

Role of Hair Follicle Transplantation in Treatment of Chronic Ulcers: A Systematic Review Article

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Abstract

Background: With a prevalence rate of 2.21 per 1,000 individuals, patients affected by chronic wounds experience considerable economic, social, and psychological burdens. Moreover, the increasing prevalence of chronic medical conditions may limit the treatment options available for specific patient populations. Standard interventions for individuals suffering from chronic ulcers encompass compression therapy, negative pressure wound therapy, and skin grafting. Recently, multipotent stem cells derived from hair follicles have gained recognition as a feasible alternative for patients for whom conventional care is insufficient.

Objective: To systematically review the literature on the role of hair follicle transplantation in the treatment of chronic lesions.

Material and Methods: PubMed, Embase, Web of Science, Cochrane Library, and Scopus were searched from their inception until January 16, 2025. Clinical trials utilizing hair follicular unit transplantation for the treatment of chronic ulcers were included. After screening the titles and abstracts of 9,692 records, ten studies were included in this review.

Results: A total of 131 cases of various types of chronic ulcers were included, primarily affecting the lower limbs. The mean age of the cases ranged from 37 to 73 years, with a predominance of males. The mean size of the ulcers ranged from 6.72 to 82.49 cm², and the duration of chronicity varied from 6 weeks to 30 years. Sixty-eight percent of the cases reported complete wound healing over a period of 18 to 24 months. Histological examination confirmed the presence of increased remodelling, neovascularization, and the appearance of adnexal structures in the dermis. No significant complications were reported. However, there are concerns regarding the risk of bias in the included records.

Conclusion: With the need for new modalities for treating chronic ulcers, hair follicle unit transplantation may be a promising alternative for cases in which standard care is not successful. Also, larger and well-designed clinical trials are needed to expand our current understanding of the underlying mechanisms of HFUs' contribution to wound healing.

Key Words: Hair follicle – Wound – Chronic ulcer – Skin graft.

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Availability of Data and Material: All data are presented in the review. Further details can be requested from the author.

Introduction

The follicular unit (FU) is an ectodermal derivative that comprises the hair follicle (HF), its associated sebaceous gland, and the arrector pili muscle. The hair follicle is divided into three sections along its length: the infundibulum, isthmus, and a non-permanent inferior segment. The inferior segment extends from the bulge to the base of the follicle. The bulge is situated where the arrector pili muscle inserts, housing niches of multipotent stem cells. The base comprises the dermal papilla and matrix cells, which exhibit the highest mitotic rate in the body [1]. In the anagen phase, the dermal papilla interacts with the bulge, signaling the proliferation of multipotent stem cells along the outer root sheath (ORS). Additionally, the bulge is regarded as an immune-privileged site where stem cells exhibit reduced expression of MHC class I and II molecules and significant expression of immunoinhibitory signals as CD200 [2,3]. Moreover, the interfollicular epidermal stem cells (epiSC) are composed of a pool of cells that originate from the basal layer of the epidermis [4]. The undifferentiated phenotype of these cells is regulated by the Wnt/ β -catenin signalling pathway [5].

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A chronic ulcer is a disruption of the epithelium that shows no signs of healing after three months [6]. Chronic leg ulcers (CLU) account for 43% of chronic skin ulcer cases, with 59% of those affected being aged 75 years or older [7]. Venous leg ulcers (VLUs) account for up to 80% of chronic leg ulcers (CLUs), resulting in significant economic and social burdens [8].

Several studies have investigated the underlying processes of chronicity in such lesions. Elevated levels of mRNA for pro-inflammatory cytokines like IL-1 β , IL-6, and TNF- α , along with reduced levels of VEGF, VEGFR2, SDF-1 α , and CXCR4, have been implicated in the impaired healing of these lesions [9,10]. The current guidelines for managing chronic ulcers involve controlling the underlying condition: vein surgery for venous lesions, surgical revascularization for arterial ulcers, and management of underlying diseases such as diabetes mellitus [11].

Additionally, autologous split-thickness skin grafting is recommended as an alternative surgical option for cases that show little to no response to conservative treatment protocols [12]. However, a failure rate of up to 30% has been reported [13]. Mini-punch skin grafts have been shown to enhance the wound healing process by incorporating the associated stem cells in the dermis and subcutaneous tissue [14]. Recently, autologous bone marrow-derived mesenchymal stem cells (BM-MSCs) have been utilized as a cell-based therapy to assist tissue regeneration in chronic wounds [15].

