Débridement and Autologous Lipotransfer for Chronic Ulceration of the Diabetic Foot and Lower Limb Improves Wound Healing

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Background: The application of autologous lipotransfer (fat grafting, lipofilling) in reconstructive surgery is steadily becoming more popular as evidence of the regenerative and reparative effects of fat becomes better known. The authors investigated the use of autologous lipotransfer for treatment of chronic diabetic and other foot and lower limb ulcers.

Methods: Twenty-six patients with nonhealing wounds were treated with surgical débridement and autologous lipotransfer (using the débridement and autologous lipotransfer method). The mean age of the wounds before intervention was 16.7 months. Wound size after débridement averaged 5.1 ± 2.6 cm^2. On average, 7.1 ± 3.3 cc of lipoaspirate was transferred into the wound area.

Results: Twenty-two of 25 wounds (88 percent) healed completely within a mean of 68.0 ± 33.0 days. A reduction of wound size by 50 percent was achieved after an average of 4 weeks. In one patient with an ulcer within particularly scarred tissues on the lower limb, a repeated session of lipotransfer led to complete wound healing after another 4 weeks.

Conclusion: The authors describe a simple and useful technique to improve wound healing in diabetic feet and chronic lower limb ulcers with a background of peripheral vascular disease, where other interventional options to achieve wound healing have failed. (*Plast. Reconstr. Surg.* 136: 1357, 2015.)

CLINICAL QUESTION/LEVEL OF EVIDENCE: Therapeutic, IV.

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THERAPEUTIC

Chronic ulceration of the foot is one of the most challenging conditions to treat for plastic surgeons. Predisposing conditions such as diabetes or peripheral vascular disease commonly hinder adequate wound healing by conservative means, and interventions such as débridement and skin grafting or vacuum-assisted closure dressings often fail, necessitating more radical interventions, which frequently end up as amputations.

Although autologous fat grafting has been shown to improve the quality[1] and regenerative potential of chronically scarred tissues[2] and burn scars,[3] the effect on wound healing of chronic wounds[4,5] and early-stage pressure ulcers[6] has only been reported on sporadically. In this study, we describe a simple and useful technique of autologous lipotransfer to improve wound healing in diabetic feet and chronic lower limb ulcers with a background of peripheral vascular disease, where other interventional options to achieve wound healing have failed.

PATIENTS AND METHODS

This study was approved by the institutional review board, and all patients gave signed informed consent. Our prospective cohort study included 30 patients, of whom four were excluded because of large wound size. Twenty-six patients (17 men and nine women) with a median age of 59 years (range, 25 to 85 years)

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Table 1. Patient Profiles and Wound Characteristics

Patient	Age (yr)	Sex	Diabetic	PVD	CRF	Wound Type	Location	Ulcer Age (mo)	Fat Used (ml)	Wound Size (cm^2)	Healed (days)
1	57	M	No	Yes	No	Chronic wound after trauma	Pretibial	9	4	1.7	95
2	67	M	No	Yes	No	Pressure sore	Plantar	1	11	5.3	80
3	25	M	No	No	No	Chronic wound after trauma	Pretibial	5	2	1.9	60
4	55	M	Yes	Yes	No	Pressure sore	Plantar	19	8	5.4	60
5	50	M	Yes	No	No	Pressure sore	Plantar	12	6	2.3	40
6	76	M	No	No	No	Chronic wound after elective surgery	Dorsal foot	2	2	2.0	50
7	40	F	No	No	No	Pressure sore	Plantar	18	5	2.0	48
8	74	M	Yes	No	Yes	Pressure sore	Plantar	3	10	8.4	70
9	46	F	No	No	No	Pressure sore	Plantar	4	15	5.5	95
10	56	F	No	No	No	Pressure sore	Plantar	72	7	3.2	+
11	51	F	Yes	No	No	Pressure sore	Plantar	9	2.5	5.4	++
12	45	F	No	No	No	Chronic wound after elective surgery	Dorsal foot	3	6	6.3	100
13	62	M	No	Yes	No	Chronic scars after fracture	Distal lower limb	6	8	3.1	40
14	52	F	Yes	Yes	No	Chronic scars after fracture	Distal lower limb	8	6	3.4	107*
15	42	F	Yes	No	No	Chronic wound after trauma	Pretibial	3	6	6.8	80
16	62	M	Yes	Yes	No	Pressure sore	Plantar	8	6	5.1	80
17	85	F	No	Yes	Yes	Pressure sore	Heel	4	9	6.9	100
18	54	M	Yes	No	No	Chronic wound after trauma	Distal lower limb	24	8	3.8	63
19	66	M	Yes	Yes	No	Pressure sore	Heel	43	2	1.4	40
20	63	M	Yes	Yes	No	Chronic venous ulcer	Distal lower limb	12	9	10.0	+++
21	68	F	Yes	Yes	Yes	Pressure sore, Charcot	Plantar	5	5	8.0	++++
22	63	M	Yes	Yes	Yes	Pressure sore, Charcot	Plantar	18	10	9.8	107
23	76	M	Yes	Yes	Yes	Chronic venous ulcer	Distal lower limb	18	6	5.3	62
24	61	M	Yes	No	No	Chronic venous ulcer	Distal lower limb	52	10	7.4	42
25	61	M	Yes	No	No	Chronic venous ulcer	Distal lower limb	52	14	9.5	51
26	56	M	Yes	Yes	No	Pressure sore	Heel	24	6	2.8	65
Mean ± SD	58.2 ± 12.6							16.7 ± 18.0	7.1 ± 3.3	5.1 ± 2.6	68.0 ± 33.0

