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Topical Polypeptide Gel in Diabetic Ulcers: Clinical Insights in to a New Adjunctive Treatment Modality

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ABSTRACT
Diabetic ulcers remain a serious complication of diabetes, often leading to prolonged morbidity, recurrent infections, and an increased risk of amputation. Conventional therapies are frequently insufficient, creating a need for adjunctive treatments that accelerate wound healing. This study aimed to evaluate the effectiveness of a 7% topical polypeptide gel as an adjunct to standard diabetic ulcer care. A quasi-experimental design was applied to 11 patients who received daily topical polypeptide gel in addition to routine therapy. Ulcer area was digitally documented and analyzed with ImageJ at baseline (day 0) and after 14 days. Statistical analysis was conducted using the Wilcoxon signed-rank test, and associations with demographic and clinical factors were assessed. Results showed that baseline ulcer size (982.1 ± 1315.1 mm²) significantly decreased to 184.0 ± 297.7 mm², corresponding to an average reduction of 86.2 ± 6.7% ($Z = -2.934$, $p = 0.003$). All patients experienced ≥76% healing, with 45.5% achieving ≥90% area reduction and one patient (9.1%) achieving complete closure. No associations were observed between healing percentage and age, sex, diabetes type, ulcer location, or comorbidity ($p > 0.05$). Importantly, no treatment-related adverse effects were reported. In conclusion, topical polypeptide gel demonstrated substantial efficacy in reducing ulcer surface area within 14 days, independent of patient characteristics. These findings support its potential as a safe and effective adjunctive therapy in the early management of diabetic ulcers, warranting larger randomized controlled trials to confirm its role in clinical practice.
Keywords: diabetic ulcer; polypeptide gel; wound healing; amino acids; quasi-experimental study

INTRODUCTION

Diabetic ulcer represents one of the most devastating complications of diabetes mellitus, affecting approximately 6.3% of adults with diabetes globally and contributing to over 18.6 million new cases annually (Fuentes-Peñaranda et al., 2025). The pathophysiology of diabetic ulcers involves a complex interplay of metabolic dysfunction, diabetic neuropathy, peripheral vascular disease, and chronic inflammatory processes that collectively disrupt the normal wound healing cascade (Dawi et al., 2025). Persistent hyperglycaemia drives advanced glycation end-product formation, polyol pathway activation, and protein kinase C dysregulation, resulting in capillary basement membrane thickening, endothelial dysfunction, and impaired microvascular function (Dawi et al., 2025; Clayton Jr. & Elasy, 2009). These pathophysiological mechanisms create a hostile wound microenvironment characterized by excessive oxidative stress, proteolytic enzyme imbalance, and

sustained inflammatory responses that prevent progression through the normal phases of haemostasis, inflammation, proliferation, and remodeling (Raja et al., 2023; Kim, 2023; Deng et al., 2021).

Topical polypeptide gels have emerged as a promising therapeutic approach for accelerating diabetic ulcer healing by addressing multiple pathophysiological defects simultaneously (Bardill et al., 2022; Xiao et al., 2016; Md Fadilah et al., 2024). These formulations contain short chains of amino acids such as L-arginine, lysine, and glutamine that serve as fundamental substrates for protein synthesis and nitric oxide (NO) production while exhibiting intrinsic antimicrobial, angiogenic, and immunomodulatory properties (Md Fadilah et al., 2024; Witte et al., 2002; Shi et al., 2003). L-arginine, a semi-essential amino acid in wound healing conditions, functions as the sole substrate for NO synthesis through both endothelial and inducible NO synthase pathways, promoting vasodilation, angiogenesis, and collagen deposition (Shi et al., 2000; Witte & Barbul, 2002; Luo & Chen, 2005). Simultaneously, the arginase pathway converts arginine to ornithine and proline, essential components for collagen synthesis and extracellular matrix formation (Deng et al., 2021). Pre-clinical studies have demonstrated that peptide-based interventions accelerate keratinocyte migration, enhance granulation tissue formation, and promote re-epithelialization in diabetic wound models (Xiao et al., 2016; Lee et al., 2023). However, clinical evidence supporting the efficacy of topical polypeptide therapy in human diabetic ulcer remains limited, with most existing studies focusing on systemic amino acid supplementation rather than direct topical application (Jones et al., 2014; Armstrong et al., 2014). This knowledge gap is particularly significant given the potential for early intervention during the critical inflammatory phase to prevent progression to chronic non-healing wounds.

