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Research Article

A Randomized Controlled Trial: Effects of Alginate Gel in the Treatment of Diabetic Foot Ulcers

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Abstract

Background: Diabetic Foot Ulcers (DFUs) are among the many complications associated with diabetes over time. Therefore, it is particularly urgent and necessary to study the intrinsic causes of foot ulcer healing, optimize existing treatment protocols further, and actively explore effective early prevention and treatment.

Methods: The study was a randomized controlled trial in which participants were randomized (1:1) to either the Alginate Care or the placebo arm. The study treatment with Alginate Care or placebo gel started at the baseline visit. The study gel (Alginate Care group) or matrix-matched placebo was applied directly to the wound bed using aseptic technique to form a complete coverage layer and extend a 1-cm coated area to the surrounding healthy skin, and after the gel had cured to form a pliable protective film, an inert standardized dressing was superimposed for secondary coverage, with dressing change intervals adjusted according to the amount of wound exudate to ensure that standardized care procedures were carried out at least 2-3 times per week. In patients with multiple wounds, the largest ulcer≥2 cm from other lesions was selected as the target wound. The primary outcome was wound closure (100% epithelialization of the wound, no drainage, no suture material, no wound dressing or adjuvant required).

Results: After 12 weeks of treatment, 7 of 40 wounds (17.5%) healed in the Alginate Care group compared with 2 of 40 (7.5%) in the placebo group.

Conclusion: In conclusion, the findings of this study provide strong evidence supporting the efficacy of Alginate Care in promoting wound healing. The significant improvements observed across multiple outcome measures suggest that Alginate Care has the potential to become a standard-of-care in wound management, offering hope for better patient outcomes and a new direction for wound care research and development.

Keywords: Alginate Gel; Bates-Jensen score; Diabetes complications; Diabetic foot ulcer; Randomized controlled trial,

Introduction

Diabetic Foot Ulcers (DFUs) are among the many complications associated with diabetes over time. Even if the ulcer is relatively shallow (UT1A, Wagner Grade 1), patients are at risk of amputation if Standard of Care (SOC) measures are ineffective [1]. Foot ulcers form and prognosis result from the interaction and joint action of many factors closely related to neurological dysfunction, extravascular lesions, and infectious conditions.[2] Therefore, it is particularly urgent and necessary to study the intrinsic causes of foot ulcer healing, optimize existing treatment protocols further, and actively explore effective early prevention and treatment. Wound healing is a finely tuned process involving various cells, including epidermal, dermal, endothelial, and immune cells, and can be divided into overlapping phases.[3] At the onset of the injury, the wound enters an inflammatory phase, during which

immune cells infiltrate the wound site; at the same time, cells from the epidermis and dermis begin to proliferate and migrate to the wound bed to fill the wound defect.[4] This is followed by a proliferative phase in which epidermal and dermal cells proliferate and migrate, further contributing to wound closure.[5] This is followed by the remodeling phase, where dermal cells undergo extracellular matrix deposition and remodeling.[6] Unlike acute wounds, the healing process of Diabetic Foot Ulcers (DFUs) and other chronic wounds is not a step-by-step linear progression from one stage to the next, as is the case with acute wounds.[7] The main characteristic of such chronic wounds is the presence of ongoing chronic inflammation [8].

Various biomaterials, including hydrogels, are used in relevant therapeutic areas and can produce significant therapeutic effects.[9] These biomaterials provide a suitable and supportive environment for the cells, which helps the cells survive and precisely regulates the release of bioactive factors.[10] Through this mechanism of action, the therapeutic efficacy of Mesenchymal Stem Cells（MSCs）can be effectively enhanced.[11] Further, this application can improve the overall wound healing status in all aspects and enhance the healing effect. Alginate dressings have been successfully marketed and used in wound care since the 1980s, when Sorbsan was introduced as a treatment option for diabetic and nutritional ulcers.[12] Since then, many different brands of dressings have been produced and commercialized. Today's dressings are available in various shapes and sizes, designed to meet multiple needs. Alginate dressings are suitable for the management of superficial wounds and lacerations, as well as for the treatment of cavities that often occur during the development of bedsores [13]. This study aimed to explore the role of alginate gel in diabetic foot healing.

