

# Clinical Approach to the Treatment of Chronic Non-Healing Wounds in Diabetes Mellitus: Efficacy of Cold Atmospheric Plasma and Modern Wound Dressings

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**Abstract** Diabetic foot (DF) is one of the most severe and socially significant complications of diabetes mellitus, associated with a high risk of infection, chronic ulceration, amputations, and subsequent disability. The prevalence of trophic ulcers in diabetes reaches 15–25%, and the risk of recurrence within 12 months exceeds 40%. The treatment of plantar ulcers remains a particularly complex clinical challenge due to their prolonged course, pronounced pain syndrome, and frequent biofilm formation. This study presents a clinical and experimental analysis of the effectiveness of a comprehensive approach to the treatment of trophic ulcers in 30 patients with DF. The treatment involved the use of cold atmospheric plasma (CAP) generated by the Plasma Skin device with the "plasma shower" nozzle in combination with modern wound dressings manufactured by HARTMANN (Atrauman Ag, Branolind N, Sorbalgon, Zetuvit Plus). The main group received CAP therapy combined with dressings, while the control group received only local dressing treatment. A phase-based selection of wound care products was employed, along with mechanical debridement, and for plantar ulcers, offloading systems by Fresco were used. The results showed that incorporating CAP into the treatment algorithm significantly accelerated granulation, reduced microbial contamination, stimulated angiogenesis (including via VEGF mediation), and decreased inflammation. These findings confirm the rationale for a comprehensive approach to treating trophic ulcers in patients with DF.

**Keywords** Diabetic foot, Trophic ulcer, Cold atmospheric plasma, Atrauman Ag, Foot offloading, HARTMANN, Sorbalgon, Biofilm, VEGF, Plasma shower

## 1. Introduction

Diabetic foot (DF) is one of the most serious and complex complications of diabetes mellitus, resulting from a combination of neuropathy, ischemia, and immunological disorders. This condition is characterized by the development of chronic wound defects that are often complicated by infection and lead to severe consequences, including lower limb amputations and reduced quality of life. According to the International Diabetes Federation (IDF), up to 25% of patients with diabetes develop foot ulcers during their lifetime, and up to 85% of all non-traumatic lower limb amputations are associated with infected trophic ulcers [1,2].

The formation of trophic ulcers in DF is a complex interplay of multiple factors. The main mechanisms include diabetic neuropathy, which leads to loss of sensation and repetitive microtrauma; peripheral arterial disease with

resulting ischemia and impaired tissue perfusion; and an immunodeficient state due to impaired leukocyte function and reduced immune response [3,4]. These changes disrupt the normal wound healing process—prolonging the inflammatory phase, reducing angiogenesis, increasing oxidative stress, and altering tissue metabolism—which contribute to the chronicity of the wound defect.

One of the key factors complicating the treatment of chronic ulcers is the formation of bacterial biofilms.

Biofilms not only sustain chronic inflammation but also hinder normal tissue repair processes, significantly reducing the effectiveness of conventional therapies [5,6].

In this context, modern methods for treating trophic ulcers in diabetic foot syndrome involve not only systemic and local pharmacological treatments but also innovative physical therapeutic modalities. One of the most promising approaches is the use of cold atmospheric plasma (CAP)—an ionized gas with a temperature below 40°C, which possesses strong antimicrobial, anti-inflammatory, and regenerative properties [7-10]. CAP disrupts bacterial biofilms, reduces the production of pro-inflammatory cytokines, stimulates angiogenesis, and activates regeneration of the cellular matrix.

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This contributes to accelerated wound healing and a reduced risk of infectious complications.

In addition to CAP, the use of modern wound dressings tailored to the phase of the wound healing process plays a crucial role in the treatment of chronic wounds in diabetic foot syndrome. Phase-oriented wound dressings maintain an optimal moist environment, regulate exudate levels, provide antimicrobial protection, and stimulate tissue repair. A wide variety of advanced dressings—ranging from alginate and hydrofiber to antimicrobial silver-impregnated dressings—have proven effective in managing trophic ulcers [11,12].

Another essential component of comprehensive treatment is adequate offloading of the affected area, especially in ulcers located on the plantar surface of the foot. Offloading reduces pressure on damaged tissues, prevents recurrent trauma, and creates favorable conditions for healing. The use of individually selected orthopedic insoles and specialized offloading devices significantly improves clinical outcomes and reduces recurrence rates [13,14].

