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Improving the Healing of Diabetic Foot Ulcers: A Real-World Insight into the Add-On Efficacy of a Topical Medical Device Based on Polynucleotides and Hyaluronic Acid

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ABSTRACT

Introduction: *Diabetic foot ulcers are rapidly becoming a social problem and a severe drain of health resources due to the current worldwide diabetes epidemic. A gel formulation of natural-origin polynucleotides (PN HPT™, Polynucleotides Highly Purified Technology) and hyaluronic acid in a topical medical device (NUCLIASKIN S, Mastelli S.r.l., Sanremo, Italy) was designed explicitly for wound bed management and extensively employed. The medical device has activating properties on dermal fibroblasts thanks to the passive replenishment of tissue reservoirs of purines, pyrimidines, nucleotides and nucleosides while preserving the ideal moist wound bed environment. The study aimed to confirm the topical medical device's long-term effectiveness and safety profile within a multi-year efficacy and safety monitoring program.*

Methods: *Retrospective comparison, in 124 patients with diabetic foot ulcers, between the usual high-quality standard of care (weekly wound cleansing and disinfection, debridement with scalpel and curette, and secondary sterile dressing) and the usual standard of care plus add-on NUCLIASKIN S gel treatment every three to six days according to the medical device's information leaflet. The primary efficacy parameter in the two retrospective cohorts was complete healing after 12 and 24 weeks; the secondary efficacy parameter was healing time.*

Results: *Compared with controls who received only the routine standard of care, the proportion of complete wound closure after 12 and 24 weeks in patients was significantly higher in the add-on cohort. Time to complete healing in the Nucliaskin S-treated cohort diverged from controls after 60 days, with significantly higher healing rates after 90 days—64% of Nucliaskin S-treated patients vs 38% of controls. There were no reports of allergic or other adverse events.*

Conclusions: *The study demonstrated that NUCLIASKIN S retains its long-standing record of excellent handiness, safety, and efficient and superior performance in facilitating the healing of the diabetic foot, a clinically troublesome and labour-intensive condition for healthcare providers, even compared to the highest-quality standard of care.*

Keywords

PN HPT™, Polynucleotides, Hyaluronic acid, Real-world study, Diabetic foot, Chronic wounds.

Introduction

The world's population structure will change substantially in 2040, with worldwide ageing steadily progressing over the following decades and only Western Africa keeping a youthful pyramidal structure until 2070 or 2080 [1]. Conversely, the demographic winter is already severe in Europe, primarily in the Mediterranean and Eastern Europe and Eastern Asia, with demographic projections spelling huge social problems related to massive migrations and threats to current standards of living [1]. Within this frightening framework, a problem that is certain to worsen is diabetic foot, a dramatic event for the quality of life and a severe drain on health resources [2]. The worldwide prevalence of diabetes is higher than 550 million people and accelerating at a faster rate in low- and middle-income countries, with an estimated 537 million between 20 and 79 years already diabetic in 2021 and an estimated 18.6 million patients per year who develop a foot ulcer worldwide each year [2,3]. About one in four diabetic patients will develop a diabetic foot ulcer in their lifetime [4]. That escalating incidence of diabetic foot ulcers means an ever-rising forced resort to minor or momentous amputations (part of the foot or above the foot, respectively), mainly due to infection and progressive gangrene. Currently, this means about 1.6 million amputations each year, with about 33% severe amputations [2,3]. The diabetic foot condition is challenging: after one year in a large prospective study, the ulcer had healed in only 46% of enrolled patients, with later recurrence in 10% of those healed subjects; 15% of patients had died, and 17% had undergone a lower extremity amputation [5]. The ulcer development involves multiple pathways leading to the organisation of a callus and frequent haemorrhage beneath it: sensory neuropathy with loss of protective nociception, motor neuropathy leading to foot and biomechanical deformities, and autonomic neuropathy with skin dryness and other viscoelastic changes are all involved (Figure 1) [2,4]. On removing the callus, the telltale full-thickness skin ulcer appears, extending into the dermis and subcutaneous tissue [2,4].