The role of hair follicle-associated stem cells (HFSCs) has been observed in the rapid re-epithelialization rate of skin grafts from the scalp compared to skin grafts from non-hairy areas. Furthermore, the slow re-epithelialization rate in the palm, sole, and areas that have lost adnexal structures after irradiation highlights the importance of hair follicles and their associated stem cells in wound healing [16]. Additionally, trials of autologous epidermal equivalents of outer root sheath keratinocytes from plucked anagen hairs for treating chronic ulcers have shown satisfactory results [17]. This review aims to systematically search the literature and summarize the current available evidence regarding the feasibility, efficacy, and safety of hair follicle transplantation in the treatment of chronic ulcers.

Material and Methods

Guidelines:

This review is conducted in accordance with the Preferred Reporting Items for Systematic Reviews

and Meta-Analyses (PRISMA) guidelines [18]. This review is registered in the PROSPERO database CRD420251012153.

Data sources and search strategy:

The search process was designed according to the methods outlined in Chapter 4 of the Cochrane Handbook for Systematic Reviews of Interventions (version 6.5) [19]. PubMed, Embase, Web of Science, Cochrane Library, and Scopus were searched from their dates of inception until January 16, 2025. The following search string was developed to retrieve relevant studies: (ulcer [Title/Abstract]) OR (wound [Title/Abstract]) OR (“diabetic ulcer” [Title/Abstract]) OR (varicose [Title/Abstract]) OR (“venous ulcer” [Title/Abstract]) AND (hair [Title/Abstract]) OR (“hair follicle” [Title/Abstract]) OR (“follicular unit” [Title/Abstract]) OR (FUT [Title/Abstract]) OR (FUE [Title/Abstract]) OR (“follicular unit extraction” [Title/Abstract]) OR (“follicular unit excision” [Title/Abstract]). The search string was translated to adapt to each database using the Polyglot tool [20]. In addition, references from the included studies and articles that cite these studies were retrieved and screened for potentially relevant articles using the Citation Chaser tool [21]. No language or publication period restrictions were applied. Duplicate records were removed using the deduplication tool [22].

Inclusion and exclusion criteria:

The retrieved records underwent screening in two stages: Title and abstract screening, followed by full-text review. Inclusion criteria included retrospective or prospective clinical studies that involved cases with chronic ulcers and specified the technique for hair follicle transplantation. Exclusion criteria comprised reviews, animal studies, in vitro studies, studies on epidermal equivalents or other skin substitutes, and studies on follicular dermal grafts.

Data extraction:

A data extraction form was created to collect the following information: Study ID (first author's name, year of publication), study duration, study country, intervention technique investigated, characteristics of the included chronic ulcer cases, and outcome measures.

Quality assessment:

The Risk of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool was used to assess the methodological quality of the included studies [23]. The ROBINS-I tool evaluates bias across five domains: bias from confounding, bias in participant selection, bias due to deviations from the intended

intervention, bias from missing data, and bias in the selection of reported results.

Data synthesis and analysis:

Due to the limited number of included studies and the anticipated high degree of heterogeneity resulting from the small sample sizes, a narrative review is presented. Quantitative measures were summarized where applicable.

Results

Search results and study selection:

The search process yielded 9,692 records. After screening titles and abstracts, followed by a full-text review of relevant articles, ten records were included in this review (Fig. 1). A summary of the included studies is presented in Table (1) [24–33].

Characteristics of studies:

The ten studies included were published between 2012 and 2024, primarily from India and Spain, with contributions from China, Taiwan, and Argentina. Most of the studies did not specify the periods during which they were conducted. However, the study by Liu et al. (2015) was conducted between 2006 and 2009 [32]. The included studies varied in design, comprising two retrospective analyses, two randomized comparative studies, two case reports, and three prospective single-arm trials. The study by Belatti et al. (2023) presented expert opinions based on the experience of a single institution regarding hair follicle transplantation into chronic ulcers in Argentina [25]. However, it has not provided details about the characteristics of the included cases or the outcome measures.

Hair transplantation techniques:

The follicular unit excision (FUE) technique utilizing motorized punches was employed in most cases. However, the studies differ based on the size of the punch used. Four studies reported outcomes from using 1mm punches to extract hair follicular units (HFU) [26–30]. Two studies used punches ranging in size between 1–3mm to extract HFUs [24,33]. Two studies compared the efficacy of using 2mm punches of HFUs versus 2mm punches from the non-hairy parts of the abdomen [25,31]. One study compared 1mm punches of HFUs versus using split-thickness skin grafting (STSG) [28]. Half of the included studies transplanted 5 HFU per cm² of the chronic lesion [26,28,30,31,33].

