site. Reprinted with permission from Wolter Kluwer Health, Inc (Philadelphia, PA).

each year.[8] For every person who undergoes total hip replacement surgery, there are 65 patients who are suffering from osteoarthritis of the hip and are being treated with nonsurgical means.

Clinical evidence of regenerative cell therapy and hip osteoarthritis demonstrate improvement in hip function and a cessation of progression of radiographic disease severity.[9] Assuming a range of 1 to 30 million patients with osteoarthritis of the hip treated with nonsurgical means, the potential for stem-cell therapy for hip osteoarthritis as an initial presurgical step in treatment is real and is poised for growth.

There are ~790,000 total knee replacements performed the United States per year with an 18% cumulative annual growth rate.[10] Despite the higher numbers of knees compared with hips performed each year, clinical results from total knee replacement demonstrate lower patient satisfaction than total hip replacement.[11] This may be due to the anatomic differences in these 2 joints. In addition, regenerative therapy appears to have promise, especially in early to mid-stage disease.[12] The average cost of total knee replacement in the United States is $20,000 per case.[13] If an alternative therapy such as regenerative cells could be used to treat this problem, significant cost savings to the healthcare system could result, on the order of $12 billion annually (Figure 4).

Regenerative Effects of Adipose-Derived Stem Cells in Plastic Surgery

Centrifugation of lipoaspirate after fat harvest through liposuction will yield 3 layers. The middle layer, also referred to as SVF, contains the ASC.[14] Another method to extract the ASC from harvested fat that is currently being utilized by plastic surgeons is the processing of nanofat and nanofat 2.0.[15,16] Nanofat is prepared by enzymatic degradation or serial mechanical filtration systems to yield high levels of viable stem cells.[17] Dermal injections or topical applications of ASC (autologous derived or off the shelf) have been observed to accelerate wound healing after fractional laser treatment.[18] There was decreased erythema at all time points and faster clearance of erythema on clinical examination.[18] Additionally, there was a 2.6-fold increase in mRNA expression of Procollagen III compared with the control group at 3 weeks.[18] Improved neocollagenesis in basic science studies offers an explanation for the observed dermal regeneration and wound healing effects when combining skin laser or microneedling treatments with ASC-based products. Despite the positive clinical effects, centrifugation and mechanical/enzymatic nanofat-processing techniques remain crude in terms of delivering consistent concentrations and total counts of viable ASCs. Devices that can generate high concentrations of ASCs will be beneficial to clinicians, patients, and academics as standardization will then be possible.

Additionally, aesthetic plastic surgeons who are considered experts in liposuction, ought to be at the forefront of technologic advances that involve fat harvest and transfer. Even if ASCs are utilized in other medical specialties (ie, orthopedics), plastic surgeons will be essential in the care of these patients to ensure minimal donor-site complications and mitigate the risk of creating iatrogenic contour deformities.

Limitations of this study include the small number of adipose samples used for fat harvest. All samples were a mix of fat from torso and thigh liposuction that would have otherwise been discarded. Potentially, specific anatomic areas may generate a more or less concentrated amount of ASC. A benefit of this study was that fat aspirated from all areas was mixed together, and thus, this represents a reasonable average of ASC derived from fat. Additionally, age and medical comorbidities may play a roll in the number of viable ASC extracted from fat using SAVE, which was out of the scope of this investigation. These 12 patients were all young and healthy volunteers. The results of this proof of concept study are encouraging and we anticipate increased motivation of many other surgeon scientists to expand upon this research in the basic science and clinical realms.

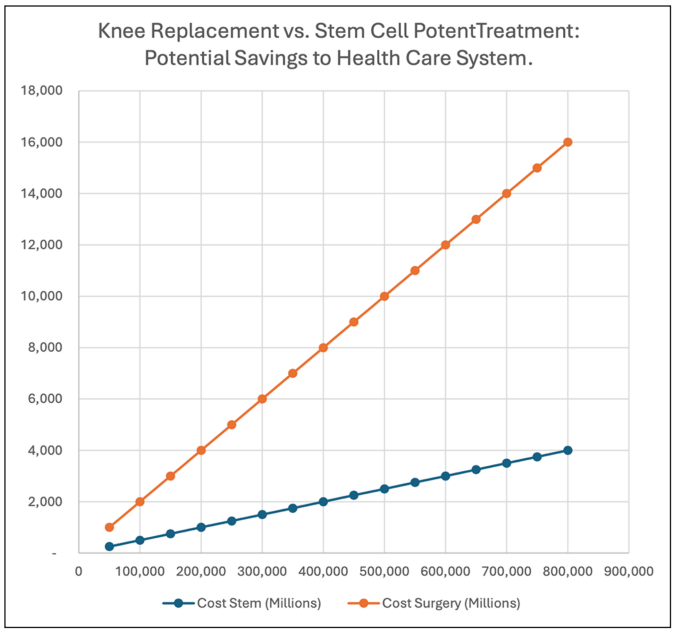

Figure 4. Potential savings using stem-cell therapy vs total knee replacement. This analysis assumes a $5000 cost for regenerative cell therapy with an average healthcare cost savings of $15,000 per knee.

