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PILOT STUDY

Research

Pilot Study: Human Adipose Tissue Allograft for Fat Pad Defects in Patients With Preulcerative Lesions

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Background: Loss or displacement of a fat pad on the foot increases plantar pressure, leading to pain and plantar ulcers. These ulcers, especially in patients with diabetic neuropathy, have high recurrence rates, often resulting in amputations. Standard of care focuses on reducing plantar pressure with shoe padding or orthotic devices, leaving the restoration of the fat pad as an unmet medical need. To address this, a human cryopreserved adipose tissue (hCAT) allograft has been developed to repair adipose tissue defects.

Methods: Scientific characterization of hCAT included assessments of its structural properties, immunogenicity, persistence, and remodeling in both in vitro and in vivo models. The incidence of adverse events and ulcer recurrence was analyzed retrospectively in 12 patients with diabetic neuropathy with preulcerative lesions who received 1.5–3.0 mL subcutaneous hCAT implants in areas with fat pad defects.

Results: When implanted in patients, hCAT remained palpable at the implantation sites, and no ulcerations occurred for an average of 6.4 months (range, 2–10 months). No product-related adverse events have been recorded to date. Long-term follow-up for implanted patients is ongoing.

Conclusions: Use of hCAT seems to be safe and potentially beneficial for managing patients at risk for plantar ulcerations. Further studies are warranted to evaluate hCAT's potential to manage patients at high risk for plantar ulcer formation.
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INTRODUCTION

The fat pad on the plantar surface of the foot provides cushioning and support to the underlying structures, especially during weight-bearing activities. When the fat pad degenerates or is displaced, it increases plantar pressure on the bones, causing pain and potentially leading to skin breakdown and ulcerations.[1]

Patients with diabetic neuropathy, in particular, are vulnerable to plantar ulcerations because their diminished sensation makes them less responsive to potential injury triggers. Motor neuropathy can also lead to muscle and fat pad atrophy, resulting in foot instability and altered gait, which increases plantar pressure and makes these patients susceptible to ulcerations.[2] Plantar ulcers frequently become infected, leading to gangrene and contributing to a high amputation rate of approximately 80% within this population.[3]

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With a high rate of amputation in patients with diabetic neuropathy, reducing plantar pressure is an essential part of wound care management for preventing plantar ulcer formation and recurrence. Current nonsurgical treatment options are limited to the use of shoe padding, inserts, and other orthotic devices.[2]

Recently, a human cryopreserved adipose tissue (hCAT) allograft has been developed for the repair, replacement, or reconstruction of adipose defects. Here, we provide scientific characterization of hCAT and describe the clinical evidence supporting its use in patients with diabetic neuropathy at high risk of plantar ulceration due to fat pad atrophy or displacement.

METHODS

A complete list of abbreviations and acronyms can be found in Supplemental Digital Content 1 (**http://links.lww.com/PRSGO/D712**).

Limitations regarding long-term follow-up inherently exist in this article type.

Disclosure statements are at the end of this article, following the correspondence information.

Related Digital Media are available in the full-text version of the article on www.PRSGlobalOpen.com.

Scientific Characterization of hCAT

Human and Animal Adipose Tissue Procurement

Human adipose tissues were provided by the National Disease Research Interchange (Philadelphia, PA) and Zen-Bio, Inc. (Durham, NC) according to their approved protocols, with written informed consent obtained.

Animal adipose tissue procurement and animal studies were conducted at Noble Life Sciences, Inc. (Woodbine, MD) after protocol approval by the Noble Life Sciences Institutional Animal Care and Use Committee. All procedures were conducted in compliance with the current versions of the animal welfare regulations.

Adipose Tissue Processing

Human (from cadaveric or lipoaspirate donors) and rat adipose tissues were stored frozen before processing. Processing steps included cutting, washing, and sieving. The processed tissue resulted in a devitalized adipose tissue particulate that can be implanted via a 20G needle. The tissues were cryopreserved in 0.5 M trehalose and 2.5% human serum albumin and subsequently stored below −40°C.

Histology and Immunohistochemistry

Histological hematoxylin and eosin (H&E) and immunohistochemical (IHC) analyses were performed at Histoserv, Inc. (Germantown, MD). For IHC staining, primary antibodies against CD206 (1:1600; Cell Signaling Technology, Danvers, MA) and von Willebrand factor (1:4000; Abcam, Cambridge, MA) were used.

Adipose Tissue Extract Preparation

Adipose tissue extracts (ATEs) were created by combining tissue with medium for cell bioassays or with phosphate-buffered saline for enzyme-linked immunosorbent assays (ELISAs) at a 1:1 (vol/vol) ratio, followed by a 2-hour incubation on a rotator and 10-minute centrifugation at 13,000 revolutions per minute.

Inflammatory Cytokine Profiling in hCAT

Inflammatory cytokines in ATEs were assessed using the 6-plex ProcartaPlex Human Inflammatory Panel (Life Technologies, Carlsbad, CA) following the manufacturer's protocol. Cytokines are listed in Table 1.