Control group:

Five studies were conducted as proof-of-concept trials without the inclusion of a comparison or control group [24,26,29,30,32]. Two studies used in-

tra-individual ulcers, which received phase-appropriate wound care, as controls [27,33]. Two studies examined ulcers by dividing them in half; one half was grafted with HFUs, while the other half received phase-appropriate wound care [25,31]. Only one study included two groups of patients in which HFUs transplantation was compared to STSG [28].

Patient selection:

The total number of cases in the included studies was 131. The male gender predominates among these cases. The mean age of the cases ranged from 37 to 73 years. Five studies did not have exclusion criteria concerning the etiological nature of the chronic ulcer [24–26,28,30]. Three studies restricted their inclusion criteria to a single etiological cause of the chronic lesions [27,29,31]. The study by Jimenez et al. (2012) included three categories of chronic ulcers: venous, diabetic, and pressure [33].

Ulcer characteristics:

The mean surface area of the examined ulcers ranged from 6.72 to 82.49cm². The duration of wound chronicity varied from 6 weeks to 30 years. Over 80% of the lesions are located on the lower limbs. The scalp is the second most common site for chronic lesions.

Outcome measure:

Nearly 68% of the chronic lesions treated by HFUs transplantation have shown complete wound closure, while 25% of the cases experienced favorable degrees of wound healing. Only one study reported data on patient satisfaction, with the majority of cases finding the trial's outcome satisfactory [24]. Additionally, Chougule et al. (2020) reported no significant association between the outcome and patients' body mass index (BMI). Three studies investigated the healed chronic lesions histologically [27,29,32], reporting increased dermal remodelling, dermal neovascularization, and the appearance of adnexal structures. Liu et al. (2015) reported increased expression of type VII collagen, while Saha et al. (2021) noted boosted expression of PECAM-1, LYVE-1, and class III β -tubulin. Meanwhile, Chougule et al. (2020) reported improvements in scar remodelling in healed lesions following HFUs transplantation. In addition, four studies noted the phenomenon of hair shaft disappearance later in the course of the healing process [29–31,33].

Quality assessment/Risk of bias assessment:

Based on the evaluation using the Risk of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool, most studies demonstrated a moderate risk of bias (Figs. 2,3).

Table (1): Summary of the included studies.

| Study I.D. | Year | Duration | Study Design | Country | Technique | Intr-individual | Patient selection | FU/cm ² | No. of cases | M/F | Mean Age |
|--------------------------------|------|-----------|---------------------------------|----------------|---|---|-------------------------------------|--------------------|--------------|---------------------------------------|--------------|
| Jimenez et al., 2012 [33] | 2012 | 2010 | Single-center trial | Spain | Experimental ulcers received 1-2 mm hair follicle punches | Two separated ulcers we involved | Diabetic, venous or pressure ulcers | 5 | 10 | 3:07 | 72.2 |
| Liu et al., 2015 [32] | 2015 | 2006-2009 | Retrospective case series study | China | FUT technique used | None | N/A | 4 | 14 | 9:05 | 60.71 |
| Martinez et al., 2016 [31] | 2016 | N/A | Randomized comparative study | Spain | 2 mm punch with hair follicle from scalp vs 2 mm punch from abdominal skin without hair | Each ulcer is divided vertically into experimental and control groups | Venous ulcers | 5 | 11 | 1:03 | 73 |
| Budamakuntla et al., 2018 [30] | 2018 | N/A | Single-center trial | India | Single-arm study using 1 mm punches | None | All causes of ulcers | 5 | 15 | 14:01 | 37.59 |
| Alam et al., 2019 [29] | 2019 | N/A | Case report | Spain | Single-arm study using 1 mm punches | None | Traumatic and surgical wounds | 10 to 17 | 2 | Males | 18 and 83 yo |
| Chougule et al., 2020 [28] | 2020 | 2016-2018 | Randomized comparative study | India | 1 mm punch with hair follicle from scalp vs STSG | Comparative study | All causes of ulcers | 5 | 40 | 3:1 in FUT group vs 4:1 in STSG group | 20-50 |
| Wong et al., 2021 [27] | 2021 | 2013 | Case report | China (Taiwan) | Single-arm study using 1 mm punches | Ulcers on the left upper back is used as control | Dystrophic epidermolysis bullosa | 2 | 1 | 0 | 54 |
| Saha et al., 2021 [26] | 2021 | N/A | Single-center trial | India | Single-arm study using 1 mm punches | None | All causes of ulcers | 5 | 10 | 9 | 40.2 |
| Belatti et al., 2023 [25] | 2023 | N/A | Single center experience | Argentina | 2 mm punch with hair follicle from scalp vs 2 mm punch from abdominal skin without hair | Ulcer divided into 2 halves. | All causes of ulcers | 2 | N/A | N/A | N/A |
| Jansen et al., 2024 [24] | 2024 | 2020-2022 | Retrospective study | Germany | Single-arm study using 2-3 mm punches | None | All causes of ulcers | 6 | 28 | 2.5 | 72.61 |