+, wound healed after 330 days; ++, patient moved away after 71 days; +++, skin grafting after 4 wk; ++++, poor compliance, refused repeated lipotransfer.
*Second lipotransfer on day 50.

had an average body mass index of 26.9 ± 10.4 kg/m^2. Sixteen of these were diabetics (type 1 or type 2), 13 had been diagnosed with peripheral vascular disease, and five had chronic renal failure (Table 1).

All patients were treated using the débridement and autologous lipotransfer method at the Department of Plastic, Reconstructive, Aesthetic and Hand Surgery at the Luisenhospital in Aachen, Germany. Inclusion criteria for adult patients were recalcitrant nonhealing lower limb ulcers (present for over 2 months); a surface dimension of larger than 2 cm^2; and causes including only venous, arterial, diabetogenic, postsurgical, posttraumatic, or pressure ulcers. All patients were recruited from the hospital's foot care clinic, where all had received standardized conservative wound dressing care by specially trained nurses but where wounds had failed to heal or had shown signs of progression of wound size. All patients had been treated before use of conventional plastic, general surgical, and vascular procedures that included débridements, vacuum-assisted closure dressings with various cycles, surgical improvement of the lower limb circulation, and other procedures that often necessitated long hospital admissions.

The locations of the chronic ulcers were as shown in Table 1. Exclusion criteria were ulcer size larger than 10 cm^2 and presence of other feasible options for treating the underlying cause of the ulcer (i.e., removal of implants, vascular surgical interventions). Patients were followed up for at least 4 months.

The primary aim of our study was to assess the time until complete wound closure was achieved. The secondary aim was to measure the time taken for a reduction in wound size by 50 percent.

Surgical Technique: Débridement and Autologous Lipotransfer Method

Débridement

According to the standard operating protocol, all ulcers underwent surgical débridement under regional or general anaesthesia. After photographic documentation, a wound swab was taken and sent for culture of organisms. The ulcers were then carefully débrided using a Volkmann spoon, sparing granulating areas, followed by careful sharp wound edge excision of a few millimeters with a scalpel. If infected bone was exposed, it was débrided to healthy and more solid bone. Hemostasis was achieved using bipolar coagulation. Wounds were then temporarily covered with gauzes soaked in Prontosan wound irrigation solution (B. Braun, Melsungen, Germany). Wound biopsy specimens were obtained if clinically indicated.

Autologous Lipotransfer

Infiltration of the standard tumescence solution (sodium chloride with adrenaline, without local anesthetic) was performed before débridement, to allow it to take effect for a few minutes. Fat harvesting from the lower abdomen ($n = 24$) or upper thigh ($n = 2$) was performed using 3.5-mm-wide liposuction cannulas (Thiebaud Biomedical Devices, Margencel, France) and the 100-cc LipiVage syringe system (Polytech Health & Aesthetics, Dieburg, Germany). The amount of lipoaspirate needed was estimated using a standard formula: 2 cc lipoaspirate per square centimeter wound size. No centrifugation of the lipoaspirate was necessary.

The lipoaspirate was then transferred into 2.5-cc Luer-lock syringes (BD, Franklin Lakes, N.J.) using a closed system (Luer Lock Adapter), followed by infiltration of the lipoaspirate with sharp 2 × 80-mm Supra Luer Lock cannulas (TSK Laboratory Japan, Tochigi-Ken, Japan) into the wound edges and sublesional injection into the bottom of the débrided ulcer, if possible. Because tissues were mostly very atrophic and scarred, sharp cannulas were used.