Methods

Study Design

The study was a randomized controlled trial in which participants were randomized (1:1) to either the Alginate Care or the placebo arm. Randomization is done by pre-prepared sealed random envelopes containing a unique three-digit random number, pre-assigned to one of the treatment groups. Figure 1 provides a flowchart of the recruitment and allocation of study participants. All participants signed an informed consent form, and the Institutional Review Boards of all participating institutions approved the study (2024-013-01).

Subjects

The main inclusion criteria for participation in the study were Diabetic patients aged 18 years or older with unhealed wounds, uninfected DFUs with a Wagner grade <3 (no osteomyelitis), and 0.5-12 cm2. Therefore, chronic diabetic foot wounds with adequate wound pre-treatment and post-surgical amputation wounds below the upper ankle were eligible for inclusion in the study. Exclusion criteria consisted of four components: possible noncompliance with study requirements, presence of necrotic tissue that could not be debrided or required amputation, exposed vessels that could not be covered or bleeding that interfered with hemodynamics (especially posterior tibial and dorsalis pedis arteries), and severely impaired coagulation.

Interventions

The study treatment with Alginate Care or placebo gel started at the baseline visit. The study gel (Alginate Care group) or matrix-matched placebo was applied directly to the wound bed using aseptic technique to form a complete coverage layer and extend a 1-cm coated area to the surrounding healthy skin, and after the gel had cured to form a pliable protective film, an inert standardized dressing was superimposed for secondary coverage, with dressing change intervals adjusted according to the amount of wound exudate to ensure that standardized care procedures were carried out at least 2-3 times per week. In patients with multiple wounds, the largest ulcer≥2 cm from other lesions was selected as the target wound.

Outcomes

The primary outcome was wound closure (100% epithelialization of the wound, no drainage, no suture material, no wound dressing or adjuvant required). The maximum study treatment period was 12 weeks. Secondary endpoints included (1) reduction in wound area. (2) at least 50% and 75% wound closure. (3) pain scores at 12 weeks. (4) Improvement in wound status as assessed by the BWAT score and the Wagner Ulcer Classification. (5) occurrence of adverse events.

Statistical Analysis

Sample Size: Based on previous data, the wound closure rate at week 10 was expected to be 50% in the placebo group and 75% in the Alginate Care group. Thirty patients per arm were needed to rule out the null hypothesis at $\alpha = 0.05$ and efficacy of 0.80. The dropout rate was 10%, so a total of 80 patients, 40 in each study arm, were needed.

Statistical Methods: Data were reported as the mean ± Standard Deviation (SD). Statistical analyses were performed using SPSS Version 26 (IBM Corp, Armonk, NY, USA). A paired t-test was used to compare the blood glucose levels before and after the intervention. Two independent sample t-tests were used to compare baseline and intervention data between groups. For count data, frequencies and percentages were presented. Two-way ANOVA was used to compare multiple groups. $p < 0.05$ was considered an indication of statistically significant differences.

Result

Baseline Characteristics of Participants

The flow of participants is illustrated in Figure 1. Initially, 100 individuals were evaluated at baseline, among which 90 fulfilled the inclusion criteria and consented to enroll in the study. These participants were then randomly assigned in a 1:1 ratio to two groups: the Alginate Care group and the placebo group. In the Alginate Care group, two participants refused cooperation and three became unreachable, leading to their withdrawal from the study. Three participants exhibited poor compliance in the placebo group, and two lost interest, resulting in their dropout. In the end, there were 40 participants in each group. As demonstrated in Table 1, all baseline indicators were comparable among the two groups, with no significant differences observed.

