

Efficacy of topical polypeptide gel in accelerating early healing of diabetic ulcers: a randomized controlled trial

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Abstract

Introduction: Diabetic ulcer (DU) remains a major health problem with high morbidity and treatment cost. Effective, rapid, and affordable treatment is essential for its management. Topical polypeptide gel has regenerative, angiogenic, and anti-inflammatory properties that may accelerate wound healing. However, clinical evidence regarding effectiveness is limited.

Methods: A double-blinded randomized controlled trial was conducted involving 26 subjects with DU, randomly allocated into an intervention group that received 7% topical polypeptide and a control group that received hydrocolloid gel. Wound healing was assessed by measuring ulcer surface area reduction on days 7, 14, and 21 compared to baseline.

Results: The polypeptide gel group demonstrated significantly greater absolute ulcer size reduction on day 7 ($p = 0.002$) and day 14 ($p = 0.004$), whereas the difference in absolute area did not reach statistical significance on day 21 ($p = 0.106$). When healing was expressed as the percentage of wound reduction from baseline, the polypeptide gel group showed significantly greater wound closure at all three time points, including day 21 (day 7: 66.4% vs. 16.8%, $p < 0.001$; day 14: 83.3% vs. 27.8%, $p < 0.001$; day 21: 92.7% vs. 41.5%, $p = 0.002$), with large effect sizes.

Conclusions: Topical 7% polypeptide gel was associated with significantly greater reduction in diabetic ulcer surface area compared with hydrocolloid gel. Although the difference in absolute area reduction did not reach statistical significance at day 21, the relative reduction from baseline remained significantly greater in the polypeptide gel group at all three time points, indicating a sustained healing advantage.

Keywords: diabetic ulcer, wound healing, polypeptide gel, amino acids, randomized controlled trial

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Introduction

Diabetes mellitus (DM) is a metabolic endocrine disorder resulting from impaired insulin function, either due to absolute insulin deficiency, known as type 1 DM, or insulin resistance, characteristic of type 2 DM (1). Poorly controlled diabetes can lead to a wide range of complications, among which diabetic ulcer (DU) is among the most common. These ulcers typically develop due to poor glycemic control, peripheral vascular disease, inadequate foot care, and neuropathy. Without appropriate management, DU can progress to osteomyelitis and even lower-limb amputation. The most frequent sites of DU are areas of the foot exposed to trauma and repetitive pressure (2).

Patients with DU require hospitalization more frequently than those with other diabetic complications. The global annual incidence of DU is estimated at 9.1 to 26.1 million cases. Approximately one-fifth of patients with diabetes are expected to develop a chronic non-healing wound such as DU during their lifetime, with recurrence rates ranging from 40% to 65% (3). The worldwide prevalence of DU is reported at 6.3%, with a prevalence of 5.5% in Asia (4). In Indonesia, the prevalence has been reported to reach 7.3%, higher than both global and regional averages (5). With the increasing prevalence of DM and an aging population, the incidence of DU continues to rise by approximately 2% annually (6). Compared to other ulcer types, DU prevalence is considerably higher, exceeding venous ulcers (1%–2%) (7) and pressure ulcers (4.4%) (8) in the elderly. Although DU can occur at any age,

the highest prevalence is observed in patients over 75 (9). Patients with flat-foot morphology, especially at the heel, are at higher risk due to disproportionate pressure distribution, which may trigger inflammation and subsequent ulcer formation (10).

Wound healing is a highly regulated process involving overlapping and complex stages of hemostasis, inflammation, proliferation, and tissue remodeling (11). In patients with DU, protein loss due to catabolism impairs wound-healing mechanisms, including reduced wound tensile strength, impaired T-cell function, diminished phagocyte activity, and lower levels of complement and antibodies. This disruption increases susceptibility to infection and delays healing. DU not only poses a high risk of amputation but also significantly reduces patients' quality of life (12). Despite advances in wound-healing research, effective DU therapy remains a major clinical challenge (11).

The economic burden of DU management is substantial. In Europe, the annual cost of DU treatment is estimated at approximately €70 million, with prolonged healing times contributing further to rising costs. Therefore, wound therapies that are both effective and affordable are urgently needed (13).

Polypeptide-based topical gels are a promising low-cost therapeutic option with encouraging outcomes. Amino acid-derived polypeptides have been reported to accelerate wound healing in traumatic and burn injuries (14). They act through multiple mechanisms, including anti-inflammatory, antimicrobial, proliferative, and angiogenic pathways (15). Essential, non-essential, and semi-essential amino acids contribute differently to wound repair (16).

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For example, arginine enhances collagen synthesis, improves blood flow through nitric oxide (NO) production, and exerts antimicrobial effects, and glutamine serves as an energy source and protects tissues against inflammatory injury (14). Taowen et al. demonstrated that polypeptides containing 81 amino acids enhanced wound healing in DU patients by promoting endothelial cell proliferation and angiogenesis (17). In an animal model, Febriani et al. identified 1 gram of polypeptide in a 10-gram gel base as the optimal dose to accelerate wound healing in diabetic Wistar rats (18).

Most previous studies have evaluated amino acid polypeptides through systemic administration, primarily oral supplementation. However, evidence on topical application in humans remains limited. Based on this background, this study was conducted to investigate the clinical effects of topical amino acid polypeptide gel compared to standard wound care on ulcer healing in patients with DU to assess its potential as an adjunctive therapeutic option.

