Therapeutic Applications of Hair Follicle Transplantation Beyond Hair Restoration: A Comprehensive Review

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BACKGROUND Hair follicle (HF) transplantation, especially through follicular unit excision (FUE), is renowned for treating androgenetic alopecia. Recent advancements have expanded its use in dermatology and plastic surgery.

OBJECTIVE This review explores FUE's broader applications beyond hair restoration, including its efficacy in treating chronic ulcers, axillary hyperhidrosis, bromhidrosis, vitiligo, and scar remodeling.

METHODS A comprehensive literature review was conducted using key medical databases, focusing on clinical research such as randomized controlled trials, retrospective studies, case series, and reports, while excluding review articles and commentaries.

RESULTS Hair follicle transplantation using the FUE technique has shown significant promise in enhancing healing in chronic ulcers and difficult to heal wounds, with cases demonstrating complete wound healing across various ulcer types. The method of sweat gland removal using FUE micropunches substantially reduced sweating and malodor in patients with axillary hyperhidrosis and bromhidrosis. In vitiligo treatment, FUE combined with other therapies showed promising repigmentation results.

CONCLUSION Follicular unit excision emerges as a versatile surgical technique demonstrating potential in various conditions beyond alopecia. The minimal complications associated with FUE across various applications highlight its safety profile. Its expanding scope in medical applications calls for further research and clinical trials to optimize its use and understand its full therapeutic potential.

Hair follicle (HF) transplantation is a surgical technique that involves the relocation of follicular units (FUs).[1] Each scalp FU may contain from 1 to 4 terminal HFs. This process requires the extraction of FUs from a designated "donor site" and their strategic insertion into another area, known as the "recipient site." There are two primary techniques of FU donor harvesting: strip harvesting and FU excision (FUE). In the former, the FU grafts are obtained through the microscopic dissection of a long and thin strip of scalp excised from the donor area, while in the latter they are harvested directly one at a time using a 0.8- to 1.0-mm circular punch. The minimal invasiveness of FUE compared to traditional methods, offering patients reduced discomfort and recovery times, marks a significant advancement over the strip harvesting technique, and FUE is currently the most common harvesting technique and has become the most widely used method among hair transplant surgeons.[1]

Traditionally used for treating androgenetic alopecia in both men and women, HF transplantation has applications that extend beyond hair restoration purposes, including various therapeutic interventions that are still being explored.

Methods

This review encompasses studies published between 2004 and 2023, offering a comprehensive analysis of advancements in FU transplantation over the past two decades. A systematic search was conducted using major medical databases, including PubMed and Scopus, to identify research focusing on the therapeutic applications of FU transplantation. Eligible studies were selected based on predefined inclusion criteria, including case series, case reports, and clinical trials, with sample sizes ranging from 1 to 20. Only studies addressing the therapeutic use of FU transplantation in medical conditions were included, while those focusing solely on cosmetic procedures, such as hair restoration for androgenetic alopecia, were excluded.

This diverse body of literature offers valuable insights into the expanding therapeutic applications of FU transplantation, emphasizing the technique's versatility and its evolution in clinical practice. The review highlights both the successes and challenges associated with the application of FU transplantation in various medical conditions.

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Hair follicle Transplantation as Therapy for Wound Healing

Wound healing, essential for maintaining the skin's barrier function, is a complex process influenced by factors such as diabetes and aging, often resulting in chronic, nonhealing wounds. Wound healing, essential for maintaining the skin's barrier function, is a complex process influenced by factors such as diabetes and aging, often resulting in chronic, nonhealing wounds. This section reviews scientific publications from the last two decades that discuss the feasibility and effectiveness of autologous HF transplantation in treating nonhealing ulcers including third-degree burns,[2] surgical defects,[3] chronic venous leg ulcers,[4,5] recessive dystrophic epidermolysis bullosa (RDEB),[6] traumatic wounds,[3,7,8] pyoderma gangrenosum,[9] diabetic ulcers,[4,8] pressure sores,[4] leprosy ulcers,[8] vasculitic ulcers,[9,10] ulcerated necrobiosis lipoidica,[9] radiodermatitis,[10] and others with unspecified causes (see **Supplemental Digital Content**, Table S1, http://links.lww.com/DSS/B597).[11] Ulcer size varied considerably, from 5.72 cm^2 [12] to 80 cm^2,[2] with durations ranging from 3 weeks[12] to as long as 40 years.[8]