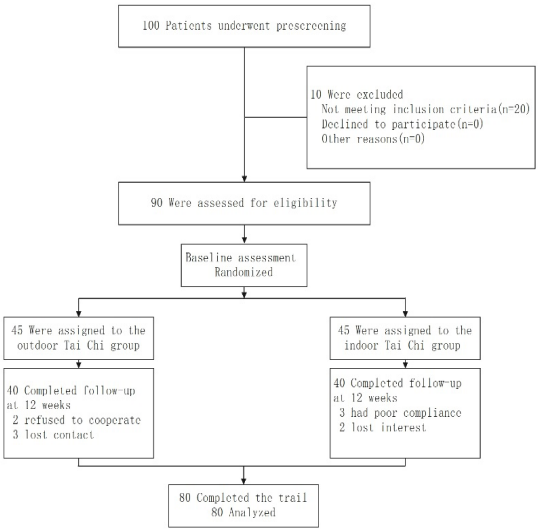

Figure 1: Flow diagram of the study participants.

Variables	AlginateCare group	placebo group	P-value
	n (%) or M±SD	n (%) or M±SD	
Age, years	64.9 ± 7.3	65.5 ± 6.9	0.517
BMI (kg/m2)	27.7 ± 3.8	27.1 ± 3.3	0.412
HbA1C (%)	7.9 ± 2.0	8.0 ± 2.1	0.388
Education			
Primary	4 (10.0)	3 (7.5)	0.451
Secondary	20 (50.0)	18 (45.0)	
High school	8 (20.0)	10 (25.0)	
University or above	8 (20.0)	9 (22.5)	
Alcohol drinking behaviora			
Yes	2 (5.0)	3 (7.5)	0.886
No	38 (95.0)	37 (92.5)	
Smoker	10 (25.0)	12 (30.0)	0.282
Duration of disease (years)	10.5 ± 3.2	11.4 ± 4.0	0.331
Number of comorbidities	2 ± 1	2 ± 1	0.638
Baseline wound area size (cm2)	2.86 ± 3.22	2.77 ± 2.57	0.337
Baseline Bates-Jensen score	37.9 ± 5.0	38.4 ± 4.2	0.285
Wound duration (months)	2.5 ± 3.3	2.1 ± 3.0	0.437

a Self-reported as drinking 3 or more alcoholic drinks (can/bottle) per typical week.

BMI = body mass index; HbA1c = glycosylated hemoglobin;

Table 1: Baseline Characteristics of the Participants.

Primary Outcomes

After 12 weeks of treatment, 7 of 40 wounds (17.5%) healed in the AlginateCare group compared with 2 of 40 (7.5%) in the placebo group (Table 2).

Secondary Outcomes

The Alginate Care group significantly outperformed the placebo group on key wound healing metrics, with a 10% improvement in complete healing (17.5% vs. 7.5%, P=0.021), a 32.5% improvement in healing above 75% (57.5% vs. 25%, P=0.013), and a doubling of wound area reduction (70.2% vs. 34.8%, P= 0.016) (Table 2). The Bates-Jensen score decreased up to three times as much as in the placebo group (-31.1% vs -10.6%, P=0.022), suggesting multidimensional improvement of the wound regarding exudate, necrotic tissue, and margin status (Table 2). Alginate Care has shown significant efficacy in promoting wound healing. This finding has important implications for developing more effective wound care products or treatments that may help reduce wound healing time, minimize the risk of infection, and improve patients' quality of life (Figure 2).

	AlginateCare group	placebo group	P-value
	n (%) or M±SD	n (%) or M±SD	
Complete wound closure: patients with event/all	7 (17.5)	3 (7.5)	0.021
75% wound closure: patients with event/all	23 (57.5)	10 (25.0)	0.013
50% wound closure: patients with event/all	4 (10.0)	8 (20.0)	0.037
Relative reduction in wound surface area (%)	70.2 ± 6.6	34.8 ± 7.1	0.016
Bates-Jensen Wound Assessment Relative change from baseline score (%)	-31.1 ± 10.5	-10.6 ± 8.8	0.022

Table 2: Study outcomes at week 12 for AlginateCare and placebo groups.