Methods

Study design

This study was a double-blind randomized controlled trial (RCT) with a pretest–posttest control group design, aimed at evaluating the effect of topical amino acid polypeptide gel on ulcer size reduction in patients with DU. The study was conducted at the Dermatology, Venereology, and Aesthetic Outpatient Clinic, the endocrinology subdivision of the Internal Medicine Outpatient Clinic, and the Thoracic and Cardiovascular Surgery Outpatient Clinic of Dr. Moewardi General Hospital in Surakarta, Indonesia, from January 2025 to May 2025. Ethical approval was obtained from the Health Research Ethics Committee of Dr. Moewardi General Hospital (no. 1.920/VIII/HREC/2024) and the Indonesian Clinical Research Registry (INA-2Y49T46A).

Subject allocation

Participants were randomly assigned into two groups using a computer-independent randomization table. The intervention group received wound dressing with 7% polypeptide gel, and the control group received wound dressing with hydrocolloid gel consisting of a mixture of pectin and sodium carboxymethylcellulose. Allocation concealment was maintained using sequentially numbered, opaque, sealed envelopes that were opened only after a participant had been enrolled and consented. The randomization sequence was generated and held by an independent investigator that was not involved in recruitment, treatment delivery, or outcome assessment. Both study gels were prepared in identical unlabeled containers with comparable color, consistency, and handling characteristics, so that the participants, treating clinicians applying the dressings, and outcome assessors were unable to distinguish the intervention from the control preparation. Blinding was therefore applied at the level of participants, care providers, and outcome assessors, and it was maintained until completion of data analysis.

Inclusion and exclusion criteria

Patients were recruited and screened at Dr. Moewardi General Hospital by clinical staff. Eligible patients were invited to participate and provided written informed consent. Inclusion criteria were age ≥ 18 years and diagnosis of Wagner grade 1–4 DUs. Exclusion

criteria were prior treatment with other wound care modalities, presence of complications such as osteomyelitis, or history of allergy to any study materials. This trial was designed as an exploratory (pilot) study, and the sample size was determined by the number of eligible patients that could be recruited within the predefined enrolment period rather than by a formal a priori power calculation. A total of 26 subjects (13 per group) were enrolled.

Gel polypeptide preparation

The polypeptide solution was prepared in collaboration with the Faculty of Pharmacy, Gadjah Mada University, and Dermama Biotechnology, certified under ISO 9001 by the British Standards Institution and with halal certification from the Indonesian Ulema Council (MUI). Amino acid analysis was performed by the Integrated Research and Testing Laboratory, Gadjah Mada University. The composition of the polypeptide included L-arginine, L-histidine, L-lysine, L-phenylalanine, L-isoleucine, L-leucine, L-tyrosine, L-methionine, L-valine, L-glutamic acid, L-aspartic acid, L-cysteine, L-threonine, L-serine, L-glycine, and L-tryptophan, with L-arginine being the most abundant component (124.59 mg/kg).

The polypeptide solution was mixed with 3% hydroxypropyl methylcellulose (HPMC) as a gelling agent. The polypeptide solution was slowly mixed with HPMC in cold water to prevent clumping, then heated to 60 to 70 °C until fully dissolved, and cooled to room temperature to form a gel. The final product was stored in airtight containers. Stability testing was conducted at the Laboratory of Extract Standardization, Faculty of Pharmacy, Muhammadiyah University of Surakarta (no. 450/SEFA-UMS/XII/24). Among the concentrations tested (5%, 7%, 10%, and 15%), the polypeptide gel with the 7% concentration formulation demonstrated optimal spreadability and stability, with consistent organoleptic properties, stable pH (3.35–3.36), good homogeneity, low adhesiveness, and reproducible spreadability. These characteristics were the main reasons why the researchers selected the 7% concentration for further use. In the control group, hydrocolloid gel was administered as the standard therapy for DU because it is widely recognized for maintaining a moist wound environment, promoting autolytic debridement, reducing pain, and serving as an evidence-based comparator in clinical trials of wound-healing interventions.

Wound care procedure

Wound cleansing began with hand hygiene and use of non-sterile gloves. Ulcers were irrigated with 0.9% NaCl solution, then compressed with sterile gauze soaked in 0.9% NaCl for 15 minutes. Necrotic tissue and slough were debrided using a sterile minor surgical set. After debridement, either polypeptide gel or hydrocolloid gel (containing pectin and sodium carboxymethylcellulose) was applied. The ulcer was covered with sterile gauze and secured with hypoallergenic plaster. The subjects in this study were instructed to change their wound dressings and apply the gel once daily at the same time. However, if the dressing became wet due to water exposure, it was permitted to replace the dressing earlier.

The gel was applied in a dose of 0.5 g per adult hand-sized wound area (finger-tip unit standard). Study subjects were supplied with a 30 g tube of polypeptide gel. Caregivers were educated and required to demonstrate correct wound care technique. Daily wound care monitoring was carried out through logbook entries completed by the patients and their families, including notes of any mild reaction or side effects the patient experienced,

and supervised by the researchers via WhatsApp (Meta Platforms Inc., Menlo Park, CA, USA) chat. In cases of severe allergic reactions (e.g., intense pruritus, swelling, erythema, or blistering), the patient was advised to discontinue the treatment and wash the affected area immediately. Safety was assessed prospectively at every scheduled visit (days 0, 7, 14, and 21) through direct clinical examination of the peri-wound skin and structured questioning for local adverse events (pruritus, erythema, edema, pain, blistering, and contact dermatitis) and any systemic complaints, supplemented by the daily patient-completed logbooks and remote supervision. All events reported were recorded with their date of onset, severity, and relationship to the study product, and reviewed by the investigators; any event prompting discontinuation was documented as a serious adverse event.