The procedure for HF transplantation into nonhealing wounds involves extracting FUs from the scalp's occipital region and inserting them into slits in the wound bed, similar to the technique used in hair restoration for baldness. Four studies used the strip harvesting technique,[11–14] while six used FUE.[3–8,12,15] The punches used in these cases typically ranged from 1.00 to 3.00 mm in size. Once extracted, the FU grafts are immediately transplanted into slits or punch holes[10] made to a depth of 4 to 5 mm in the wound bed under local anesthesia. The size of the slits/holes corresponds to the diameter of the FU graft, and the insertion can be done using implanters[4] or using fine-tipped forceps (Figure 1). The optimal graft density for effective healing is not yet established, but a minimum of 2 grafts per cm^2 is suggested if a 2 mm punch is used for harvesting.[10]

After transplantation, Vaseline dressing and therapeutic compression bandages are used to aid the healing process.

Most studies reported improved healing in all treated patients (see **Supplemental Digital Content**, http://links.lww.com/DSS/B597). However, there was significant variation in the degree of improvement and healing rate, underscoring the need to consider individual health conditions and the specific ulcer's cause when evaluating the therapy's efficacy. For example, in one study[7] involving 15 patients and 17 ulcers, a reduction of over 75% in ulcer area was observed in 3 patients, while five others showed a reduction of 50% to 75% by the 18-week end point. However, two patients did not respond to HF transplantation. One of these nonresponders required surgery for varicose veins, suggesting a complicating factor in healing. The other nonresponder, who had pyoderma gangrenosum with venous stasis, illustrates the challenges of treating wounds in certain medical conditions. A recent study on 28 patients reported high patient satisfaction, as evidenced by an 81% willingness to undergo the procedure again.[9]

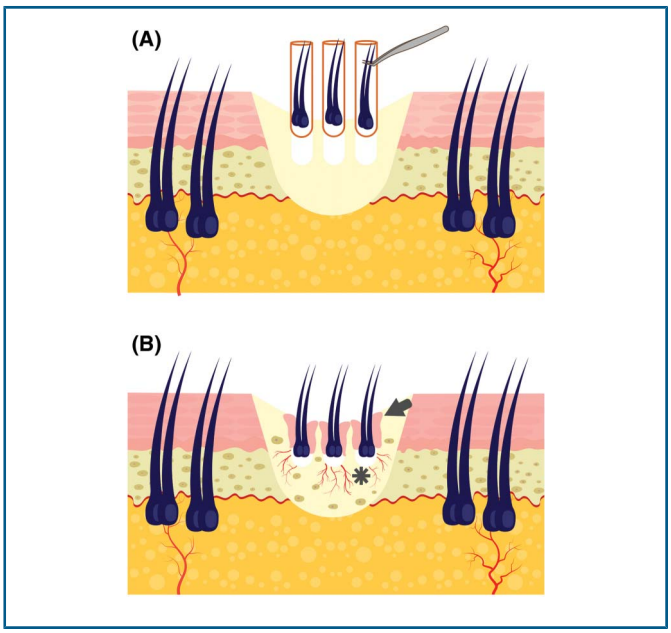

Figure 1. Hair follicle grafting therapy promotes reemergence of critical skin components in chronic nonhealing wounds. (A) Transplantation of HF grafts into the center of chronic ulcer. (B) Advanced healing several weeks' post-transplantation. Hair follicle graft not only stimulates reepithelialization of wounds but also increase blood vessels, nerve fibers, fat-producing cells, and sweat glands (Saha and colleagues).[8]

Five studies[7,13–16] reported complete healing within 1 to 3 months, although 1 challenging case involving a chronic ulcer caused by iatrogenic formalin injection[12] required 6 months for complete healing, attributed to the wound's unique etiology.