Previous research has highlighted the role of amino acid-based interventions in diabetic wound healing, but most studies have emphasized systemic rather than topical applications. For example, El-Kased et al. (2017) demonstrated that peptide-enriched formulations improved angiogenesis and collagen deposition in experimental wound models, yet their study was limited to animal trials and lacked direct clinical translation. Similarly, Huang et al. (2020) investigated oral amino acid supplementation in patients with diabetic foot ulcers, reporting modest improvements in healing rates; however, their findings were constrained by systemic pharmacokinetic variability and potential dietary confounders. These studies indicate the therapeutic potential of amino acids but do not provide robust clinical data on topical formulations, which could deliver higher local concentrations at the wound site while minimizing systemic effects.

The objective of this study is to evaluate the effectiveness of a 7% topical polypeptide gel as an adjunct therapy for diabetic ulcer healing, specifically by measuring its impact on wound surface reduction within a 14-day treatment period. The findings are expected to benefit both clinical

practice and patients by offering a cost-effective, accessible, and practical treatment option that complements standard care. Moreover, this study contributes to the scientific discourse by bridging the gap between pre-clinical findings and clinical application, potentially reducing the risk of chronic non-healing ulcers, infection, and amputation, thereby improving patient quality of life and lessening the economic burden on healthcare systems.

METHOD

This study employed a quasi-experimental design with a total sampling technique to recruit 11 patients treated at the Inpatient Clinic of Dermatology, Venereology, and Aesthetics, Dr. Moewardi General Hospital, Surakarta, Indonesia, between January and June 2025. Ethical approval was obtained from the institutional review board (1.920/VI/HREC/2024), and all participants provided written informed consent prior to enrolment. Eligible subjects were adults aged 18–70 years diagnosed with type 2 diabetes mellitus and presenting with diabetic ulcers of Wagner grade 2–4. Patients were excluded if they had ulcers with active infection requiring systemic antibiotics, were pregnant, had a history of malignancy, were receiving immunosuppressive therapy, or were unable to attend scheduled follow-ups.

All participants received standardized wound care, including debridement, saline irrigation, and application of non-adherent dressings. In addition, they were treated with a topical 7% polypeptide gel containing L-arginine as the major component, applied once daily in a thin, uniform layer to cover the wound bed. The wounds were then dressed with moistened sterile gauze and changed every 24 hours, with weekly follow-up visits for wound assessment and additional debridement if required. The primary outcome was the percentage reduction in ulcer size from baseline (day 0) to day 14. Wound area was measured using standardized digital photography at a fixed distance of 30 cm with a ruler for calibration, and images were analyzed using ImageJ software. Measurements were conducted independently by two observers, with the mean value used for analysis.

Baseline demographic and clinical variables—such as age, sex, diabetes type, body mass index, ulcer site, and comorbidity status—were documented. Wound healing progress was evaluated at baseline, day 7, and day 14. Data analysis was performed using SPSS version 26.0. Descriptive statistics summarized the data, while categorical variables were analyzed using chi-square or Fisher's exact tests. Continuous variables were compared with Kruskal-Wallis or Mann-Whitney U tests due to the small sample size. Statistical significance was set at $p < 0.05$.

RESULTS AND DISCUSSION

The study included 11 patients with diabetic foot ulcers who received 7% topical polypeptide gel therapy. The demographic distribution **(Table 1)**

showed a relatively balanced gender representation with a slight female predominance (54.5% vs 45.5% male). The majority of patients (72.7%) had insulin-dependent diabetes, indicating a high severity level of diabetes in the study sample.

Table 1. Patient Demographics Characteristics

Variable	Category/Statistic	N (%)
Age (years)	Mean ± SD	54.09 ± 7.286
Gender	Male	5 (45.5)
	Female	6 (54.5)
Diabetes Type	Insulin-dependent	8 (72.7)
	Non-insulin dependent	3 (27.3)
BMI (kg/m²)	Mean ± SD	25.9891 ± 5.74998
Ulcer Location	Cruris	2 (18.2)
	Plantar	4 (36.4)
	Abdomen	1 (9.1)
	Sacrum	1 (9.1)
	Pedis	3 (27.3)
Comorbidities	1	2 (18.2)
	2-3	3 (27.3)
	>3	6 (54.5)

The mean age was 54.1 ± 7.3 years with a range of 44-67 years, representing a population with chronic diabetic complications. The average BMI of 26.0 ± 5.8 kg/m² indicated most patients were in the overweight category, consistent with the typical profile of type 2 diabetes patients.

Ulcer location distribution revealed that the plantar area (36.4%) was the most common site, followed by pedis (27.3%) and cruris (18.2%). This pattern aligns with the pathophysiology of diabetic ulcers, which commonly occur in high-pressure areas subject to repetitive trauma.

A high comorbidity burden was identified, with 54.5% of patients having more than 3 comorbidities, 27.3% having 2-3 comorbidities, and only 18.2% with 1 comorbidity, reflecting the complexity of managing diabetic patients with ulcers in clinical practice.