Wound size measurement and analysis

Wound size assessment was conducted by two independent evaluators: the principal investigator (blinded to treatment allocation) and an external observer. The ulcer was photographed with a ruler as a reference scale at baseline (day 0), day 7, day 14, and day 21. Treatment was discontinued once complete closure was achieved, or after 21 days.

The primary outcome was the reduction in ulcer area. Ulcer area is a validated predictive indicator of DU healing, with early surface area reduction strongly correlating with overall healing time. Digital imaging was performed, and images were analyzed using ImageJ software version 1.53 (National Institutes of Health, Bethesda, MD, USA) with scale calibration. Digital imaging was used because it provides non-contact, reliable, and accurate measurements. The baseline ulcer area of every wound was recorded on day 0 and used as the reference for all subsequent measurements. Wound healing was expressed as the absolute reduction in ulcer surface area (mm²) and percentage of wound reduction (%) compared to the baseline of the wound area on day 0.

Statistical analysis

Data were analyzed using SPSS version 26 (IBM Corp., Armonk, NY, USA). A *p*-value < 0.05 was considered statistically significant. Interrater reliability of wound measurements was tested using the kappa statistic. Demographic data, including age, BMI, sex, DM type, comorbidities, and bacterial isolates, were summarized using descriptive statistics. The distribution of continuous variables was assessed using the Shapiro–Wilk test. Because the change in ulcer surface area was not normally distributed and the group sizes were small, between-group comparisons of the reduction in ulcer area at each time point (ΔH_7 , ΔH_{14} , and ΔH_{21} relative to baseline) were performed using the non-parametric Mann–Whitney *U* test. We acknowledge that a repeated-measures or linear mixed-effects model would more fully exploit the longitudinal structure of the data by modeling all time points simultaneously while accounting for within-subject correlation; such an approach is recommended for future, larger studies. To aid interpretation beyond statistical significance, the effect size for each between-group comparison was estimated using the rank-biserial correlation derived from the Mann–Whitney *U* statistic, and 95% confidence intervals for the between-group difference in means were obtained by bootstrap resampling. Effect sizes and confidence intervals are reported alongside *p*-values.

Results

Baseline characteristics of study subjects

A total of 26 subjects with DU were enrolled in this study, with 13 allocated to the treatment group and 13 to the control group. Table 1 presents the baseline characteristic of the study subjects. The mean age was 54.2 years in the treatment group and 54.1 years in the control group. The treatment group was slightly dominated by females (53.8%) compared to males (46.2%), whereas the control group had a higher proportion of males (53.8%) than females (46.2%). Both groups were predominantly composed of subjects with normal BMI. In the treatment group, insulin-dependent DM (69.2%) was more common than non-insulin-dependent (30.8%), whereas the control group had a higher prevalence of non-insulin-dependent DM (53.8%) compared to insulin-dependent (46.2%). The mean wound area for the treatment group was 901.62 mm² compared to 1,542.29 mm² in the control group.

Regarding ulcer grading, most subjects in the treatment group presented with Wagner grade 2 ulcers (76.9%), followed by grade 3 (15.4%) and grade 4 (7.7%). In the control group, grade 2 ulcers were also the most frequent (69.2%), followed by grade 3 (30.8%). All subjects had comorbidities. The most frequent comorbidities in the treatment group were hypertension (46.2%) and peripheral arterial disease (46.2%), whereas in the control group cardiovascular disease (46.2%) and hypertension (30.8%) were most common (Table 2). Gram-stained ulcer smears revealed positive dominance of Gram-positive bacteria in only two subjects in the treatment group (15.4%) and one subject in the control group (7.7%). The most frequent ulcer location was the plantar region (38.5%) in the treatment group and the crural region (38.5%) in the control group. No adverse events or discomfort were reported in either group.

Table 1 | Baseline characteristics.

Characteristics	Treatment group (<i>n</i> = 13)	Control group (<i>n</i> = 13)	<i>p</i>
Age (years)	54.2 ± 6.7	54.1 ± 10.6	0.965
Sex			0.695
Male	6 (46.2%)	7 (53.8%)	
Female	7 (53.8%)	6 (46.2%)	
Body mass index			0.688
Underweight	1 (7.7%)	2 (15.4%)	
Normoweight	6 (46.2%)	6 (46.2%)	
Pre-obesity	3 (23.1%)	4 (30.8%)	
Obesity	3 (23.1%)	1 (7.7%)	
DM type			0.234
Insulin-dependent	9 (69.2%)	6 (46.2%)	
Non-insulin-dependent	4 (30.8%)	7 (53.8%)	
Wagner grades			0.645
2	10 (76.9%)	9 (69.2%)	
3	2 (15.4%)	4 (30.8%)	
4	1 (7.7%)	0 (0.0%)	
Complicating bacteria			0.539
Significant growth	2 (15.4%)	1 (7.7%)	
No significant growth	11 (84.6%)	12 (92.3%)	
Ulcer location			0.105
Cruris	3 (23.1%)	5 (38.5%)	
Plantar	5 (38.5%)	1 (7.7%)	
Abdomen	1 (7.7%)	0 (0.0%)	
Sacrum	1 (7.7%)	0 (0.0%)	
Pedis	3 (23.1%)	7 (53.8%)	
Baseline wound area (mm ²)	901.6	1542.3	0.505

DM = diabetes mellitus.

Table 2 | Comorbidities of the study subjects.