Activation of THP-1 and Human Peripheral Blood Mononuclear Cells by hCAT In Vitro

In vitro immunogenicity of hCAT was investigated through the activation of immune cells THP-1 or human peripheral blood mononuclear cells (hPBMCs) in cocultures with 25% ATEs representing 0.25-mL tissue. Activation of THP-1 cells and hPBMCs was assessed by detecting tumor necrosis factor-α (TNF-α), interleukin (IL)-1β, and IL-6 using human ProcartaPlex Simplex Kits (Life Technologies), following the manufacturer's protocols.

Immunogenicity In Vivo

Cryopreserved adipose tissue (CAT) immunogenicity in vivo was assessed by detecting anti-CAT antibodies in blood serum via ELISA. An allogeneic rat CAT (rCAT) surrogate was used to mirror clinical hCAT applications. Immunogenicity testing was conducted within a nonalcoholic steatohepatitis model in obese Zucker rats, as part of Britecyte, Inc.'s liver disease therapeutics program.[10] Six male obese Zucker rats (8–10 weeks old) were subcutaneously treated with 2 mL rCAT, whereas a control group received phosphate-buffered saline. Blood serum samples were collected 4 weeks post-treatment to detect antiallogeneic rCAT antibodies.

Detection of antiallogeneic rCAT antibodies in rat serum was performed by ELISA. Reagents were from the DuoSet ELISA Ancillary Reagent Kit 2 (R&D Systems, Minneapolis, MN). Rat serum samples were titrated using 2-fold dilutions ranging from 1:100 (1%) to 6400 (0.016%) on an ELISA plate coated with 4 µg/mL of the rCAT extract. The presence of antibodies was detected using goat anti-rat immunoglobulin G antibodies conjugated with horseradish peroxidase (1:1000 dilution; R&D Systems, Minneapolis, MN), followed by the tetramethylbenzidine substrate.

hCAT Remodeling In Vivo After Subcutaneous Implantation

At day 0, 6 male Sprague-Dawley (SD) rats, aged 4–5 weeks, received 0.5 mL/point hCAT subcutaneously in 4 locations on the dorsum (2 mL total). Blood serum and hCAT implants were collected on days 3, 7, 10, 14, 21, and 28 postimplantation. The hCAT implants were photographed and weighed. The hCAT specimens were fixed in 10% neutral-buffered formalin for histological and IHC analyses.

Clinical Evaluation of hCAT

hCAT Commercial Product Description

hCAT (Liposana, Britecyte, Inc., Frederick, MD) is manufactured by Britecyte's partner, LifeLink Foundation, Inc. (Tampa, FL), hCAT (Liposana, Britecyte, Inc., Frederick, MD) is regulated as a human cells, tissues, and cellular and tissue-based product under Section 361 of the Public Health Service Act and Title 21, CFR Part 1271. It is intended for use in the repair, replacement, or reconstruction of adipose defects and has a shelf life of 5 years if stored at −40°C or colder. Storage between −20°C and −40°C is limited to 6 months.[11]

Takeaways

Question: Can implantation of human cryopreserved adipose tissue (hCAT) allograft in areas of fat pad defects in patients with diabetic neuropathy at risk for plantar ulcerations prevent ulcer formation?

Findings: No ulcerations were observed in any of the 12 patients who received hCAT implantation with an average follow-up of 6.4 months (range, 2–10 months). In addition, no product-related adverse events were reported.

Meaning: The use of hCAT should be considered part of the standard of care for managing patients at risk of ulcerations. The hCAT allograft is a promising solution that can provide an ulcer-free, higher quality of life for patients in need.

Table 1. Inflammatory Cytokines in hCAT Versus Fresh Human Adipose Tissue

	hCAT		Fresh Human Adipose Tissue†	
Cytokine	Cytokine Level (Mean ± SD, pg/g Tissue)*	Range (Lowest–Highest, pg/g Tissue)*	Cytokine Level (Mean or Range, pg/g Tissue)	References
IL-1β	Below quantitation	N/A	5.15–528.39	4
			0–1000	5
IL-6	339 ± 181	49–641	100–300	5
			2220‡	6
			85.8§	7
G-CSF	Below quantitation	N/A	0–1200	5
			3.43‖	8
			75.9§	7
IFN-γ	Below quantitation	N/A	0–100	5
			Below quantitation¶	9
TNF-α	Below quantitation	N/A	30–100**	N/A**
			7.76–133.68	4
			50–500	5
			105.6§	7
MIG	Below quantitation	N/A	4375.8§	7

*hCAT extracts derived from 10 different donors were tested.
†Cytokine levels in fresh human adipose tissue are reported in the literature. Fresh human adipose tissue—collected tissues were washed several times to reduce the presence of blood.
‡Cytokine levels in Cavallo et al[6] are shown for 0.2 mL tissue/mL. Data were adjusted to pg/g tissue by multiplying mean values in the article by 5.
§Cytokine levels in Nava et al[7] are shown for 3 mL tissue in 9 mL medium (~0.3 mL/mL). Data for lipoaspirates were adjusted to pg/g tissue by multiplying mean values in the article by 3.3.
‖Cytokine levels in Yu et al[8] are shown for ~7mL tissue/mL. Data were adjusted to pg/g tissue by dividing mean values by 7.
¶IFN-γ level in Munro et al[9] is for mouse adipose tissue.
**Data are generated by the authors of this study.
G-CSF, granulocyte colony stimulating factor; IFN-γ, interferon gamma; MIG, monokine induced by IFN-γ; N/A, not applicable.