Table (1): Continued.

| Study I.D. | Mean Ulcer size | Chronicity duration | Lower limb | Complete closure | Partial closure | No effect | Duration for closure | Histological evidence | Phenomenon |
|--------------------------------|--|---------------------|------------|------------------|-----------------|-----------|---|---|--|
| Jimenez et al., 2012 [33] | 36.8 | 1-30 years | 10 | 0 | 10 | 0 | Significant 27.1% reduction in the experimental group in comparison with 6.5% in the control group at wk 18. | Improved dermal organization and neovascularization | Lesser amount of exudate, improved granulation tissue, wound border reactivation. Disappearance of hairs by wk 4 |
| Liu et al., 2015 [32] | 74.14 | Up to 13 years | 11 | 11 | 0 | 0 | Re-epithelization started at wk. 5 and completed at 2 months | At wk 16, epidermis, dermis and adnexal structures were observed | Recipient scar tissue was more elastic |
| Martinez et al., 2016 [31] | Average of the half 12 cm ² | 6 years | 11 | 0 | 11 | 0 | Significant 75.15% (23.03%) reduction in experimental group, 33.07% (46.17%) reduction in control group at wk. 18 | N/A | Improvement in granulation tissue, wound border reactivation and disappearance of hair shafts by week 9 |
| Budamakundla et al., 2018 [30] | 6.72 | 9 months | 15 | 7 | 6 | 2 | 18 weeks | N/A | Later disappearance of hair shafts from the recipient area |
| Alam et al., 2019 [29] | 5.7 and 40.5 | 3 months | 0 | 2 | 0 | 0 | 1 month in traumatic wound, 5 months in surgical wounds | More dermal remodeling in the central part of the scar than the periphery | Central part of the scar is more red, fibrotic and covered by hairs than the periphery |
| Chougule et al., 2020 [28] | 10 to 40 | N/A | 0 | 40 | 0 | 0 | 5 wks. in HFUT vs 4 wks. in STSG | N/A | N/A |
| Wong et al., 2021 [27] | N/A | 54 years | 0 | 1 | 0 | 0 | 6 months | Positive expression of Type VII collagen | N/A |
| Saha et al., 2021 [26] | 10 | 6 weeks-40 years | 10 | 10 | 0 | 0 | Up to 3 months | Re-emergence of blood vessels (PECAM-1), lymph vascular structures (LYVE-1), class III β -tubulin | N/A |
| Belatti et al., 2023 [25] | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Jansen et al., 2024 [24] | 82.49 | 22.46 years | 21 | 16 | 6 | 6 | Variable up to 14 months | N/A | N/A |

