

Tissue Augmentation with Allograft Adipose Matrix For the Diabetic Foot in Remission

Tala B. Shahin, BS*
 Kairavi V. Vaishnav, BS*
 Marcy Watchman, BS*
 Vignesh Subbian, PhD†
 Ethan Larson, MD*
 Evangelia Chnari, PhD‡
 David G. Armstrong, DPM,
 MD, PhD*§

Background: Repetitive stress on the neuropathic plantar foot is the primary cause of diabetic foot ulcers. After healing, recurrence is common. Modulating plantar pressure has been associated with extension of ulcer free days. Therefore, the goal of this study was to determine the effects of an injectable allograft adipose matrix in providing a protective padding and reducing the pressure in the plantar foot.

Methods: After healing his recurrent ulcer using total contact casting, a 71-year-old man with a 9-year history of recurrent diabetic foot ulcers was treated with injection of allograft adipose matrix, procured from donated human tissue. This was delivered under postulcerative callus on the weight-bearing surface of the distal end of the first ray resection. As is standard in our clinic for tissue augmentation procedures, our patient underwent serial plantar pressure mapping using an in-shoe pressure monitoring system.

Results: There was a 76.8% decrease in the mean peak pressure due to the fat matrix injected into the second metatarsal region and a 70.1% decrease in mean peak pressure for the first ray resection at the site of the postulcerative callus. By 2 months postoperatively, there was no evidence of residual callus. This extended out to the end of clinical follow-up at 4 months.

Conclusion: The results from this preliminary experience suggest that allograft adipose matrix delivered to the high risk diabetic foot may have promise in reducing tissue stress over pre- and postulcerative lesions. This may ultimately assist the clinician in extending ulcer-free days for patients in diabetic foot remission. (*Plast Reconstr Surg Glob Open* 2017;6:e1555; doi: 10.1097/GOX.0000000000001555; Published online 23 October 2017.)

INTRODUCTION

Lower extremity complications of diabetes, particularly diabetic foot ulcers, continue to constitute a common and complex constellation of pathology.¹ After healing, reulceration is common. Approximately 40%, 66%, and 75% of people will have a recurrent ulcer at

1, 3, and 5 years, respectively. Extending ulcer-free and activity-rich days in diabetic foot ulcer remission is important, as data suggest that quality of life and resource utilization can both be improved.² The use of fat grafting has been instituted by our group as a means of redistributing shear and normal stress of the foot after remission of plantar diabetic foot ulcers.³

Although still limited, there has been an increase in interest in adipose grafting over the past decade. Zuk et al.⁴ reported that processed lipoaspirate expressed unique activity distinct to mesenchymal stem cells. This lipoaspirate has shown to maintain its volume over time.⁵⁻⁸ Furthermore, Nicoletti et al.⁹ reported on 4 patients with autologous adipose tissue grafting success in distribution of plantar weight-bearing patterns in patients with traumatic soft-tissue loss. This corresponds well with our clinical experience.³

Decellularized adipose matrix has recently been the focus of preclinical characterization as a potential solution for soft-tissue defect filling.^{10,11,12} Allograft adipose matrix

From the *Department of Surgery, University of Arizona, Tucson, Ariz.; †Department of Biomedical Engineering, University of Arizona, Tucson, Ariz.; and ‡Research and Development, Musculoskeletal Transplant Foundation (MTF), Edison, N.J.

Received for publication August 1, 2017; accepted September 8, 2017.

The present address for D.G.A. is the Department of Surgery, Keck School of Medicine of University of Southern California, Los Angeles, Calif.

Copyright © 2017 The Authors. Published by Wolters Kluwer Health, Inc. on behalf of The American Society of Plastic Surgeons. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

DOI: 10.1097/GOX.0000000000001555

Supplemental digital content is available for this article. Clickable URL citations appear in the text.