Comorbidities	Treatment group (n = 13)	Control group (n = 13)	p
CVD	1 (7.7%)	6 (46.2%)	0.423
AKI	1 (7.7%)	2 (15.4%)	
CKD	3 (23.1%)	2 (15.4%)	
Hypertension	6 (46.2%)	4 (30.8%)	
Pleural effusion	1 (7.7%)	0 (0.0%)	
PAD	6 (46.2%)	2 (15.4%)	
Anemia	2 (15.4%)	1 (7.7%)	
Dyslipidemia	3 (23.1%)	2 (15.4%)	
Hyperuricemia	5 (38.5%)	0 (0.0%)	
Electrolyte imbalance	2 (15.4%)	0 (0.0%)	
Dementia	1 (7.7%)	0 (0.0%)	
Hypoalbuminemia	2 (15.4%)	0 (0.0%)	
Hypercoagulopathy	1 (7.7%)	0 (0.0%)	
CLI	0 (0.0%)	3 (23.1%)	
DVT	1 (7.7%)	1 (7.7%)	
Stroke	0 (0.0%)	2 (15.4%)	
Bullous pemphigoid	0 (0.0%)	1 (7.7%)	
Parkinson	0 (0.0%)	1 (7.7%)	
Pneumonia	0 (0.0%)	1 (7.7%)	

AKI = acute kidney injury, CKD = chronic kidney disease, CLI = critical limb ischemia, CVD = cardiovascular disease, DVT = deep vein thrombosis, PAD = peripheral arterial disease.

Note. Comorbidities refer to conditions other than the primary disease; subjects may present with more than one comorbidity.

Interrater agreement for wound size assessment

To ensure reliability of ulcer size measurement, a kappa test was performed between two independent assessors. The interrater reliability was excellent, with κ values of 0.92 at baseline (H0), 0.96 at day 7 (H7), 1.00 at day 14 (H14), and 1.00 at day 21 (H21), indicating very strong agreement (Table 3).

Table 3 | Interrater reliability of wound size.

Observer	κ
H0	0.92
H7	0.96
H14	1.00
H21	1.00

H = day.

Differences in ulcer surface area reduction between groups

The analysis of ulcer surface area reduction was conducted by comparing changes between H7 and H0, H14 and H0, and H21 and H0. We also compared the percentage of wound reduction. Significant differences were observed in $\Delta H7$ and $\Delta H14$ between the treatment and control groups; in addition, $\Delta H21$ showed a difference in wound size but did not reach statistical significance. The mean reduction in ulcer surface area at $\Delta H7$ was 570.7 mm² in the treatment group versus 71.9 mm² in the control group (95% confidence interval [CI] 163.6–944.7 mm²; effect size = 0.75; $p = 0.002$). At $\Delta H14$, the mean reduction was 723.0 mm² in the treatment group compared to 146.4 mm² in the control group (95% CI 147.1–1,135.6 mm²; effect size = 0.70; $p = 0.004$). At $\Delta H21$, reductions were 806.0 mm² in the treatment group and 300.3 mm² in the control group (95% CI –3.8 to 1,138.4 mm²; effect size = 0.43; $p = 0.106$; Fig. 1). Notably, two subjects each in the treatment and control groups achieved complete ulcer closure. When expressed as percentage reduction relative to baseline, the treatment group showed a greater relative reduction than the control group at day 7 (66.4% vs. 16.8%; 95% CI 32.3%–63.7%; effect size = 0.85; $p < 0.001$), day 14 (83.3% vs. 27.8%; 95% CI 39.1%–69.0%; effect

size = 0.85; $p < 0.001$), and day 21 (92.7% vs. 41.5%; 95% CI 33.6%–66.2%; effect size = 0.72; $p = 0.002$; Fig. 2). Wound progress in the treatment and control groups can be seen in Figures 3 and 4.

Discussion

This study demonstrated a significantly greater wound size reduction in the treatment group than in the control group at day 7 and day 14. Although the difference in absolute ulcer area was not statistically significant at day 21, the relative reduction from baseline remained significantly greater in the treatment group at all three time points, indicating that the early healing advantage was sustained through day 21. Our study results indicate that the polypeptide gel was superior to the hydrocolloid gel containing pectin and sodium carboxymethylcellulose, particularly during the early phases of wound healing. This finding supports our hypothesis that topical application of polypeptide gel accelerates ulcer size reduction in patients with DU. The results are consistent with previous studies. Taowen et al. reported that polypeptides containing 81 amino acids improved healing outcomes in DU patients (17), and Xing et al. demonstrated that injectable polypeptide hydrogel enhanced wound closure in streptozotocin-induced diabetic mice through angiogenesis (19). Likewise, Sun et al. showed that the short-chain peptide RL-QN15 promoted re-epithelialization and angiogenesis in diabetic wounds, partly by upregulating vascular endothelial growth factor beta (VEGF- β) expression (20). In our study, the polypeptide gel formulation, primarily composed of L-arginine (7% in HPMC gel), along with other amino acids, likely

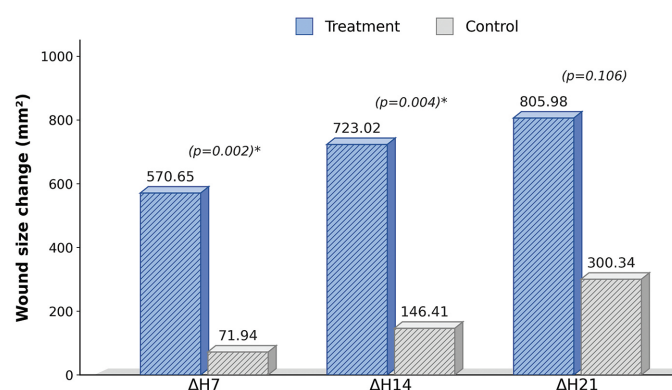


Figure 1 | Comparison of wound size changes (mm²) between the treatment and control groups.