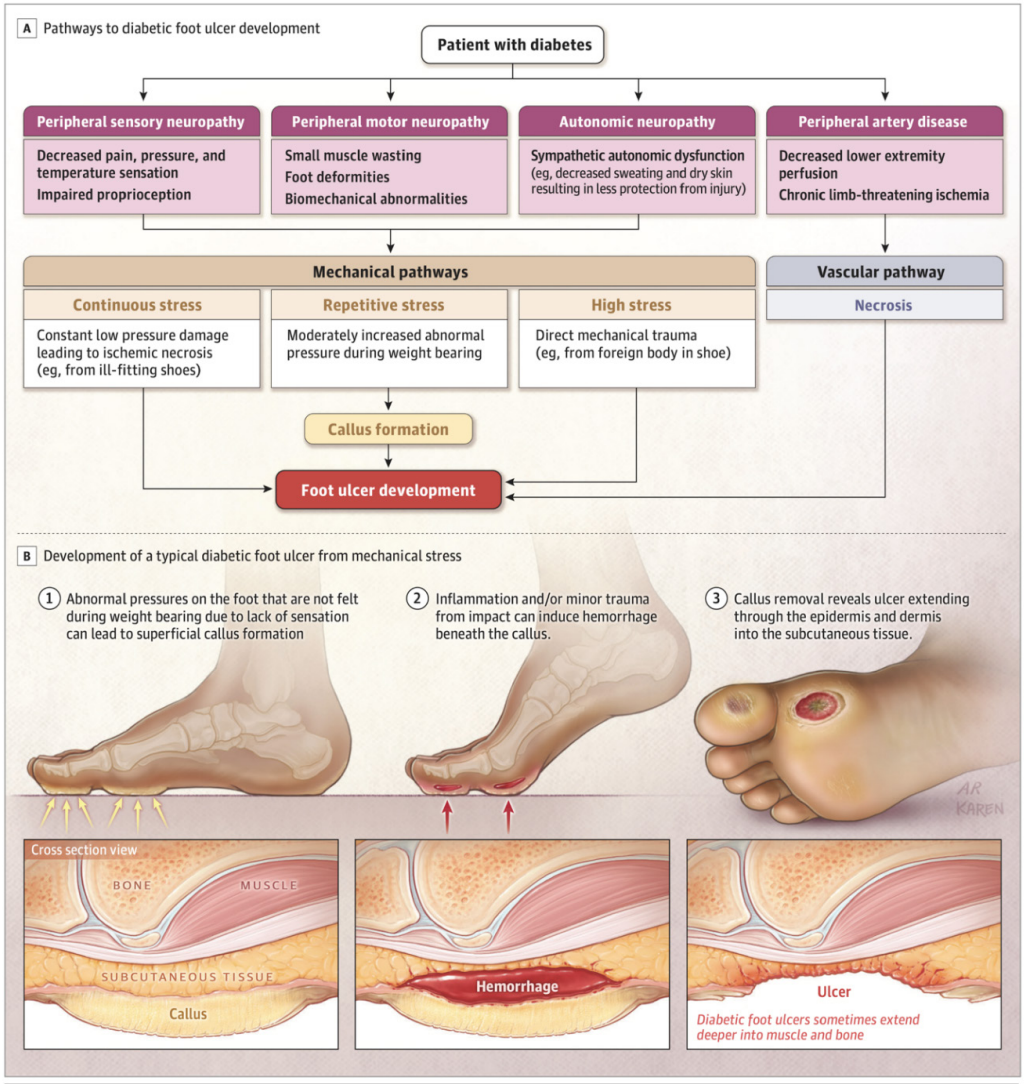

Figure 1: Pathophysiology of diabetic ulcer development. Image reproduced from Ref. 2, open access article distributed under the terms of the Creative Commons CC BY—unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