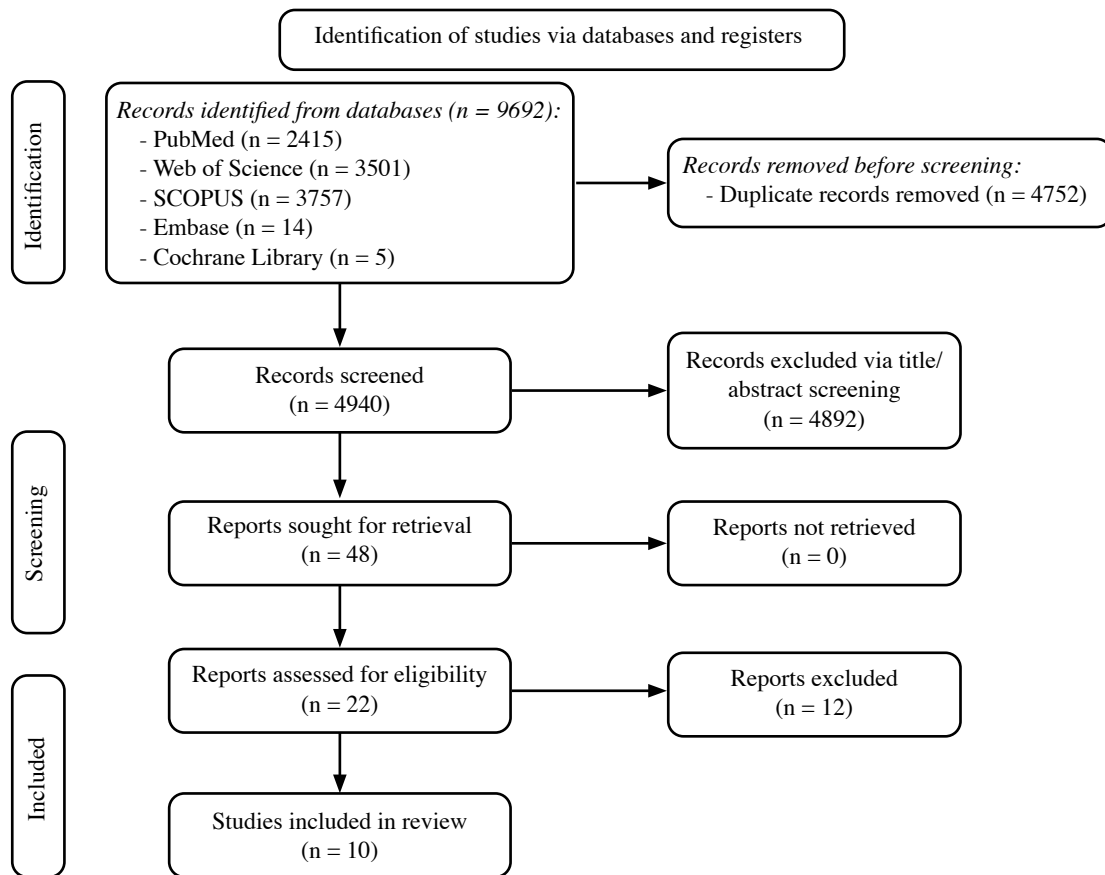


Fig. (1): PRISMA flowchart of the search process.

| | | Risk of bias domains | | | | | |
|-------|---------------------------|----------------------|----|----|----|----|---------|
| | | D1 | D2 | D3 | D4 | D5 | Overall |
| Study | Jansen et al., 2024 | ⊖ | ⊕ | ⊕ | ⊖ | ⊖ | ⊖ |
| | Belatti et al., 2023 | ? | ? | ? | ? | ? | ? |
| | Saha et al., 2021 | ⊖ | ⊕ | ⊕ | ⊖ | ⊕ | ⊖ |
| | Wong et al., 2021 | ⊗ | ⊕ | ⊗ | ⊖ | ⊖ | ⊗ |
| | Chougule et al., 2020 | ⊖ | ⊕ | ⊖ | ⊖ | ⊕ | ⊖ |
| | Alam et al., 2019 | ⊗ | ⊕ | ⊖ | ⊖ | ⊖ | ⊖ |
| | Budamakuntla et al., 2018 | ⊖ | ⊕ | ⊕ | ⊖ | ⊖ | ⊖ |
| | Martinez et al., 2016 | ⊗ | ⊕ | ⊕ | ⊖ | ⊖ | ⊖ |
| | Liu et al., 2015 | ⊗ | ⊕ | ⊕ | ⊖ | ⊖ | ⊖ |
| | Jimenez et al., 2012 | ⊖ | ⊕ | ⊕ | ⊖ | ⊕ | ⊖ |

Domains:

D1: Bias arising from the randomization process.

D2: Bias due to deviations from intended intervention.

D3: Bias due to missing outcome data.

D4: Bias in measurement of the outcome.

D5: Bias in selection of the reported result.

Judgement

⊗ High

⊖ Some concerns

⊕ Low

⊛ No information

Fig. (2): Risk of bias chart of the included studies.

