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CASE REPORT

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Adipose tissue allograft for the management of a pre-ulcerative plantar lesion in a diabetic neuropathic patient

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Key Clinical Message

This case describes a minimally invasive implantation of cryopreserved human adipose tissue allograft (CAT) in a diabetic neuropathic patient with a pre-ulcerative plantar lesion. No re-ulceration or adverse events have occurred out to 9 months. CAT provides healthcare providers with an option to manage patients at risk for plantar ulcers.

KEYWORDS

adipose tissue, allograft, diabetic, fat pad, neuropathic, plantar ulcer

1 | INTRODUCTION

The fat pad on the bottom of the foot serves as a cushion and shock absorber, providing support, and safeguarding the underlying structures of the foot during weight-bearing activities. Atrophy of the fat pad occurs when the adipose tissue diminishes or becomes displaced, resulting in increased plantar pressure on the bones and leading to pain, disability, and potential ulcerations.[1]

Certain patient populations are at higher risk of plantar ulcerations, especially those with significant comorbidities such as diabetes and peripheral neuropathy. In diabetic neuropathic patients, lesions frequently become infected, leading to gangrene and, in severe cases, amputation. Neuropathic patients experience muscle and fat pad atrophy, which leads to foot instability and an altered gait, resulting in high plantar pressure and subsequent tissue breakdown and ulcer formation.[2] Plantar ulcers are the primary cause of amputations in patients with diabetic neuropathy, with a reported limb amputation rate exceeding 80% in this population.[3]

Given the high rate of ulcer-related amputations, preventing the formation and recurrence of an ulcer is an essential part of wound care management. For plantar ulcers, which represent approximately 50% of all ulcers, minimizing pressure is crucial in preventing the formation, and recurrence of such ulcers.[4] Yet, available management options remain limited. Conservative approaches for fat pad atrophy include activity adjustments, casting, and the use of shoe pads or other orthotic devices designed to alleviate localized foot pressure. Although helpful to some extent, these therapies do not address fat pad deficiency in areas of high pressure, which is one of the main underlying causes of plantar ulcers. Consequently, the reconstruction of adipose tissue remains an unmet medical need. A desirable solution should be able to restore fat pad integrity. Clinicians have thus explored available options to volumize fat pads such as silicone, collagen-and hyaluronic acid (HA)-based dermal fillers, and autologous adipose tissue.[5–13]

The use of silicone for the plantar fat pad has been described as early as the 1960s, with some cases reporting

positive outcomes.[5,6] However, regulatory issues and safety concerns have prevented its widespread use. More recently, dermal fillers, primarily used for cosmetic procedures in the face and hands, have been applied to the foot. This is a relatively newer use with limited outcomes reported in the literature. While pain reduction has been observed, these outcomes have generally been restricted to non-diabetic patients.[7,8]

Autologous fat grafting, widely used for soft tissue cosmetic and reconstructive procedures, has also recently been applied to address fat pad atrophy and has shown promising outcomes.[11–13] However, most published data describe autologous fat grafting in patients with painful fat pad atrophy, with only a few clinical cases reporting its use in diabetic patients with a history of plantar ulcers.[14,15] Although limited, these data support the concept of using adipose in preventing reulcerations. Unfortunately, autologous adipose has several limitations. Autologous adipose tissue is not readily available, as it requires a surgical procedure for tissue harvesting, which can potentially lead to donor site morbidity. Additionally, clinical outcomes are highly variable due to differences in tissue harvesting and processing techniques, as well as variations in tissue quality among patients.[16–20] These differences, along with yet unidentified factors, may contribute to the high resorption rate of grafted autologous adipose tissue, leading to rapid volume loss, and poor clinical outcomes.[21]

To address the limitations of current management options, an off-the-shelf cryopreserved human adipose tissue allograft (CAT) has emerged as a viable alternative for the management of fat pad atrophy and other conditions involving adipose defects.[22] Immunogenic components are eliminated from CAT during the proprietary tissue processing, allowing allogeneic use of CAT. CAT retains the inherent structure and cushioning function of the native tissue and is intended to repair adipose tissue defects.[22]

This clinical case evaluates the utilization of CAT in a high-risk diabetic neuropathic patient susceptible to plantar ulcer formation. The implantation of CAT in a diabetic neuropathic patient with a pre-ulcerative lesion due to fat pad atrophy prevented recurrence for 9 months without any adverse events. Long-term follow-up is ongoing. This is the very first case describing the clinical use of CAT for a diabetic neuropathic patient at high risk of ulcer recurrence.

