Diabetic Foot: Wound Healing, Amputation Decision, and Innovative Developments

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Abstract

Aim: To review the effects of diabetes-related diseases on the healing process and amputation decision in diabetic foot ulcers (DFU), negative pressure wound therapy (NPWT) results, and current treatment approaches.

Methods: The study was planned as retrospective and cross-sectional. Data of patients who were admitted to our clinic due to DFU and were treated were examined. A total of 38 patients were included in the study. The results of patients (n=19) who underwent periodic debridement and classic dressing were compared with the results of patients (n=19) who underwent NPWT. Healing in patients was achieved by amputation (n=8), repair with partial thickness grafts or flaps (n=10), and secondary epithelialization development (n=10). The effect of diabetes-related peripheral arterial disease (PAD), cardiovascular disease (CVD), chronic kidney disease (CKD), diabetic retinopathy (DRP), and previous amputation history (AH) on recovery time was examined. The predictive importance of diabetes-related diseases for amputation was investigated.

Results: It was determined that diabetes-related diseases caused a delay in wound healing. [PAD ($p<0.044$), CVD ($p<0.016$), CKD ($p<0.001$), DRP ($p<0.001$)], The delay in wound healing was evident in the presence of CKD and DRP. Wound healing time was not affected in patients with AH ($p>0.05$). The incidence of PAD was higher in patients who underwent amputation. There was no significant difference between NPWT (mean 67 days) and the classic dressing group (mean 73 days) in terms of healing time ($p>0.05$).

Conclusions: In the presence of diabetes-related diseases, wound healing time was prolonged. This effect was more evident in the presence of DRP and CKD. This may be explained by microvascular disease, but larger series studies are needed. Wound healing was not affected in patients with AH. The incidence of PAD was found to be higher in patients who underwent amputation. Improving the care conditions of patients with diabetes and accessing treatment facilities will reduce DFU and amputation rates. No difference was found between NPWT and classic dressing in terms of healing time. However, it was observed that NBWT increased the development of granulation in the wound, reduction of edema, wound contraction, and the chance of success of the graft or flap surgery. Innovative studies are needed to develop optimum wound surfactant molecules in this regard.

Keywords: *Diabetic foot ulcer, wound healing, amputation, diabetes-related diseases*

1. Introduction

The main problem in the development of diabetic foot ulcer (DFU) is microangiopathy. DFU and lower extremity amputation (LEA) are independent risk factors associated with early death[1]. The 5-year survival rate in patients with diabetes who develop lower extremity complications is worse than in patients with many common types of cancer[2]. Duration of diabetes, glycemic control, and epigenetic features are the most effective factors in the development of complications[3]. The development of micro and macrovascular complications in diabetes is an independent risk factor in the development of DFU. Today, despite the advances made in elucidating the potential mechanisms underlying DFU (physiologic, pathologic, cellular, molecular signaling pathway, and epigenetics), the same parallelism has not been achieved in its treatment. The fact that the wound is associated with complex pathogenic factors makes the treatment difficult. Especially in a wound complicated by infection and combined with vascular insufficiency, the failure rate in treatment will increase if both infection and microvascular insufficiency cannot be managed simultaneously.

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Studies show that major amputations are not the solution. Therefore, wound care, which is the step before amputation, is very important for patients with diabetic foot. Developed as an alternative to traditional wound treatment, NPWT has made this process more transparent by understanding many mechanisms in wound healing. Studies have shown that NPWT increases granulation tissue, accelerates wound healing by increasing local blood flow, and removes exudate and proinflammatory cytokines from the environment. In wound healing, NPWT acts by causing contraction in the wound with negative pressure applied to the surface, protecting the wound from external micro-organisms, keeping the wound warm and moist, drawing exudate in the soft tissue, reducing edema in the wound, and increasing cellular proliferation[4].

The study aimed to investigate the effect of diabetes-related diseases (PAD, CVD, CKD, DRP), previous amputation history, and NPWT on the healing process and amputation decision.

2. Materials and methods

The study was planned as retrospective and cross-sectional. Information about patients who applied to our clinic due to diabetic foot between 2008 and 2011 was retrospectively reviewed. A total of 38 patients were included in the study.

Patients with a follow-up period of less than 1 year, oncology patients, patients with systemic connective tissue disease, patients receiving immunosuppressive therapy, and pregnant patients were excluded from the study.

Approval for the study was received from the ethics committee of our institution. Informed consent was obtained from all patients in accordance with the Declaration of Helsinki. The study was started after receiving ethics committee approval.