The mainstay of diabetic foot ulcer management is regular ulcer debridement to eliminate the nonviable wound bed and wound edge tissue, including the excess callus on the periphery, nonviable dermal tissue, foreign materials and bacterial residues. From a multidisciplinary team perspective, improving control of blood glucose, haemoglobin A_{1c} levels and infections and considering revascularisation in case of peripheral artery disease are collateral requirements; educating the patient about proper self-care, regular foot inspections, and treatment for callus and other pre-ulcerative signs will help to prevent recidives [2,6]. Wound treatments may accelerate healing. Among the available options, NUCLIASKIN S (Mastelli S.r.l., Sanremo, Italy) is a Class-III CE-marked medical device conceived for wound dressing and tissue protection in the E phase of the TIME protocol of wound bed management. Nucliaskin S is a viscoelastic, isotonic gel formulation of natural-origin polynucleotides (PN HPT™, Polynucleotides Highly Purified Technology) and hyaluronic acid (HA) in sterile 2-mL pre-filled glass syringes without needle for topical administration [7-9]. Regardless of aetiology, the advanced NUCLIASKIN S medication promotes faster and physiological regeneration and repair of skin lesions and ulcers with no noticeable signs of infection like post-surgical or post-traumatic injuries, burns, bedsores, and diabetic, venous, arteriolar and mixed-origin ulcers. NUCLIASKIN S can be combined with elastic compression; moreover, it facilitates the adhesion of biological membranes, skin substitutes and autografts [7-9].

Clinically, PN HPT™ have hydrating and activating properties on dermal fibroblasts based on the passive replenishment of tissue reservoirs of nucleotides, nucleosides, and nitrogen bases [10,11]. Collaterally, HA enhances the hydration of the extracellular matrix, an essential prerequisite for fibroblast vitality and wound healing [12]. Therefore, the device ensures the environment is steadily moist and ideal for accelerating the physiological repair of chronic torpid skin lesions and ulcers, with polynucleotides acting as passive activators of spontaneous tissue regeneration.

Materials and Methods

Study design

Retrospective, purely observational real-world data collection in 124 adult diabetic patients with grade-A2 Texas foot ulcers, treated between 2015 and 2023 in the ARNAS Civico excellence centre in Palermo. The standard diabetic foot management protocol envisaged weekly evaluations of the healing process and wound closure status. Before the retrospective data collection, 62 patients had undergone the high-quality, weekly standard of care that is routine in the study centre ("Controls"); 62 patients had received the usual standard of care and add-on Nucliaskin S ("Add-on gel"). A hundred per cent re-epithelialisation with no wound drainage, as determined by the treating physician, was the definition of complete wound closure.

Standard of care in the retrospective "Controls" cohort — Weekly wound cleansing and disinfection, debridement with scalpel and curette, and application of a secondary sterile dressing and sterile gauze.

Add-on treatment in the retrospective "Add-on gel" cohort — Gel applied topically to the wound bed and margins every three to six days according to the medical device's information leaflet [13].

Primary efficacy parameter — Complete healing after 12 and 24 weeks, expressed as per cent of the retrospective cohorts.

Secondary efficacy parameter — Time to complete healing in days.

Safety assessment — Incidence throughout the study period of adverse events, including severe events and infections, based on spontaneous patient reporting and objective evaluations, reported as per cent of patients.

Statistical comparisons — 2x2 χ^2 test for proportions for the primary efficacy parameter; Kaplan-Meier survival analysis for the secondary efficacy parameter. Five per cent significance level for all analyses.