$\Delta H7$ = change in ulcer area from baseline to day 7, $\Delta H14$ = change from baseline to day 14, $\Delta H21$ = change from baseline to day 21.

* = statistically significant with the Mann-Whitney test, data presented as mean $\pm$ standard deviation.

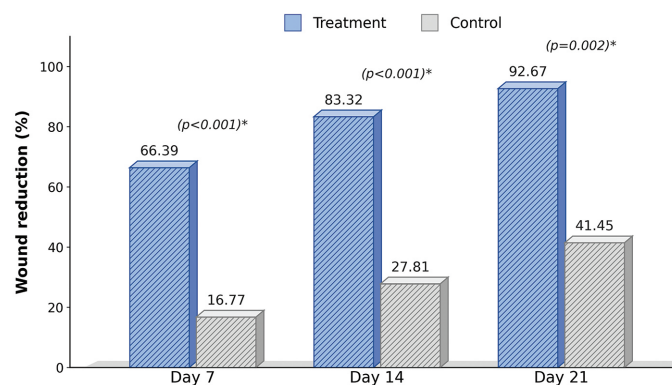


Figure 2 | Comparison of wound size reduction (%) between the treatment and control groups.

* = statistically significant with the Mann-Whitney test, data presented as mean $\pm$ standard deviation.

provided synergistic wound-healing benefits.

Delayed wound healing in DU is multifactorial, mainly driven by hyperglycemia, oxidative stress, neuropathy, and impaired angiogenesis (21–23). Chronic hyperglycemia induces excessive

reactive oxygen species (ROS) formation, advanced glycation end-product accumulation, endothelial dysfunction, and impaired nitrogen oxide (NO) bioavailability, leading to persistent inflammation, ischemia, and poor remodeling (24–26). Neuropathy ex-

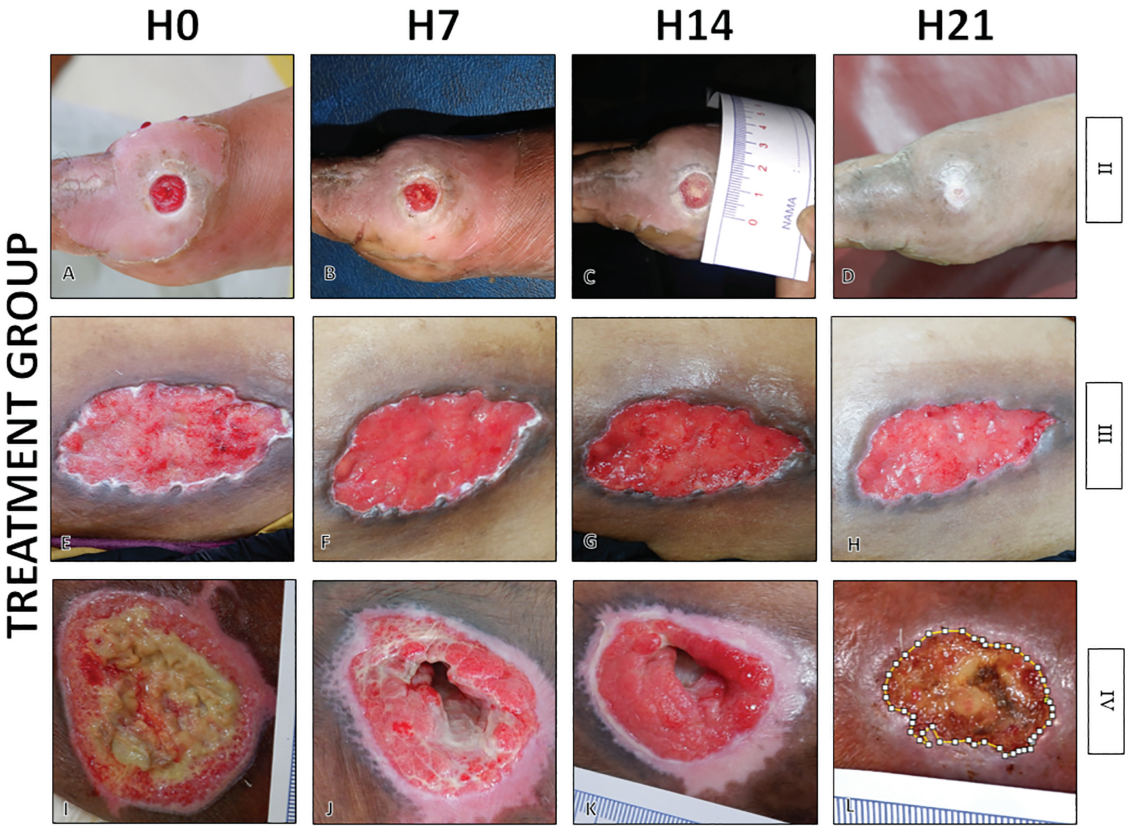


Figure 3 | Wound progress in the treatment group.
H0 = baseline (day 0), H7 = day 7, H14 = day 14, H21 = day 21.