The patients' age, sex, duration of diabetes, recovery time, treatments administered, and presence of comorbid diseases were examined retrospectively. Data were accessed from the archive, patient files and information processing system.

Healing: Ensuring epithelial continuity with no discharge or signs of infection in the wound was considered as the absence of an open wound.

Peripheral artery disease (PAD): Ankle brachial index (ABI) less than 0.90.

Chronic kidney disease (CKD): Albuminuria greater than 30 mg/g creatinine and estimated glomerular filtration rate (tGFR) less than 60 mL/min/1.73.

Cardiovascular disease (CVD): Presence of hypertension, coronary artery disease, and heart failure.

Diabetic retinopathy (DRP): Monitoring the changes due to nonproliferative retinopathy within the borders of the retina and proliferative retinopathy extending into the vitreous during fundus examination.

History of amputation (AH): Major or minor limb loss in the lower or upper extremities at any stage of life in a patient with diabetes.

Negative pressure wound therapy (NBWT): This was applied to the wound after debridement and irregulation, if necessary, and NBWT changed every 3 days, until the wound was ready for surgery or until dermal healing was completed.

Classic dressing: After the necessary debridement and irregulation of the wound, dressings was changed daily and used until the wound was ready for surgery or until dermal healing was completed. Sterile gauze was applied to the wound surface after moistening it with isotonic solution.

2.1. Statistical Analysis

Normality control of continuous variables was evaluated using the Shapiro-Wilk test. The independent sample t-test was used in cases that showed normal distribution, and the Mann-Whitney U test was used in cases that did not. Fisher's exact test was used to analyze categorical data. The analysis of the data was evaluated in the Statistica version 13.5.0.17 program. The statistical significance level was accepted as 0.05.

3. Results

The average age of the patients included in the study was 53.6 (min 31–max 85) years. There were 14 female patients and 24 male patients. The average diabetes duration of the patients was 12.8 (range, 1 - 25) years.

There was a history of PAD in 39% of the patients, CVD in 65%, CKD in 42%, DRP in 63%, and AH in 21%. It was determined that the healing time (days) prolonged with the presence of PAD ($p<0.044$), DRP ($p<0.001$), CKD ($p<0.001$) and CVD ($p<0.016$). It was found that the delay in wound healing was quite evident in the presence of DRP and CKD. Wound healing time was not affected in patients with AH ($p>0.05$). (Table 1)

Table 1

Recovery times in the presence of diabetes-related diseases and amputation history

		n	Mean±SD	Median [IQR]	Min-Max	p
DRP	No	14	52.86±12.30	55 [41.25-65.5]	37-73	<0.001[a]
	Yes	24	73.08±13.36	73 [67-84.5]	35-90	
CKD	No	22	56.82±13.00	62.5 [42-67]	35-73	<0.001[a]
	Yes	16	77.75±11.78	80.5 [68.5-87]	46-90	
PAD	No	23	61.39±16.32	67 [42-73]	35-90	0.044[b]
	Yes	15	72.13±14.09	73 [67-87]	44-90	
CVD	No	13	56.23±16.37	60 [40.5-67]	37-85	0.016[a]
	Yes	25	70.52±14.10	67 [66-82.5]	35-90	
AH	No	30	65.03±16.77	67 [52.75-77.5]	35-90	0.665[b]
	Yes	8	67.88±14.55	67 [58-81]	42-87	

a:Mann-Whitney U test. B:Independent Samples t-test, IQR:Interquartile Range

Table 2

Amputation rates in diabetes-related diseases

		Amputation				Total		
		Yes		No				
		n	%	n	%	n	%	p
DRP	No	10	33.3	4	50.0	14	36.8	0.433
	Yes	20	66.7	4	50.0	24	63.2	
CKD	No	17	56.7	5	62.5	22	57.9	0.999
	Yes	13	43.3	3	37.5	16	42.1	
PAD	No	21	70.0	2	25.0	23	60.5	0.039
	Yes	9	30.0	6	75.0	15	39.5	
CVD	No	12	40.0	1	12.5	13	34.2	0.222
	Yes	18	60.0	7	87.5	25	65.8	

p: Fisher's exact test

Of the patients who underwent amputation (n=8), 50% had DRP, 37% had CKD, 75% had PAD, and 87.5% had CVD. When patients with and without amputation were compared, it was determined that PAD was important in the amputation decision (p=0.039). (Table 2)

