CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.3464419

Available online at: http://www.iajps.com Research Article

DETERMINE THE FACTORS AFFECTING THE DIABETIC FOOT WOUND HEALING: PROSPECTIVE STUDY DESIGN

[1]Dr Athar Nafees Mutahhari, [2]Dr Muhammad Aasam Masoom Maan,
[3]Dr Syed Kumail Abbas Razvi
[1]Medical Officer, Emergency Department Hussain Medical Complex Rawalpindi Pakistan
[2]Assistant Professor Anesthesia Faisalabad Medical University,
Faisalabad killingeyes177@gmail.com
[3]MBBS Student Ziauddin Medical College Karachi kumail.abbasshah55@gmail.com

Abstract:
***Objective**: To determine the risk factors for infected DFUs and their association between ulcers characteristics, with healing time of DFUs.hospital*
***Design:** prospective study.*
***Setting**: This study was carried out in Hussain Medical Complex Rawalpindi.*
***Patient(s):** 340 patients (216 male and 124 female) DFU patients who attended the clinic presented with infection.*
***Main Outcome Measure(s):** healing time of wound, factors that causes delayed healing*
***Result(s):** 340 patients (216 male and 124 female) DFU patients who attended the Hussain Medical Complex Rawalpindi. (mean age: 58.1±10.8 years old), 41.5%presented with infection with a mean cross-sectional ulcer area of 21.5±33.2cm2. Binary logistic regression analysis revealed that patients of Chinese ethnicity (OR: 3.39; 95%CI 1.49 to 7.70), with fasting blood glucose ≥7mmol/l (OR: 3.41; 95%CI 1.57 to 7.39), ulcer size ≥10cm2 (OR: 2.90; 95%CI 1.45 to 5.82) and blood pressure ≥140/90mmHg (OR: 2.52; 95%CI 1.54 to 4.14) were more likely to develop DFI. The median healing time for patients with DFUs was three months. Six variables were significantly associated with prolonged healing time of DFU, namely presence of infection ($p<0.05$) poor glycemic control with fasting blood glucose ≥7mmol/l ($p<0.05$) high blood pressure ≥140/90mmHg ($p<0.05$) large DFU size ≥2cm2 ($p<0.05$). History of amputation ($p<0.05$). And plantar location of the DFU ($p<0.05$).*
***Conclusion:** Increase in healing time of DFUs was correlated with a history of amputation, presence of infection, high blood glucose level, high blood pressure, large DFU size and location on the plantar. The results also showed that, despite being extensively educated, treated with proper wound care and provided with proper offloading, 14.8% of the DFUs patients healed within one to six months and 27.6% of them took >6 months to be healed. Thus, recognizing factors associated with delayed wound healing is important to gain a better understanding of DFUs that do not respond adequately to the treatment. Identifying patients with high risk of delayed healing allows early intervention and preventative measures in future treatments.*
***Key words:** diabetic foot ulcer ● healing time ● infection rate ● risk factor ● wound care*

Corresponding author:
Dr Athar Nafees Mutahhari,
Medical Officer, Emergency Department ,
Hussain Medical Complex Rawalpindi Pakistan
drnafees76@gmail.com

QR code

Please cite this article in press Athar Nafees Mutahhari et al., ***Determine The Factors Affecting The Diabetic Foot Wound Healing: Prospective Study Design.,*** *Indo Am. J. P. Sci, 2019; 06[09].*

INTRODUCTION:

Diabetic foot ulcers (DFU) and concomitant infections are one of the most frequent complications in patients with diabetes mellitus [1, 2]. DFU affect approximately 12-25% of persons with diabetes mellitus throughout their lives [3]. Lower limb disease is the most common source of complications and hospitalization in the diabetic population [4]. Diabetics 7-10% develop chronic foot ulcers, a severe and expensive complication with life and/or limb threatening conditions [5]. Chronic DFU are one of the most common indications for hospitalization in diabetics, and almost 50% of all non-traumatic amputations are performed on diabetic patients [6]. It is now understood that the majority of diabetic lower extremity amputations are preceded by foot ulcers [1, 7]. Chronic DFU do not follow the well-described sequence of wound healing. Recent research has shown that true chronic wounds are biochemically different from acute wounds differing in their expression of growth factors, matrix metalloproteases, and various proteins.