The objective of this study was to provide clinical justification for the effectiveness of using cold atmospheric plasma in combination with HARTMANN wound dressings and mandatory offloading of the plantar surface in the treatment of trophic ulcers in patients with diabetic foot syndrome.

### Pathophysiology of Trophic Ulcers

In diabetic patients, the wound healing process is impaired at all stages, resulting in chronic, hard-to-treat wounds. A key pathophysiological factor is suppressed fibroblast activity—cells responsible for synthesizing collagen and extracellular matrix components essential for granulation tissue formation. There is also a disruption in the expression of growth factors, particularly vascular endothelial growth factor (VEGF), which plays a central role in angiogenesis and microcirculation restoration at the site of injury. As a result, the reparative potential of tissues is reduced, and the formation of new blood vessels is slowed, critically impairing oxygen and nutrient delivery to the wound bed [15,16,17].

Chronic inflammation is another significant aspect of the pathophysiology of diabetic ulcers. In diabetes, there is a hyperexpression of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ). These cytokines sustain the inflammatory process by activating the transcription factor NF- $\kappa$ B and other signaling pathways, which prevents the wound from transitioning from the inflammatory to the reparative phase. This dysregulation results in the prolonged presence of inflammatory cells in the wound, damage to surrounding tissues, and delayed epithelialization [18,19].

A particularly important factor in the chronicity of trophic ulcers is the formation of bacterial biofilms—structured communities of microorganisms encased in an extracellular polymeric substance. Biofilms protect bacteria from antibiotics and immune defenses, promote persistent inflammation, and enhance resistance to treatment. They significantly reduce the effectiveness of conventional therapies and are among the leading causes of recurrence and complications in diabetic

foot syndrome [20,21,22].

Additionally, various external and local factors further worsen wound conditions and impede healing. Maceration of the wound edges, caused by excessive or improperly managed exudate, leads to tissue softening and an increased risk of microtrauma. Repetitive trauma due to improper pressure distribution on the foot and hyperkeratosis—excessive thickening of the stratum corneum—cause mechanical damage to tissues and disrupt normal regenerative processes. The lack of adequate offloading of the affected area significantly increases pressure on the ulcerative defect, impeding healing and contributing to chronicity [19,20,21].

Thus, the pathophysiological cascade leading to the formation and chronicity of trophic ulcers in diabetic patients is multifactorial and requires a comprehensive treatment approach aimed at addressing both intrinsic (microcirculatory and immune disorders) and extrinsic (infectious and mechanical) factors.

## 2. Methods

This study was conducted at the Podiatric Center (Diabetic Foot Clinic). A total of 30 patients with type 2 diabetes mellitus of more than 5 years' duration were included. Inclusion criteria comprised the presence of trophic foot ulcers persisting for at least four weeks, indicating a chronic wound process. Patients with clinical signs of osteomyelitis, critical limb ischemia, gangrene, systemic infections, or severe somatic diseases that could influence wound healing were excluded in order to avoid bias in the results [3,23].

Patients were randomized into two equal groups using computer-generated random numbers. The main group ( $n = 15$ ) received cold atmospheric plasma (CAP) therapy three times per week, in combination with HARTMANN wound dressings, selected based on the phase-oriented approach — i.e., choosing dressings appropriate to the wound phase (inflammation, exudation, granulation, epithelialization). The control group ( $n = 15$ ) underwent standard wound care using HARTMANN dressings tailored to wound phase but without CAP therapy [24,25].

To objectively assess the effectiveness of therapy, the following methods were employed:

- Clinical examination and photographic documentation of the ulcers to monitor visible changes and healing dynamics;
- Planimetry — measurement of ulcer surface area to objectively evaluate wound contraction over time [26];
- Microbiological culture to identify pathogenic microflora and assess the efficacy of antimicrobial therapy;
- Biochemical markers of inflammation and repair, including C-reactive protein (CRP), interleukin-6 (IL-6) — a key pro-inflammatory cytokine, and vascular endothelial growth factor (VEGF), which reflects angiogenic activity [27,28];
- A general clinical inflammation marker — erythrocyte sedimentation rate (ESR).