Interestingly, two randomized controlled trials,[4,5] which compared scalp hair-bearing grafts to punch grafts from nonhairy abdominal skin on the same ulcer, confirmed that HF scalp HF punch grafts were more effective in accelerating the healing of chronic ulcers (Figure 2).

A notable case report highlighted the efficacy of HF transplantation in a patient with RDEB[6] (Figure 3). Recessive dystrophic epidermolysis bullosa is a rare genetic disorder characterized by extreme skin fragility, leading to chronic wounds from even minor trauma.[17] The prognosis depends on the severity of symptoms, with potential complications affecting life expectancy. Currently, no cure exists, and treatments focus on symptom management, including wound care, pain control, and nutritional support.[17]

The patient underwent eight sessions of FUE transplantation over 6 years (360 FUs transplanted), resulting in healing of most ulcers. This case underscores the potential of HF transplantation in managing complex and recurrent bullous and ulcerative conditions.[6]

Regarding complications, the overall incidence of issues associated with HF transplantation in chronic wounds was

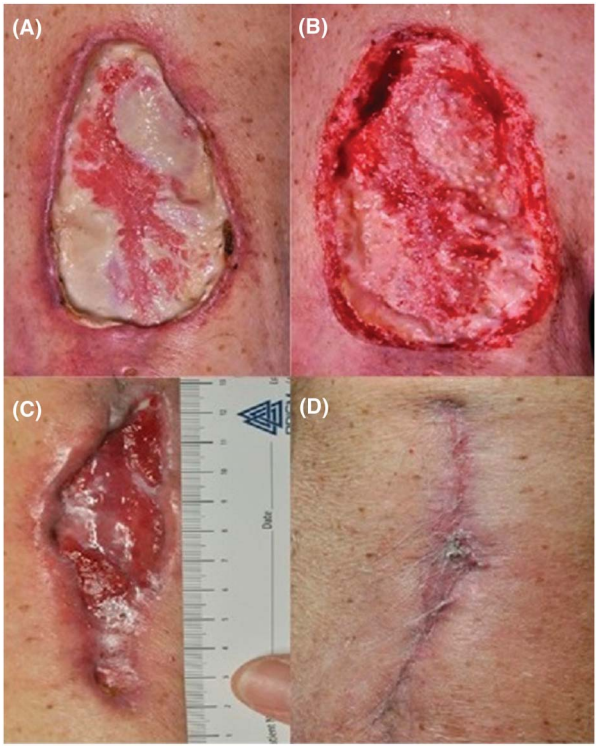

Figure 2. Healing of a recalcitrant chronic ulcer after FU transplantation. (A) Initial condition of a wound caused by an unintended iatrogenic formalin injection. (B) Immediate postop figure showing 400 scalp-derived FU grafts implanted into the wound bed. (C) Noticeable wound healing response observed at 3 months. (D) By 6 months' post-transplant, the wound had fully healed, displaying hair growth predominantly at the scar's center. The scar's edge blends seamlessly with adjacent skin, contrasting with the center's increased fibrotic texture. (Reprinted with permission from Alam and colleagues.)[12] FU, follicular unit.

low. Only one study[5] reported a postoperative complication, which was successfully managed with wound dressing and antibiotics. Other studies reported no significant complications or minor issues unrelated to the transplantation process.

A common question concerns the fate of hair shafts in the wounds. In standard hair transplants, the graft survival rate is estimated to be around 80% to 100% at 6 to 12 months.[4,11,18] However, in chronic wounds, most authors observed a notable decrease in hair regrowth after transplant.[9,15]

This reduction in hair regrowth is possibly due to the unique wound environment, which may signal the transplanted follicular cells to prioritize wound repair over hair shaft production.[16,19] The hypothesis was first suggested by Jahoda and Reynolds in 2001[20] and further supported by Aamar and colleagues,[21] who showed that during wound healing, follicular dermal sheath cells migrate toward the wound and do not contribute directly to hair regrowth.