CONCLUSIONS

SAVE is a novel fat-processing technique with high stem-cell extraction that shows promise from a regulatory, yield, time efficiency, and cost perspective. Clinical studies are needed using regenerative cells from this platform, which will help better define their efficacy and economic efficiency in both large- and small-volume regenerative settings.

Disclosures

Dr Del Vecchio receives royalties from MicroAire (Charlottesville, VA). Dr Vranis is a consultant for InMode Ltd (Irvine, CA). Dr Alevrogianni has no disclosures. Dr Theodorou received royalties from Thieme Medical Publishing (New York, NY).

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REFERENCES

1. Zuk PA, Zhu M, Mizuno H, et al. Multilineage cells from human adipose tissue: implications for cell-based therapies. *Tissue Eng*. 2001;7:211-228. doi: 10.1089/107632701300062859
2. Klinger M, Klinger F, Caviggioli F, et al. Fat grafting for treatment of facial scars. *Clin Plast Surg*. 2020;47:131-138. doi: 10.1016/j.cps.2019.09.002
3. Zhu M, Zhou Z, Chen Y, et al. Supplementation of fat grafts with adipose-derived regenerative cells improves long-term graft retention. *Ann Plast Surg*. 2010;64:222-228. doi: 10.1097/SAP.0b013e31819ae05c
4. FDA Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use Guidance for Industry and Food and Drug Administration Staff. Accessed September 5, 2024. https://www.fda.gov/media/109176/download
5. Aronowitz J, Lockhart R, Hakakian C. Mechanical versus enzymatic isolation of stromal vascular fraction cells from adipose tissue. *Springerplus*. 2015;4:713. doi: 10.1186/s40064-015-1509-2
6. DelVecchio D, Rohrich R. A classification of clinical fat grafting: different problems, different solutions. *Plast Reconstr Surg*. 2012;130:511-522. doi: 10.1097/PRS.0b013e31825dbf8a
7. Centers for Disease Control. Incidence of Hip Osteoarthritis, USA. Accessed September 5, 2024. https://www.cdc.gov/arthritis/types/osteoarthritis.htm
8. Total Hip Replacement Statistics, USA. American College of Rheumatology. Accessed September 5, 2024. https://rheumatology.org/patients/joint-replacement-surgery
9. Mao L, Jiang P, Lei X, et al. Efficacy and safety of stem cell therapy for the early-stage osteonecrosis of femoral head: a systematic review and meta-analysis of randomized controlled trials. *Stem Cell Res Ther*. 2020;11:445. doi: 10.1186/s13287-020-01956-5
10. Total Knee Replacement Statistics, USA. American College of Rheumatology. Accessed September 5, 2024. https://rheumatology.org/patients/joint-replacement-surgery
11. Bourne R, Chesworth B, Davis A, et al. Patient satisfaction after total knee arthroplasty: who is satisfied and who is not? *Clin Orthop Relat Res*. 2010;468:57-63. doi: 10.1007/s11999-009-1119-9
12. Sultan M, Shaikh M, Chowdhry N. Comparative analysis of knee joint replacement and stem cells therapy treatment for knee osteoarthritis using statistical techniques. *Res Med Eng Sci*. 2020;8:887-897. doi: 10.1186/s40001-018-0349-2
13. Samuel G. Understanding Knee Replacement Costs: What's on the Bill? Accessed September 5, 2024. https://www.healthline.com/health/total-knee-replacement-surgery/understanding-costs
14. Miller MQ, Dighe A, Cui Q, Park SS, Christophel JJ. Regenerative medicine in facial plastic and reconstructive surgery: a review. *JAMA Facial Plast Surg*. 2016;18:391-394. doi: 10.1001/jamafacial.2016.0913
15. Jeyaraman M, Muthu S, Sharma S, Ganta C, Ranjan R, Jha SK. Nanofat: a therapeutic paradigm in regenerative medicine. *World J Stem Cells*. 2021;13:1733-1746. doi: 10.4252/wjsc.v13.i11.1733
16. Menkes S, Luca M, Soldati G, Polla L. Subcutaneous injections of nanofat adipose-derived stem cell grafting in facial rejuvenation. *Plast Reconstr Surg Glob Open*. 2020;8:E2550. doi: 10.1097/GOX.0000000000002550
17. Crowley JS, Liu A, Dobke M. Regenerative and stem cell-based techniques for facial rejuvenation. *Exp Biol Med*. 2021;246:1829-1837. doi: 10.1177/15353702211020701
18. Zhou BR, Xu Y, Xu Y, et al. The effect of conditioned media of adipose-derived stem cells on wound healing after ablative fractional carbon dioxide laser resurfacing. *Biomed Res Int*. 2013;2013:519126. doi: 10.1155/2013/519126
19. Baptista LS, do Amaral RJFC, Carias RBV, Aniceto M, Claudio-da-Silva C, Borojevic R. An alternative method for the isolation of mesenchymal stromal cells derived from lipoaspirate samples. *Cytotherapy*. 2009;11:706-715. doi: 10.3109/14653240902981144
20. Shah FS, Wu X, Dietrich M, Rood J, Gimble JM. A non-enzymatic method for isolating human adipose tissue-derived stromal stem cells. *Cytotherapy*. 2013;15:979-985. doi: 10.1016/j.jcyt.2013.04.001
21. Markarian CF, Frey GZ, Silveira MD, et al. Isolation of adipose-derived stem cells: a comparison among different methods. *Biotechnol Lett*. 2014;36:693-702. doi: 10.1007/s10529-013-1425-x
22. Raposio E, Caruana G, Bonomini S, Libondi G. A novel and effective strategy for the isolation of adipose-derived stem cells: minimally manipulated adipose-derived stem cells for more rapid and safe stem cell therapy. *Plast Reconstr Surg*. 2014;133:1406-1409. doi: 10.1097/PRS.0000000000000170
23. Mitchell JB, McIntosh K, Zvonic S, et al. Immunophenotype of human adipose-derived cells: temporal changes in stromal-associated and stem cell–associated markers. *Stem Cells*. 2006;24:376-385. doi: 10.1634/stemcells.2005-0234
24. Aust L, Devlin B, Foster SJ, et al. Yield of human adipose-derived adult stem cells from liposuction aspirates. *Cytotherapy*. 2004;6:7-14. doi: 10.1080/14653240310004539
25. Yoshimura K, Shigeura T, Matsumoto D, et al. Characterization of freshly isolated and cultured cells derived from the fatty and fluid portions of liposuction aspirates. *J Cell Physiol*. 2006;208:64-76. doi: 10.1002/jcp.20636
26. Suga H, Eto H, Aoi N, et al. Adipose tissue remodeling under ischemia: death of adipocytes and activation of stem/progenitor cells. *Plast Reconstr Surg*. 2010;126:1911-1923. doi: 10.1097/PRS.0b013e3181f4468b
27. Condé-Green A, Rodriguez RL, Slezak S, Singh DP, Goldberg NH, McLenithan J. Comparison between stromal vascular cells' isolation with enzymatic