Wound assessment was conducted every 3 days, allowing timely adjustments to therapeutic measures, reassessment of dressing types, and optimization of cold atmospheric plasma (CAP) parameters. Frequent monitoring helped in early detection of complications and improved the overall effectiveness of the treatment protocol.

In addition to the above methods, the study also included cytological analysis of cellular changes in the wound, enabling a deeper morphological assessment of tissue state and therapy efficacy. Cytological material was obtained by gently scraping the wound edges using a sterile spatula or soft brush. Specimens were fixed and stained using standard techniques (Papanicolaou, Romanowsky–Giemsa), followed by microscopic evaluation of cell composition, the number of inflammatory cells (neutrophils, macrophages), presence of fibroblasts, signs of epithelial cell proliferation, as well as bacterial flora and inflammatory features [29].

Cytological analysis provided additional insight into the dynamics of inflammatory and reparative processes at the cellular level, offering further evidence of CAP's ability to reduce inflammation and stimulate tissue regeneration, corroborating clinical and laboratory findings.

The use of these diagnostic tools complies with current clinical research standards in the treatment of diabetic ulcers, ensuring reliable and reproducible data that are essential for evaluating the effectiveness of emerging therapeutic technologies [30].

### Debridement and Wound Condition Monitoring

Debridement is one of the most important and integral stages in the comprehensive treatment of chronic trophic ulcers, including diabetic wounds. The primary objective of this procedure is the removal of all non-viable tissue, such as necrotic material, fibrin deposits, hyperkeratosis, and bacterial biofilms, which contribute to sustained inflammation and obstruct normal wound healing [30]. Eliminating these barriers enables the wound to transition from chronic inflammation to the active phases of granulation and epithelialization, significantly accelerating tissue repair [31].

In the study conducted at the Podiatric Center's specialized Diabetic Foot Care Unit, debridement was primarily performed using mechanical methods with sterile surgical instruments — scalpels, curettes, and scissors. The procedure was carried out on an outpatient basis 1–2 times per week, depending on the extent of necrotic tissue and the stage of the wound healing process. Prior to debridement, the wound underwent superficial antiseptic treatment using octenidine-based solutions, which offer a broad spectrum of antibacterial activity without significant cytotoxic effects on granulation tissue [32,33].

Special attention was given to the choice of antiseptics based on the wound healing phase. During the granulation and epithelialization stages, the use of aggressive and drying agents (e.g., Betadine, iodophores, hydrogen peroxide) was avoided, as modern research suggests that such agents may inhibit angiogenesis, impede keratinocyte migration, and increase cell apoptosis, thereby delaying regeneration

[34,35]. Instead, preference was given to gentle, hydrophilic dressings and low-cytotoxicity antiseptics that support a moist wound microenvironment conducive to healing.

Wound condition monitoring was conducted every 3 days, with systematic assessment of the following parameters:

- The volume and nature of wound exudate (serous, purulent, hemorrhagic), serving as indicators of inflammatory activity and potential infection;
- The color, texture, and density of granulation tissue, reflecting the quality and speed of new connective tissue and blood vessel formation;
- The presence of fibrinous plaque, hyperkeratosis, and signs of infection (edema, erythema, local hyperthermia);
- The degree of epithelialization at the wound edges, indicating wound closure progress and epithelial cell migration;
- Visual inspection with photographic documentation, providing objective records of wound dynamics and allowing for planimetric analysis.



**Figure 1.** A trophic ulcer developed in the area of scar tissue that had formed following surgical drainage of a phlegmon



**Figure 2.** Condition of the trophic ulcer after surgical necrectomy. Treatment included the use of Hartmann wound dressings and cold atmospheric plasma therapy



**Figure 3.** Trophic ulcer: staged wound care and dressing changes throughout healing



**Figure 4.** Trophic ulcer: staged wound care and dressing changes throughout healing



**Figure 5.** Trophic ulcer: staged wound care and dressing changes throughout healing

This process is clearly illustrated by a series of clinical

photographs showing the same patient's foot at different stages of treatment and healing — starting from the initial examination and surgical necrectomy, through sequential wound care procedures and dressings involving cold atmospheric plasma therapy, to the final stage of epithelialization (Figures 1–5).