In terms of healing time, the difference between NPWT (mean 67 days) and the classic dressing group (mean 73 days) was not significant (p>0.05). However, a significant reduction in extremity edema was observed in patients who underwent NPWT. Macroscopically, an increase in wound contraction and granulation tissue was observed. (Table 3)

Table 3

Healing time NPWT and classic dressing

	n	Mean±SD	Median [IQR]	Min-Max	p
NBWT	19	68.79±9.43	67 [67-67]	55-90	0.665
Classic dressing	19	62.47±20.7	73 [42-83]	35-89	

p:Mann-Whitney U test, IQR:Interquartile Range

4. Discussion

It is known that the prevalence of PAD in diabetes is between 20% and 50%[5]. In studies, PAD has been found to be associated with delayed wound healing, infection and increased amputation rates[6-7]. When patients with and without amputation were compared, it was understood that the presence of PAD was important in the decision for amputation. The predictive importance of PAD for amputation can be more clearly understood through larger series of studies. However, it was seen that wound healing was delayed in the presence of PAD.

In prospective clinical studies, CVD has been associated with severe DRP, end-stage CKD, delayed healing of ischemic ulcers, rapid progression, amputation, and mortality[8]. In our study, it was determined that DFU recovery time (days) increased in the presence of diabetes-related PAD, DRP, CVD, and CKD. This effect was quite evident in the presence of DRP and CKD. This result may be explained by microvascular disease because microvascular disease associated with diabetes is pathognomic, especially in the development of DRP and CKD, and is important in predicting prognosis[9]. No information could be found in the literature regarding the risk of microvascular disease and DFU development and its predictive importance for amputation.

The lifetime risk of lower extremity amputation in patients with diabetes is approximately 25%[10]. In our study, the prevalence of amputation was 21%. The presence of diabetes-related PAD, DRP, CVD, and CKD creates an increased risk for foot ulcers and lower extremity amputations. These data was supported by the results of our study. In our study, the incidence of PAD was found to be high in patients with AH.

Studies have shown that the greatest risk for amputation is low socioeconomic status and poor self-care[11]. The strongest clinical indicator in the development of DFU is the presence of a previous foot ulcer or AH[12]. However, there is no information about whether it affects the healing time. We determined that the wound healing rate was not affected in patients with AH.

The most important factor playing a role in diabetic wound pathology is cellular aging. Senescent cells have a phenotype that produces a secretome rich in pro-inflammatory cytokines and tissue-degrading proteases. Chronic wound microenvironment, high levels of inflammation, and oxidative stress induce cell aging[13]. Applying negative pressure to the wound appears to be very effective in restructuring cells, ensuring matrix regeneration, and removing inflammation mediators from the environment. However, there is no consensus on the effectiveness of NPWT in the treatment of DFU.

There are studies indicating that it does not contribute to shortening recovery time. On the other hand, there are also studies indicating that NPWT shortens the recovery period, but is not cost-effective[14]. Some studies report that it increases the granulation tissue and increases the chance of graft success in post-graft application[15]. One of the aims of NPWT is to prepare the wound for surgery as soon as possible. The clinically expected result may not be complete wound closure. It is an intermediate step in completely closing the wound and aims to shorten the hospital stay[16].

In our study, no statistically significant difference was found between the NPWT group (mean days) and the classic dressing group (mean days) in terms of recovery time (p>0.05). Negative pressure applied physically to the wound at optimum pressure and frequency reduces the bacterial load by drawing exudate. However, the most important parameter of NPWT's antibacterial effect is the surface contact material. Polyurethane sponge containing silver nitrate is frequently used. In studies conducted on this subject, the results of using polyurethane sponges containing boric acid as wound contact material in NPWT are remarkable. Innovative developments in wound healing have shown that boric acid is an effective molecule, especially in chronic wounds[17].

5. Conclusion

As a result of our study, diabetes-related diseases prolonged the recovery time of wound healing. The presence of DRP and CKD prolonged the healing time the most. It was understood that the recovery time was not affected in patients with AH. However, the incidence of PAD was found to be high in patients who underwent amputation. NPWT did not affect the healing rate in DFU. However, decreased edema, increased granulation, and contraction effects on the wound were observed. DFU is a preventable disease. The socioeconomic conditions of patients with diabetes should be improved and the conditions for accessing care facilities should be regulated. Finally, funds allocated for DFU research are insufficient. In this regard, innovative studies on wound healing should be supported.

Statement of ethics

The study was approved by the local ethics committee (ESH/GOEK 2011/206).

Conflict of interest statement

The authors declare that they have no financial conflict of interest with regard to the content of this report.

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