2 | CASE HISTORY

A 57-year-old male with a medical history including diabetes mellitus (DM), neuropathy, chronic kidney disease (CKD), obesity, multiple myeloma (MM), and a previous partial calcanectomy of the left heel, as well as a history of osteomyelitis and recurrent plantar ulcers, presented to the office with a callus pre-ulcerative lesion. He was selected to receive CAT implantation in the area of the lesion.

3 | METHODS

CAT is a cryopreserved human adipose tissue allograft that retains the native tissue architecture. It is a commercially available product that is regulated by the Food and Drug Administration (FDA) as a human cells, tissues, and cellular and tissue-based product (HCT/P) under Section 361 of the Public Health Service (PHS) Act and Title 21, Code of Federal Regulations (CFR) Part 1271. CAT is processed from donated subcutaneous abdominal adipose tissue derived from cadaveric donors.

Per the product insert, CAT (Liposana™, Britecyte, Inc., Frederick, MD) is manufactured in partnership with LifeLink Tissue Bank. LifeLink Tissue Bank is accredited by the American Association of Tissue Banks (AATB), registered with the FDA and Health Canada, licensed by the states of Florida, California, Maryland, and New York, and registered with the states of Delaware and Oregon. LifeLink adheres to the criteria for donor screening, recovery, processing, and distribution of allografts required by these organizations and all applicable regulations set forth by the FDA. All tissue is recovered and processed under aseptic conditions from carefully screened donors. Comprehensive serologic testing is performed on each donor. In addition, numerous microbiologic cultures are performed and evaluated at tissue recovery and allograft packaging. Communicable disease testing was performed by a laboratory registered with FDA to perform donor testing and certified to perform such testing on human specimens under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) and 42 CFR part 493.[22]

CAT is supplied as a 1.5 mL unit packaged in a sterile cryogenic vial with a screw cap, contained within two chevron-type peel pouches. Both pouches and the vial have been sterilized. CAT is shipped on dry ice and must be maintained at the recommended temperature until ready for use. It has a shelf life of 5 years if stored at −40°C or colder. Storage between −20°C to −40°C is limited to 6 months.

To prepare CAT, the outer pouch is removed, leaving the vial in the inner pouch on a clean surface. The product should thaw for approximately 30 minutes before use. Once thawed, the vial is retrieved from the pouch. After shaking the vial, CAT is immediately withdrawn using a syringe with an 18G needle. Once the product is in the syringe, the 18G needle is replaced with a new sterile needle. Although the recommended needle size is 20G, a 21G needle was used for implantation in this case. Figure 1 shows CAT within the vial and its subsequent withdrawal.

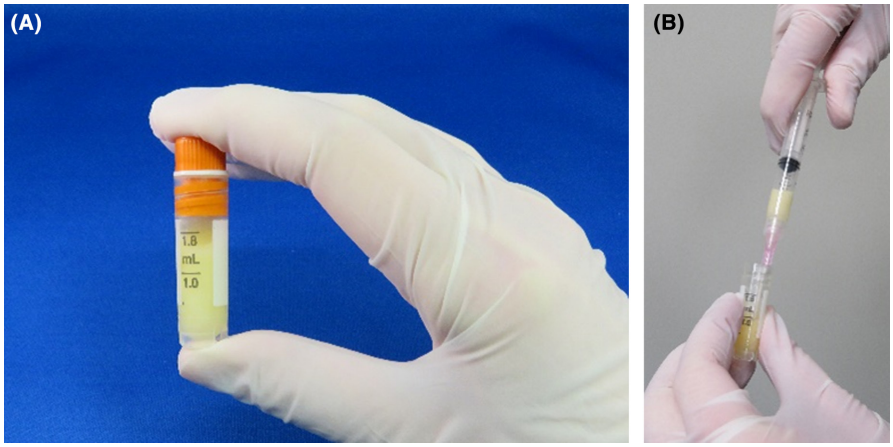

FIGURE 1 (A) CAT supplied in a cryogenic vial and (B) its subsequent withdrawal from the vial into a 3 mL syringe prior to implantation.