The fat was infiltrated with a threading technique using minimal pressure, in the direction from the surrounding areas (approximately 1 cm from the wound edge) toward the ulcer, or parallel to the wound edges, to avoid contaminating the surrounding tissues because of possible infection present in the wound. Fat was infiltrated retrogradely into the tunnels left by the cannula with each slow push. The amount of fat used was controlled by observing the surrounding skin (by avoiding blanching) and fat starting to fill the ulcer surface. Care had to be taken not to overinfiltrate the wound edges, as this might have caused further necrosis of the tissue and fat because of increased pressure. In the study, an average of 7.1 ± 3.3 cc of lipoaspirate was transferred. Fat that spilled into the crater of the wound was left in situ up to the edge of the skin, to act as a biological "dressing," which might have further influenced the wound milieu positively because of, for example, the presence of growth factors (Fig. 1).

The wounds were then covered with a sterile silicone wound dressing (Mepitel; Mölnlycke, Erkrath-Unterfeldhaus, Germany) and a vacuum-assisted closure dressing (polyvinyl alcohol foam) was applied (Lohmann & Rauscher, Schönau an

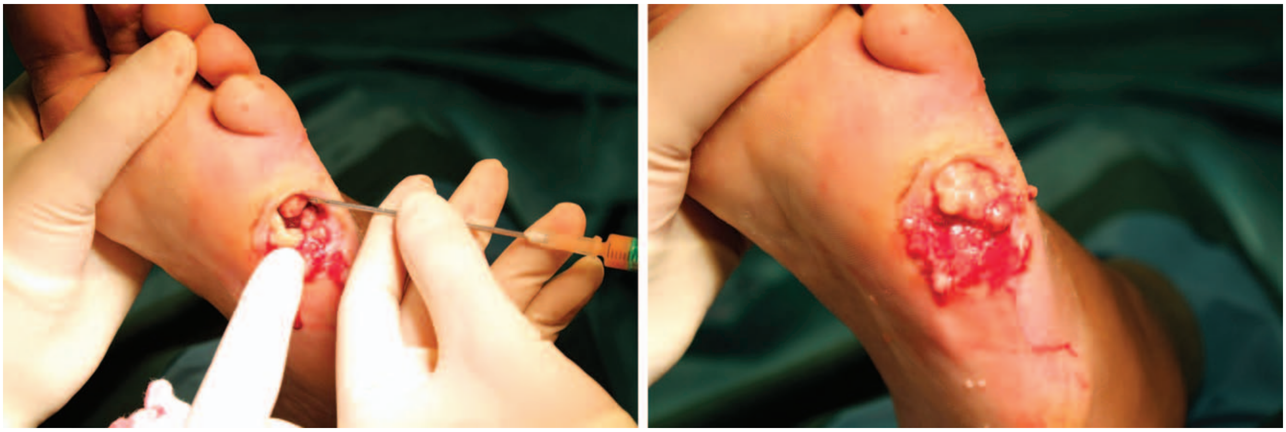

Fig. 1. Débridement and autologous lipotransfer into the ulcer base after débridement using a sharp cannula (*left*), and fat left within the base and crater of the wound (*right*).

der Triesting, Austria). Negative pressure was set at continuous mode at −90 mmHg for 24 hours, followed by intermittent negative pressure of −80 and −30 mmHg for 5 and 2 minutes, respectively. Patients received perioperative and postoperative antibiotics guided by positive culture results and sensitivities. Average operating time was 29 ± 6 minutes.

Aftercare

Strict bedrest was maintained and the dressing kept in place for 4 to 5 days. On postoperative day 5, the first change of dressing was performed and wounds were assessed. Photographic documentation of the healing progress and two measurements of wound size were performed. The wounds were then irrigated with Octenisept aqueous wound antiseptic (Schülke & Mayr, Norderstedt, Germany) and dressed using Suprasorb H plates (Lohmann & Rauscher). Antibiotic cover was continued for another week according to intraoperative swab results. Further dressing changes were recorded on postoperative days 7, 10, 14, and 21 and then weekly until complete wound healing. The same person, who was not the operating surgeon, performed standardized measurements of all wounds during follow-up in the foot care clinic. All photographs were later evaluated and the wounds measured again using a scale in the photograph, to ascertain the accuracy of the clinical readings. Limited weight bearing was instructed and orthopedic shoe support (WCS Wound Care Shoe System, Darco International, Inc., Huntington, W.Va.) applied from day 5 until wound healing was complete.