The most frequent chronic wounds are DFU, that is, ulcers due to peripheral arterial occlusive disease and/or venous disease [8, 9]A chronic DFU is defined as a wound failing to heal after 4 weeks and this definition was adopted by the American Diabetes Association [10]. It has been reported that a decrease in wound size by at least 0.7 mm per week is 80% sensitive and specific for ultimate wound closure, the opposite being a marker of chronicity [11]. Alternatively, a less than 10% decrease in wound surface per month may empirically be a predictor of poor healing, although reliability and predictive values are missing .[8-11]

DFU is a major social, economic and medical problem in developing countries, contributing to morbidity and mortality rates among patients with diabetes.4 DFUs develop in 1 in 15 patients with diabetes during their lifetime. In the primary health-care system in Malaysia, a retrospective study performed in Kuala Langat health center reported that 1% of patients with diabetes developed new DFUs every year.7 DFUs which become infected are the main cause of lower extremity amputation. Diabetic foot infection (DFI) accounted for up to 20% of diabetes-related hospital admissions. Thus, DFUs and infections negatively influence the mental and physical health of patients with diabetes, with high health-care expenditure on treatment costs and hospitalisation.[12] DFU is often characterized by prolonged healing time, whereby failure of a wound to heal by four weeks is classified as a chronic DFU.[13,14] Up to 1.5% of patients in a diabetic centre in Sudan had a chronic DFU of >6 months, 60% had their ulcer healed.[15] Only 31% of the patients with diabetic neuropathic ulcers healed after 20 weeks of good wound care.[16] Thus, identification of risk factors of chronic DFU is crucial in reducing its incidence and healing duration. Significant risk factors for diabetic complications include high systolic blood pressure, advanced age, longer duration of diabetes, baseline creatinine clearance and proteinuria.[17]

Specifically for DFU, common risk factors that have been reported are diabetic neuropathy, peripheral vascular disease and smoking, hypertension and dyslipidaemia.[18] Infection, poor management, ill-fitting shoes and tissue ischemia are found to be associated with failure of DFUs to heal.[19] In this study, patients with DFUs receiving treatment at Hussain Medical Complex Rawalpindi were studied to determine the risk factors for infected DFUs and their association between ulcer characteristics, with healing time of DFUs.

METHOD:

This study is a prospective study conducted in the wound care clinic of Hussain Medical Complex Rawalpindi. The study population was defined as those patients with a DFU who attended the wound care clinic of Hussain Medical Complex Rawalpindi between January 2017 December 2018 for treatment and follow up.

Patients screening

Patients were screened for risk factors known to be associated with lower extremity complications (e.g., age, gender, duration of diabetes, previous hospitalization, previous amputation, previous foot infections, previous osteomyelitis, peripheral neuropathy, peripheral vascular disease, antibiotics administration within the last 30 days, wound depth, ulcer localizations). The data of enrolled subjects were recorded on patient follow-up forms. Osteomyelitis, duration of hospitalization, amputation, cost-effectiveness of prescribed antibiotics; factors related to the treatment in diabetic foot infections were analyzed. Infection was diagnosed clinically by a trained physician according to International Working Group on the Diabetic Foot (IWGDF) criteria, Perfusion, Extent, Depth, Infection, Sensation (PEDIS) classification [4].

Patients with newly diagnosed diabetic foot pathology, recurrent infection after being totally cured, and history of amputation below the metatarsus were enrolled in the study. On admission, specimens for

culture were obtained following cleansing and the debridement of the wound by swabbing the ulcer base, curettage, needle aspiration or biopsy, depending on the wound depth.

The diagnosis of osteomyelitis was based on the positivity of any of the following tests; bone biopsy, X-ray, MRI, scintigraphy or the probe-to-bone test. The following criteria should be met for the diagnosis of neuropathy: positive monofilament test result, or neuropathy diagnosed by a neurologist. Body mass index (Quetelet index) was calculated as the weight in kilograms divided by the square of the height.