The area was prepped with Betadine solution before implantation. As the patient was densely neuropathic, a local anesthetic was not required. Once the patient was ready and CAT was loaded into the syringe, all air bubbles were carefully removed. Figure 2 shows the patient receiving a subcutaneous implant of 1.5 mL CAT in the left heel during an office visit. CAT was implanted as a bolus underneath the pre-ulcerative lesion avoiding subcutaneous nerves and blood vessels. After implantation, the patient was offloaded in an offloading boot (Foot Defender®, Defender Ops, Miami, FL).

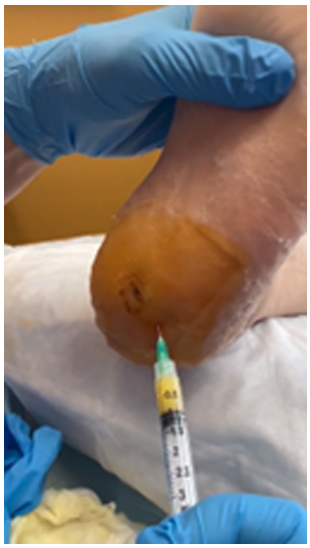

FIGURE 2 Patient receiving the subcutaneous CAT implantation.

4 | CONCLUSION AND RESULTS

The primary clinical outcome was incidence of ulcer recurrence at the site of CAT implantation. Safety outcomes included the product-related number and types of adverse events and serious adverse events. The patient returned for outcomes assessment at 1 week, 2 weeks, 5 weeks, 6 months, 7.5 months, and 9 months postimplantation.

Two weeks after implantation, the patient was able to be transitioned to a custom brace and diabetic shoes. At the 9-month follow-up, no ulcer formation was observed, and CAT remained palpable, with the callus having disappeared at the site of the pre-ulcerative lesion. Figure 3 shows the area of pre-ulcerative lesion at the Baseline implant visit, the 6-month follow-up visit, and the 9-month follow-up visit. The patient is still being followed for longer term outcomes.

5 | DISCUSSION

Diabetic neuropathic patients face a heightened risk of plantar ulcerations due to fat pad atrophy or displacement. In 1983, a study found that all diabetic neuropathic patients with previous ulcerations had abnormally high pressure at the ulcer site.[23] This elevated plantar pressure is a primary trigger for ulcer formation and contributes to the high amputation rate of over 80% in diabetic neuropathic patients.[3] Plantar ulcers account for about 50% of foot ulcers seen in specialized clinics and are particularly challenging to prevent due to weight-bearing biomechanics and the lack of pain perception in neuropathic patients.[4] The recurrence rate for plantar ulcers ranges from 20% to 80% within just 2 months postclosure.[24]

The correlation between elevated plantar pressures and the onset of foot ulcers in the diabetic neuropathic patient population has spurred research into additional management modalities aimed at reducing plantar pressure. Current approaches to reducing plantar pressure in patients with fat pad atrophy are limited. Conservative options include prescriptive footwear and padding. In cases of foot deformities, surgical corrections such as osteotomies or tendon balancing are required. Another approach,

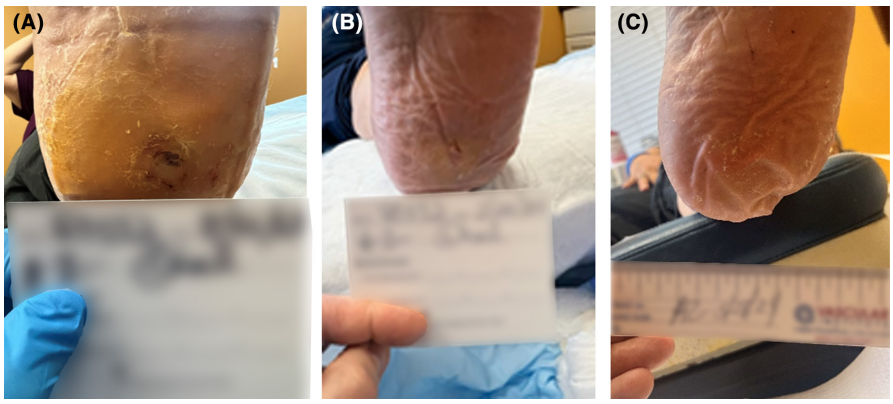

FIGURE 3 (A) Pre-ulcerative lesion site on the left heel foot prior to CAT implantation, (B) the implantation site at 6 months follow-up, and (C) at 9 months follow-up.

involving the use of fillers, has also been described in the literature.