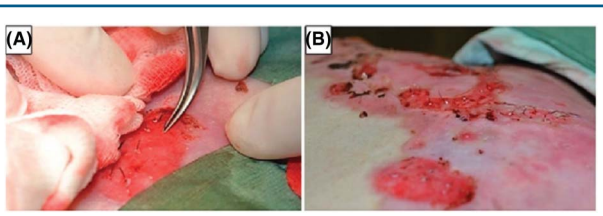

Figure 3. Chronic nonhealing ulcers in a patient with RDEB. (A) HF grafts were inserted into slits created by an 18-gauge needle. (B) Immediately after transplantation. (Reprinted with permission from Wong and colleagues.)[25] HF, hair follicle; RDEB, recessive dystrophic epidermolysis bullosa.

The Role of Follicular Unit Excision in Treating Axillary Hyperhidrosis and Bromhidrosis

Follicular unit excision has been suggested as a new method for treating axillary hyperhidrosis and bromhidrosis. Due to the close anatomical relationship between sweat glands and the HFs,[22] the removal of FUs by FUE micropunches also removes sweat glands during extraction.[23,24] This approach was first explored by Schambach and colleagues[25] in a study with 6 patients who had axillary hyperhidrosis. Using a 0.9-mm punch, they removed about 70% of the FUs from one axilla, leaving the other as a control. The study showed an 80% reduction in sweating within 3 months, and three patients also reported significant improvement in bromhidrosis, a condition involving unpleasant body odor linked to excessive sweating (Figure 4).

Li and colleagues conducted a similar study, focusing on bromhidrosis in 20 patients.[26] They used a 1-mm punch to extract axillary FUs with the FUE method. Malodor was measured using a 10-point visual analogue scale, showing significant improvements. Postoperative complications were minimal, highlighting the procedure's safety and patient-friendly nature.

In conclusion, the effectiveness, minimal complications, and short recovery time make axillary FUE an appealing option for treating hyperhidrosis and bromhidrosis. However, further studies are needed to confirm its broader applicability and long-term outcomes.

The Scar Remodeling Effect of Hair Follicle Transplantation

The use of hair transplantation (HT) to treat alopecic areas of noninflammatory scarring alopecia (resulting from burns, trauma, surgery, etc.) is well established.[27,28] Transplanted hair grafts effectively camouflage alopecic areas, providing aesthetic improvement. However, a recently explored aspect of this therapy is the remodeling effect of transplanted follicles on scar tissue.[29,30] In other words, transplanting HFs not only improves the appearance of the scar by adding hair coverage but also induces structural changes in the fibrotic tissue.

Recent evidence from Plotczyk and colleagues[29] demonstrated these effects at microscopic and transcriptomic levels. In a study involving 3 patients with linear surgical scalp scars, biopsies were taken before and 2, 4, and

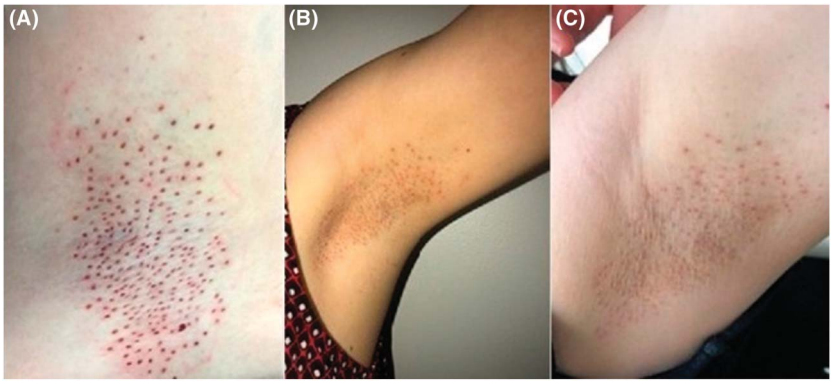

Figure 4. Progression of healing after FU excision for the treatment of axillary hyperhidrosis. (A) Immediate postoperative condition. This photo captures the immediate aftermath of FU excision surgery. The subject is shown with visible 1 mm wounds. (B) Early signs of healing 2 days postsurgery. (C) 1 week after the surgical procedure. The axillary region is shown with significantly reduced redness, indicating substantial progress in the healing process. (Reprinted with permission from Wong and colleagues.)[25] FU, follicular unit.