RESULTS

Wound size after débridement averaged 5.1 ± 2.6 cm^2 (range, 2.1 to 10.0 cm^2). Of the 26 wounds, the average treatment period before débridement and autologous lipotransfer intervention was 16.7 ± 17.9 months (range, 2 to 72 months). All patients had previously undergone various unsuccessful attempts to surgically improve the wound. One patient (patient 11) showed very good wound healing progress (almost 75 percent reduction in wound size after 60 days), but moved away after 71 days and thus any further follow-up was not possible. She was excluded from computations of the final results.

Twenty-two of 25 wounds (88 percent) healed completely within a mean of 68.0 ± 33.0 days (range, 40 to 107 days), resulting in stable tissues (Fig. 2). An average wound size reduction of 50 percent was achieved 4 weeks after intervention (Fig. 3).

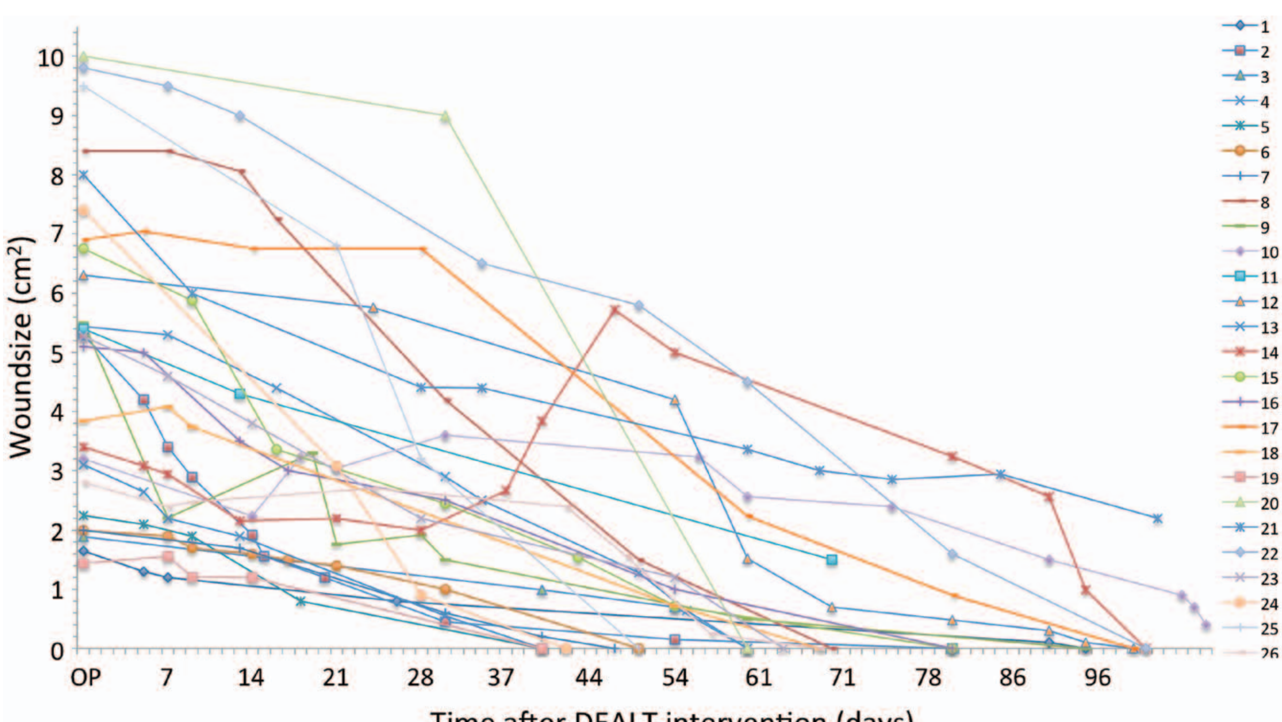

Fig. 2. Reduction of wound size (in square centimeters) over time (in days) following the débridement and autologous lipotransfer (*DEALT*) intervention for chronic wounds in 26 patients.