Based on these observations, decisions were made regarding the type of dressing — transitioning from absorbent dressings (e.g., alginates) to hydrogels — and the use of antiseptic or epithelialization-promoting agents. A key aspect of care was determining the optimal timing for initiating cold atmospheric plasma (CAP) therapy, ensuring maximum synergy between treatment modalities [36].

This individualized, phase-based approach to chronic wound management, grounded in regular monitoring and treatment adjustment, fully aligns with modern principles of gerontopodiatry and diabetology. Such a protocol enhances treatment efficacy, reduces the risk of complications such as secondary infection or ulcer progression, and shortens the overall healing time [37,38].

Furthermore, recent studies emphasize the importance of integrating comprehensive wound care strategies, including microcirculation optimization and the use of advanced wound dressings with antimicrobial and regenerative properties — an approach that was also employed in the present study using HARTMANN products [39,40].

#### **Cold Atmospheric Plasma: Mechanisms of Action**

Cold Atmospheric Plasma (CAP) is a physical state of matter in which a neutral gas becomes partially ionized under the influence of high-frequency electrical discharge. Despite the ionization, the gas temperature remains below 40°C, making CAP safe for medical applications, including use on open wounds. CAP consists of reactive oxygen and nitrogen species (ROS and RNS), ions, electrons, UV radiation, ozone, peroxides, as well as weak electromagnetic fields and electric currents [41,42].

Due to its complex physicochemical interactions, CAP exerts significant biological effects on various components of chronic wound pathogenesis. Below are the key mechanisms of CAP action, as demonstrated in both clinical and experimental studies:

##### **1. Antimicrobial Action**

CAP exhibits a broad spectrum of antimicrobial activity due to the generation of ROS and RNS, which induce oxidative damage to pathogen cell membranes, proteins, and DNA. A particularly important feature of CAP is its ability to disrupt mature biofilms, which are typically resistant to antibiotics and antiseptics. Studies have confirmed CAP's effectiveness against strains such as *Staphylococcus aureus* (including MRSA), *Pseudomonas aeruginosa*, *Candida albicans*, and other microorganisms commonly found in infected chronic ulcers [43–46].

##### **2. Anti-inflammatory Action**

CAP modulates the inflammatory response by reducing levels of pro-inflammatory cytokines, including interleukin-1 $\beta$

(IL-1 $\beta$ ) and tumor necrosis factor-alpha (TNF- $\alpha$ ). It also inhibits the activity of the transcription factor NF- $\kappa$ B, which plays a central role in maintaining chronic inflammation. This leads to a reduction in inflammatory infiltration, edema, and pain, which is particularly beneficial in the context of non-healing chronic wounds [47,48].

### 3. Stimulation of Angiogenesis

CAP enhances the expression of hypoxia-inducible factor HIF-1 $\alpha$  and vascular endothelial growth factor (VEGF), promoting the formation of new capillaries in the damaged area and improving microcirculation. This enhances the delivery of oxygen and nutrients to tissues, which is critical for the transition from the inflammatory to the proliferative phase of wound healing [49,50].

### 4. Reparative and Regenerative Effects

CAP stimulates fibroblast activity, increases collagen synthesis, and supports the formation of extracellular matrix components. It also accelerates epithelial cell proliferation and migration, facilitating rapid re-epithelialization of the wound surface. These processes are fundamental for restoring skin integrity and forming mature granulation tissue [41,50].

### Technical Parameters and Tolerability of the Procedure

In this study, a certified Plasma Skin device with a "plasma shower" nozzle was used. The treatment was applied three times per week, with each session lasting 5 minutes. All patients tolerated the procedure well, with no local or systemic side effects reported. The absence of burns, pain, or irritation supports the conclusion that cold plasma is a safe physical treatment modality, suitable even for patients with sensitive skin or comorbid conditions [51].

### Offloading of Plantar Ulcers

Offloading is a fundamental and essential component of the comprehensive treatment of plantar ulcers in patients with diabetic foot syndrome and other chronic skin conditions of the foot. Its goal is to reduce or completely eliminate pressure and friction at the wound site, thus preventing repeated trauma and creating optimal conditions for tissue repair [52].

In this study, all patients in both the intervention and control groups received offloading within the first 24 hours after enrollment into the clinical protocol, in accordance with the leading international guidelines for diabetic ulcer management [38,53]. Timely initiation of offloading is considered one of the key factors in improving treatment outcomes and reducing the recurrence rate of ulcerative lesions.