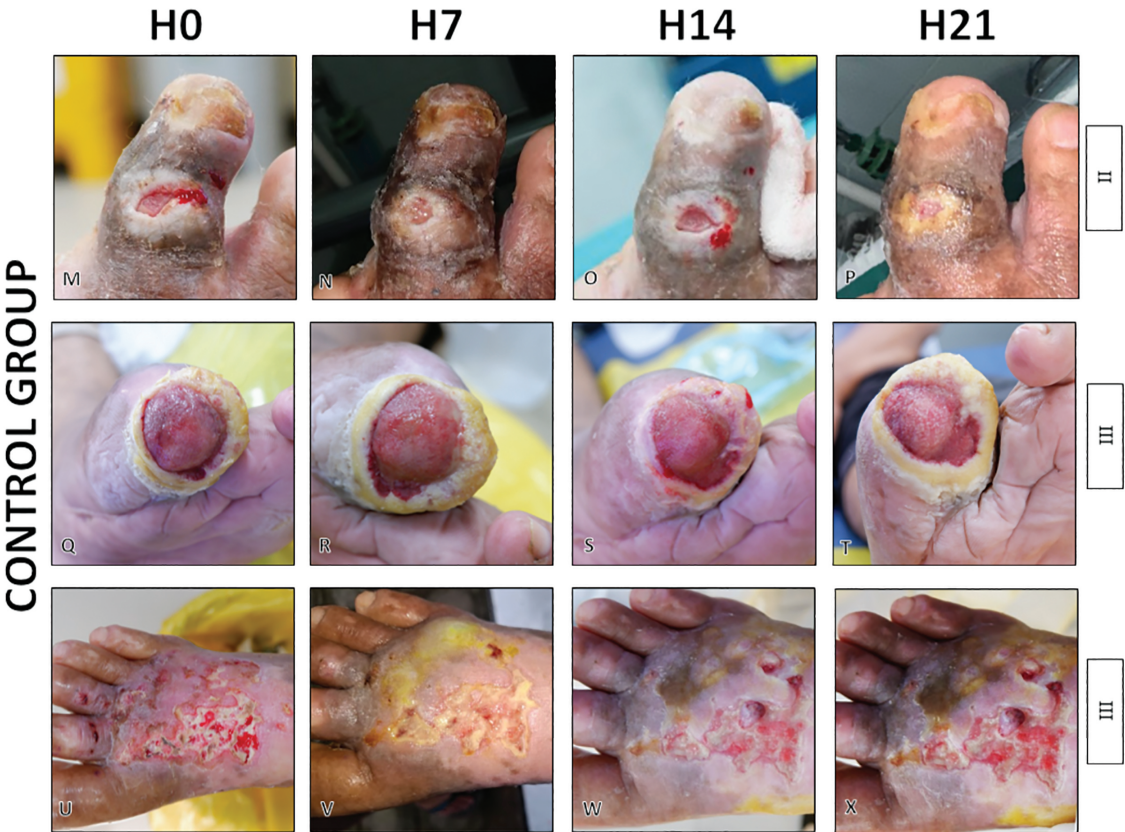


Figure 4 | Wound progress in the control group.
H0 = baseline (day 0), H7 = day 7, H14 = day 14, H21 = day 21.

acerbates these conditions through sensory loss, biomechanical changes, and reduced immune responses (27). Against this background, polypeptides may exert therapeutic effects by enhancing angiogenesis, reducing inflammation, providing antimicrobial action, and stimulating fibroblast and keratinocyte proliferation (28, 29). L-arginine serves as a substrate for NO synthesis, thereby promoting vasodilation, oxygen delivery, and collagen deposition (30). Other amino acids such as glutamine, alanine, and phenylalanine may support anti-inflammatory processes and angiogenesis. In addition, antimicrobial peptides (AMPs) derived from amino acids such as arginine are effective in reducing infection risk with minimal antimicrobial resistance (31, 32).

The greater early response in the polypeptide treatment group was most evident at day 7, when the inflammatory phase predominates in DU. The treatment group showed greater reduction in ulcer size. We hypothesize that this may reflect anti-inflammatory and antimicrobial properties of polypeptides reported in preclinical work, such as downregulation of interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)- α , and induction of IL-4 and IL-10; however, these mediators were not measured in this study, and so any such mechanism remains speculative. At day 14, the treatment group again demonstrated greater wound reduction, a pattern that could be consistent with accelerated angiogenesis, fibroblast proliferation, and collagen deposition during the proliferative phase, although these processes were likewise not directly assessed. At day 21, the absolute reduction in ulcer area remained greater in the treatment group but did not reach statistical significance. This loss of significance in absolute terms most plausibly reflects the larger and markedly more variable baseline wounds in the control group, in which a few substantially larger ulcers inflated the variance of absolute change and reduced statistical power, rather than a true convergence of healing between the groups. Consistent with this interpretation, when healing was expressed as the percentage reduction from baseline, which normalizes for initial ulcer size, the treatment group retained significantly greater wound closure at day 21, representing a large effect. Residual between-group differences in absolute healing at this stage may additionally be influenced by systemic factors such as poor glycemic control, impaired vascularization, and diabetic neuropathy (33–35). Several studies have reported that peptide-based therapies exert their strongest effects during the inflammatory and proliferative phases of wound healing, and that the magnitude of the absolute between-group difference may narrow during the remodeling phase (20, 30). Moreover, control treatments such as hydrocolloid gels also provide a favorable healing environment that can accelerate wound closure in later stages (36). Systemic factors, including glycemic control and vascular comorbidities, further influence outcomes in DU (33, 34). Finally, the limited sample size of this trial may have reduced statistical power to detect a difference in absolute area at day 21, as similarly noted in other wound-healing studies (11). Nevertheless, the relative reduction from baseline remained significantly greater in the treatment group at day 21, indicating that the treatment advantage was maintained when differences in baseline ulcer size were taken into account.