Study Design and Patient Population

Clinical outcomes of hCAT were evaluated in a single-center case series. Patients with a history of plantar ulcers and preulcerative lesions, defined by callus formation despite proper offloading (eg, diabetic shoes), were selected for hCAT implantation. Between August 2023 and April 2024, 12 patients received hCAT implants.

Informed consent was obtained from each patient before implantation. Deidentified data were collected from medical charts in accordance with the Health Insurance Portability and Accountability Act of 1996. The study followed ethical guidelines from the Declaration of Helsinki, and institutional review board approval was waived as it was a retrospective study.

hCAT Management

The areas of preulcerative lesions were prepared with Betadine solution before implantation. For patients with painful neuropathy, a local anesthetic was used. The callus in the lesion area was then shaved down with a scalpel. Each patient received a subcutaneous hCAT implant of 1.5 mL of using a 21G needle in the area under and around the preulcerative lesion. All patients were offloaded with diabetic shoes, except 2 patients who used an offloading boot (Foot Defender, Defender Ops, Miami, FL). Additional hCAT implantation was at the investigator's discretion, typically based on callus reappearance or a large fat pad defect requiring greater than 1.5 mL hCAT. Patients were then instructed to reduce activity and limit weight-bearing for 2–3 days. Patients who could not limit activity were advised to wear their prescribed diabetic molded shoes or boots.

Clinical Outcomes and Follow-up

The clinical outcomes included hCAT-related adverse events (AEs) and the incidence of ulcer formation at the site of hCAT implantation. Patients were followed up at 1, 3, 6, and 9 months, when applicable. All patients are continuing to be followed up for longer-term outcomes with a frequency of every 2–3 months.

Statistical Analysis

GraphPad Prism and Microsoft Excel were used for calculations of mean and SDs. The Student *t* test was used for statistical analysis, and a *P* value of less than 0.05 was considered significant.

RESULTS

Scientific

Histologically, adipose tissue consists of large, oval-, or polyhedral-shaped cells (adipocytes) with thin cytoplasmic membranes and an extracellular matrix between cells. The nuclei are crescent-shaped and compressed to the cell periphery. In H&E-stained sections, adipocytes seem clear due to the dissolution of cytoplasmic fat by organic solvents during preparation. H&E-stained images show that the structure of processed tissue before cryopreservation and hCAT postthaw is consistent with native fresh adipose tissue (Fig. 1).

The immunogenicity of hCAT in vitro was assessed by inflammatory cytokine detection in hCAT extracts (ATEs) and immune cell activation by ATEs. Among the 6 key inflammatory cytokines analyzed, only IL-6 was

detectable in hCAT, ranging from 49 to 641 pg/g tissue (Table 1). In contrast, fresh adipose contains detectable levels of inflammatory cytokines including IL-1β and TNF-α (Table 1). Results of cell cultures indicated that ATEs did not activate immune cells, which was detected by the release of IL-1β, IL-6, or TNF- α by THP-1 cells (Fig. 2A) or by hPBMCs (Fig. 2B). A slight increase in IL-6 observed in the coculture of THP-1 cells with ATEs compared with THP-1 cells alone is attributed to the presence of IL-6 in ATEs (Table 1). Due to the known immunogenicity of decellularized human scaffolds in animals, CAT immunogenicity in vivo was investigated using an allogeneic rCAT surrogate, which mirrored the clinical use of hCAT in patients.[12,13] Results demonstrated that no antiallogeneic rCAT antibodies were detected in blood serum 4 weeks postimplantation in rats (Fig. 3). For the other in vivo experiments, hCAT was tested.

The implantation of hCAT was well tolerated, with no animal deaths, abnormalities, or weight loss observed (data not shown). Blood chemistry values were within reported historical ranges for SD rats (data not shown). The hCAT grafts persisted for the entire study duration (4 weeks) at the implantation sites with their appearance at each time point depicted in Supplemental Digital Content 2A. (**See figure, Supplemental Digital Content 2,** which displays the visual appearance and weight of hCAT in vivo. Visual appearance of hCAT at different time points after subcutaneous implantation in SD rats. A, One representative hCAT graft on day 7 postimplantation is embedded in rat connective tissue [black asterisk] with visible blood vessels on the surface