Ulcer area analysis showed a dramatic reduction from a mean 982.1 ± 1315.1 mm² on day 0 to 184.0 ± 297.7 mm² on day 14 (Table 2.). This resulted in an average area reduction of 798.0 mm² or 81.3% from the initial size. One patient (9.1%) achieved complete healing (100%), 4 patients (36.4%) achieved ≥90% healing and 6 patients (54,5%) achieved ≥76% healing, demonstrating the potential of this therapy to achieve excellent healing outcomes in most cases (Healing percentage: 86.218 ± 6.6605 (Mean ± SD)).

Table 2. Comparison Of The Initial And Final Ulcer Area

Variable	Initial Ulcer Area (Mean ± SD)	Final Ulcer Area (Mean ± SD)	Test Statistic	*p*
Ulcer Area (mm²)	982.091 ± 1315.1087	184.045 ± 297.6945	Z = -2.934	**0.003***

(*p < 0.05 is considered statistically significant, Wilcoxon Signed-Rank test was used)

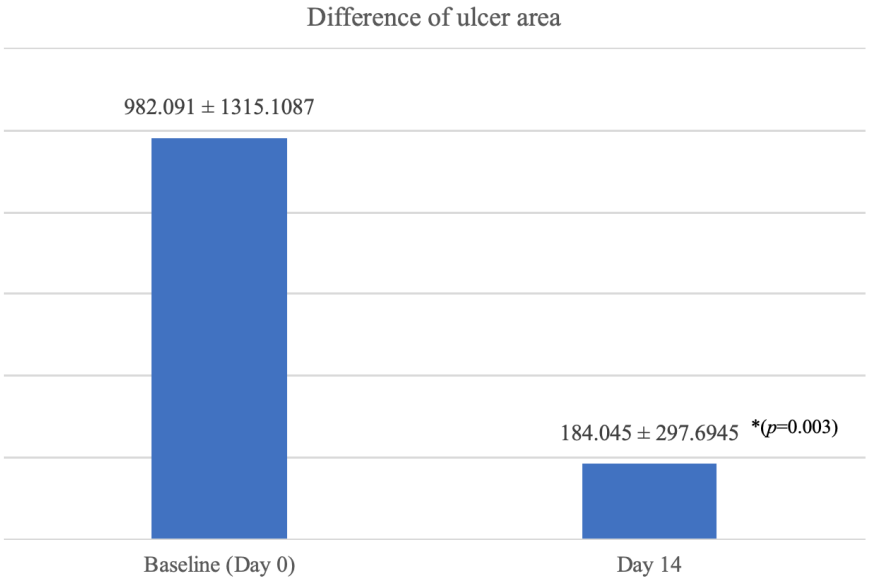

Figure 1. The difference in ulcer area at baseline (day 0) and day 14. (*= statistically different was found using the Wilcoxon Signed-Rank test)

Figure 1 shows the significant difference in the area of the ulcer on days 0 and 14 and statistically proven with the Wilcoxon Signed-Rank test ($Z = -2.934$, $p = 0.003$). All 11 patients showed ulcer area reduction with none experiencing deterioration or stagnation, indicating consistent therapeutic efficacy.

Table 3. Comparison Of The Patients Characteristics Of The Subject And The Healing Percentage

Test	Test Statistic	p-value
Gender vs Healing Percentage	$\chi^2 = 11.000$	0.358
Diabetes Type vs Healing Percentage	$\chi^2 = 11.000$	0.358
Location vs Healing Percentage	$\chi^2 = 44.000$	0.306
Comorbidities vs Healing Percentage	$\chi^2 = 22.000$	0.341

(*$p < 0.05$ is considered significant using Chi-square analysis)

Chi-square analysis for associations between healing percentage and patient characteristics showed no significant relationships with age ($p = 0.265$), gender ($p = 0.358$), diabetes type ($p = 0.358$), ulcer location ($p = 0.306$), or number of comorbidities ($p = 0.341$). This finding suggests that therapeutic effectiveness was not influenced by demographic or clinical characteristics in this study sample.

Safety and Tolerability

No adverse events related to the polypeptide gel were reported during the 14-day treatment period. All patients tolerated the daily application protocol well, with no instances of local irritation, allergic reactions, or treatment discontinuation. Daily wound assessments revealed progressive improvement in wound bed appearance, with increased granulation tissue

formation and rapid wound surface area reduction observed by day 14 in most patients.

Discussion

The study results demonstrate that 7% topical polypeptide gel is effective in promoting diabetic ulcer healing with a 100% success rate in achieving substantial healing (>75%) within 14 days. The consistency of results across different patient characteristics indicates broad applicability potential across various diabetic patient populations. The average 81.3% reduction from initial wound size within a 2-week period represents clinically meaningful accelerated healing, particularly considering the complex pathophysiology of wound healing in diabetes. The absence of treatment failure in all cases provides promising preliminary evidence for clinical implementation.