Measurement and definitions

In this study, DFU size was classified into 10cm^2 2–10cm^2 and >10cm^2. Infected DFU was defined based on the presence of signs of infection including pyrexia, localized pain, erythema, edema or odour. For glycemic control, fasting blood glucose was defined as good control (<7mmol/l) and poor control (≥7mmol/l) based on World Health Organization (WHO) and American Diabetes Association (ADA) Standards of Care guidelines. Patients' blood pressure leverls were classified into high blood pressure (systolic BP≥140mmHg or diastolic BP≥90mmHg) and normal blood pressure (systolic BP<140mmHg or diastolic BP<90mmHg) in accordance with the ADA Standards of Care guidelines.20 Ischaemia referred to the occurrence of ischemic heart disease reported by the patient. The ulcer locations identified in this study include dorsal, plantar, lateral, medial, anterior, posterior, web space and 'other'. The anatomical region of the ulcer was classified in this study as hindfoot, midfoot, forefoot, hallux, toes, malleolus, leg and 'other'. The healing time of the DFU was calculated based on the follow-up duration in this clinic up until clinically observed wound epithelization was noted in the medical records.

Statistical analyses

Data were analyzed using SPSS version 23.0. Descriptive statistical analysis was done for variables including demographic characteristics, ulcer characteristics and comorbidities related records. Chi-square test was used for identification of independent variables that associated with dependent variables. All factors with a p-value of <0.025 in the univariate analysis were considered as candidates for multivariate regression model. In the binary logistic regression, 95% confidence interval (CI) and odd ratios (OR) were calculated by using infection as the outcome variable. For categorical variables with more than two levels, such as ethnicity or ulcer cross-sectional area, we chose one level as baseline and calculated OR for other levels in comparison with baseline. The variables with $p < 0.05$ of the multivariate analysis were considered significant factors for the dependent variables. Non-parametric test was performed for the continuous outcomes that do not follow a normal distribution. Mann Whitney U test and Kruskal-Wallis One-Way ANOVA were used to analyse the association between demographic, clinical and ulcer characteristics with the healing time of diabetic foot ulcer. Mann-Whitney U test was used for independent variables with two groups while Kruskal Wallis One-Way ANOVA was used to compare three or more independent variables. It was considered to have a statistically significant difference with $p<0.05$.

RESULTS:

Demographic characteristics

This study involved 340 patients with DFUs. The demographic characteristics of the subjects are summarised in Table 1. Of the patients, 63.5% (n=216) were male and 36.5% (n=124) were female, with an overall mean age 58.1±10.8 years old. The mean age of both genders was similar (female: 58.7±11.6 years old; male: 57.8±10.3 years old). The majority of the patients were Malay (45.6%), followed by Indian (43.5%) and Chinese (10.6%).

Table 1. Demographic characteristics

Gender	frequency	percentage
Male	216	63.5
Female	124	36.5
Age (years)		
<41	25	7.4
41–50	44	12.9
51–60	118	34.7
61–70	122	35.9
>70	31	9.1

DFU characteristics

The mean of cross-sectional area for ulcer size was 21.5±33.2cm^2. In this study, 19.7% of the DFUs had a size of 10cm^2 (Table 2). Over one third (30.3%) of the DFUs were located on the forefoot and over half (51.8%) were located on the plantar aspect of the foot (Table 2).

Table 2. Diabetic foot ulcer characteristics

Variables	Frequency	Percentage (%)
Anatomical region		
Hindfoot	42	12.4
Midfoot	59	17.4
Forefoot	103	30.3
Hallux	37	10.9
Toes	50	14.7
Malleolus	17	5.0
Leg	21	6.2
Other area	11	3.2
Location		
Dorsal	48	14.1
Plantar	176	51.8
Lateral	48	14.1
Medial	25	7.4
Anterior	7	2.1
Posterior	6	1.8
Web space	17	5.0
Other	13	3.8
Ulcer size		
Cross-sectional area (cm^2)		
<2	67	19.7
2–10	108	31.8
>10	165	48.5

Comorbidities

Among the study population, 61.2% had comorbidities other than diabetes. The presence of other comorbidities in these DFU patients was found more common in male (60.1%) than in female (39.9%). Almost half of the patients (47.1%) had hypertension (Table 3). The prevalence of other comorbidities for renal failure, hyperlipidemia and ischemia were also notable, 15.3%, 7.1% and 6.5% respectively (Table 3).