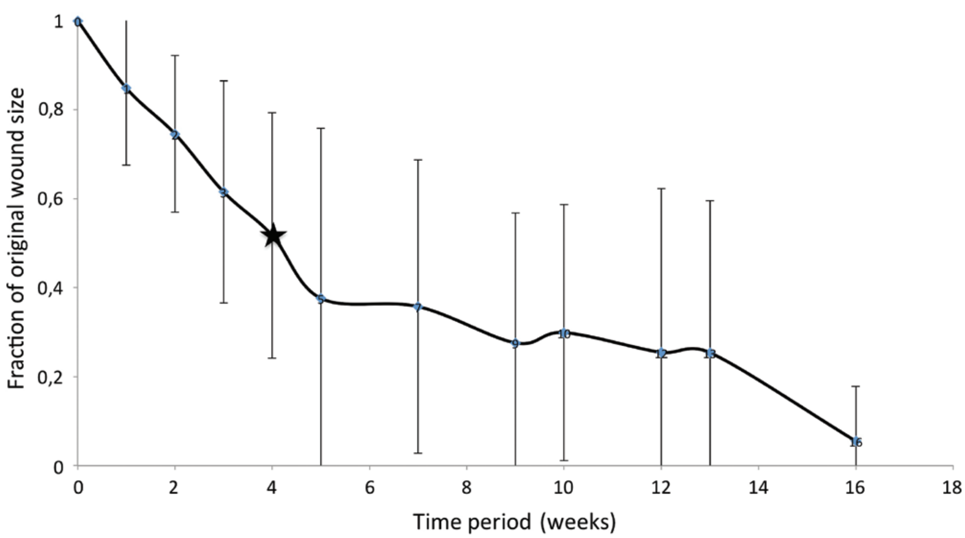

Fig. 3. Reduction of average wound size in percentage of original size over time (in weeks). After 4 weeks, wound size was reduced on average by 50 percent (*star*).

In one patient, a repeated session of lipofilling led to complete wound healing: patient 14, who had a chronically open wound on her lower tibia surrounded by an area of chronic scarring following a compound fracture and repeated infections, showed initial improvement for 4 weeks, then progression of wound size; however, after a repeated lipotransfer session on day 50 after the initial procedure, she achieved complete wound healing and stable tissues on day 107.

Three patients did not achieve complete closure according to the protocol after the 4-month observation period. Patient 20 (a 63-year-old diabetic) presented with a very large (3.6 × 2.8 cm), painful chronic venous stasis ulcer on his left medial lower limb, present for over 12 months. After the débridement and autologous lipotransfer method did not achieve the desired wound size reduction after 4 weeks, a skin graft was performed onto the newly formed granulation tissue covering the wound ground and wound edges. This resulted in excellent healing and pain-free, stable tissues within 2 weeks (Fig. 4).

Patient 21 was a 68-year-old diabetic with Charcot deformity and a mal perforans ulcer extending from the plantar across to the lateral dorsal aspect of her foot (8 cm^2). Initial débridement and autologous lipotransfer improved the depth of the ulcer (2 cm) considerably, and granulation tissue had started to close the connection to the dorsal wound opening. Despite very close follow-up and provision of an electric wheelchair, compliance was challenging, resulting in stagnation of the wound healing process. The patient refused a repeated lipotransfer session. Patient 10 showed considerable improvement of her initial pressure

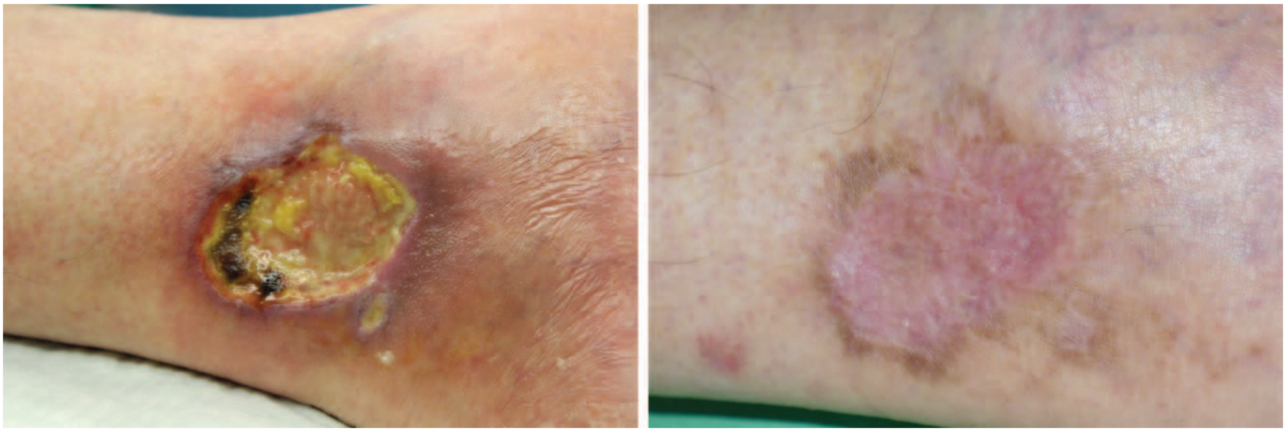

Fig. 4. A painful chronic stasis ulcer present for 12 months (*left*), healed completely after débridement and autologous lipotransfer and split-thickness skin grafting (*right*).

