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Barrier Protective Effect of the Cream Consisting of a Mixture of Zinc and Silver in the Treatment of Diabetic Foot Wounds

Diyabetik Ayak Yaralarının Tedavisinde Çinko ve Gümüş Karışımından Oluşan Kremin Bariyer Koruyucu Etkisi

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ABSTRACT

Objectives: Diabetes mellitus is an endocrine disease that damages a wide variety of cell types with increased serum glucose. Diabetic foot ulcers, one of the complications of the disease, are the most well-known. These ulcers, which result in significant morbidity and mortality, affect 25% of patients with diabetes during the lifetime. Diabetic foot ulcers are a health problem due to their resistance to healing. Therefore, a new and good drug to be developed for this disease is of great importance.

Methods: In this study, a cream containing silver and zinc was applied to diabetic foot patients (n=25).

Results: The findings of this study revealed the antimicrobial properties of the application rich in silver and zinc in the diabetic foot. Significant effects on wound healing were demonstrated by follow-up at 1 week, 2 weeks, 1 month, 3 months, and 6 months. In this process, wound characteristics were evaluated based on features such as side tissue and wound depth.

Conclusion: Data stated that the cream is a therapeutic treatment tool that can be used in the clinic.

Keywords: Diabetic wound; silver; topical treatment; wound healing; zinc.

ÖZET

Amaç: Diabetes mellitus, artan serum glukozu ile çok çeşitli hücre tiplerine zarar veren endokrin bir hastalıktır. Hastalığın komplikasyonlarından biri olan diyabetik ayak ülserleri en bilinenleridir. Önemli morbidite ve mortalite ile sonuçlanan bu ülserler, diyabetli hastaların %25'ini yaşamları boyunca etkilemektedir. Diyabetik ayak ülserleri, iyileşmeye karşı dirençleri nedeniyle bir sağlık sorunudur. Bu nedenle bu hastalık için geliştirilecek yeni ve iyi bir ilaç büyük önem taşımaktadır.

Yöntem: Bu çalışmada diyabetik ayak hastalarına (n=25) gümüş ve çinko içeren krem uygulandı.

Bulgular: Bu çalışmanın bulguları, diyabetik ayakta gümüş ve çinkodan zengin uygulamanın antimikrobiyal özelliklerini ortaya koydu. Yara iyileşmesi üzerinde önemli etkiler 1 hafta, 2 hafta, 1 ay, 3 ay ve 6 ayda yapılan takiplerle gösterilmiştir. Bu süreçte yan doku ve yara derinliği gibi özelliklere göre yara özellikleri değerlendirildi.

Sonuç: Veriler, kremin klinikte kullanılabilecek bir tedavi edici tedavi aracı olduğunu belirtti.

Anahtar sözcükler: Yara iyileşmesi; gümüş; çinko; diyabetik yara; topikal tedavi.

Diabetes mellitus is an endocrine disease with serious effects on the health systems all around the world. Increased serum glucose damages a wide variety of cell types.[1] Diabetic foot ulcers are one of the well-known complications of diabetes. These ulcers are associated with significant morbidity and mortality.[2] Besides, the ulcers affect 25% of the patients with diabetes for all their lives. Diabetic foot ulcers constitute an important health problem due to resistance to recovery relating to the combination of both internal and external factors.[3] The pathophysiology of diabetic foot ulcers depends on neuropathy, trauma, and peripheral arterial occlusive disease. Once a foot ulcer emerges, the limb starts to have a high risk for invasive infection. When a vascular disease is observed, the patient is considered to have critical limb ischemia. Amputation can be applied in advanced stages.[4] Standard practices in diabetic foot ulcers include surgical debridement, exudate control dressing, vascular evaluation, and infection control.[5]

Species such as Peptostreptococcus and Bacteroides have a role in the infection of diabetic foot ulcers.[6] This infection leads to superficial cellulitis, chronic osteomyelitis, and lower extremity amputations with gangrene.[7] Staphylococcus aureus, Enterococcus faecalis, and Pseudomonas aeruginosa are among the predominant pathogens. Serious infections caused by drug-resistant organisms require broad-spectrum antimicrobials that target aggressive Gram-negative aerobes and obligate anaerobes.[8] In addition to systemic antibiotics, topical treatments such as silver and zinc are applied.