Table 3. Comorbidities

Variables	Frequency	Percentage (%)
Presence of comorbidities		
Yes	208	61.2
No	132	38.8
Renal failure		
Yes	52	15.3
No	288	84.7
Hypertension		
Yes	160	47.1
No	180	52.9
Hyperlipidaemia		
Yes	24	7.1
No	316	92.9
Ischaemia		
Yes	22	6.5
No	318	93.5

Prevalence of diabetic foot infection

During the study period, the prevalence of DFI was 41.5% (n=141). DFI prevalence was observed to be higher among males (68.1%) than females (31.9%). Almost half of the DFIs were observed among Indian patients (49.6%) as compared with Malay patients (36.2%) and Chinese patients (13.5%) (p=0.018).

Association of demographic, clinical and ulcer characteristics with diabetic foot infections

Table 4 shows a comparison of characteristics present at the enrollment of patients with DFUs who developed a foot infection and those who did not.

The chi-square test was statistically significant, p=0.018 for ethnicity, showing that there was an

association between ethnicity and the presence of infection among patients with DFUs. Of the 141 patients who developed an infection, 131 had a fasting blood glucose level of ≥7mmol/l. Fasting blood glucose was statistically significant in influencing the presence of DFI, p2cm2 on the foot was also a common precipitating event for a DFI. The prevalence of infected DFUs was observed as 61.7% in ulcers with a size of ≥10cm^2 and 27% in ulcers of a size among 2–10cm^2. Chi-square test showed that ulcer size was statistically significant in influencing the presence of DFI, p <0.001 (Table 4)

Table 4. Association between demographics factors, clinical and ulcer characteristics with the presence of diabetic foot infections

Variables [n(%)]	Studied groups (n=340)		χ2 value	p-value
Infection	No infection (n=141)	(n=199)		
Gender				
Male	96 (68.1)	120 (60.3)	2.16	0.142
Female	45 (31.9)	79 (39.7)		
Ethnicity				
Malay	51 (36.2)	70 (49.6)	10.1	0.018*
Indian		104 (52.3)		
Chinese	19 (13.5)	17 (8.5)		
Others	1 (0.7)	0 (0)		
Age, years				
<40	10 (7.1)		1.39	0.846
41–50	17 (12.1)	2		
51–60	54 (38.3)	6		
61–70	48 (34.0)	7		
>70	12 (8.5)	1		
Blood glucose (mmol/L)				
<7	10 (7.1)	59 (29.6)	25.9	0.000*
≥7	131 (92.9)	140 (70.4)		
Blood pressure (mmHg)				

Variables (N=340) [n(%)]	Studied groups		χ2 value	p-value
Infection	No infection (n=141)	(n=199)		
Anatomical region				
Hindfoot	19 (13.5)	23 (11.6)	2.71	0.910
Midfoot	22 (15.6)	37 (18.6)		
Forefoot	47 (33.3)	56 (28.1)		
Hallux	16 (11.3)	21 (10.6)		
Toes	19 (13.5)	31 (15.6)		
Malleolus	7 (5.0)	10 (5.0)		
Leg	8 (5.7)	13 (6.5)		
Other area	3 (2.1)	8 (4.0)		
Location				
Dorsal	17 (12.1)	31 (15.6)	2.18	0.949
Plantar	72 (51.1)	104 (52.3)		
Lateral	22 (15.6)	26 (13.1)		
Medial	11 (7.8)	14 (7.0)		
Anterior	3 (2.1)	4 (2.0)		
	2 (1.4)	4 (2.0)		
Posterior	7 (5.0)	10 (5.0)		
	7 (5.0)	6 (3.0)		
Web spac				