The control group received a hydrocolloid gel consisting of pectin and sodium carboxymethylcellulose, a dressing that has been widely applied for chronic wound management. It has been shown to provide a moist healing environment, promote angiogenesis, and facilitate autolytic debridement (36). Our findings suggest that polypeptide gel may offer a greater early wound-healing benefit at a substantially lower cost (Rp 13,500 / \$0.82 vs.

Rp 172,600 / \$10.68 per 30 g), supporting its potential as a cost-effective adjunctive option for DU management that warrants confirmation in larger trials. Importantly, no adverse events were reported with polypeptide gel use, consistent with previous reports of its favorable safety profile, although the small sample limits the precision of this safety estimate. However, high concentrations of free amino acids have been associated with cytotoxicity, underscoring the need for careful formulation (37).

However, several limitations should be acknowledged. First, this was a small, single-center, exploratory trial without a prior power calculation. It was therefore likely underpowered to detect between-group differences at later time points, and the non-significant result at day 21 should be interpreted as inconclusive rather than as evidence of no effect. Second, several baseline wound and patient characteristics that may influence healing—including ulcer duration, glycemic control, vascular status, infection status, and off-loading strategy—were not fully captured or reported, which limits the ability to exclude residual confounding. These variables should be measured and reported in future studies. Third, between-group comparisons relied on the Mann–Whitney U test applied separately at each time point rather than a repeated-measures or mixed-effects model that would account for the within-subject correlation across visits. A longitudinal modeling approach is recommended for subsequent trials. Finally, angiographic examination was not performed to evaluate vascular involvement, which could influence wound-healing outcomes; future studies should consider angiographic evaluation to better assess the role of vascular status in wound repair.

Conclusions

In this small exploratory randomized controlled trial, topical 7% polypeptide gel was associated with a significantly greater relative reduction in DU surface area than hydrocolloid gel throughout the 21-day observation period. When healing was expressed as the percentage of wound reduction from baseline, the treatment group consistently and significantly achieved greater wound closure at every timepoint, with each comparison representing a large effect size. This sustained advantage in relative healing, together with the gel being well tolerated and substantially less expensive than the comparator, suggests that it may be a promising low-cost adjunctive option for DU management. Nevertheless, because of the small sample size and exploratory design, and given that the corresponding difference in absolute area change did not reach statistical significance at day 21, these findings should be regarded as preliminary. Larger, adequately powered, longer-term trials with detailed baseline characterization are needed before any firm clinical recommendation can be made.