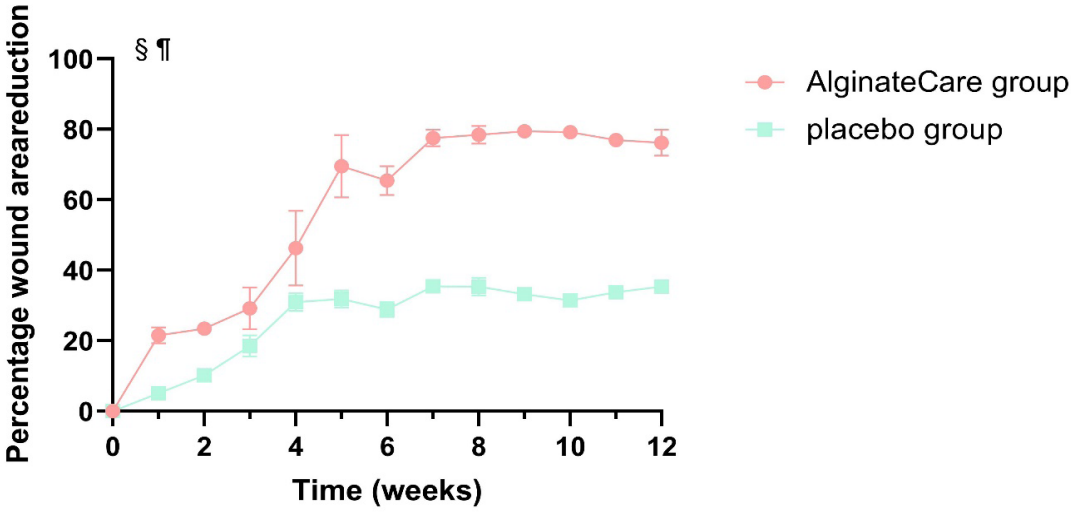

Figure 2: Weekly healing rates by treatment group.

Discussion

According to the trial's primary endpoint, a significantly higher percentage of wounds in the Alginate Care group were healed after 12 weeks. The odds of healing were more than twice as high as those of the control group. Over the past 10 years, the wound healing community has seen the emergence of many new cellular and/or tissue-based products (CPTs).[14] In this study, the difference in percent wound healing between the Alginate Care and the control groups (10%) was comparable to the difference in DFU wound severity in many other RCT studies in similar populations.[15]. Alginate is a natural polysaccharide mainly derived from brown algae.[16] It is good in biocompatibility, degradability, and water absorption, and has a wide range of applications in wound care, tissue engineering, and drug delivery.[17] Alginate gels exhibit unique advantages in the biomedical field due to their highly hydrated properties and porous microstructure, making them potentially ideal materials for numerous cutting-edge applications such as drug delivery systems, tissue engineering scaffolds, and wound healing enhancers [18].

Vascular pathology is a primary factor in developing Diabetic Foot Ulcers (DFUs).[19] In patients with T2DM, hyperglycemia exacerbates damage to the vascular endothelium.[20] This exacerbation of endothelial damage is further compounded by a reduction in anticoagulant properties, which intensifies atherosclerosis formation and progression.[21] Following the onset of atherosclerosis, atherosclerotic plaques develop, leading to significant calcium deposition within the blood vessels of affected patients, thereby influencing the pathological course of atherosclerotic plaque formation [22]. Elevated blood sugar levels in individuals with diabetes mellitus (DM) aggravate damage to the vascular endothelial layer.[23] Moreover, this condition diminishes anticoagulant functions, thereby accelerating the development and advancement of atherosclerosis.[24] As atherosclerosis progresses, it gives rise to atherosclerotic plaques, resulting in substantial calcium accumulation within patients' blood vessels, impacting the progression of atherosclerotic plaque formation [25].