In 2018, Foumenteze et al. described the use of an HA dermal filler to treat metatarsalgia from wearing high-heeled shoes. Improvements were seen between Baseline and 6 months for time to onset of pain, time between onset of pain and intolerable pain, and pain sensation. However, none of these subjects were diabetic neuropathic patients.[10] In 2000, in a randomized double-blind controlled study, van Schie et al. described the use of liquid silicone injections in diabetic feet to reduce risk factors for ulceration. Twenty-eight diabetic neuropathic patients received several injections of silicone in the plantar surface of the foot. Results showed a significant increase in plantar thickness for the patients who received silicone and a corresponding decrease in pressure for up to 12 months.[6]

Though these studies have demonstrated some clinical effectiveness of fillers, a lack of long-term durability data and safety concerns remain major factors limiting their widespread use. The most significant adverse response is migration from the injection site to other parts of the foot, causing inflammation and pain, which may necessitate surgical excisio.[5,6]

Recent studies have explored the use of autologous adipose tissue in fat pad atrophy management. In 2016, Luu et al. described a case involving a 37-year-old man with diabetes and neuropathy who had a history of gangrene and a 5th ray amputation. He developed a chronic ulcer that eventually healed but left him with residual fat pad atrophy and pre-ulcerative lesions. Fat grafting was utilized, and the patient was able to return to normal footwear within 4 weeks with no reported recurrence of the ulcer at 6 weeks.[14] Also in 2016, Gusenoff et al. conducted a prospective, randomized, clinical trial focusing on patients with painful fat pad atrophy. After 1 year, the fat grafting group showed improved foot function, reduced pain, and better performance in daily activities compared to the conservative management group.[25]

While autologous adipose shows positive clinical outcomes, this modality has multiple limitations: it requires a surgical procedure, poses potential donor site morbidity, and yields variable results due to resorption of the adipose tissue.[17,18] This resorption is linked to differences in tissue harvesting and processing techniques, as well as variations in tissue quality among patients.[21] In addition, a certification is required for healthcare providers to be able to harvest autologous adipose tissue, which significantly restricts the number of physicians who can perform autologous adipose procedures.

In a slightly different context, Kress et al. conducted a retrospective chart review in 2023 of 17 feet in 15 patients, primarily diabetic and neuropathic, who had undergone either autologous fat grafting or received an allograft adipose matrix due to recurrent ulcerations. Eleven patients received autologous fat grafts, and four patients received an allograft adipose matrix (Leneva®, MTF Biologics, Edison, NJ). Only two patients implanted with the allograft adipose matrix were diabetic, and two were spina bifida patients. An average follow-up was 6.9 months for all patients. No complications or recurrent ulcerations were reported. For three patients who received the adipose allograft matrix the follow up was 1 month for two patients and 5 months for one patient.[15]

Allograft adipose matrix is a decellularized delipidized adipose-derived extracellular matrix. Because adipocytes, the main cell type in adipose that stores lipids and provide cushioning, are removed from the tissue in the allograft adipose matrix, this product does not retain the structure and cushioning function of the native adipose tissue. Tissue regeneration after the allograft adipose matrix implantation relies on host cell migration and graft remodeling, which takes approximately 3 months.[26]

Recent advances in tissue processing and preservation have led to the development of CAT, a commercially available, off-the-shelf cryopreserved adipose tissue allograft intended for use in the repair, replacement, or reconstruction of adipose tissue defects.[22] CAT is produced using a novel proprietary technology, which enables retention of the structure and function of native tissue while eliminating immunogenic components. CAT is a devitalized human

adipose tissue. Devitalization is a step of the CAT processing method, used to reduce tissue immunogenicity.[27] For retention of adipose tissue integrity, CAT is preserved in trehalose. Trehalose is a disaccharide of glucose that is widely used for the preservation of cells and tissues including adipose.[28]

CAT can be implanted via a minimally invasive technique in any healthcare setting. The preparation of CAT for implantation takes just a few minutes and involves thawing a vial of CAT and withdrawing it into a syringe. No special syringes or needles are required. CAT is an alternative option to autologous fat grafting without its limitations: it allows for fast preparation and implantation, involves no adipose harvesting donor site morbidity, and provides an unlimited amount available for use at any time with lot-to-lot consistency, which leads to reproducible clinical outcomes.