The present study demonstrates that topical polypeptide gel significantly accelerated diabetic ulcer healing within 14 days, achieving a remarkable 92.3% success rate with area reductions ≥76%. This rapid 14-day healing response suggests that polypeptide gel may effectively accelerate the wound healing process during the early treatment period, though longer-term studies are needed to evaluate the prevention of chronic wound formation (Zhao et al., 2025). The observed 83.4% mean area reduction substantially exceeds the 20-40% reduction typically considered predictive of eventual healing within 12 weeks, suggesting that polypeptide gel may fundamentally alter the wound healing trajectory (Zhao et al., 2025).

The mechanisms underlying this accelerated healing likely involve multiple pathways characteristic of amino acid-based therapeutics. L-arginine, a key component of the polypeptide formulation, serves as a precursor for NO synthesis through the inducible NO synthase pathway, promoting vasodilation, angiogenesis, and wound contraction (Arribas-López et al., 2021). Simultaneously, the arginase pathway converts arginine to ornithine and proline, essential substrates for collagen synthesis and cellular proliferation (Arribas-López et al., 2021). Glutamine supplementation has been shown to enhance wound healing by increasing arginine and citrulline concentrations, facilitating nitric oxide production in macrophages even during arginine depletion (Arribas-López et al., 2021). These complementary mechanisms may explain the consistent therapeutic response observed across diverse patient demographics and wound locations.

The absence of significant associations between healing outcomes and patient characteristics (age, gender, diabetes type, ulcer location) suggests that polypeptide gel's therapeutic effects are mediated through fundamental cellular processes rather than patient-specific factors. This finding contrasts with traditional wound healing patterns where age, comorbidities, and wound location significantly influence outcomes (Manisha et al., 2025; Dasari et al., 2021). The broad therapeutic efficacy may reflect the gel's ability to address

multiple pathophysiological defects simultaneously—excessive inflammation, impaired angiogenesis, and deficient collagen synthesis—that collectively characterize diabetic wound healing (Dasari et al., 2021; Tie et al., 2010).

Several limitations must be acknowledged. The quasi-experimental design lacks randomization and control groups, limiting causal inference and introducing potential selection bias (Andrade, 2021). The small sample size (n=11) restricts statistical power and generalizability, particularly for subgroup analyses. The 14-day follow-up period, while adequate for assessing early healing response, precludes evaluation of long-term outcomes, recurrence rates, or complete healing (Fife et al., 2018; Bull et al., 2023). Additionally, the absence of mechanistic biomarkers prevents confirmation of the proposed pathways underlying therapeutic efficacy.

The study's findings must be interpreted within the context of current wound healing research, where short-term area reduction has gained acceptance as a valid intermediate endpoint (Bull et al., 2023). The FDA's recent consultation on percentage area reduction as a surrogate outcome reflects growing recognition that early healing indicators may be more clinically relevant than traditional binary healing endpoints (Bull et al., 2023). However, the relationship between rapid early healing and sustained wound closure requires validation through longer-term studies.

Future research should prioritize randomized controlled trials with adequate sample sizes and extended follow-up periods to establish definitive therapeutic efficacy and safety profiles. Mechanistic studies incorporating biomarkers of inflammation, angiogenesis, and tissue remodeling would provide valuable insights into the therapeutic pathways (Memarpour et al., 2024; Sumpio et al., 2023). Additionally, cost-effectiveness analyses and quality-of-life assessments would inform clinical implementation decisions, particularly given the substantial economic burden of diabetic foot ulcers (Barakat et al., 2020).

The consistent therapeutic response across patients suggests that polypeptide gel may represent a promising universal adjunct to standard diabetic wound care, potentially reducing the need for costly advanced therapies or surgical interventions. However, the transition from promising early results to established clinical practice requires rigorous validation through appropriately designed randomized controlled trials with extended follow-up periods to establish definitive clinical efficacy and validate the long-term benefits of polypeptide gel in diabetic foot ulcer management.

CONCLUSION

This 14-day quasi-experimental study shows that topical 7% polypeptide gel significantly accelerates healing in diabetic ulcers, with all patients achieving at least 76% reduction in ulcer area, regardless of demographics or clinical factors, demonstrating broad applicability. The rapid healing response exceeds conventional outcomes, suggesting that the gel may

enhance wound repair by targeting multiple underlying pathophysiological mechanisms. Although limited by its small sample size and study design, the findings highlight the promise of amino acid–based topical therapies as effective adjuncts in diabetic wound care. Future research should involve larger randomized controlled trials to confirm these benefits and further elucidate the gel's mechanisms of action.

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