In addition, people with Diabetes Mellitus (DM) often have the following conditions: narrowing of the blood vessels, the walls of which become rough and uneven, and an increase in the levels of fibrinogen and globulin. [26] The increase in fibrinogen and globulin makes the blood thicker and slows blood flow. [27] The slowing of blood flow, in turn, triggers a change in the hemodynamics of the patient's body. This change in hemodynamics further increases the risk of foot ulcers. [28] However, until a foot ulcer develops, the patient often has no conscious symptoms. It is not until the ulcer develops that the patient may notice anything. In patients with Diabetic Foot Ulcers (DFUs), the reduced blood supply to the extremity can severely impair wound healing, increasing the risk of foot lesions and infection [29].

Angiogenesis occurs in the third stage of wound healing.[30] Generating new capillaries, especially the formation of tortuous micro vessels, depends on the synergistic action of numerous factors such as Vascular Endothelial Growth factor (VEGF) and basic fibroblast growth factor.[31] Alginate delivers angiogenic growth factors and extracellular matrix directly to the wound to supplement deficiencies or normalize imbalances present in chronic wounds. [32] This process is not driven by these factors alone; the prior transient inflammatory response, as well as the rearrangement of the cytoskeleton, are also key elements that are integral to ensuring its proper progression. [33] Our clinical findings suggest that angiogenesis may be rapid, as the wound area shrinks considerably on average within the first week.

The Bates-Jensen score, a validated tool for assessing wound status across multiple dimensions including exudate, necrotic tissue, and margin status, also showed a marked improvement in the Alginate Care group. [34] The score decreased by up to three times more than in the placebo group (-31.1% vs. -10.6%, P=0.022), suggesting a multidimensional enhancement in wound healing. This comprehensive improvement is crucial as it addresses the physical aspects of wound healing and the underlying biological processes that contribute to wound progression and resolution.

Conclusion

In conclusion, the findings of this study provide strong evidence supporting the efficacy of Alginate Care in promoting wound healing. The significant improvements observed across multiple outcome measures suggest that Alginate Care has the potential to become a standard-of-care in wound management, offering hope for better patient outcomes and a new direction for wound care research and development.

References

1. Armstrong DG (2023) Diabetic Foot Ulcers: A Review. Jama 330: 62-75.
2. Dayya D (2022) Debridement of Diabetic Foot Ulcers. Adv Wound Care (New Rochelle) 11: 666-686.
3. Qiang L (2021) Keratinocyte autophagy enables the activation of keratinocytes and fibroblastsand facilitates wound healing. Autophagy 17: 2128-2143.
4. Maruyama M (2020) Modulation of the Inflammatory Response and Bone Healing. Front Endocrinol (Lausanne) 11: 386.
5. Jiang J (2024) The mechano-chemical circuit in fibroblasts and dendritic cells drives basal cell proliferation in psoriasis. Cell Rep 43: 114513.
6. Talbott HE (2022) Wound healing, fibroblast heterogeneity, and fibrosis. Cell Stem Cell 29: 1161-1180.

7. Chang M, Nguyen TT (2021) Strategy for Treatment of Infected Diabetic Foot Ulcers. Acc Chem Res 54: 1080-1093.

8. Wilkinson HN, Hardman MJ (2020) Wound healing: cellular mechanisms and pathological outcomes. Open Biol 10: 200223.

9. Ho TC (2022) Hydrogels: Properties and Applications in Biomedicine. Molecules 27.

10. Golebiowska AA (2024) Decellularized extracellular matrix biomaterials for regenerative therapies: Advances, challenges and clinical prospects. Bioact Mater 32: 98-123.

11. Liu J (2022) Mesenchymal stem cells and their microenvironment. Stem Cell Res Ther 13: 429.

12. Ahmed A, Getti G, Boateng J (2021) Medicated multi-targeted alginate-based dressings for potential treatment of mixed bacterial-fungal infections in diabetic foot ulcers. Int J Pharm 606: 120903.