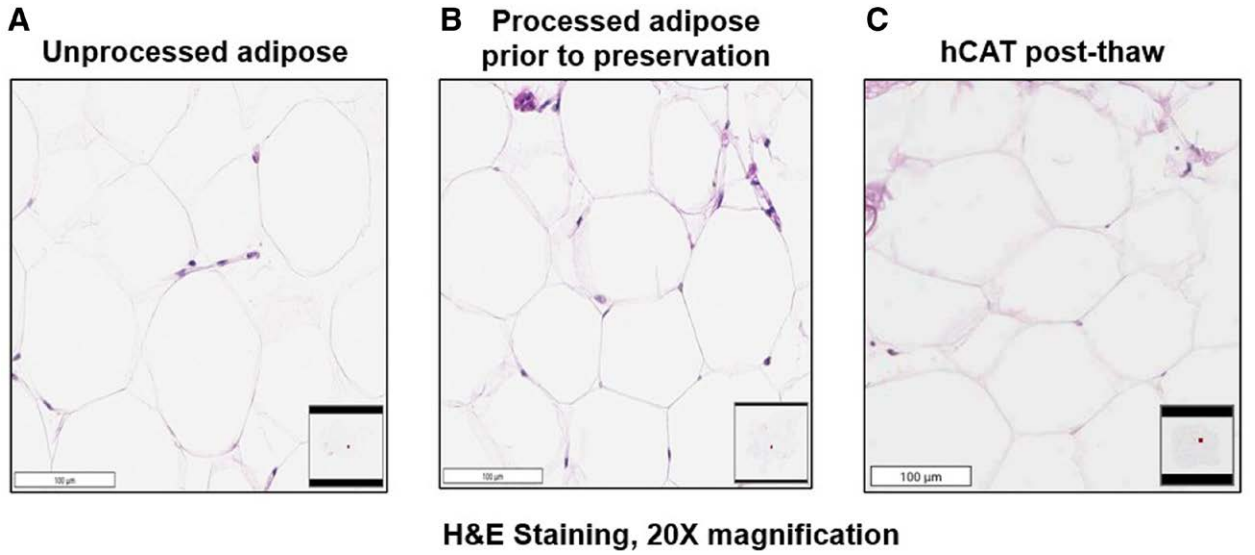

Fig. 1. The hCAT allograft retains the structural integrity of native adipose tissue. The structure of fresh unprocessed adipose tissue (A), processed adipose tissue before cryopreservation (B), and hCAT postthaw (C) was evaluated histologically using H&E staining. Microphotographs of H&E-stained tissue sections show that there are no significant differences between fresh adipose tissue and hCAT.

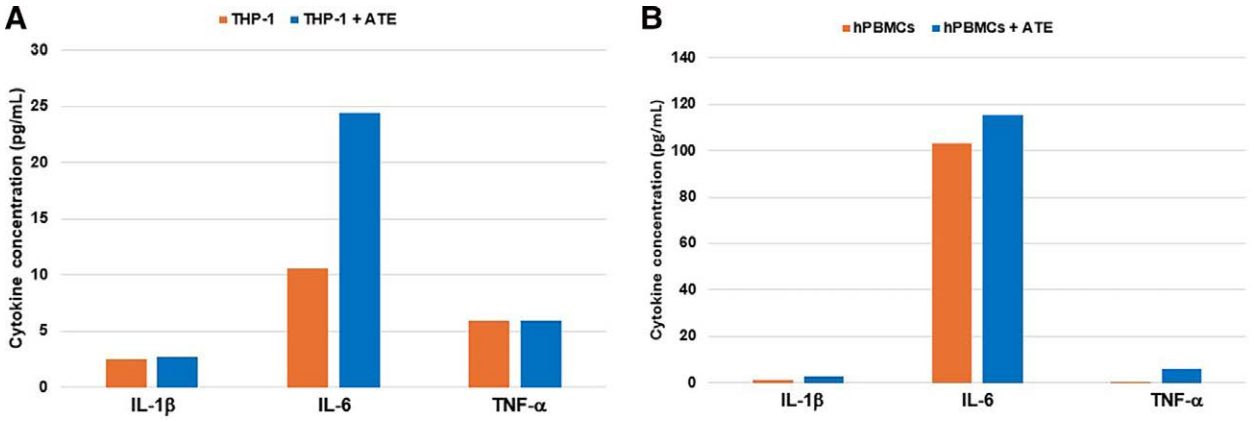

Fig. 2. ATEs from hCAT do not trigger secretion of inflammatory cytokines by THP-1 cells (A) and by hPBMCs (B). Concentrations of inflammatory cytokines IL-1β, IL-6, and TNF-α in culture supernatants were measured. Results for 1 representative experiment are shown.

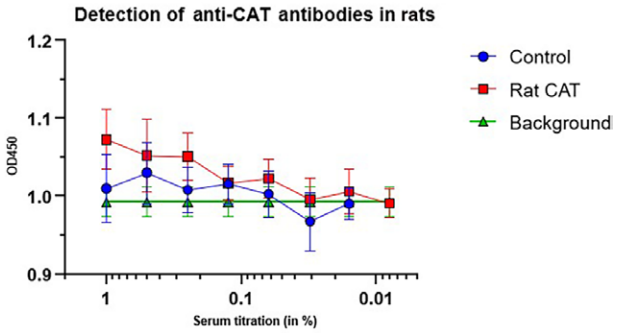

Fig. 3. Allogeneic rCAT does not trigger anti-rCAT antibody formation. Sprague-Dawley rCAT (2 mL per rat) was subcutaneously implanted in obese Zucker rats. Four weeks after implantation, blood serum was collected and tested for the presence of antiallogeneic rCAT antibodies. Control: serum from rats treated with phosphate buffer saline. Background: ELISA wells without serum. Graphs show mean ± SD, OD at 450 nm for each serum concentration (N = 6 rats per each group). OD, optical density.