Fig. 5. A 74-year-old diabetic man with chronic renal failure and mal perforans ulcer for over 4 months (*left*), 30 days postoperatively (*center*), and with stable tissues 70 days after débridement and lipotransfer (*right*).

ulcer (3.2 cm^2) present for over 6 years on a background of chronic scarring (childhood burns and prosthesis on her foot), with all previous surgical interventions having failed. The ulcer completely filled up with stable tissue by day 90; however, an attempt to graft skin after 3 months (wound size, 2.4 cm^2) failed to achieve complete reepithelialization. The wound continued to decrease in size until, after 8 months (now 0.9 cm^2), another skin graft was attempted unsuccessfully. Repeated lipotransfer at 10 months finally resulted in closure of the wound 4 weeks later.

Most patients were followed up for another 3 months after wound healing, which showed stable, soft tissues in all patients who healed, with no recurrence. There were no complications. Figures 5 through 8 show the typical findings before and after fat transplantation using the débridement and autologous lipotransfer method.

DISCUSSION

Chronic ulcers on the lower limb constitute a particularly challenging situation with a high risk of morbidity for the patient, often associated with recurrent surgical débridement and, eventually, amputations in a compromised vascularized environment. This study shows the enormous effects of autologous lipotransfer on wound healing as a relatively easy-to-perform, cost-effective, and well-tolerated procedure.

In this challenging patient population, close guidance of the patients and repeated encouragement to comply with the wound dressing protocol and pressure point prophylaxis are essential to achieve complete wound healing. Even in noncompliant patients, the débridement and autologous lipotransfer method has been shown to improve the depth and size of the ulcer to an extent that it is flush with the skin surface.

However, complete reepithelialization can be difficult and slow to achieve in these patients. To enhance reepithelialization, the application of Reverdin grafts[7,8] or "pinch micrografts"[9] is appealing, as it is a simple technique that provides additional keratinocytes to the wound bed. Reverdin grafts are small disks of full-thickness micro–skin grafts containing an island of epidermis and dermis surrounded by epidermis on the edges. They can be distributed sparingly onto the wound bed and promote epithelialization of the wound. We found it very helpful in patients on whom we operated following conclusion of this study.

In retrospect and with our newly gained experience, a repeated lipotransfer session can be performed after 4 weeks, if we do not observe any further decrease in wound size or formation of granulation tissue. As shown in this study, even in large wounds measuring more than 10 cm^2, the débridement and autologous lipotransfer method can achieve a well-vascularized wound bed on which skin grafts take much easier compared with an initially atrophic, chronic wound environment.

It is important to keep in mind that cancerous tissue can be a cause for nonhealing wounds. In this study, biopsy specimens were taken only if, based on the clinical findings, malignancy had to