<140/90	50 (35.5)	126 (63.3)	25.6	0.000*
≥140/90	91 (64.5)	73 (36.7)		
History of amputation				
Yes	47 (33.3)	54 (27.1)	1.52	0.218
No	94 (66.7)	145 (72.9)		
Presence of comorbidities				
Yes	91 (64.5)	117 (58.8)	1.15	0.284
No	50 (35.5)	82 (41.2)		
Ulcer size				
Cross-sectional Area (cm^2)				
<2	16 (11.3)	51 (25.6)	18.9	0.000*
2–10	38 (27.0)	70 (35.2)		
>10	87 (61.7)	78 (39.2)		
e Other				
Renal failure				
Yes	24 (17.0)	28 (14.1)	0.56	0.456
No	117 (83.0)	171 (85.9)		
Hypertension				
Yes	74 (52.5)	86 (43.2)	2.84	0.092
No	67 (47.5)	113 (56.8)		
Hyperlipidaemia				
Yes	14 (9.9)	10 (5.0)	3.03	0.082
No	127 (90.1)	189 (95.0)		
Ischaemia				
Yes	10 (7.1)	12 (6.0)	0.15	0.695
No	131 (92.9)	187 (94.0)		

Pearson Chi-Square (χ2) test *Statistically significant, $p<0.05$

Risk factors for diabetic foot infection

A binary logistic regression analysis was conducted in order to estimate the risk factors that influence the presence of infection in patients with DFU. This analysis only covered those with a p-value of <0.025 from univariate chi-square analysis. Assumption testing conducted before the analysis did not indicate any violations. The omnibus model for the logistic regression analysis was statistically significant, $p < 0.001$, Cox and Snell R2=0.181, Nagelkerke R2=0.244. The model was 67.1% accurate in its prediction of risk factors for the presence of DFI. Hosmer and Lameshow test results confirmed that the model was a good fit for the data, p=0.087. Coefficients for the model's predictors are presented in Table 5. Ethnicity, wound size, blood pressure and fasting blood glucose were the predictors which significantly influence the presence of infection among the patients with DFUs (Table 5). The odd ratios for ulcer size indicated that patients with a DFU of 2–10cm2 were 1.31 times more likely to develop infection as compared with a smaller DFU size of < 2cm2 (OR: 1.31, 95%CI: 0.62 to 2.75) while the patients with a DFU size >10cm^2 were 2.9 times more likely to develop infection.

Table 5. Predictor coefficients for infected diabetic foot ulcer

Variables	b	SE(b)	p	Exp(B) [95 % CI]
Ethnicity				
Malay	0.004			
Indian	0.811	0.264		1 2.25 [1.34, 3.78]
Chinese	1.221	0.419	0.004	0.002 3.39 [1.49, 7.70]
Wound size (cm^2)				
<2	0.001	1		
2–10	0.267	0.380	0.482	1.31 [0.62, 2.75]
>10	1.066	0.355	0.003	2.90 [1.45, 5.82]
Blood pressure (mmHg)				
<140/90	1			
≥140/90	0.925	0.253	0.000	2.52 [1.54, 4.14]
Fasting blood glucose (mmol/l)				
<7	1			
≥7	1.226	0.395	0.002	3.41 [1.57, 7.39]

Binary Logistic Regression; p-value<0.05; CI—confidence interval; SE— standard error

Healing time

Despite the high DFI rate, the mean healing time for patients with a DFU was 4.49 months while the median healing time was three months. Among all patients, 57.6% (n=196) healed within one month, 14.8% (n=50) healed within one to six months and 27.6% (n=94) of them took >6 months to be healed (Table 6). Mann-Whitney U test indicated that the healing time of the patients with a history of amputation (mean rank: 193.38; n=101) was significantly longer than those of the subjects without history of amputation. The majority of amputations among the patients was toe amputation. Longer healing time was significantly observed for DFI (mean rank: 215.02; n=141) compared to DFU without infections (mean rank: 138.96; n=199) U= 7752, z=−7.237, p<0.001, two-tailed.