Zinc is an ion with antimicrobial and anti-inflammatory properties. The zinc can be applied topically to skin lesions.[9] It has been demonstrated that zinc can also be used in diabetic wounds.[10] In addition, silver has antibacterial effects on wounds. Silver is thought to be used for diabetic foot lesions.[11] Antimicrobial activity was observed in a study that zinc and silver were used together. This complex was well-tolerated and stimulated healthy recovery.[12]

Patients with diabetic feet were selected in this study. A cream containing silver and zinc was applied. The findings of this study demonstrated the antimicrobial properties of the application rich in silver and zinc in diabetic feet. The positive effects on wound healing have been demonstrated. It is stated that the cream is a therapeutic treatment tool that can be used in the clinic.

Methods

Patient Population

The primary outcome of this study was ulcer healing. This study required 25 patients for the protocol to produce clinically meaningful results. The study was conducted prospectively between December 2019 and December 2020, in the Plastic Surgery Wound Care Department of Fatih Sultan Mehmet Training and Research Hospital. This study was approved by the Ethics Committee of the hospital, with the number 2019/12.

The inclusion criteria are as follows: (1) Patients with a diagnosis of diabetes and diabetic foot. (2) Patients with diabetic foot ulcers with Grades II, III, and IV according to the Meggitt-Wagner classification system[13] (Table 1). (3) Collaboration of patients or their relatives who can complete the consent form according to the study protocol and have regular weekly visits. (4) Age >20 years old.

Exclusion criteria have consisted of the following: (1) Diabetic foot ulcers with necrotic tissue that could not be treated with adequate debridement. (2) Diabetic foot ulcers with clinically evident evidence of infection. Ulcers that are progressive surrounded by a hardened red border, warm or tender, with purulent exudates, or with a foul odor.[14,15] (3) Patients with Grade V diabetic foot ulcers according to the Meggitt-Wagner classification system. (4) Patients with a known history of hypersensitivity to any part of the drugs or products used in this study. (5) Patients with accompanying

Table 1. Meggitt-Wagner classification

Grade 0	Non-open lesions on the skin
Grade 1	There is a superficial ulcer that does not penetrate the deeper layers.
Grade 2	The ulcer is deeper and reaches the tendon, bone, or joint capsule.
Grade 3	Deeper tissues are involved and there is usually an abscess, osteomyelitis, or tendinitis that extends through the midfoot compartments of the tendon sheaths.
Grade 4	Gangrene occurs in the fingers, toes, and/or part of the forefoot. Gangrene may be wet or dry, infected, or non-infected.
Grade 5	Gangrene involving the whole foot or a sufficient part of the foot.

extravascular problems or systemic infections. (6) Patients with a history of glucose-6-phosphate dehydrogenase deficiency.[16]

Sample Size Estimation

The required number of patients in this study was estimated using the following equation:

$n=([Z_{\alpha/2}*SD]/d)^2$ that n is the population per group; SD, standard deviation; d, margin of error; and α, probability of type I error.

Study Design

The patients included in the study were randomly divided into two groups. The population consisted of a control group and a study group. The study duration was 6 months for each patient followed. The data were compared with the demographic data of the patients. Study group treatment consisted of the application of silver-zinc sulfadiazine cream. Visits were scheduled for each patient until the 6-month period for the study was completed. Cream applications were made during the visits. Wounds were debrided as needed to remove all necrotic tissue.

Evaluation Criteria

Demographic data including age, gender, wound grade, and location, and the number of debridement procedures was collected. Information was obtained about comorbid conditions such as peripheral vascular disease and chronic renal failure. Systolic and diastolic blood pressures of the patients were measured. At the beginning of this study, wound size was determined using the VISITRAK wound measurement system and wound photography. Deep wound and peri-wound tissue cultures were collected. The tissue around the wound was examined. Diabetic foot ulcer characteristics and healing rate were assessed using the PUSH version 3.0 score.[17] PUSH score ranged from 0 to 17 according to ulcer surface area (length-width), amount of exudate, and tissue type characteristics. The decrease in the PUSH score was considered as an indicator of ulcer healing. After cleaning the wound, it was examined and scored by an independent person. The wound was measured and evaluated for changes in wound size, grade, tissue properties, and amount of exudate.

Statistical Analysis

Data were analyzed using SPSS version 23 SPSS, Chicago, IL, USA. Frequency distribution (number and percentage) for categorical variables and descriptive statistics (mean, standard deviation, median, and quartiles) for numerical variables were given. Compliance with the assumption of normal distribution for numerical variables was checked with the Shapiro–Wilk test. It was determined that the variables were not suitable for the normal distribution. The Mann–Whitney U-test was used to examine the difference between the two groups. Friedman's test was used to examine the difference between the time periods. In cases where the differences between the time periods were significant, the differences between the time periods were determined by looking at P values with Bonferroni correction. Spearman correlation coefficient was used to analyze the relationship between numerical variables. $P<0.05$ was preferred for the statistical significance.