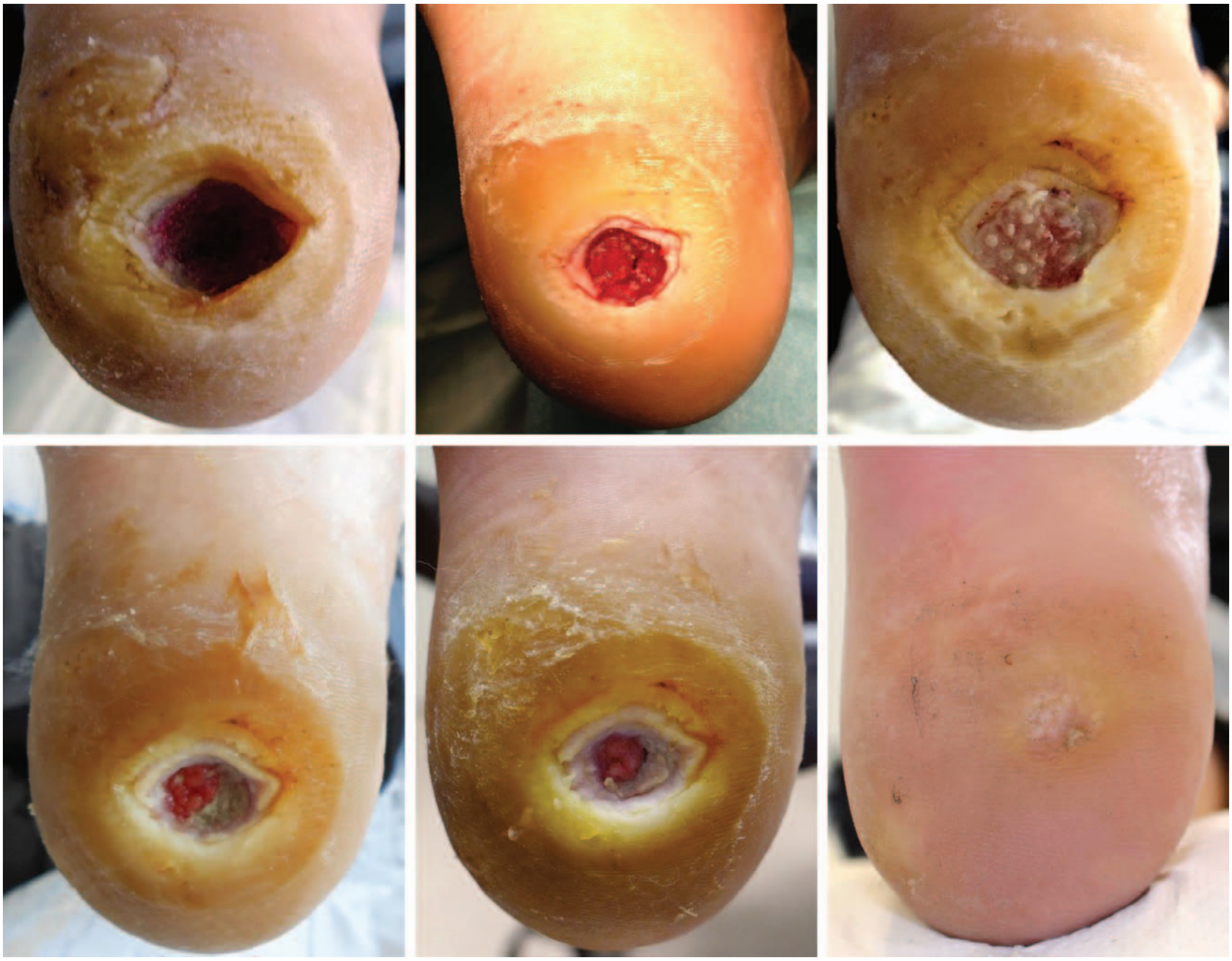

Fig. 6. A 46-year-old woman with chronic pressure ulcer of the right foot for over 1 year, after débridement (*above*, *left*); after lipotransfer (*above*, *center*); on day 6 postoperatively (*above*, *right*); on days 10 and 21 postoperatively, showing granulation tissue (*below*, *left* and *center*); and after 95 days, showing complete reepithelialization (*below*, *right*).

be ruled out. All of the histologic specimens were tumor-free.

Although the clinical effects of autologous lipotransfer are encouraging, the reasons for this are still a matter of research. As the lipoaspirate forms a physical scaffold surrounding the ulcer, it may aid the surrounding tissue to serve as a matrix for new cells to migrate and grow, neovascularization to take place, and granulation tissue to form.

Recently, Nicoletti et al. described their results after lipofilling in four patients with unstable skin of the weight-bearing area of the sole of the foot.[10] A regenerative boost and enhancement of local wound repair is attributed to fat grafts.[11,12] The regenerative capacity of fat grafts is demonstrated in various experimental and a few clinical studies.[1,13] Possible beneficial influences of adipose-derived stem cells were described in wound healing and skin transplantation,[14] and in treatment of chronic ulcers of lower limbs in patients with peripheral arterial disease.[13] Adipose-derived stem cells have been shown to have a positive impact on wound healing, as they are attracted to the wound site and influence wound healing processes by means of paracrine mechanisms and fusion and differentiation, for example, into keratinocytes or fibroblasts.[15] In addition, studies have shown that adipokines such as leptin[16] and adiponectin[17] may have important wound healing properties. Wound closure in full-thickness wounds in diabetic mice was achieved by topical adiponectin treatment.[18] The amount of adiponectin used in that study is stored in approximately 2 g of autologous fat. Topical leptin enhances gene expression of type I and type III collagen and synthesis of collagen in wound tissue and accelerates wound healing.[16] These findings emphasize the beneficial effect of fat transplantation for skin homeostasis at the site of implantation.[1]

Fig. 7. A 55-year-old diabetic patient with pressure sore for 19 months (*left*), 7 weeks after 8 ml of lipotransfer (*center*), and with a closed wound after 10 weeks (*right*).