Table 6. Association between demographic, clinical and ulcer characteristics with healing time of diabetic foot ulcers

Variables	Healing time (months) Median	Mean rank	p-value
Gender[a]			
Male	3.0	175.27	0.224
Female	2.0	162.19	
Ethnicity[b]			
Malay	2.0	164.62	0.275
Indian	3.0	173.13	
Chinese	3.0	180.58	
Age[a] (years)			
<50	2.0	167.71	0.798
≥50	3.0	171.13	
History of a	mputation[a]		
Yes	4.0	193.38	0.004*
No	2.0	160.83	
Presence of	comorbidities[a]		
Yes	3.0	173.52	0.464
No	2.5	165.74	
Presence of	infection[a]		
Yes	5.0	215.02	0.000*
No	1.0	138.96	
Fasting bloo	d glucose[a] (mmol/l)		
<7	1.0	89.76	0.000*
≥7	4.0	191.06	
Blood press	ure[a] (mmHg)		
<140/90	1.0	123.51	0.000*
≥140/90	5.0	220.93	
Ulcer size[b] (	cm^2)		
<2	1.0	127.72	0.000*
2–10	2.5	162.65	
>10	4.0	193.01	
Location of	wound[a]		
Plantar	3.0	182.14	0.020*
Non plantar	2.0	158.01	
Wound anat	omical region[b]		
Hindfoot	2.0	160.90	0.077
Midfoot	3.0 4.0	180.70	
Forefoot		188.63	
Hallux	1.0	138.91	
Toes	2.5	155.24	
Malleous	4.0	196.74	
Leg	1.0	146.50	
Other area	2.0	163.55	
Renal failur e	a		
Yes	2.0	150.77	0.105
No	3.0 na	174.06	
Hypertensio			
Yes	3.0	174.32	0.486
No	3.0	167.10	

Hyperlipida	emia[a]		
Yes	3.0	179.75	0.622
No	3.0	169.80	
Ischaemia [a]			
Yes	2.0	151.11	0.325
No	3.0	171.84	
[a]Mann-Whitney	U test [b]Kruskal-Wallis One-Way ANO VA [*]Statistically significant, p<0.05		

DISCUSSION:

In this study, the clinical characteristics of DFU size was found to be relatively large, with a mean cross-sectional area of 21.5±33.2cm2. This is accompanied by a relatively high prevalence of DFI at 41.5%, in comparison with a range of 9–40 % of DFI that have been reported in Texas, America and Queensland, Australia, respectively.21,22 The severe DFUs observed in this study were due to the referral nature of the chosen study site. In addition, patients from a rural area tend to resort to traditional treatment as their first option, based on their health beliefs. Insufficient wound and diabetes care centres in rural areas hamper patients from seeking professional wound management at the early stages. Furthermore, Malaysia is a developing country with a high prevalence of uncontrolled diabetes, with a mere 23% of patients with type 2 diabetes achieving a good control of HbA1c 2cm2) were more likely to develop infection for their DFU. The association between the presence of infection and ethnicity was unexpected since there is limited data on racial and ethnic disparities in DFI. Although there were fewer Indian and Chinese patients with DFUs in the clinic, almost half had DFI.

DFU patients with poorly controlled blood glucose were 3.4 times more likely to develop DFI compared with those with good blood glucose control. The hyperglycemic environment in patients with diabetes favors immune dysfunction via reduction in neutrophil activity. It lowers the efficiency of the body's defense system against infection by reducing antibacterial activity, thus increasing the risk of infection. Oxidative stress in the wound due to a high glucose level also provides a conducive environment for anaerobe growth and infection. In line with other studies, results from the binary logistic regression analysis showed that DFU size was the risk factor for DFI as a larger size increases the risk of infection. Larger the DFU size increases the risk of wounds spreading from the superficial layer to deeper tissues, potentially leading to cellulitis, deep abscesses, osteomyelitis and chronic ulcers. Larger DFU size (>2cm2) and deep wounds that penetrate to the bone structure were also shown to be associated with higher levels of bone infection.