Various methods and devices were used to ensure maximum offloading effectiveness:

- Custom orthopedic insoles, designed according to the patient's foot anatomy and ulcer location. These insoles help redistribute plantar pressure, reduce load on the affected area, and provide cushioning during walking. Modern insole materials offer optimal support and durability [54].

- Fresco foam and felt offloading elements — specialized orthopedic components made of lightweight, elastic, and high-quality materials. These elements exhibit excellent shock-absorbing properties, significantly reducing dynamic and static pressure on the plantar surface, especially in the ulcer zone. Their porous structure and softness absorb impact and reduce friction while walking, thereby minimizing the risk of further tissue damage and accelerating wound healing [55,56].

Felt elements by Fresco provide stable and gentle offloading, adapting to the individual anatomy of the foot, which is especially important in cases of deformities or hyperkeratosis. Fresco foam materials, in addition to cushioning, offer moisture-wicking and breathable properties, maintaining an optimal skin microclimate and preventing maceration or secondary infections. Their lightweight and flexible design increases patient comfort and adherence, while custom adjustability allows for the creation of personalized offloading systems [57].

Offloading effectiveness was assessed at each visit through visual evaluation of the wound and consideration of patients' subjective feedback. If necessary, orthopedic devices were adjusted to achieve optimal offloading and prevent new injuries [58].

The implementation of offloading allowed for the elimination of local pressure at the wound site, creating a favorable microenvironment for reparative processes while reducing the risk of recurrence, infectious complications, and necrosis of surrounding tissues. In addition, systematic offloading contributed to improved microcirculation and reduction of inflammation in the wound area, further stimulating healing [59].

Thus, plantar ulcer offloading using Fresco foam and felt materials is a key component of a multidisciplinary approach to diabetic foot treatment, which includes not only local therapy but also metabolic correction, glycemic control, and patient education [60].

### Wound Dressings (HARTMANN)

The modern approach to chronic wound management, including trophic ulcers in diabetic foot syndrome, involves a phase-specific selection of wound dressings tailored to the stage of the healing process. The company HARTMANN has developed a wide range of specialized dressings that provide effective protection, wound sanitation, and healing stimulation, in line with evidence-based medicine.

#### 1. Exudative Phase — Sorbalgon

A dressing made from calcium alginate derived from brown seaweed. Upon contact with exudate, it forms a soft gel-like substrate, which facilitates gentle wound cleansing, minimizes tissue trauma during dressing changes, and maintains a moist environment essential for activating reparative processes [61,62].

#### 2. Inflammatory Phase — Zetuvit Plus

A modern, multi-layer absorbent dressing with high fluid retention capacity and a soft silicone contact surface. It



effectively controls maceration of surrounding tissue, reduces edema, and protects wound margins. The silicone border provides reliable yet atraumatic fixation, even with frequent dressing changes, which is particularly important for patients with sensitive skin [62,63].

### 3. Granulation Phase with Infection Risk — Atrauman Ag

A nonwoven dressing impregnated with silver compounds, offering prolonged antimicrobial action effective against a wide range of microorganisms, including resistant strains. The material does not adhere to the wound surface, thereby minimizing pain and the risk of re-traumatizing granulation tissue [63,64].

### 4. Epithelialization Phase — Branolind N

A mesh-based ointment dressing containing Peruvian balsam, known for its regenerative and antiseptic properties. It allows oxygen permeability, does not interfere with epithelialization, and promotes the formation of a thin, resilient epithelial layer while reducing scarring [64]. Such a sequential application of wound dressings ensures physiologically optimal conditions for healing at each stage, improving outcomes and reducing the rate of chronicity and recurrence. Maintaining a moist environment, controlling microbial colonization, and stimulating cellular regeneration—all of these mechanisms are implemented as part of a comprehensive therapy tailored to the phases of the wound process [65].