Our clinically observed improvements after autologous fat transplantation in wound healing are in line with reports on treatment of fibrosis of the skin.[1,2] The results might be explained by the release of stored growth factors and wound healing–related peptides.[19–21] Adipose-derived stem cells have an angiogenic cytokine profile, as they contain vascular endothelial growth factor, platelet-derived growth factor, and basic fibroblast growth factor, and they can induce tissue neovascularization. This function is enhanced even under hypoxia.[22] Furthermore, adipose-derived stem cells may inhibit the production of inflammatory cytokines and stimulate the production of antiinflammatory cytokines. This is why adipose-derived stem cells probably enhance wound healing in hypoxic tissue.[23] Adipose-derived stem cells have shown enhancement of wound healing in diabetic rats,[14] and increasing knowledge is available about the general potential of mesenchymal stem cells in wound repair.[24] Currently, a Phase I trial is being conducted for treatment of nonrevascularizable

Fig. 8. Lipotransfer using the débridement and autologous lipotransfer method in a pretibial ulcer present for 5 months (*left*), and healed wound with stable tissues after 60 days (*right*).

critical limb ischemia, based on intramuscular injection of adipose-derived stem cells.[25] However, the use of adipose-derived stem cells is not the only approach for cell therapy of ischemic tissue. There are several studies on the effect of bone marrow–derived cells on critical limb ischemia. A meta-analysis by Teraa et al. emphasizes the promising potential of bone marrow–derived cell therapy in critical limb ischemia patients.[26]

The cultivation of adipose cell suspensions or stem cell enhancement is regulated by restrictive governmental regulations in Germany and many other countries.[27] Therefore, a protocol based on cell isolation to enrich adipose-derived stem cell content such as Marino et al. described[13] would not be possible without approval by official regulatory authorities. Harvesting plain fat is simple and minimally invasive, and as our results show, augmentation of stem cells is not necessary. Thus, simultaneous harvesting and transplantation of simple fat grafts is more appealing, as it saves operating time and resources.

Cervelli et al.[28] added platelet-rich plasma to enhance the wound healing properties of fat grafts. They used platelet gel from a small volume of blood (9 to 18 ml) followed by injection of fat grafts obtained with the Coleman technique for reconstructing the three-dimensional projection and superficial density of tissues. Their results demonstrated the efficacy of combining these two treatments but, again, we have been able to show that this combination is not necessary to achieve wound closure.

A vacuum-assisted closure dressing was used in this study because of the ease of wound care (no dressing change necessary for 4 to 5 days), and to enhance patient compliance with bedrest. As all patients had been treated with varying cycles of negative-pressure therapy (vacuum-assisted closure) dressings in the past with no positive effect on wound healing, the application in this study at low and intermittent pressures for 4 to 5 days was probably not responsible for the good outcomes in this study. Clinical experience and studies of successfully treated cases of wounds and ulcers[29] or chronic diabetic foot ulcers[30] show a potential effect of vacuum-assisted closure dressing on wound healing. Nevertheless, there is still a paucity of evidence indicating a positive effect on wound healing with débridement and vacuum-assisted closure alone in the management of chronic wounds, as a Cochrane review showed: in seven randomized controlled trials with 205 participants that examined the benefits of vacuum-assisted closure therapy in the management of chronic wounds,[31] there was only one study[32] that was able to find significant improvements. That study included only seven wounds in six patients, applying a negative pressure of −125 mmHg. Nevertheless, there are some recommendations to use reduced negative pressure in diabetic foot ulcer patients, as these patients do not tolerate maximum pressures.[31]

Pressure-free dressings and relative immobilization have been shown in other studies to enhance survival of fat grafts,[33] which can be likened to the protocols used for skin grafts. In this study, autologous lipotransfer (fat grafting, lipofilling) has been shown to allow wound healing in chronic, previously nonhealing ulcers in diabetic patients within 2 to 3 months, resulting in stable tissues. Integral to the healing process is the protection of granulation tissue by minimizing weight bearing on the wounds by use of special orthopedic shoes or inlays. The study has also shown that larger wounds can still benefit from lipotransfer by allowing formation of granulation tissue that can later be skin grafted. Further prospective studies are underway to compare randomized patients treated with lipotransfer to a control method. Results of histologic biopsies will give further insights into the responsible factors within the lipoaspirate influencing the wound healing.

CONCLUSIONS

Autologous fat grafts are able to achieve wound healing in nonhealing ulcers of the lower limbs. With this study, we have been able to demonstrate that addition of platelet-rich plasma or stem cell isolation is not necessary, which not only saves cost but also makes this therapeutic option possible in many countries that rigorously regulate stem cell injections or even modification of fat grafts, and clinical environments where resources are scarce. The presented débridement and autologous lipotransfer method is quick, easy to perform, and does not require an expensive setup in the operating room.

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