Results

Table 1 illustrates the demographics of the two retrospective cohorts; only the gender and age distributions were slightly unbalanced. Fifteen patients (24.2%) were no more than 60 years old in the "Add-on gel" cohort *vs* 18 controls (29.0%), leading to a slight difference in the two mean ages; however, the two median ages were very similar. Most patients of the "Add-on gel" group had suffered from ulcers of toes and soles (38.7% and 21.0%, respectively), followed by lesions of the right or left foot, including heels and ankles (17.7%), ulcers of stumps after previous amputations (9.7%), and ulcers of the interdigital spaces (4.8%). One patient had suffered from leg lesions (1.6%).

Table 1: Demographics of the two retrospective cohorts.

	Controls	Add-on gel
Retrospective patients (n)	62	62
Mean age (years ± SEM)	68.1 ± 11.90	66.5 ± 10.2 *
Median age (years)	67.5	66.5 *
Age range	39 to 93	43 to 86 *
Male gender (n, %)	41 (66.1%)	49 (79.0%)

* *Ages missing in two patients.* SEM = standard error of the mean.

As usual in long diabetic foot studies developing over many months, follow-up attrition was conspicuous in both retrospective groups due to high mortality, hospitalisations for infectious and septic complications and amputations, and many patients lost to follow-up for unspecified reasons. Table 2 summarises the reasons for dropouts in the two retrospective cohorts.

Table 2: Number and reasons for the dropouts recorded during or after treatment.

	Controls	Add-on gel
Total dropouts (n, %)	12 (19.4%)	10 (16.1%)
Infections and sepsis	4	5
Diabetic foot treatment stopped due to other pathologies	1	2
Lost during follow-up for unspecified reasons	6	2
Death before healing	1	1

Figure 2 illustrates the outcomes for the primary efficacy parameter, complete healing rates, in the two retrospective cohorts. Compared with controls who had received only the routine weekly standard of care, the proportions of patients who had achieved complete wound closure after 12 and 24 weeks were significantly higher in the cohort of patients who had also received the add-on Nucliaskin S topical treatment. In the add-on Nucliaskin S topical treatment cohort, complete healing time, the secondary efficacy parameter, started to diverge from controls after 60 days (Figure 3), with significantly higher healing rates after 90 days—64% of Nucliaskin S-treated patients *vs* 38% of controls. There were no allergic or other adverse events.

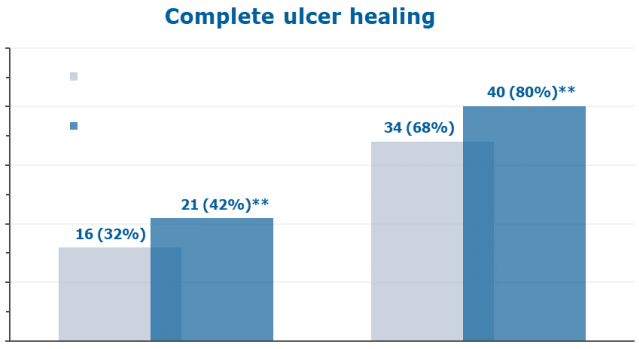

Figure 2: Complete wound healing after 12 and 24 weeks (primary efficacy parameter) in the two comparative retrospective cohorts.
** p=0.02 vs usual standard of care.

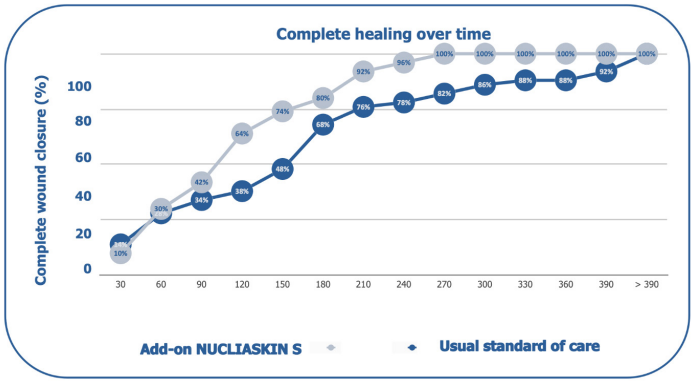

Figure 3: Progression of complete wound healing during the follow-up period (secondary efficacy parameter) in the two comparative retrospective cohorts (cumulative patients showing complete healing at each consecutive month). Difference between Kaplan-Meier curves: ** p=0.02.