## 3. Results

Upon completion of the 4-week treatment course, statistically and clinically significant differences were observed between the main group (CAP + HARTMANN dressings) and the control group:

- The average reduction in ulcer area in the main group was 62.4%, compared to 32.8% in the control group ( $p < 0.01$ ), indicating a marked acceleration of reparative processes with combination therapy. Wound size began to decrease as early as day 10–12 of treatment.
- The formation of mature granulation tissue (visually and based on cytological criteria) was observed in 86% of patients in the main group, versus 40% in the control group, confirming the role of CAP and appropriately selected dressings in promoting the transition from inflammation to proliferation.
- C-reactive protein (CRP) levels decreased from 28 to 10 mg/L in the main group, compared to a reduction to 19 mg/L in the control group, reflecting a more pronounced anti-inflammatory effect of CAP therapy.
- Interleukin-6 (IL-6), a key mediator of chronic inflammation, decreased from 18.4 to 9.6 pg/mL in the main group, while in the control group, the average level remained at 13.1 pg/mL.
- Vascular endothelial growth factor (VEGF), which promotes angiogenesis, increased from 57 to 104 pg/mL in the main group, demonstrating enhanced microcirculation and vascularization at the ulcer site.

- Microbiological cultures on day 21 remained positive in only 33% of patients in the main group, versus 73% in the control group, confirming the antiseptic efficacy of the combined approach (CAP + Atrauman Ag).

Additional confirmation was provided by cytological analysis, which revealed a reduction in neutrophils and the emergence of active fibroblasts.

## 4. Discussion

The integration of cold atmospheric plasma (CAP) and a phase-oriented selection of wound dressings demonstrated significant advantages in the treatment of trophic ulcers in patients with diabetic foot syndrome. The findings confirm that this combination produces multifactorial therapeutic effects: it accelerates wound debridement, stimulates granulation tissue formation, reduces microbial load, and lowers inflammatory background.

The clinically significant reduction in ulcer size, improvement in inflammatory biomarkers (CRP, IL-6), and increase in VEGF levels in the main group indicate activation of reparative and angiogenic processes under the influence of CAP. One of the key factors in the success of combination therapy was the proper organization of the wound dressing process. The use of HARTMANN dressings in accordance with the phases of the wound healing process ensured not only optimal moisture balance but also fulfilled a number of additional functions—antimicrobial protection (Atrauman Ag), effective exudate management (Sorbalgon, Zetuvit Plus Silicone Border), and stimulation of epithelialization (Branolind N). This individualized approach to dressing selection significantly increased treatment efficacy, minimized the risk of maceration and secondary infection, and shortened ulcer healing time.

Particular attention should be paid to offloading the foot, which is critically important in the presence of plantar ulcers. The use of offloading materials eliminated pressure on the wound surface, reduced the risk of progression of soft tissue damage, and improved microcirculation in the affected area. This confirms that without adequate offloading, even the most advanced technologies and dressings lose their effectiveness.

Thus, the presented approach combines elements of both innovative and evidence-based medicine, providing comprehensive targeting of the key pathophysiological mechanisms of chronic wounds. It has strong potential for clinical implementation, especially in specialized diabetic foot clinics and outpatient chronic wound treatment centers.

## 5. Conclusions

Based on the conducted study, it can be concluded that the use of cold atmospheric plasma (CAP) as part of combination therapy for trophic ulcers in diabetic foot syndrome significantly increases clinical efficacy. In combination with phase-oriented HARTMANN dressings and mandatory offloading of the plantar surface, CAP therapy provides

pronounced antimicrobial, anti-inflammatory, and regenerative effects, initiates active tissue recovery, shortens healing time, reduces the risk of infectious complications, and improves the overall condition of patients.

This therapeutic approach affects not only the symptoms, but also the pathogenetic mechanisms of the chronic wound process. Biochemical and cytological data confirm reduced inflammation, angiogenesis activation, and enhanced tissue repair. Practical implementation of this method in an outpatient or day-hospital setting does not require complex equipment and can be easily adopted by most healthcare facilities.

The safety and tolerability of CAP therapy, along with the convenience and effectiveness of modern dressings, make this treatment scheme widely applicable. The method aligns with the principles of personalized medicine and holds high potential for inclusion in clinical guidelines for the treatment of chronic ulcers in patients with diabetic foot syndrome.

In summary, comprehensive therapy incorporating CAP, phase-specific dressings, and plantar offloading can be considered a promising direction in modern wound management, fully aligned with evidence-based standards and aimed at improving the quality of life for patients with diabetic complications. The method is safe, suitable for outpatient practice, and can be recommended for inclusion in clinical guidelines.

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