of hCAT [black arrow]; and weight of hCAT grafts at different time points postimplantation. C, Combined weight for 4 hCAT grafts is shown at each time point. Time point 0: 2 g of hCAT was implanted, **http://links.lww.com/PRSGO/D713**.) The yellow color of the grafts, due to vitamin A (carotene) in human adipose tissue, gradually diminished over time. Visually, postimplantation, hCAT became vascularized, with blood vessels visible on the graft surface by day 7, and the grafts embedded into host connective tissues (**Supplemental Digital Content 2B, http://links.lww.com/PRSGO/D713**). The weight of hCAT grafts did not significantly change over time postimplantation after a minor drop at day 3 (**Supplemental Digital Content 2C**, **http://links.lww.com/PRSGO/D713**). Fluctuations in graft weight between time points were attributed to challenges in distinguishing hCAT from host connective tissues attached to the grafts.

Histologically, before implantation, hCAT did not contain rat macrophages, neutrophils, or lymphocytes (Fig. 4A). However, as early as day 3 postimplantation, these cells were observed infiltrating hCAT (Fig. 4B, black circle in image 4). Many of the cells detected in hCAT were CD206-positive M2 macrophages (Fig. 4B, image 6). Areas rich in M2 macrophages also had a high number of newly formed blood vessels (Fig. 4B, image 5), originating from rats. No blood vessels or M2 macrophages were detected in hCAT before implantation (Fig. 4A, images 2 and 3). M2 macrophages were still detected in hCAT at day 28 postimplantation, the final time point in the study, hCAT was not resorbed (**Supplemental Digital Content 2, http://links.lww.com/PRSGO/D713**); it was remodeled by M2 macrophages by taking up lipids released from hCAT adipocytes (Fig. 5, red arrows).

Clinical

The hCAT was prepared for implantation per the steps outlined in Supplemental Digital Content 3. (**See figure, Supplemental Digital Content 3,** which displays the preparation of hCAT [Liposana] for implantation, **http://links.lww.com/PRSGO/D714**.) Of the 12 patients who received hCAT, 10 (83%) were men and 2 (17%) were women with an average age of 67 years (range, 42–85 years). All were diabetic neuropathic patients with peripheral vascular disease. Other significant comorbidities included lymphedema (25%), chronic kidney disease (17%), and obesity (17%). All patients had a history of plantar ulcers, with 11 of them having a history of recurrent ulceration. Table 2 shows a summary of patient demographics and hCAT administration details. Three patients received hCAT implants in a metatarsal head, 3 in a metatarsal base, 5 in a submetatarsal head, and 1 in the heel.

Patients have been followed up for clinical outcomes for an average of 6.4 months (range, 2–10 months). Eight patients were administered hCAT once. Four patients received an additional 1.5 mL of hCAT after the initial application. One patient received a second hCAT application at 8 weeks due to a large defect size, another at 5 months due to pain, and 2 more at 6 months due to callus formation. The patient who experienced pain had it before the first implant, which subsided shortly after the hCAT implant but returned after 5 months. The pain subsequently subsided again after the second implantation. To date, there have been no ulcerations or hCAT-related AEs reported. For all patients, hCAT has remained palpable at the site of implantation. Four representative cases of patients who received hCAT are highlighted in Figure 6.

DISCUSSION

The use of fat grafts for soft tissue repair and reconstruction was pioneered by Neuber in 1893.[14] Historically, allogeneic adipose has not been widely used due to immunogenicity concerns, with only 2 cases described in the literature.[15] One case involved a fat graft from a matched brother to treat a radiation-induced ulcer, whereas another described breast augmentation with a cadaveric fat graft, which was explanted 15 years later due to pain, though there was no evidence of immunologic rejection.[16,17] These cases suggested the potential for clinical use of allogeneic adipose tissue.

A novel adipose processing technology now allows for the allogeneic use of adipose tissue, and hCAT is the first commercially available human adipose allograft using this technology. The hCAT allograft retains the structure and function of native tissue while eliminating immunogenic components, making it suitable for use in adipose tissue defects or damage.

Devitalization is a part of the hCAT manufacturing process, which is a common approach to reduce tissue antigenicity.[18] The developed manufacturing process ensures that immunogenic components such as lymph nodes and blood cells are removed, but retains adipocytes, the primary cell type in adipose tissue (Fig. 1). Experiments conducted using in vitro and in vivo models confirmed that hCAT does not contain proinflammatory