digestion and mechanical processing of aspirated adipose tissue. *Plast Reconstr Surg*. 2014;134:54. doi: 10.1097/01.prs.0000455394.06800.62
28. Fraser JK, Hicok KC, Shanahan R, Zhu M, Miller S, Arm DM. The Celution® system: automated processing of adipose-derived regenerative cells in a functionally closed system. *Adv Wound Care (New Rochelle)*. 2014;3:38-45. doi: 10.1089/wound.2012.0408
29. Lin K, Matsubara Y, Masuda Y, et al. Characterization of adipose tissue-derived cells isolated with the Celution™ system. *Cytotherapy*. 2008;10:417-426. doi: 10.1080/14653240801982979
30. Aronowitz JA, Ellenhorn JD. Adipose stromal vascular fraction isolation: a head-to-head comparison of four commercial cell separation systems. *Plast Reconstr Surg*. 2013;132:932e-939e. doi: 10.1097/PRS.0b013e3182a80652
31. Doi K, Tanaka S, Iida H, et al. Stromal vascular fraction isolated from lipo-aspirates using an automated processing system: bench and bed analysis. *J Tissue Eng Regen Med*. 2013;7:864-870. doi: 10.1002/term.1478
32. Williams SK, Kosnik PE, Kleinert LB, Vossman EM, Lye KD, Shine MH. Adipose stromal vascular fraction cells isolated using an automated point of care system improve the patency of expanded polytetrafluoroethylene vascular grafts. *Tissue Eng Part A*. 2013;19:1295-1302. doi: 10.1089/ten.tea.2012.031
33. Güven S, Karagianni M, Schwalbe M, et al. Validation of an automated procedure to isolate human adipose tissue–derived cells by using the Sepax® technology. *Tissue Eng Part C Methods*. 2012;18:575-582. doi: 10.1089/ten.tec.2011.0617
34. Vilaboa SDA, Navarro-Palou M, Llull R. Age influence on stromal vascular fraction cell yield obtained from human lipoaspirates. *Cytotherapy*. 2014;16:1092-1097. doi: 10.1016/j.jcyt.2014.02.007
35. Millan A, Landerholm T, Chapman JR. Comparison between collagenase adipose digestion and Stromacell mechanical dissociation for mesenchymal stem cell separation. *McNair Scholars J CSUS*. 2014;15:86-101.
36. Wang L, Lu Y, Luo X, et al. [Cell-assisted lipotransfer for breast augmentation: a report of 18 patients]. *Zhonghua Zheng Xing Wai Ke Za Zhi*. 2012;28:1-6.