(AAM) is the extracellular matrix component of allograft adipose tissue after the lipid and the cellular components have been removed. When properly processed, the endogenous components (matrix proteins, growth factors, cytokines) are preserved.^{13,14} Collagen IV is a key component in the thick matrix (basal lamina) surrounding the adipocytes and plays an important role in adipocyte survival. Collagen VI is also specific to adipocytes and binds strongly to Collagen IV, an interaction linked to the anchoring of the basement membrane to cells.^{14,15} Adiponectin, leptin, angiopoietin, insulin growth factor-1, and fibroblast growth factor-1 and -2 are adipogenic and angiogenic factors naturally found in adipose tissue that support neovascularization, stem cell differentiation to adipocytes, and modulation of glucose and lipid metabolism.^{16,17} When implanted in pre-clinical models, the natural factors that are retained in the matrix support host cell infiltration and revascularization of the matrix (either with or without the addition of cells).¹⁰⁻¹² Recently, AAM derived from human donors is also being evaluated for clinical use. A 16-week pilot study to assess short-term local skin and volume changes using an injectable AAM in the subcutaneous space in the dorsum of the wrist has recently been completed.¹⁸ Another clinical assessment of AAM in abdominoplasty patients is in progress with histopathological evaluation of adipogenesis being the primary outcome measure and safety/adverse events the secondary measure.¹⁹ Acellular adipose tissue intended for the repair of soft-tissue defects is also being assessed for safety

and tolerability in healthy volunteers in a phase I prospective study.²⁰

To our knowledge, there are no reports in the literature detailing experience with this therapy in the high risk foot. The goal of this article was to present an initial clinical experience of plantar tissue augmentation using a decellularized AAM in patients with recently healed diabetic foot ulcers to assess potential plantar pressure reduction, with the ultimate goal of reducing the risk of reulceration.

METHODS

Case Presentation

We abstracted the medical records of a 71-year-old gentleman with a 40-year history of type 2 diabetes who presented for care of a recently healed but frequently recurring diabetic foot ulcer. He had been treated according to our clinic protocol, which consists of custom shoes and molded multilaminar multidurometer insoles, frequent return visits (every 2–3 months) with callus debridement and instructions for home monitoring.

Measurement of Plantar Pressure

To determine the location of peak pressure, the F-Scan in shoe system (Tekscan Inc. Boston, Mass.) was used.²¹⁻²³ The F-scan pressure sensor, fit to size so not to interfere with the patient's pressure mapping, was placed in the pa-

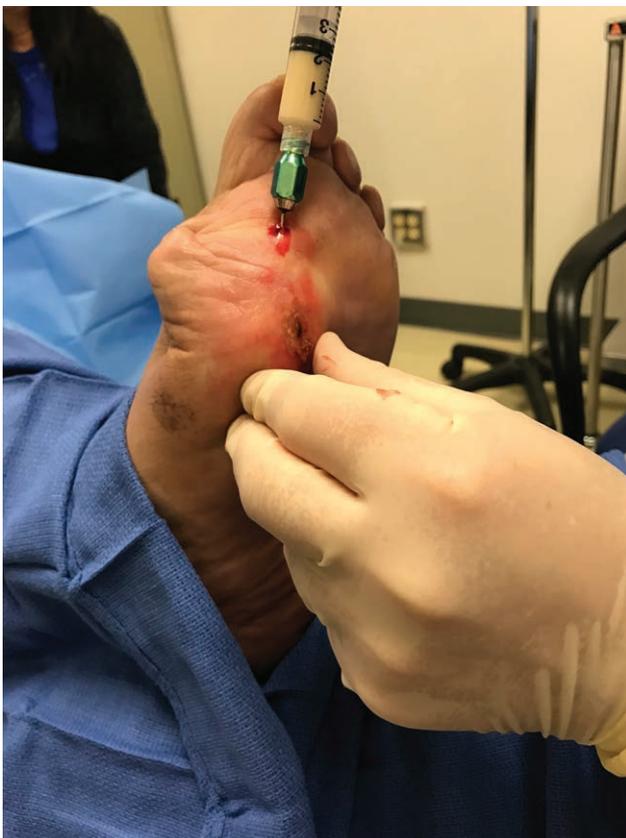


Fig. 1. Fat is injected deep to the wound in multiple passes and in multiple depths with microdroplet deposition technique.