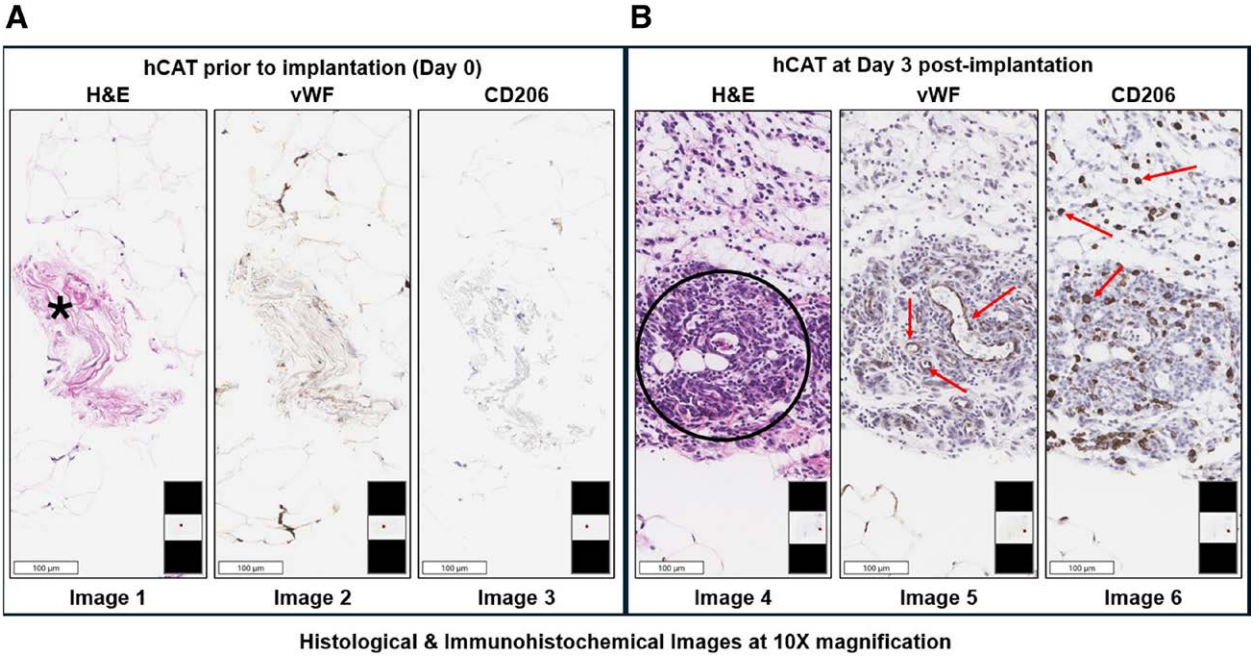

Fig. 4. Histological evaluation of hCAT structure, vascularization, and the presence of M2 macrophages. A, Images 1–3 show stained tissues on day 0 before implantation. B, Images 4–6 show stained tissues on day 3 postimplantation. On day 0 before implantation, there are no detectable blood vessels (vWF) and M2 macrophages (CD206) in the hCAT. The black asterisk on image 1 shows a collagen-rich area in hCAT (A). On Day 3 postimplantation, high numbers of blood vessels (image 5, red arrows) and M2 macrophages (image 6, red arrows) are present in hCAT; the black circle on the H&E images (image 4) shows an area infiltrated predominantly by rat macrophages, many of which are M2 macrophages (image 6, red arrows). vWF, von Willebrand factor.

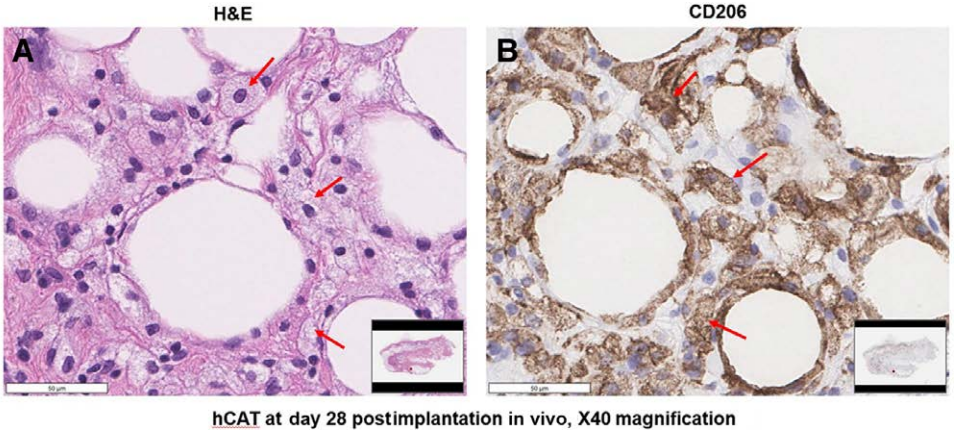

Fig. 5. Histological evaluation of hCAT structure (A) and the presence of M2 macrophages on day 28 postimplantation in vivo (B). There are high numbers of cells filled with lipid droplets (A), which are CD206-positive M2 macrophages (B). Red arrows point to cells filled with lipid droplets (A) and to M2 macrophages (B).

cytokines (Table 1) and does not elicit an immune response (Fig. 2). In contrast, fresh adipose tissue contains high levels of proinflammatory cytokines (Table 1), and the presence of proinflammatory cytokines in adipose tissue-derived products may have a negative effect on clinical outcomes.[6]

Due to the known immunogenicity of decellularized human scaffolds in animals, CAT immunogenicity in vivo was investigated using an allogeneic rCAT surrogate, mirroring the clinical use of hCAT in patients.[12,13] No antiallogeneic rCAT antibodies were detected in blood serum 4 weeks postimplantation in rats (Fig. 3). Despite the anticipated immune response to hCAT in other in vivo experiments, the clinical product was evaluated in immune-competent animals to gather valuable insights into how it behaves in a fully functioning immune system.