Results

A total of 25 patients who met the criteria were included in this study. One patient was excluded due to his/her death within the study. Finally, 24 patients were included in the study. The patients completed the 6-month weekly period of the study. The demographic distributions of the patients are indicated in Table 2. The images of diabetic foot ulcers obtained from the patients are presented in Figure 1.

The closure rate in the 3rd and 6th months was higher than the closure rate in the 1st week ($p<0.05$). The rate of closure in the 3rd and 6th months of the wounds with Grade 2 or Grade 3 was increased compared to the closure rate in the 1st week ($p<0.05$). In men, the closure rate at the 3rd and 6th months was higher than the closure rate at the 1st week ($p<0.05$) (Table 3).

A significant difference was observed between wound characteristics in terms of wound closure rates ($p<0.05$). Wound closure rates of patients with dry necrotic wound characteristics were always significantly higher than those with exudative wound characteristics ($p<0.05$). The closure rate of dry necrotic wounds in the 6th month was higher than the closure rate in the 1st week ($p<0.05$), whereas the closure rate of the exudative wounds in the 3rd and 6th months was higher than the closure rate in the 1st week ($p<0.05$). A significant difference was detected between the tissues around the wound in terms of wound closure

Table 2. Demographic distribution

	Med±SD	Med (25–75)
Wound area	33.75±34.81	22.5 (6.5–48)
Age	61.13±10.85	59 (53.5–66)
Diastolic blood pressure	94.88±26.12	91 (85–116.5)
Systolic blood pressure	126.33±20.55	126 (112.5–142.5)
ABI score	0.75±0.16	0.75 (0.66–0.86)
	n	%
Wound feature		
Dry necrotic	15	63
Exudative	9	38
Wound tissue		
Hard tissue	13	54
Erythematous	11	46
Deep tissue culture positivity		
No	5	21
Yes	19	79
Culture result in the wound surrounding tissue		
No	16	67
Yes	8	33
Gender		
Male	16	67
Woman	8	33
Diagnosis		
DM	1	4
DM+PVD	21	88
DM+PVD+CRF	2	8
Amputation requirement		
No	11	46
Yes	13	54
Wound grade		
Grade 2	18	75
Grade 3	5	21
Grade 4	1	4

PVD: Peripheral vascular disease; CRF: Chronic renal failure; DM: Diabetes mellitus.

rates in the 1st week, 2nd week, 1st month, and 3rd month ($p<0.05$). Accordingly, wound closure rates in the 1st week, 2nd week, 1st month, and 3rd month were significantly higher in the intact tissue around the wound than in those with erythematous tissue around the wound. In the erythematous tissue around the wound, the closure rate in the 3rd and 6th months increased compared to the closure rate in the 1st week ($p<0.05$).

In patients with culture growth in the deep wound, the closure rate at the 3rd and 6th months was higher than the closure rate at the 1st week ($p<0.05$). Wound closure rates of those with culture growth in the surrounding tissue were always significantly higher than those without culture growth in the surrounding tissue ($p<0.05$). The closure rate in the 3rd and 6th months of the patients with or without culture growth in the surrounding tissue was increased compared to the closure rate at the 1st week ($p<0.05$). A significant difference was found in terms of wound closure rates in the 1st week, 2nd week, 1st month, and 3rd month between amputation cases ($p<0.05$). However, there was no significant difference in wound closure rates in the 6th month ($p>0.05$). Wound closure rates in the 1st week, 2nd week, 1st month, and 3rd month were significantly higher than those without amputation. There was no significant change in the closure rate of amputated patients according to time ($p>0.05$). In patients without amputation, closure rate at the 3rd and 6th months was higher than the 1st week ($p<0.05$).

As a result of the analysis, a significant negative correlation was determined between the ABI score and the wound closure rates at the 1st week (Table 4), ($p<0.05$). There was no significant correlation between age, systolic blood pressure, and diastolic blood pressure, and wound closure rates ($p>0.05$).