6 months after HT into the scar. The results showed a notable increase in epidermal thickness, improved interdigitation of the epidermal–dermal junction, enhanced dermal vascularization, and remodeling of the dermal fibrosis. The procedure reduced the proportion of thick collagen fibers and their alignment, significantly impacting the scar's matrix structure. This morphologic shift was accompanied by changes in the transcriptomic profile before and after HT, revealing a transition toward a healthier phenotype. Transcriptomic analysis revealed changes in cytokine levels, with reduced profibrotic factors such as TGF-β1, IL-13, and IL-6, indicating a direct effect of HT in decreasing fibrosis and contributing to scar remodeling. These improvements were noticeable as early as 2 months and became more pronounced by 6 months postprocedure impact[29] (Figure 5).

In the context of scarring alopecia due to burns, a study with 18 patients highlighted the benefits of HT combined with nanofat grafting on scar tissue.[30]

Importantly, these studies also emphasize the relative safety of HF transplantation, which is associated with minimal complications. This is a clear advantage, especially when considering its application in scar remodeling,[29] vitiligo,[31] and acne keloidalis nuchae (AKN),[32] where other treatments may present higher risks. The low complication rate strengthens the case for its broader use as a therapeutic option.

The introduction of HFs contributed to improvements in scar stiffness, flexibility, and pigmentation, making the scarred skin more natural in appearance and feel. Enhanced vascularization was also observed, suggesting healthier skin.

In conclusion, these findings emphasize that HT not only restores hair growth but also significantly improves the physical and aesthetic properties of scar tissue.

Follicular Unit Excision for the Treatment of Vitiligo

Recent studies have demonstrated the effectiveness of FUE in treating vitiligo, a skin condition affecting around 2% of the global population.[33] FUE, which uses pigmented terminal scalp HFs rich in melanocytes, has shown particular promise in repigmenting vitiliginous skin by utilizing the melanocytes' ability to migrate and restore pigmentation. This offers a compelling alternative to traditional mini grafting techniques.[31]

In a study by Thakur and colleagues[31] involving 63 patients, FUE showed strong results, with 72.1% of participants achieving excellent color matching in their vitiligo patches. The method has proven especially effective for treating areas with leucotrichia.[34] Chouhan and colleagues documented complete repigmentation in a patient within 12 weeks using body HT via FUE, with a density of 6 to 8 FU/cm.[2,35] A study by Elazim and colleagues[36] with 53 patients highlighted the potential of combining FUE with treatments like topical calcipotriol betamethasone dipropionate or Narrowband-UVB phototherapy, which resulted in early and favorable repigmentation outcomes.

The outer root sheath cell suspension technique has also expanded therapeutic options for vitiligo,[34] although further research is needed to refine these methods.[37,38]

The debate over the comparative efficacy of FUE punch grafting versus the traditional mini punch grafting technique for vitiligo remains ongoing, with no clear consensus on which method is superior.[38–45]

The primary difference between the techniques is the donor source: FUE uses scalp follicles, while mini punch grafting draws from the thighs or buttocks. Consequently, the FUE punch graft is composed mainly of terminal pigmented HFs plus a little dermis and pigmented epidermis, while the mini punch graft is composed mainly of dermal tissue and pigmented epidermis with occasional fragments of vellus HFs. The choice between the two depends on factors such as surgeon expertise, patient preference, and cost. Ongoing research aims to refine these techniques to improve their efficacy and accessibility for more vitiligo patients.