Discussion

Foot ulcers are highly susceptible to rapidly spreading infection, leading to overwhelming tissue destruction and a high mortality risk. An ulcer precedes 85% of amputations in diabetic patients, with the amputation risk increasing with advancing age—threefold in patients aged 45-74 and sevenfold in those over 75 [14,15]. Preventing foot ulceration and early and effective treatment of developing lesions are paramount. Suppose foot ulcers are developing or are already apparent. The concept summarised in the "TIME" acronym conceived in the early 2000s — tissue debridement, infection and/or inflammation, moisture balance, edge effect — is ideal for efficient wound bed preparation [7-9]. "T" or tissue debridement refers to the method best suited for the patient (enzymatic, autolytic, surgical, mechanical) to isolate viable from nonviable tissues and areas of necrosis, slough or eschar [7-9]. In the event of infection or inflammation ("I"), antibiogram-guided systemic antibiotics and local antimicrobials will help to eliminate barriers to wound healing. "M" stands for moist wound healing: reversing any wound bed dryness and desiccation or excessive moisture or maceration at wound edges and around the wound. At last, the edge effect ("E"): the wound edges should appear attached, open, and regularly contracting as a marker of sound wound management [7-9]. The topical medical device proved helpful when applied in the "E" phase of the TIME wound care paradigm. Several studies suggest that the PN HPT™/HA combination of Nucliaskin S allows complete wound repair without side effects more rapidly than the topical application of hyaluronic acid alone [16-19]. PN HPT™ reorganise three-dimensionally in the wound areas, acting as potent yet passive fibroblast activators and facilitating the deposition of new collagen and proelastin fibres in a newly produced dermal matrix [10,11]. Moreover, PN HPT™ are devoid of toxicological liabilities at the topically administered dose [19].

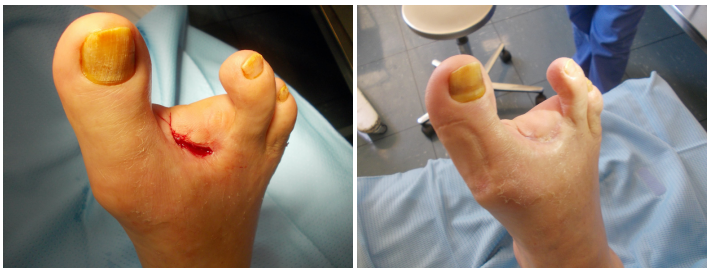

Figure 4: Healing after six months of add-on NUCLIASKIN S treatment; right-foot stump in a 66-year-old patient with severe diabetes and poor compliance to antidiabetic therapy.

The study confirms those previous results in comparison with the routine high-quality standard of care of the author's reference centre, achieving a higher rate of complete healing of diabetic ulcers already after three months.

The NUCLIASKIN S secondary efficacy parameter outcomes, time to complete healing, are at least as significant. Rapid healing means less pain and improved mobility; it also means shortening the time window of vulnerability to nasty microorganisms, thus

reducing the risks of cellulitis, osteomyelitis, tissue necrosis requiring amputation, and sepsis [10,11]. A dramatic comparison of a severe diabetic foot situation before and after add-on NUCLIASKIN S treatment concisely yet exhaustively describes the value of the topical PN HPT™/HA medical device (Figure 4).

Conclusions

The results of this retrospective study demonstrated that, when compared with high-quality wound care, the topical add-on application of Nucliaskin S, a medical device based on the co-formulation of natural-origin polynucleotides (PN HPT™, Polynucleotides Highly Purified Technology) and hyaluronic acid, accelerates the time to wound healing and decreases the risk of dangerous open-wound complications.

Acknowledgements

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