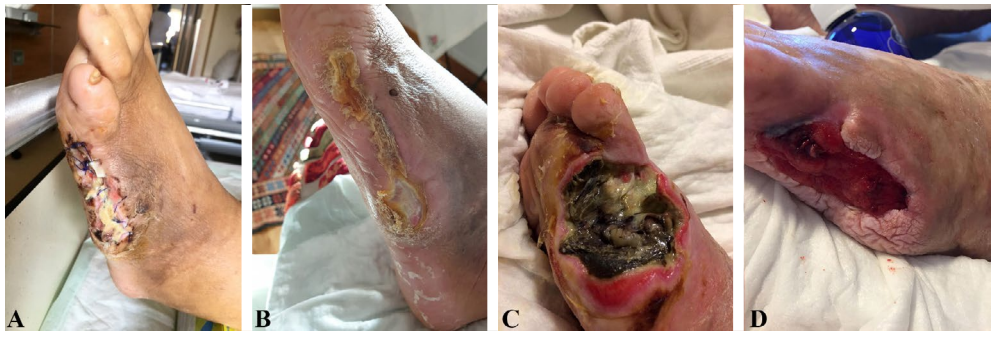

Figure 1. Photographs of diabetic foot ulcers. In **(a, b)**, improvement is indicated in the patient that has not been amputated. **(c, d)** The improvement in the amputated patient.

Table 3. Analysis of the data

	1 week		2 weeks		1 month		3 months		6 months		Test/P1
	Med±SD	Med (25–75)	Med±SD	Med (25–75)	Med±SD	Med (25–75)	Med±SD	Med (25–75)	Med±SD	Med (25–75)	
Wound feature											
Dry necrotic	83.7±34.7b	100 (100–100)	88.6±27.7	100 (100–100)	94.1±14.0	100 (100–100)	98.8±4.8	100 (100–100)	100±0a	100 (100–100)	11.719/0.020*
Exudative	31.0±31.6b	15.7 (14.3–35.4)	44.7±33.7	33.3 (30–48.6)	61.6±32.9	61.9 (53.6–85.7)	78.7±27.3a	87.5 (61.9–100)	75.4±29.1a	85.7 (58.3–100)	24.303/0.000*
Test/P2	−2.861/0.007*		−2.697/0.015*		−2.864/0.008*		−2.626/0.048*		−3.149/0.025*		
Wound side tissue											
Sturdy	88.4±29.4	100 (100–100)	92.1±24.4	100 (100–100)	97.1±7.5	100 (100–100)	100±0	100 (100–100)	100±0	100 (100–100)	7.892/0.096
Erythematous	35.1±36.3b	15.7 (6.3–60)	48.5±34.9	33.3 (30–100)	64.0±32.0	61.9 (50–100)	80.8±25.3a	87.5 (61.9–100)	79.9±27.9a	100 (58.3–100)	28.048/0.000*
Test/P2	−3.001/0.005*		−2.782/0.011*		−3.073/0.005*		−2.970/0.022*		−2.651/0.063		
Deep wound culture											
No	100±0	100 (100–100)	100±0	100 (100–100)	100±0	100 (100–100)	100±0	100 (100–100)	100±0	100 (100–100)	0.000/1.000
Yes	54.4±42.3b	42.9 (14.3–100)	64.8±37.8	85.7 (31.3–100)	77.2±29.2	85.7 (60.4–100)	88.9±21.2a	100 (82.1–100)	88.4±23.2a	100 (85.7–100)	35.782/0.000*
Test/P2	−2.132/0.053		−1.985/0.075		−1.985/0.075		−1.402/0.297		−1.251/0.406		
Cultured wound side tissue											
No	80.5±35.8b	100 (71.4–100)	85.1±30.1	100 (92.9–100)	92.4±15.2	100 (92.86–100)	98.8±4.5a	100 (100–100)	100±0a	100 (100–100)	15.467/0.004*
Yes	30.8±33.8b	15 (10.3–47.7)	46.1±35.8	35.4 (20.6–74.3)	61.0±35.2	61.2 (39.8–92.9)	76.0±27.9a	84.8 (58.0–100)	72.4±29.5a	79.3 (45.8–100)	20.850/0.000*
Test/P2	−2.638/0.013*		−2.359/0.032*		−2.565/0.019*		−2.938/0.023*		−3.449/0.013*		
Gender											
Men	55.4±43.3b	51.4 (10.3–100)	65.6±39.4	92.9 (30.6–100)	75.9±31.2	92.9 (57–100)	86.8±22.6a	100 (81.7–100)	86.2±24.7a	100 (79.3–100)	28.339/0.000*
Women	81.0±35.6	100 (66.7–100)	85.2±27.6	100 (74.3–100)	94.1±12.1	100 (92.9–100)	100±0	100 (100–100)	100±0	100 (100–100)	7.892/0.096
Test/P2	1.436/0.192		1.402/0.214		1.470/0.192		1.932/0.153		1.725/0.238		
Diagnosis											
DM	6.3±	6.25 (6.3–6.3)	31.25±	31.3 (31.3–31.3)	50±	50 (50–50)	81.3±	81.3 (81.3–81.3)	100±	100 (100–100)	-
DM+PVD	68.0±39.6b	100 (33.3–100)	75.7±34.8	100 (37.5–100)	86.5±21.1	100 (76–100)	94.6±13.1a	100 (100–100)	92.6±18.2	100 (100–100)	29.693/0.000*
DM+PVD+CRF	50.0±70.7	50 (0–100)	55.6±62.9	55.6 (11.1–100)	50.0±70.71	50 (0–100)	61.1±55.0	61.1 (22.2–100)	66.7±47.1	66.7 (33.3–100)	-
Test/P	-		-		-		-		-		
Amputation											
No	33.5±35.5b	15.7 (6.3–42.9)	47.1±33.0	33.3 (30–85.7)	62.7±30.6	61.9 (50–85.7)	80.8±25.6a	87.5 (61.9–100)	79.9±27.9a	100 (58.3–100)	29.526/0.000*
Yes	89.7±27.5	100 (100–100)	93.2±24.4	100 (100–100)	98.2±6.7	100 (100–100)	100±0	100 (100–100)	100±0	100 (100–100)	6.759/0.149
Test/P2	3.064/0.004*		3.268/0.002*		3.591/0.001*		2.970/0.022*		2.651/0.063		
Wound grade											
Grade 2	74.2±39.6b	100 (42.9–100)	81.7±33.9	100 (85.7–100)	88.9±21.7	100 (85.7–100)	94.3±14.0a	100 (100–100)	93.7±19.0a	100 (100–100)	18.604/0.001*
Grade 3	19.8±14.7b	15.7 (14.3–33.3)	32.1±13.7	33.3 (30–37.5)	53.3±32.1	60.4 (53.6–66.7)	78.4±32.36a	87.5 (82.1–100)	78.4±27.6a	85.7 (72.9–100)	18.042/0.001*
Grade 4	100±	100 (100–100)	100±	100 (100–100)	100±	100 (100–100)	100±	100 (100–100)	100±	100 (100–100)	-
Test/P	-		-		-		-		-		
TOTAL	63.9±42.0b	100 (15–100)	72.1±36.5	100 (33.3–100)	81.9±27.5	100 (64.3–100)	91.2±19.3a	100 (93.8–100)	90.8±21.0a	100 (100–100)	35.782/0.000*