Follicular Unit Excision in Acne Keloidalis Nuchae

A recent case report has shown the effectiveness of FUE in treating acne keloidalis (AKN).[32] The technique focuses on removing HFs from the center of AKN papules and has

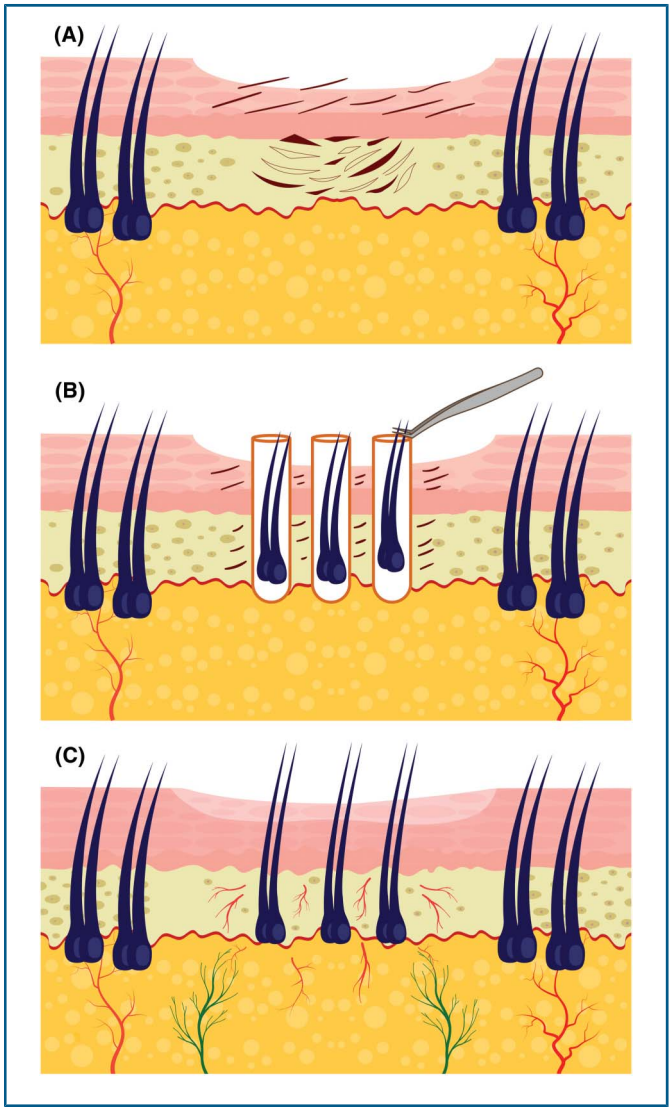

Figure 5. Scar remodeling effects through HFs grafting (Plotczyk and colleagues[29]). (A) This first illustration depicts the scar tissue before intervention: the epidermis appears thin and flat, and there is a decrease in nerve fibers and blood supply. (B) Hair follicle grafts are transplanted directly into the middle of the scar. (C) Changes in the scar post HF transplantation: The epidermal thickness is increased, and the interdigitating epidermal–dermal junction shows an undulating basal membrane that reflects the complex interaction between these two layers, a Stark contrast to the straight line seen in the first illustration. The dermal cell density is increased, as well as the vascularization (depicted through the emergence of red branches weaving through the dermis) and innervation (green branches illustrate the rich appearance of innervation, signifying the restoration of sensory and autonomic functions to the area). HF, Hair follicle.

proven useful for patients who are not candidates for treatments like laser hair removal or drug therapy. In a study, 3 patients were treated using 17 G, 18 G, or 19 G punches to remove single FUs from the papules. Between 95 and 135 grafts were extracted from the nape area, which remained lesion-free during follow-up.

However, the study's small sample size limits the findings. Further research with a larger patient cohort is needed to provide more definitive conclusions and clarify FUE's role in treating AKN.[32]

Discussion

Hair follicle transplantation, traditionally used for treating androgenetic alopecia, is now being applied to a wider range of therapeutic uses. This expansion is largely due to the properties of HFs and advancements in the FUE technique. The accessibility of scalp HFs and their diverse cellular composition, including epithelial, mesenchymal, vascular, neural, immune, and stem cells, make them a valuable resource for regenerative therapies.

The development of FUE reflects a broader trend in medicine, where procedures initially designed for cosmetic purposes, in this case hair restoration, are being adapted for medical treatments. This shift highlights the potential for existing methodologies to find renewed applications in health care.