13. McDermott ER, Bowers Z, Nuelle JA (2022) The Application of Hyaluronic Acid/Alginate Sheet to Flexor Pollicis Longus Tendon Repair to Prevent Adhesion Formation: A Second Look. Cureus 14: e33147.

14. Sen CK (2023) Human Wound and Its Burden: Updated 2022 Compendium of Estimates. Adv Wound Care (New Rochelle) 12: 657-670.

15. Zhou DR (2021) The effectiveness and safety of recombinant human growth hormone combined with alginate dressing in the treatment of diabetic foot ulcer: A protocol for systematic review and meta-analysis. Medicine (Baltimore) 100: e23984.

16. Anjana K, Arunkumar K (2024) Brown algae biomass for fucoxanthin, fucoidan and alginate; update review on structure, biosynthesis, biological activities and extraction valorisation. Int J Biol Macromol 280: 135632.

17. Peng W (2022) Recent progress of collagen, chitosan, alginate and other hydrogels in skin repair and wound dressing applications. Int J Biol Macromol 208: 400-408.

18. Zhang M, Zhao X (2020) Alginate hydrogel dressings for advanced wound management. Int J Biol Macromol 162: 1414-1428.

19. Deng H (2023) Mechanisms of diabetic foot ulceration: A review. J Diabetes 15: 299-312.

20. Alzamil NM (2020) Suppression of type 2 diabetes mellitus-induced aortic ultrastructural alterations in rats by insulin: an association of vascular injury biomarkers. Ultrastruct Pathol 44: 316-323.

21. Gorzelak-Pabis P (2021) Rivaroxaban protects from the oxysterol-induced damage and inflammatory activation of the vascular endothelium. Tissue Barriers 9: 1956284.

22. Pedro-Botet J, Climent E, Benaiges D (2020) Atherosclerosis and inflammation. New therapeutic approaches. Med Clin (Barc) 155: 256-262.

23. Yang DR (2024) Endothelial dysfunction in vascular complications of diabetes: a comprehensive review of mechanisms and implications. Front Endocrinol (Lausanne) 15: 1359255.

24. Espinola-Klein C (2022) When and How to Combine Antiplatelet and Anticoagulant Drugs? Hamostaseologie 42: 73-79.

25. Villa-Bellosta R (2024) Vascular Calcification: A Passive Process That Requires Active Inhibition. Biology (Basel) 13.

26. Jin K (2025) The correlation between the atherogenic index of plasma and the severity of coronary artery disease in acute myocardial infarction patients under different glucose metabolic states. Sci Rep 15: 6128.

27. Udovenko A (2023) Formation and elimination of soluble fibrin and D-dimer in the bloodstream. Croat Med J 64: 421-429.

28. Tran MM, Haley MN (2021) Does exercise improve healing of diabetic foot ulcers? A systematic review. J Foot Ankle Res 14: 19.

29. Aitcheson SM (2021) Skin Wound Healing: Normal Macrophage Function and Macrophage Dysfunction in Diabetic Wounds. Molecules 26.

30. Chen T, Wang K, Sun Z (2025) New insights into the role of ubiquitination in angiogenesis (Review). Int J Mol Med 55.

31. Tang L, Xu GT, Zhang JF (2023) Inflammation in diabetic retinopathy: possible roles in pathogenesis and potential implications for therapy. Neural Regen Res 18: 976-982.

32. Niu X (2024) ZIF-8-modified hydrogel sequentially delivers angiogenic and osteogenic growth factors to accelerate vascularized bone regeneration. J Control Release 374: 154-170.

33. Grada A, Phillips TJ (2022) Nutrition and cutaneous wound healing. Clin Dermatol 40: 103-113.

34. Gupta S (2023) Wound Assessment Using Bates Jensen Wound Assessment Tool in Acute Musculoskeletal Injury Following Low-Cost Wall-Mounted Negative-Pressure Wound Therapy Application. Indian J Orthop 57: 948-95K.