[a,b]Indicaes the differences between the means of the groups (a=the highest mean). 1: Friedman test; 2: Mann–Whitney U-test; *p<0.05.

Table 4. Examination of the relationship between the scales

	1 week	2 weeks	1 month	3 months	6 months
Age					
r	0.202	0.240	0.283	0.295	0.167
P	0.345	0.258	0.180	0.162	0.437
Diastolic blood pressure					
r	−0.131	−0.049	−0.080	−0.285	−0.138
P	0.541	0.821	0.710	0.177	0.520
Systolic blood pressure					
r	0.264	0.314	0.270	-0.063	-0.045
P	0.213	0.135	0.201	0.769	0.835
ABI					
r	−0.426	−0.324	−0.344	−0.329	−0.188
P	0.038*	0.123	0.100	0.117	0.380

r: Spearman correlation coefficient; *p<0.05.

Discussion

In the study, patients with diabetic feet were selected according to the criteria. Creams containing silver and zinc were applied to the individuals. The effect of the cream on infections in the diabetic foot was investigated. Healing of ulcers has been observed. In the measurements, it was determined that the creams had antimicrobial properties. It has been demonstrated that the cream has a healing effect on wounds by changes in the amount of exudates and wound radius.

Diabetic foot ulcers remain a common problem among diabetic patients. Diabetic foot ulcers cause a significant loss of workload and financial burden. This is a global public health problem today. The ulcers can cause tissue loss with amputation.[18] Silver and zinc have been used in wound care given their antimicrobial properties. After cleaning with normal saline solution, the cream was applied to the wound surface once a day. This can place a significant burden on patients and caregivers for time-consuming treatments. In one study, patient and caregiver quality of life was analyzed by a questionnaire. Quality of life is improved in patients with healed ulcers. Patients with persistent ulcers reported having a poor quality of life. Caregivers experienced more emotional difficulties with poorly healing wounds.[19] The daily available treatment methods can positively affect the quality of life by reducing the burden of the patient and caregiver. These methods can help reduce job loss. The cream in the study can be applied easily. In this way, it can shorten the patient's return to normal life by reducing the therapy load.