Fig. 2. Cross hatching is used to promote vascularity and ensure no large puddles form.



Video Graphic 1. See video, Supplemental Digital Content 1, which demonstrates the multiple depth layering microdroplet technique, <http://links.lww.com/PRSGO/A594>.

patient's shoe. The system was then calibrated specifically to the patient, taking into account the patient's body mass as the applied force. The patient was then asked to walk back and forth the length of the corridor, approximately 30 meters, so the patient feels comfortable when ambulating. This also allows the sensors to warm up once calibrated, because insole temperature can influence final measurements.^{24,25} Once the patient was ambulating comfortably and the F-Scan was calibrated, the ambulatory measurements were then recorded in real time.

Preparation of AAM

Allograft adipose matrix provided by the Musculoskeletal Transplant Foundation was prepared from donated human adipose tissue, processed aseptically to remove lipid and cells, disinfect and reduce in size to create an injectable formulation. The dehydrated tissue matrix was

prepared as described per the package insert directions. Using sterile technique, the AAM is rehydrated using 1.2 ml of sterile saline for each 1.5 ml final volume of AAM. A total of 5 syringes of 1.5 ml each were prepared of the AAM, which provided 7.5 ml in total.

AAM Placement

The patient's foot was then scrubbed, prepped, and draped using aseptic sterile technique. Local anesthesia was infiltrated just proximal to the left foot plantar first metatarsal phalangeal joint peak pressure site. Using a #11 blade, a small puncture incision was created at the plantar distal most aspect of the first metatarsal phalangeal joint. A blunt tip 20 gauge cannula was then inserted into the surgical site and the AAM was slowly and carefully infiltrated into the subcutaneous planes using the modified Coleman technique.²⁶ The cannula was blunt tipped to follow the natural tissue planes when inserted, rather than forming new channels if the tissue were sharp. While withdrawing the cannula, the AAM was injected into the channel created by the cannula. Once the entire 7.5 ml of AAM was injected, the incision site was dressed with Dermabond. This procedure is demonstrated in Video 1 and Figures 1, 2 (see video, Supplemental Digital Content 1, which demonstrates the multiple depth layering microdroplet technique, <http://links.lww.com/PRSGO/A594>).

RESULTS

There was a 76.8% decrease in mean peak pressure under the second metatarsal region, and a 70.1% decrease in mean peak pressure for the distal end of the first ray resection at the site of the postulcerative callus. These data are illustrated in Figure 3. By 2 months postoperatively, there was no evidence of residual callus. This extended out to the end of clinical follow-up at 4 months. Clinical results are demonstrated in Figures 4, 5.

THE EFFECT OF THE ACELLULAR FAT GRAFT ON PEAK PRESSURE IN TWO DIFFERENT LOCATIONS OF THE PATIENT'S FOOT

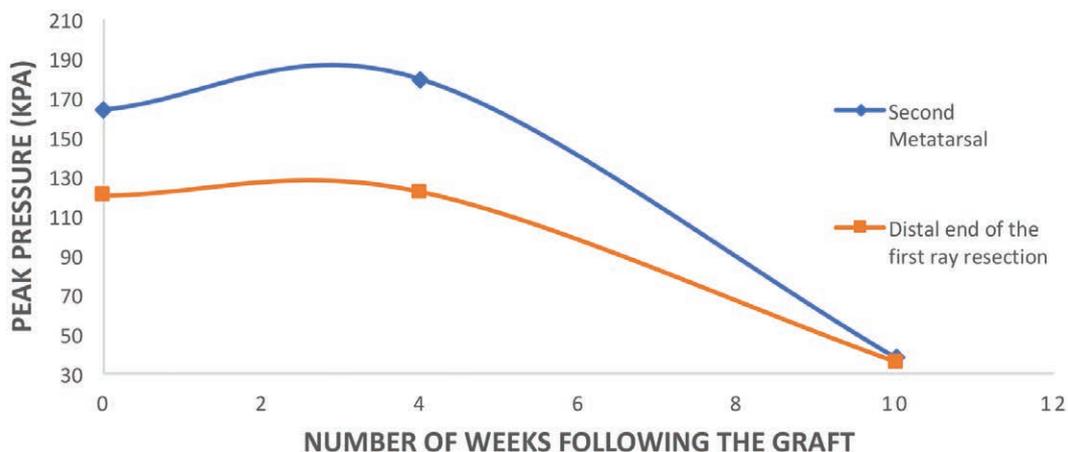


Fig. 3. Reduction in plantar pressure following acellular grafting of postulcerative lesion.