Postimplantation, hCAT does not resorb but integrates and remodels within the host tissue (**Supplemental Digital**

Table 2. Summary of Patient Demographics and hCAT Administration

Case	Sex	Age, y	Medical History	Implant Location	Follow-up, mo*
1	M	82	DM, painful neuropathy, PVD, hammertoe, equinus, ankle fusion, biomechanical deformity on right foot	R second metatarsal head	10
2	M	57	DM, neuropathy, PVD, CKD, obesity, MM, partial calcanectomy left heel, previous osteomyelitis	L heel	10
3	M	65	DM, neuropathy, PVD, equinus, multiple digit amputations on both feet	R fourth metatarsal head	9
4	M	85	DM, neuropathy, PVD, equinus, ray amputations on the right foot, digit amputations on left foot	L fifth metatarsal base	9
5	M	65	DM, neuropathy, PVD, obesity, lymphedema, equinus, previous osteomyelitis of the right foot	R second submetatarsal head	8
6	M	67	DM, neuropathy, PVD, CKD, lymphedema, smoker, equinus, hallux limitus of left foot	L fifth metatarsal base	7.5
7	M	75	DM, neuropathy, PVD, left drop foot	L fifth metatarsal base	7.5
8	F	67	DM, neuropathy, PVD, spina bifida, equinus, fifth toe amputation of the right foot	R fifth submetatarsal head	4.5
9	M	59	DM, neuropathy, PVD, smoker, right ankle fused, equinus	R first and fifth metatarsal head	3
10	F	78	DM, severe neuropathy, PVD, psoriatic arthritis	R submetatarsal head	3
11	M	62	DM, neuropathy, PVD, hallux rigidus of the right foot, equinus, lymphedema	R first submetatarsal head	3
12	M	42	DM, neuropathy, PVD	L fourth submetatarsal head	2

*As of June 15, 2024.
CKD, chronic kidney disease; DM, diabetes mellitus; F, female; M, male; MM, multiple myeloma; PVD, peripheral vascular disease.