Today, various methods are used for the foot with diabetes. Off-loading at the ulcer site is an important treatment strategy. In one study, the physical load on the wound was reduced. Reductions in ulcer surface area were observed.[20] Application of the cream in this treatment regimen can accelerate wound healing. Wound debridement is frequently performed in the diabetic foot. In one study, fibrin and necrotic tissue debridement were made from the ulcer surface. Bacterial load and fibrin coverage decreased.[21,22] Application of the cream after debridement can stimulate tissue regeneration. Combining it with silver- and zinc-based antimicrobial applications can reduce the risk of infection. The cream in our study can be applied in addition to the current treatments. It can help with controlling the wound for infection.

One study investigated pathogens in diabetic foot infection. The most well-known pathogens in superficial and deep samples were S. aureus (36.9%), Gram-negative bacilli (24.6%), and β-hemolytic streptococci (19.5%). Septicemia was predominantly caused by S. aureus and β-hemolytic streptococci.[23] The antimicrobial effects of silver and zinc can prevent system complications. In one study, silver foam dressing was used against diabetic foot ulcers. Wound condition and scoring have improved. Treatment resulted in decreases in the bioburden of pathogenic organisms such as Enterobacteriaceae species, P. aeruginosa, and S. aureus.[24] The use of zinc with silver may contribute to higher antimicrobial effects. The data in our study indicate that the cream can be used against pathogens. In addition to the antimicrobial feature, the shrinkage of the wound can prevent the proliferation of bacteria.

In one study, a silver-containing cream was applied to diabetic foot ulcers. Ulcers healed at a rate of 81.8%.[25] Silver-based topical applications can accelerate wound closure. One study analyzed the effects of silver sulfadiazine cream. Wound width and thickness decreased after the application. Ulcers healed in an average of 43 days.[26] Accelerating wound healing can reduce the risk of infection. In a mouse study, zinc was used in the ulcer area. Skin wound healing, tissue remodeling, and new vessel formation are accelerated.[27] Zinc therapy can contribute to the formation of a healthy tissue skeleton. In one study, a silver- and zinc-based cream was applied. Bacterial count was reduced through antimicrobial activity. It did not cause resistance by infecting organisms. It has been observed to stimulate the healthy healing process.[12] Using the cream in daily life can reduce the complications of infection. The silver- and zinc-based application in our study gave positive results in the treatment process. This may be related to the antimicrobial properties of silver and zinc. It can have a stimulating effect on tissue regeneration when used together. According to our statistical results, according to our results after 6 weeks, we concluded that the transformation of post-cream wounds into chronic wounds decreased in our study.

The disease has led to increased care costs. High hospital costs per diabetic foot ulcer admission have been recorded.[28] Cost-effective treatment approaches can reduce the burden of the disease in the health-care system. Workforce loss due to illness can be prevented. The cream in our study can provide the necessary approach. It can enable diabetic amputation to be treated before it occurs.

There are many factors that have an impact on wound healing, including relieving pressure, improving nutritional status, general condition of the patient, and wound management. Many of these factors appear difficult to control but can be managed with appropriate randomization. One of the limitations of our study is the lack of biopsy results after the amputation. Biopsy results and changes in vascular and nerve structure can be examined in future studies. Another limitation is the lack of monitoring of glycohemoglobin (HbA1c) values. HbA1c may be a parameter in examining the systematic effects of the cream. In our study, none of the patients were required major amputation. Completion of amputation and simultaneous application of cream contributed to infection control when appropriate demarcation lines were formed.

Conclusion

Data in the literature indicate that silver- and zinc-based applications can heal ulcers. The antimicrobial properties can prevent complications from an infection. Accelerating the healing process can reduce the burden of the disease. Shrinkage of the wound can reduce the risk of coinfection. Daily use of the cream can improve the quality of life.

Disclosures

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – H.M.A., P.K.; Design – P.K., H.M.A.; Supervision – P.K., H.M.A.; Materials – H.M.A., P.K.; Data collection – H.M.A., P.K.; Analysis and interpretation – P.K., H.M.A.; Literature search – P.K., H.M.A.; Writing – P.K., H.M.A.; Critical review – P.K., H.M.A.

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