Fig. 4. Four weeks following grafting demonstrating resolution of preulcerative callus.



Fig. 5. Four months, postoperatively.

DISCUSSION AND CONCLUSION

The results from this preliminary experience suggests that AAM delivered to the high-risk diabetic foot may have promise in reducing tissue stress over pre- and postulcerative lesions. This may ultimately assist the clinician in extending ulcer-free days for patients in diabetic foot remission.

We were initially surprised by the lack of change in plantar pressure at 4 weeks, as our current experience in using standard autograft lipofilling has shown some reduction in pressure by that time. This may be related to insufficient time to maturation.

We were also surprised by the significant reduction in pressure at the site of the region of interest in this patient (70%). Our work and that of Mueller et al.^{27,28} have shown that far more invasive soft-tissue procedures such as Achilles tendon lengthenings have provided only a fraction of this correction. We believe that a long-term study is required to see if this kind of pressure reduction is durable and reproducible.

In summary, these initial data support the concept of tissue augmentation utilizing this novel modality. We look forward to further works that will confirm or refute these data.

Kairavi V. Vaishnav, BS
 Department of Surgery
 University of Arizona
 1501 N Campbell Avenue, Room 4402
 Tucson, AZ
 E-mail: kairaviv@email.arizona.edu

REFERENCES

1. Armstrong DG, Boulton AJM, Bus SA. Diabetic foot ulcers and their recurrence. *N Engl J Med.* 2017;376:2367–2375.
2. Skrepnek GH, Mills JL Sr, Lavery LA, et al. Health care service and outcomes among an estimated 6.7 million ambulatory care diabetic foot cases in the U.S. *Diabetes Care.* 2017;40:936–942.
3. Luu CA, Larson E, Rankin TM, et al. Plantar fat grafting and tendon balancing for the diabetic foot ulcer in remission. *Plast Reconstr Surg Glob Open.* 2016;4:e810.
4. Zuk PA, Zhu M, Ashjian P, et al. Human adipose tissue is a source of multipotent stem cells. *Mol Biol Cell.* 2002;13:4279–4295.
5. Choi M, Small K, Levovitz C, et al. The volumetric analysis of fat graft survival in breast reconstruction. *Plast Reconstr Surg.* 2013;131:185–191.
6. Doren EL, Parikh RP, Laronga C, et al. Sequelae of fat grafting postmastectomy: an algorithm for management of fat necrosis. *Eplasty.* 2012;12:e53. Available at <https://www.ncbi.nlm.nih.gov/pubmed/23308300>. Accessed August 1, 2017.
7. Losken A, Pinell XA, Sikoro K, et al. Autologous fat grafting in secondary breast reconstruction. *Ann Plast Surg.* 2011;66:518–522.
8. Delaporte T, Delay E, Toussoun G, et al. Breast volume reconstruction by lipomodelling technique: about 15 consecutive cases. *Annales de Chirurgie Plastique et Esthétique.* 2009;54:303–316. Available at <http://europepmc.org/abstract/med/19237233>.
9. Nicoletti G, Brenta F, Jaber O, et al. Lipofilling for functional reconstruction of the sole of the foot. *Foot (Edinb).* 2014;24:21–27.
10. Han TT, Toutounji S, Amsden BG, et al. Adipose-derived stromal cells mediate *in vivo* adipogenesis, angiogenesis and inflammation in decellularized adipose tissue bioscaffolds. *Biomaterials.* 2015;72:125–137.