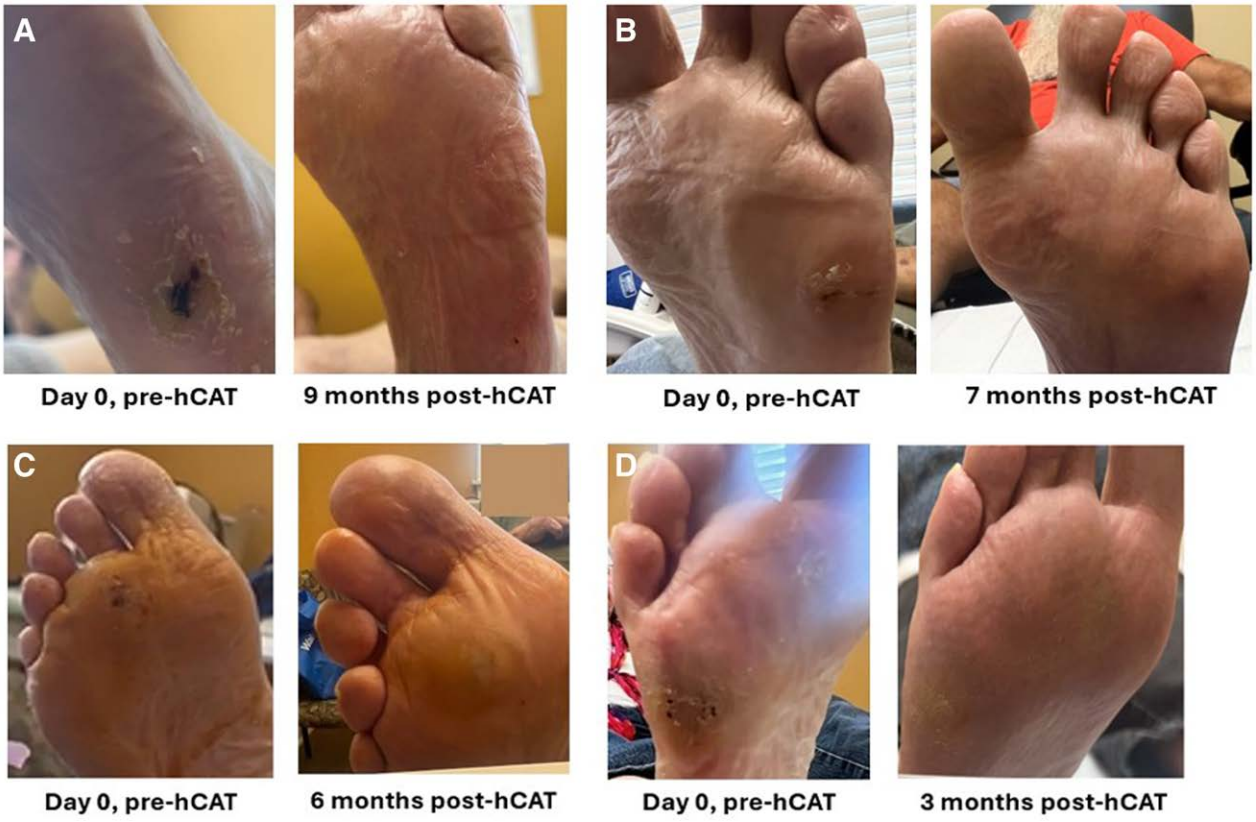

Fig. 6. Representative diabetic neuropathic hCAT patient cases. A, An 85-year-old man with a history of PVD and multiple digit amputations at day 0 and 9 months follow-up. B, A 75-year-old man with PVD and left drop foot at day 0 and 7 months follow-up. C, An 82-year-old man with PVD, previous ankle fusion, and a biomechanical deformity on the right foot at day 0 and 6 months follow-up. D, A 78-year-old woman with PVD and psoriatic arthritis at day 0 and 3 months follow-up. All the patients presented with preulcerative calluses that disappeared at their respective follow-up visits. PVD, peripheral vascular disease.

Content 2A, C, http://links.lww.com/PRSGO/D713). M2 macrophages, known for their anti-inflammatory and pro-angiogenic properties, were abundant in hCAT implants, with new blood vessel formation observed as early as day 3 (Fig. 4B).[12,19] The literature suggests that early macrophage infiltration in fat grafts supports blood vessel formation, stem cell recruitment, and fat graft retention.[20] These findings align with studies on human cartilage implants, where immune cells, including M2 macrophages, infiltrated the tissue, preserving the implant's volume and mechanical properties without resorption, similar to hCAT.[21]

The hCAT allograft is a unique commercially available adipose tissue allograft. In contrast to 2 other products, allograft adipose matrix (Leneva and Renuva, MTF Biologics, Edison, NJ), which preserves only the extracellular matrix, hCAT retains adipocytes, providing structural support and cushioning.[22,23] Although blood vessel formation in allograft adipose matrices begins 3 weeks postimplantation in immunocompromised mice, hCAT shows faster remodeling, with blood vessel formation detected as early as day 3 (Fig. 4B).[24]

The hCAT allograft is designed for the repair, replacement, or reconstruction of adipose tissue defects, such as fat pad atrophy, a condition common in patients with diabetic neuropathy that increases the risk of plantar ulceration. In this study, 12 patients with diabetic neuropathy received hCAT, with no reported ulcer formation, recurrence, or AEs. The average follow-up time was more than 6 months, with the longest being 10 months.

Current strategies for alleviating plantar pressure in patients with fat pad atrophy are limited. Conservative measures include prescribing specialized footwear and padding. In severe cases, surgical interventions may be necessary to address foot defects.[25] Autologous fat grafting has emerged as another viable treatment option for fat pad atrophy; however, its primary use is typically for painful fat pad atrophy in patients without diabetes.[14,26–31]

Gusenoff et al[30] conducted a prospective, randomized clinical trial on patients with painful fat pad atrophy. After 1 year, patients who received fat grafting showed improved foot function and less pain compared with those who received conservative treatment.

In 2017, Raposio et al[32] studied 8 patients with chronic heel pain after surgery for the adult flatfoot deformity. These patients underwent autologous subcutaneous heel fat grafting, and pain levels significantly decreased from baseline to 6 months postprocedure.

In patients with diabetes, autologous adipose use is rare. Luu et al[25] reported a case of a 37-year-old diabetic man with neuropathy, gangrene, and a prior fifth-ray amputation. Fat grafting around a preulcerative lesion allowed him to resume wearing normal footwear within 4 weeks, with no ulcer recurrence at 6 weeks.

In another study, Kress et al[31] reviewed 17 feet in 15 patients, mostly diabetic and neuropathic, who underwent fat grafting for recurrent ulcerations. Eleven patients received autologous fat grafts, and 4 received an allograft adipose matrix (Leneva, MTF Biologics). After an average follow-up of 6.9 months, no complications or recurrent ulcerations were reported.

Although autologous adipose tissue offers promising outcomes, it requires an additional procedure to harvest fat, potentially leading to donor site morbidity. Results can be unpredictable due to adipose resorption, which is attributed to variations in harvesting and processing techniques as well as the quality of the patient's adipose.[33] The hCAT allograft is an alternative option to autologous fat grafting without these limitations: it allows for fast preparation and implantation, involves no adipose harvesting donor site morbidity, and is subjected to a validated manufacturing process that ensures lot-to-lot consistency, which should result in more predictable and consistent clinical outcomes.

CONCLUSIONS

The positive outcomes observed in this study suggest that hCAT is a promising approach for managing patients with adipose defects who are at high risk of ulceration or recurrence. Long-term follow-up for all patients is currently ongoing. Future studies with larger sample sizes and extended follow-up periods are warranted to further assess the clinical effectiveness and durability of the effect.

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DISCLOSURES

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