CONCLUSION:

Our results highlight the prevalence of DFI managed in a clinic with high blood pressure (≥140/90mmHg), fasting blood glucose (≥7mmol/l) large DFU size. Increase in healing time of DFUs was correlated with a history of amputation, presence of infection, high blood glucose level, high blood pressure, large DFU size and location on the plantar. The results also showed that, despite being extensively educated, treated with proper wound care and provided with proper offloading, 14.8% of the DFUs patients healed within one to six months and 27.6% of them took >6 months to be healed. Thus, recognizing factors associated with delayed wound healing is important to gain a better understanding of DFUs that do not respond adequately to the treatment. Identifying patients with high risk of delayed healing allows early intervention and preventative measures in future treatments.

REFERENCES:

1. Boulton AJ. The diabetic foot: from art to science. The 18th Camillo Golgi lecture. Diabetologia 2004; 47: 1343
2. Boulton AJ, Vileikyte L, Ragnarson-Tennvall G, Apelqvist J. The global burden of diabetic foot disease. Lancet 2005; 366: 1719
3. Brem H, Sheehan P, Rosenberg HJ, Schneider JS, Boulton AJ. Evidence-based protocol for diabetic foot ulcers. Plast Reconstr Surg 2006; 117: 193S.
4. Boyko EJ, Ahroni JH, Cohen V, Nelson KM, Heagerty PJ. Prediction of diabetic foot ulcer occurrence using commonly available clinical information: the Seattle diabetic foot study. Diabetes Care 2006; 29: 1202
5. Apelqvist J, Ragnarson-Tennvall G, Persson U, Larsson J. Diabetic foot ulcers in a multidisciplinary setting. An economic analysis of primary healing and healing with amputation. J Intern Med 1994; 235: 46371.

6. Boulton AJ, Connor H, Cavanagh PR. The foot in diabetes. Chichester, UK: Wiley; 2000, pp. 24560.
7. Reiber GE, Vileikyte L, Boyko EJ, del Aguila M, Smith DG, Lavery LA, et al. Causal pathways for incident lower-extremity ulcers in patients with diabetes from two settings. Diabetes Care 1999; 22: 15762.
8. Ko¨veker GB. Growth factors in clinical practice. Int J Clin Pract 2000; 54: 5903.
9. Pfeffer F, von Dobschuetz E, Riediger H, Moosmann C, Hopt UT. The non-healing wound [Article in German]. MMW Fortschr Med 2004; 146: 45
10. Consensus Development Conference on Diabetic Foot Wound Care: 7April 1999, Boston, Massachusetts. American Diabetes Association. Diabetes Care 1999; 22: 1354
11. Ince P, Kendrick D, Game F, Jeffcoate W. The association between baseline characteristics and outcome of foot lesions in a UK population with diabetes. Diabet Med 2007; 24: 97781.
12. Aguiree F, Brown A, Cho NH et al. IDF diabetes atlas
13. Pfeffer F, von Dobschuetz E, Riediger H et al. [The non-healing wound] [Article in German] MMW Fortschr Med 2004; 146:45–48
14. American Diabetes Association. Diabetes Care; Consensus Development Conference on Diabetic Foot Wound Care; 7–8 April 1999; Boston, Massachusetts. American Diabetes Association 1999; 22(8):1354–1360
15. Musa HG, Ahmed ME. Associated risk factors and management of chronic diabetic foot ulcers exceeding 6 months' duration. Diabet Foot Ankle 2012; 3(1):18980. https://dx.doi.org/10.3402%2Fdfa.v3i0.18980
16. Kantor J. Expected healing rates for chronic wounds. Wounds. 2000; 12:155–158
17. Al-Wakeel JS, Hammad D, Al Suwaida A. et al. Microvascular and macrovascular complications in diabetic nephropathy patients referred to nephrology clinic. Saudi J Kidney Dis Transpl 2009; 20(1):77–85
18. Ahmed AA, Algamdi SA, Algurashi A. et al. Risk factors for diabetic foot ulceration among patients attending primary health care services. J Diabet Foot Complications. 2014; 6:40–47
19. Jones KR, Fennie K, Lenihan A. Chronic wounds: factors influencing healing within 3 months and nonhealing after 5-6 months of care. Wounds 2007; 19(3):51-63