The studies reviewed here, covering HF transplantation for wound healing, axillary hyperhidrosis, bromhidrosis, scar remodeling, vitiligo, and AKN, demonstrate the therapeutic potential of FUE.

Of all these indications, however, it is in the healing of chronic or hard-to-heal wounds, where HF transplantation shows most promise as a useful therapy, especially in conditions as prevalent and costly as chronic leg ulcers. To put things in perspective, it is estimated that one in every 100 adults will suffer from chronic venous leg ulcers at some point in their lifetime,[46] and the mean total cost of a chronic venous leg ulcer per year and patient in Germany has been estimated to be 9,569 euros.[47] The authors believe that one of the reasons why HF transplantation as a therapy for wounds is still underutilized is because of the difficulty of harvesting FU grafts with a 1 mm size punch, which requires specific surgical skills and instrumentation developed by hair surgeons. However, this hurdle can be overcome by transplanting 2 to 3 mm HF punch grafts, which are much easier to harvest, only require punch biopsies biopsy and instrumentation familiar to any dermatologic surgeon, and which have also shown good results.[5,9,10]

Concerning the mechanistic explanations behind the wound healing role of the HF graft, it can be speculated that one of the reasons could be the abundance of epithelial and mesenchymal stem cells in the transplanted anagen follicles. In this regard, it is well known that in response to a skin injury, epithelial bulge stem cells migrate out of the follicle, differentiate into epidermal progenitor cells, and contribute to restoration of the epidermis.[48,49] Likewise, mesenchymal dermal sheath cells appear to participate in the wound healing response, moving out of the follicles into the wound bed, where they contribute to dermal fibroblasts and myofibroblasts.[20,21,50] In addition to this, a still undefined paracrine effect between the transplanted HFs and the wound microenvironment is also suspected, supported by the intriguing clinical observation that the reepithelialization of the wound not only originates around the transplanted HF grafts but also from the margins of the wound, the so-called "wound edge effect."[4,5,9]

In addition, it is important to highlight the work of Saha and colleagues,[8] who demonstrated that HF grafts transplanted into the ulcer not only stimulate its healing but also increase the amount of blood vessels, lymphatic structures, nerve fibers, and sweat glands, thus reestablishing key functions in the healed skin, such as sweating and sensitivity (Figure 1B). These observations, however, are expected given the fact that eccrine coils, adipocytes, and a rich vascularization and innervation are present in the microscopic anatomy of a FU graft.[22]

An important question to be answered regarding the technical aspect of the procedure concerns the minimum number of HF grafts that need to be transplanted in the wound bed per cm^2 in order to reach an optimal healing response. This number, which obviously depends on the size of the punch graft, has been empirically established as 2 to 5 HF grafts per cm^2 when using a 2 mm punch for harvesting,[4,5,10] but has not been established using 1-mm punches. Another question that remains to be answered is whether the implantation of these HF grafts should be done homogeneously or preferentially in the periphery of the ulcer in order to induce epithelial bridging with the edges of the wound. These questions, as well as better standardization of the technical procedure, will undoubtedly be resolved as further clinical experience is gained with this form of therapy.

The minimal complications reported also reinforce its safety profile and clinical utility.[45] This is particularly significant for conditions like chronic ulcers[4] and RDEB,[6] which can have serious health consequences. However, complications can occur, especially when FUE is performed by untrained physicians or improperly delegated, highlighting the need for skilled and ethical practice.

In conclusion, HF transplantation, especially through the FUE technique, is emerging as a valuable tool in therapeutic interventions, especially in the management of chronic and hard-to-heal ulcers. Further research with larger sample sizes is needed to fully assess its effectiveness, safety, and long-term outcomes. Expanding this research could validate the current applications of FUE and possibly extend its therapeutic potential. As for future directions, it is imperative to bring together basic researchers and clinicians to investigate and ultimately decipher the population of HF cells that contribute most in the stimulation of wound healing as well as to elucidate the molecular bases of the paracrine healing effect observed in the transplanted follicular graft.

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