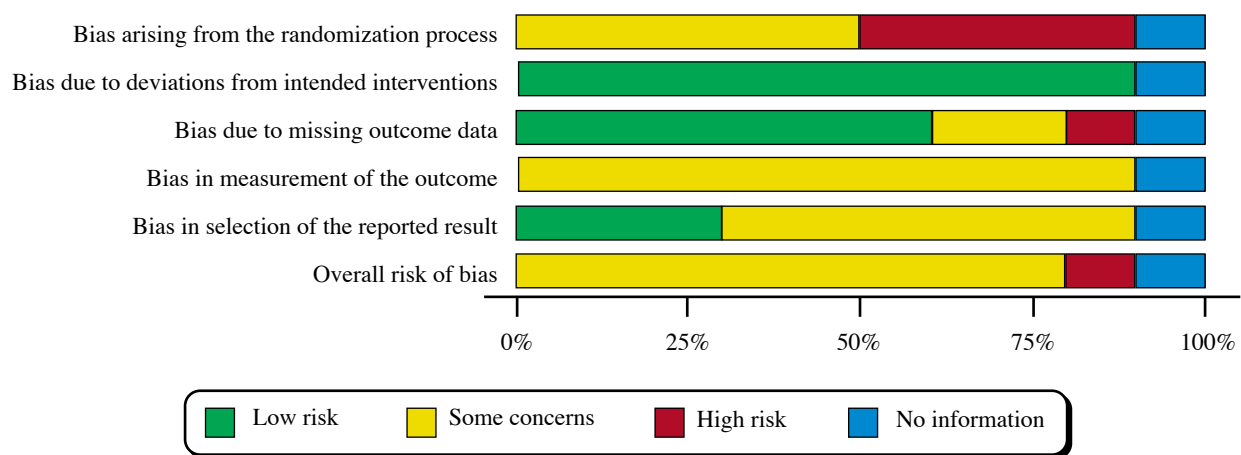


Fig. (3): Summary diagram of the risk of bias of the included studies.

Discussion

This review offers a systematic summary of the current literature regarding the potential healing effects of hair follicle transplantation in chronic lesions. It encompasses ten studies from five different countries. The heterogeneity in the methodological approaches employed by each study complicates the determination of the effect of hair follicles in the chronic wound bed. Additionally, various sizes of punches were utilized. As a result, it is still unclear whether the healing effects observed in these trials were attributable to the multipotent stem cells found in the hair follicular units or the interfollicular stem cells from the basal layer of the epidermis located between the hair follicles [34]. Moreover, the ability to perform the procedure of HFU transplantation into chronic wounds in a single session and by a single team makes this technique a valuable alternative for patients with comorbid conditions. Additionally, the number of HFUs required per square centimeter, which can alter the chronic wound microenvironment and provide the necessary stem cells and growth factors for healing, has not been established on solid reasoning. Furthermore, the control groups used to compare the outcome measures could not be standardized. Moreover, the limited number of cases involved in these trials increases the risk of bias in the reported results and diminishes their quality. Additionally, including cases at the extremes of age may have affected the ability to generalize the reported outcome measures to the broader population of patients with chronic wounds. Including cases with specific etiological factors for chronicity may also have influenced the reported outcome measures. Furthermore, the effect of the duration of chronicity on the wound bed and its subsequent effects on the transplanted hair follicles could not be investigated. Obesity is

also a contributing factor that affects the healing capacity of chronic wounds. Despite the increase in adipocyte size, this growth does not typically see a corresponding increase in the number of blood vessels for adequate vascularization [35]. Only one study has investigated the effect of BMI on wound healing after HFUs transplantation. Furthermore, the histopathological changes that accompany the healing of chronic wounds after HFUs transplantation require further investigation.

The increasing percentage of elderly individuals with chronic wound conditions makes chronic wounds an intriguing scientific topic to explore. In the United States, 2% of the population is affected by chronic wounds, which accounts for a total annual cost of 20 to 25 billion USD [36,37]. In Europe, 2-3% of the total healthcare budget is dedicated to treating patients with chronic wounds, with 27-50% of acute hospital beds occupied by patients with a wound on any given day [38]. This anticipated rise in cases of chronic wounds will place additional burdens on healthcare systems, highlighting the need to explore new and innovative techniques for managing these wounds.

To the best of my knowledge, this narrative review on the clinical application of hair follicle transplantation in chronic wounds is the first to examine the available studies in this area of interest. Due to limitations in the included studies, this review also has several restrictions. First, it is confined to studies published in the literature. Ongoing trials and larger studies may significantly impact our understanding of the efficacy of HFUs transplantation in chronic lesions. Additionally, publication bias may affect the results, as studies reporting negative outcome measures might be underrepresented in the literature.

Conclusion:

Hair follicle transplantation using the follicular unit excision technique shows promising results for alleviating the burden on patients with chronic, intractable wounds. The ease of use and prompt availability make HFU transplantation a suitable alternative for cases with limited efficacy of the usual standards of care. However, well-designed, large-scale trials are needed to enhance our understanding of the underlying molecular and cellular mechanisms involved in the healing of chronic wound beds after HFU transplantation.

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