To date, 17 patients—primarily diabetic neuropathic individuals with both open and closed ulcers—at the Ocean County Foot & Ankle Surgical Associates practice have received a CAT implant, with most undergoing only one implantation. Follow-up data extending up to 11 months show that the product remains palpable at the implantation site. These preliminary data suggest that diabetic neuropathic patients with plantar pre-ulcerative lesions, a history of plantar ulcers, newly closed or open plantar ulcers, post-traumatic and post-surgical patients with adipose deficiencies, and a wide range of individuals with metatarsal or heel pain may qualify for and benefit from CAT.

In this case report, subcutaneous implantation of CAT was evaluated in a diabetic neuropathic patient at high risk of plantar ulcer formation. The patient had a history of recurrent plantar ulcers and presented with a pre-ulcerative lesion (Figure 3A). Similar to the case reported by Luu et al., there has been no incidence of ulcer recurrence or complications.[14] While the Luu et al. case was followed for only 6 weeks, this CAT patient has been followed for 9 months. CAT has remained palpable throughout the 9-month follow-up, indicating the longevity of the implanted CAT.

Currently, CAT is the only adipose allograft available to health care providers that retains the structure and cushioning function of native adipose tissue. The favorable outcomes observed in this clinical case suggest that CAT is a promising approach for managing diabetic neuropathic patients at risk of plantar ulcerations. Long-term follow-up for the treated patient is currently ongoing. Future studies with larger sample sizes and extended follow-up are warranted to further evaluate the clinical effectiveness and ulcer-free duration.

AUTHOR CONTRIBUTIONS

Matthew J. Regulski: Conceptualization; data curation; writing – review and editing. **Molly C. Saunders:** Conceptualization; writing – original draft; writing – review and editing. **Sharron E. McCulloch:** Conceptualization; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

MJR has not received any financial compensation from Britecyte. MCS and SEM are employees of Britecyte.

DATA AVAILABILITY STATEMENT

Research data are not shared.

CONSENT

Written informed consent from the patient has been obtained to permit the submission of data for publication.

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REFERENCES

1. Dalal S, Widgerow AD, Evans GR. The plantar fat pad and the diabetic foot—a review. *Int Wound J*. 2015;12(6):636-640. doi:10.1111/iwj.12173
2. Kwon OY, Mueller MJ. Walking patterns used to reduce forefoot plantar pressures in people with diabetic neuropathies. *Phys Ther*. 2001;81(2):828-835. doi:10.1093/ptj/81.2.828
3. Pecoraro RE, Reiber GE, Burgess EM. Pathways to diabetic limb amputation. *Basis for Prevention Diabetes Care*. 1990;13(5):513-521. doi:10.2337/diacare.13.5.513
4. Prompers L, Huijberts M, Apelqvist J, et al. High prevalence of ischaemia, infection and serious comorbidity in patients with diabetic foot disease in Europe. Baseline results from the Eurodiale study. *Diabetologia*. 2007;50(1):18-25. doi:10.1007/s00125-006-0491-1
5. Balkin SW. Injectable silicone and the foot: a 41-year clinical and histologic history. *Dermatologic Surg*. 2005;31(11):1555-1560. doi:10.2310/6350.2005.31241
6. van Schie CH, Whalley A, Vileikyte L, Wignall T, Hollis S, Boulton AJ. Efficacy of injected liquid silicone in the diabetic foot to reduce risk factors for ulceration: a randomized double-blind placebo-controlled trial. *Diabetes Care*. 2000;23(5):634-638. doi:10.2337/diacare.23.5.634
7. Miller A. Filler in the foot: treatment of plantar fat pad atrophy with dermal fillers. *J Aesthet Nurs*. 2021;10(1):6-11. doi:10.12968/joan.2021.10.Sup1.6
8. Ali NS, Hoss E, Kollipara R, Goldman MP. Hyaluronic acid filler for treatment of metatarsal fat pad atrophy. *Dermatologic Surg*. 2021;47(7):1034-1035. doi:10.1097/DSS.0000000000002999
9. Salvatore L, Natali ML, Brunetti C, Sannino A, Gallo N. An update on the clinical efficacy and safety of collagen injectables for aesthetic and regenerative medicine applications. *Polymers*. 2023;15(4):1020. doi:10.3390/polym15041020