11. Young DA, Bajaj V, Christman KL. Decellularized adipose matrix hydrogels stimulate in vivo neovascularization and adipose formation. *J Biomed Mater Res A*. 2014;102:1641–1651.
12. Wu I, Nahas Z, Kimmerling KA, et al. An injectable adipose matrix for soft-tissue reconstruction. *Plast Reconstr Surg*. 2012;129:1247–1257.
13. Banyard DA, Borad V, Amezcua E, et al. Preparation, characterization, and clinical implications of human decellularized adipose tissue extracellular matrix (hDAM): a comprehensive review. *Aesthet Surg J*. 2016;36:349–357.
14. Sano H, Orbay H, Terashi H, et al. Acellular adipose matrix as a natural scaffold for tissue engineering. *J Plast Reconstr Aesthet Surg*. 2014;67:99–106.
15. Mariman EC, Wang P. Adipocyte extracellular matrix composition, dynamics and role in obesity. *Cell Mol Life Sci*. 2010;67:1277–1292.
16. Chandran M, Phillips SA, Ciaraldi T, et al. Adiponectin: more than just another fat cell hormone? *Diabetes Care*. 2003;26:2442–2450. Available at <https://www.ncbi.nlm.nih.gov/pubmed/12882876>. Accessed August 1, 2017.
17. Lowe CE, O’Rahilly S, Rochford JJ. Adipogenesis at a glance. *J Cell Sci*. 2011;124:2681–2686.
18. Allograft adipose matrix (AAM) in subcutaneous dorsal wrist—full text view—ClinicalTrials.gov. Available at <https://www.clinicaltrials.gov/ct2/show/NCT02445118?term=adipose+matrix&rank=1>. Accessed June 12, 2017.
19. In-vivo assessment of adipose allograft extracellular matrix in abdominoplasty patients—full text view—ClinicalTrials.gov. Available at <https://www.clinicaltrials.gov/ct2/show/NCT02845180?term=adipose+matrix&rank=2>. Accessed August 1, 2017.
20. Safety study of acellular adipose tissue for soft tissue reconstruction. Available at <https://clinicaltrials.gov/ct2/show/NCT02817984>. Accessed July 24, 2017.
21. Ahroni JH, Boyko EJ, Forsberg R. Reliability of F-scan in-shoe measurements of plantar pressure. *Foot Ankle Int*. 1998;19:668–673.
22. Randolph AL, Nelson M, Akkapeddi S, et al. Reliability of measurements of pressures applied on the foot during walking by a computerized insole sensor system. *Arch Phys Med Rehabil*. 2000;81:573–578. Available at <https://www.ncbi.nlm.nih.gov/pubmed/10807094>. Accessed August 1, 2017.
23. Vidmar G, Novak P. Reliability of in-shoe plantar pressure measurements in rheumatoid arthritis patients. *Int J Rehabil Res*. 2009;32:36–40.
24. Randolph AL, Nelson M, deAraujo MP, et al. Use of computerized insole sensor system to evaluate the efficacy of a modified ankle-foot orthosis for redistributing heel pressures. *Arch Phys Med Rehabil*. 1999;80:801–804. Available at <https://www.ncbi.nlm.nih.gov/pubmed/10414765>. Accessed August 1, 2017.
25. Luo ZP, Berglund LJ, An KN. Validation of F-Scan pressure sensor system: a technical note. *J Rehabil Res Dev*. 1998;35:186–191. Available at <https://www.ncbi.nlm.nih.gov/pubmed/9651890>. Accessed August 1, 2017.
26. Coleman SR. Facial recontouring with lipostructure. *Clin Plast Surg*. 1997;24:347–367. Available at <https://www.ncbi.nlm.nih.gov/pubmed/9142473>. Accessed August 1, 2017.
27. Armstrong DG, Stacpoole-Shea S, Nguyen H, et al. Lengthening of the Achilles tendon in diabetic patients who are at high risk for ulceration of the foot. *J Bone Joint Surg Am*. 1999;81:535–538. Available at <https://www.ncbi.nlm.nih.gov/pubmed/10225799>. Accessed August 1, 2017.
28. Mueller MJ, Sinacore DR, Hastings MK, et al. Effect of Achilles tendon lengthening on neuropathic plantar ulcers. A randomized clinical trial. *J Bone Joint Surg Am*. 2003;85-A:1436–1445.