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References

- Kumar A, Arora A, Sharma P, Anikhindi SA, Bansal N, Singla V. Is diabetes mellitus associated with mortality and severity of COVID-19? A meta-analysis. *Diabetes Metab Syndr*. 2020;14:535–45.
- Raja JM, Maturana MA, Kayali S, Khouzam A, Efeovbokhan N. Diabetic foot ulcer: a comprehensive review of pathophysiology and management modalities. *World J Clin Cases*. 2023;11:1684–93.
- Chang M, Nguyen TT. Strategy for treatment of infected diabetic foot ulcers. *Acc Chem Res*. 2021;54:1080–93.
- Zhang P, Lu J, Jing Y, Tang S, Zhu D, Bi Y. Global epidemiology of diabetic foot ulceration: a systematic review and meta-analysis. *Ann Med*. 2017;49:106–16.
- Yunir E, Tahapary DL, Tarigan TJE, Harbuwono DS, Oktavianda YD, Kristanti M. Non-vascular contributing factors of diabetic foot ulcer severity in national referral hospital of Indonesia. *J Diabetes Metab Disord*. 2021;20:805–13.
- Hatem MA, Kamal DM, Yusuf KA. Diabetic foot limb threatening infections: case series and management review. *Int J Surg Open*. 2022;48:100568.
- Schul MW, Melin MM, Keaton TJ. Venous leg ulcers and prevalence of surgically correctable reflux disease in a national registry. *J Vasc Surg Venous Lymphat Disord*. 2023;11:511–6.
- Hernández-Martínez-Esparza E, Santesmases-Masana R, Román E, Abades Porcel M, Torner Busquet A, Berenguer Pérez M, et al. Prevalence and characteristics of older people with pressure ulcers and legs ulcers, in nursing homes in Barcelona. *J Tissue Viability*. 2021;30:108–15.
- Rosinha P, Saraiva M, Ferreira L, Garrido S, Carvalho A, Freitas C. A retrospective cohort study on diabetic foot disease: ascertainment of ulcer locations by age group. *Cureus*. 2022;14:e28189.
- Gupta S, Singh G, Chanda A. Prediction of diabetic foot ulcer progression: a computational study. *Biomed Phys Eng Express*. 2021;7:065020.
- Miraj SS, Kurian SJ, Rodrigues GS, Saravu K, Rao M, Raychaudhuri SP, et al. Phototherapy in diabetic foot ulcers: a promising strategy for effective wound healing. *J Am Nutr Assoc*. 2023;42:295–310.
- Glover K, Stratakos AC, Varadi A, Lamprou DA. 3D scaffolds in the treatment of diabetic foot ulcers: new trends vs conventional approaches. *Int J Pharm*. 2021;599:120423.
- Popescu V, Cauni V, Petrutescu MS, Rustin MM, Bocai R, Turculet CR. Chronic wound management: from gauze to homologous cellular matrix. *Biomedicines*. 2023;11:2457.
- Arribas-López E, Zand N, Ojo O, Snowden MJ, Kochhar T. The effect of amino acids on wound healing: a systematic review and meta-analysis on arginine and glutamine. *Nutrients*. 2021;13:2498.
- Luo Y, Song Y. Mechanism of antimicrobial peptides: antimicrobial, anti-inflammatory and antibiofilm activities. *Int J Mol Sci*. 2021;22:11401.
- Church DD, Hirsch KR, Park S, Kim IY, Gwin JA, Pasiakos SM, et al. Essential amino acids and protein synthesis: insights into maximizing the muscle and whole-body response to feeding. *Nutrients*. 2020;12:3717.
- Taowen P, Shuyuan F, Xiaoli S, Annan W, Feng Q, Yizhong Z. Study on the action mechanism of the peptide compounds of Wuguchong on diabetic ulcers, based on UHPLC-Q-TOF-MS, network pharmacology and experimental validation. *J Ethnopharmacol*. 2022;288:114974.
- Febriani D, Mulianto N, Kusumawardani A, Julianto I, Wardhani IAP. Optimal dose of gell peptide for diabetic wound healing. *Syntax Lit J Ilm Indones*. 2023;8:4453–62.
- Xing C, Hou L, Sun C, Chen H, Li Y, Li L. Injectable polypeptide/chitosan hydrogel with loaded stem cells and rapid gelation promoting angiogenesis for diabetic wound healing. *Int J Biol Macromol*. 2025;306:141578.
- Sun D, Guo K, Liu N, Li Y, Li Y, Hu Y. Peptide RL-QN15 promotes wound healing of diabetic foot ulcers through p38 mitogen-activated protein kinase and smad3/miR-4482-3p/vascular endothelial growth factor B axis. *Burns Trauma*. 2023;11:tkado35.
- Davis FM, Kimball A, Boniakowski A, Gallagher K. Dysfunctional wound healing in diabetic foot ulcers: new crossroads. *Curr Diab Rep*. 2018;18:2.
- Deng L, Du C, Song P, Chen T, Rui S, Armstrong DG, et al. The role of oxidative stress and antioxidants in diabetic wound healing. *Oxid Med Cell Longev*. 2021;2021:8852759.
- Li J, Yan H, Xiang R, Yang W, Ye J, Yin R. ATP secretion and metabolism in regulating pancreatic beta cell functions and hepatic glycolipid metabolism. *Front Physiol*. 2022;13:918042.
- Kim J. The pathophysiology of diabetic foot: a narrative review. *J Yeungnam Med Sci*. 2023;40:328–34.
- González P, Lozano P, Ros G, Solano F. Hyperglycemia and oxidative stress: an integral, updated and critical overview of their metabolic interconnections. *Int J Mol Sci*. 2023;24:9352.
- Huang F, Lu X, Yang Y, Yang Y, Li Y, Kuai L. Microenvironment-based diabetic foot ulcer nanomedicine. *Adv Sci*. 2023;10:2203308.
- McDermott K, Fang M, Boulton AJM, Selvin E, Hicks CW. Etiology, epidemiology, and disparities in the burden of diabetic foot ulcers. *Diabetes Care*. 2023;46:209–21.
- Aquib M, Sharma T, Giri VP, Rao A. Peptides in chronic wound healing: fighting infections and facilitating diabetic wound management. *J Drug Deliv Sci Technol*. 2025;105:106599.
- Md Fadilah NI, Shahabudin NA, Mohd Razif RA, Sanyal A, Ghosh A, Baharin KI, et al. Discovery of bioactive peptides as therapeutic agents for skin wound repair. *J Tissue Eng*. 2024;15:20417314241280359.
- Arana V, Paz Y, González A, Méndez V, Méndez JD. Healing of diabetic foot ulcers in L-arginine-treated patients. *Biomed Pharmacother*. 2004;58:588–97.
- Malone-Povolny MJ, Maloney SE, Schoenfish MH. Nitric oxide therapy for diabetic wound healing. *Adv Healthc Mater*. 2019;8:1801210.
- Wu G, Meininger CJ, McNeal CJ, Bazer FW, Rhoads JM. Role of L-arginine in nitric oxide synthesis and health in humans. *Adv Exp Med Biol*. 2021;1332:167–87.
- Xiang J, Wang S, He Y, Xu L, Zhang S, Tang Z. Reasonable glycemic control would help wound healing during the treatment of diabetic foot ulcers. *Diabetes Ther*. 2019;10:95–105.
- Wang K, Wang Y, Shi W, Shen K, Tao K, Ling R, et al. Diagnosis and treatment of diabetic foot ulcer complicated with lower extremity vasculopathy: consensus recommendation from the Chinese Medical Association (CMA), Chinese Medical Doctor Association (CMDA). *Diabetes Metab Res Rev*. 2024;40:e3776.
- Soewondo P. *Hidup sehat dengan diabetes*. 3rd ed. Jakarta: Pusat Diabetes dan Lipid RSCM-FK UI; 2017. Indonesian.
- Kanikireddy V, Varaprasad K, Jayaramudu T, Karthikeyan C, Sadiku R. Carboxymethyl cellulose-based materials for infection control and wound healing: a review. *Int J Biol Macromol*. 2020;164:963–75.
- Giliomee J, Toit LC, Kumar P, Klumperman B, Choonara YE. Evaluation of composition effects on the physicochemical and biological properties of polypeptide-based hydrogels for potential application in wound healing. *Polymers (Basel)*. 2021;13:1828.