10. Foumenteze JP, Simpson H, Kerrouche N. Hyaluronic acid filler injections under the metatarsal heads provide a significant and long-lasting improvement in metatarsalgia from wearing high-heeled shoes. *Dermatologic Surg*. 2018;44(7):994-1001. doi:10.1097/DSS.0000000000001470
11. Billings E Jr, May JW Jr. Historical review and present status of free fat graft auto transplantation in plastic and reconstructive surgery. *Plast Reconstr Surg*. 1989;83:368-381. doi:10.1097/00006534-198902000-00033
12. Malik D, Luck J, Smith OJ, Mosahebi A. A systematic review of autologous fat grafting in the treatment of acute and chronic cutaneous wounds. *Plast Reconstr Surg Glob Open*. 2020;8(5):e2835. doi:10.1097/GOX.0000000000002835
13. Phan K, Lin MJ. Autologous fat grafting for plantar fasciitis. *J Cutan Aesthet Surg*. 2022;15(1):97-98. doi:10.4103/JCAS.JCAS_206_20
14. Luu CA, Larson E, Rankin TM, Pappalardo JL, Slepian MJ, Armstrong DG. Plantar fat grafting and tendon balancing for the diabetic foot ulcer in remission. *Plast Reconstr Surg Glob Open*. 2016;4(7):e810. doi:10.1097/GOX.0000000000000813
15. Kress GT, Swerdlow M, Mohan N, Patel K, Shin L. Remission strategies with fat grafting to prevent recurrence of pedal ulcerations and pain: a case series. *Plast Reconstr Surg Glob Open*. 2023;11(9):e5232. doi:10.1097/GOX.0000000000005232
16. Fontes T, Brandão I, Negrão R, Martins MJ, Monteiro R. Autologous fat grafting: harvesting techniques. *Ann Med Surg (Lond)*. 2018;13(36):212-218. doi:10.1016/j.amsu.2018.11.005
17. Wederfoort JLM, Hebels SA, Heuts EM, van der Hulst RRWJ, Piatkowski AA. Donor site complications and satisfaction in autologous fat grafting for breast reconstruction: a systematic review. *J Plast Reconstr Aesthet Surg*. 2022;75(4):1316-1327. doi:10.1016/j.bjps.2022.01.029
18. Rohrich RJ, Sorokin ES, Brown SA. In search of improved fat transfer viability: a quantitative analysis of the role of centrifugation and harvest site. *Plast Reconstr Surg*. 2004;113(1):391-397. doi:10.1097/01.PRS.0000097293.56504.00
19. Pu LL. Towards more rationalized approach to autologous fat grafting. *J Plast Reconstr Aesthet Surg*. 2012;65(4):413-419. doi:10.1016/j.bjps.2011.09.033
20. Bellini E, Grieco MP, Raposio E. The science behind autologous fat grafting. *Ann Med Surg (Lond)*. 2017;24:65-73. doi:10.1016/j.amsu.2017.11.001
21. Doornaert M, Colle J, De Maere E, et al. Autologous fat grafting: latest insights. *Ann Med Surg (Lond)*. 2018;37:47-53. Published 2018 Oct 16. doi:10.1016/j.amsu.2018.10.016
22. *Liposana™ Package Insert*. Britecyte, Inc.; 2024.
23. Boulton AJ, Hardisty CA, Betts RP, et al. Dynamic foot pressure and other studies as diagnostic and management aids in diabetic neuropathy. *Diabetes Care*. 1983;6:26-33. doi:10.2337/diacare.6.1.26
24. Armstrong DG, Boulton AJM, Bus SA. Diabetic foot ulcers and their recurrence. *N Engl J Med*. 2017;376(24):2367-2375. doi:10.1056/NEJMra1615439
25. Gusenoff JA, Mitchell RT, Jeong K, Wukich DK, Gusenoff BR. Autologous fat grafting for pedal fat pad atrophy: a prospective randomized clinical trial. *Plast Reconstr Surg*. 2016;138(5):1099-1108. doi:10.1097/PRS.0000000000002667
26. Kokai LE, Schilling BK, Chnari E, et al. Injectable allograft adipose matrix supports adipogenic tissue remodeling in the nude mouse and human. *Plast Reconstr Surg*. 2019;143(2):299e-309e. doi:10.1097/PRS.0000000000005269
27. Wingenfeld C, Egli RJ, Hempfing A, Ganz R, Leunig M. Cryopreservation of osteochondral allografts: dimethyl sulfoxide promotes angiogenesis and immune tolerance in mice. *J Bone Joint Surg Am*. 2002;84(8):1420-1429.
28. Crowley CA, Smith WPW, Seah KTM, et al. Cryopreservation of human adipose tissues and adipose-derived stem cells with DMSO and/or trehalose: a systematic review. *Cells*. 2021;10(7):1837. doi:10.3390/cells10071837

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