RISK OF NON-HEALING IN ISCHEMIC VERSUS NEUROPATHIC DIABETIC FOOT ULCERS IN RELATION TO GRADE, STAGE OF INFECTION AND TREATMENT PROTOCOL: A FOLLOW-UP STUDY

Hafiza Ammarah Sadiq,[1] Mehwish Iftikhar,[2] Rajia Liaqat,[3] Amna Rizvi,[4] Azhar Hussain,[5] Muhammad Ijaz Bhatti,[6] Ahmed Zafar Khan,[7] Aysha Zafar,[8] Fatima Javed[9]

Abstract

Background & Objectives: Diabetic foot ulcer (DFU) is a potentially crippling consequence of diabetic foot disease. Aim of this study was to determine the risk of non-healing in ischemic as compared to neuropathic diabetic foot ulcers in relation to its grade and stage of infection.

Methods: This prospective non-interventional study was conducted from July 2019 to February 2020 in Diabetes Management Center, Services Hospital Lahore Pakistan. Patients presenting with DFU were assessed for neurological and vascular status in the lower limbs. Ulcer grading was determined by Wagner's and Texas classification. Patients were followed up to 2-6 months for healing status of the diabetic foot ulcer.

Results: Of 132 patients, 97 (73%) patients presented with neuropathic ulcer and 35 (27%) were having ischemic ulcers. Most participants were aged between 40-59 years. Based on Wagner's ulcer classification, it was observed that patient with score 2 had three times more likely to have their ulcer healed compared to those with score 1 and 3 [OR =3.09(95% CI:0.62-15.38, P=0.17)]. Kaplan-Meier survival curves showed that healing pattern among ischemic ulcer is considerably better compared to neuropathic foot ulcers. The evidence of equal survival hypothesis using Log-rank (Mantel Cox) test was statistically significant ($p<0.001$). No statistically significant difference in healing pattern through time was found across Wagner's scoring categories.

Conclusion: Peripheral neuropathy was the commonest pathology underlying DFU presenting at our tertiary level diabetes clinic. Early detection of neuropathy and timely foot care may help prevent ulceration with its often-grave consequences.

Key words: Diabetic foot ulcer, Neuropathy, Ischemia, Neuro-ischemic foot ulcer, Wound infection

How to cite: *Sadiq HA, Iftikhar M. Liaqat R, Rizvi A, Hussain A, Bhatti MI, Khan AZ, Zafar A, Javed F.* Risk of Non-healing in Ischemic Versus Neuropathic Diabetic Foot Ulcers in Relation to Grade, Stage of Infection and Treatment Protocol: A Follow-up Study *JAIMC 2023; 21(1): 4-8*

1. *Al-Aleem Medical College/ Gulab Devi Hospital Lahore Pakistan*
2,4. *Department of Endocrinology, Services Institute of Medical Sciences Lahore Pakistan*
3. *Department of Pathology, Al-Aleem Medical College/ Gulab Devi Hospital Lahore Pakistan*
5. *Department of Gastroenterology, Services Institute of Medical Sciences Lahore, Pakistan*
6. *Department of Cardiology, Al-Aleem Medical College/ Gulab Devi Hospital Lahore Pakistan*
7. *University College/ School of Medicine Dublin, Ireland*
8. *Khalifa University College of Medicine and Health Sciences, UAE*
9. *CMH Lahore Pakistan*

Correspondence:
Dr. Hafiza Ammarah Sadiq, *Senior Registrar Al Aleem Medical College, Gulab Devi Hospital Lahore.*

Submission Date: 12-01-2023
1st Revision Date: 14-03-2023
Acceptance Date: 25-03-2023

The term "diabetic foot" refers to a condition where the foot of a patient suffering from diabetes develops various levels of ulceration, infection, or damage to the deeper tissues, typically linked with peripheral vascular disease or neurological abnormalities in the lower extremity. A diabetic foot ulcer (DFU) is a full thickness dermal wound below the level of the ankle on exposed or weight-bearing parts of the foot in a patient suffering from diabetes. Diabetic foot disease begins with an infection progressing to foot ulcers, gangrene, foot deformities, and finally may result in amputations. The cost to the individual patient, his family and society, in terms of loss of mobility, low quality of

life, loss of income, and cost of treatment is huge.[1,2] Prevalence of DFU is 6.3% globally,[3] whereas lifetime incidence of foot ulcer in a diabetic person can reach up to 25%.[4] In Pakistan, diabetic foot disease prevalence ranges from 4% to 10%, and the amputation rate after developing foot ulcers is between 8% and 21%.[5] The cost of care of diabetic foot syndrome (DFS) increases significantly following the appearance of foot ulcers. In the first year, it is 5.4 times higher than for diabetic patients without foot ulcers, and in the second year, it is 2.8 times higher.[6] The management of diabetic foot disease costs between 9 to 13$ billion in USA due to lost earning potential and treatment costs.[7] Although hospital stays have become shorter due to better surgical treatment and the use of improved glycemic control and multidisciplinary strategies; the number of major lower extremity amputations has not decreased.[8]

The development of a diabetic foot ulcer is the outcome of various pathological processes, including underlying diseases like peripheral vascular and neuropathy and poor glycemic control; each of which contributes to its genesis and progression. When someone has chronic high blood sugar levels, it triggers a series of metabolic pathways downstream. These pathways include excessive release of cytokines, formation of more advanced glycation end products, increased activity in the polyol pathway, activation of protein kinase C, and a higher level of oxidative stress. Over time, these deranged metabolic processes lead to the development of vascular insufficiency and nerve damage.[9] Furthermore, when the blood flow to the skin is inadequate due to micro vascular insufficiency, it causes arteries and arterioles of the skin to contract abnormally.[10]

Diabetic foot ulcers usually begin at vulnerable spots which are abnormal plantar pressure points occurring as a result of foot deformity, which is a long-term sequel of diabetic peripheral neuropathy.[11-13] Direct consequences of foot ulcers include chronic non-healing ulcers, osteomyelitis, systemic sepsis, amputation and even death. In addition, worsening of glycemic control occurs as a consequence of mobility restriction and wound infection, which in turn leads to progression of other diabetic complications.[14]

Optimum management of foot ulcer requires an accurate ulcer evaluation. This involves assessment of ulcer severity, presence of infection and the underlying patho-physiological condition.[15] Many systems for ulcer severity grading have been described, but the most widely used grading systems are the Wagner's classification and the University of Texas ulcer grading systems. The former system grades ulcer by its depth and presence of gangrene, while the latter also considers the presence of infection and underlying ischemia.[16] The presence of infection can be assessed clinically and confirmed on wound cultures. The patho-physiological categorization is based upon assessment for the presence of peripheral vascular ischemia and peripheral neuropathy. The former may be tested clinically by checking the ankle brachial pressure index or by peripheral arterial Doppler ultrasound, while the latter evaluation is usually done by peripheral sensory examination using at least a 10g monofilament and tuning fork, and more formally by biothesiometry or nerve conduction studies.[17,18] Previous studies have shown that the vast majority of diabetic foot ulcers occur in neuropathic and neuro-ischemic feet, while purely ischemic ulcers are less common.[19] Some authors have indicated that neuropathic ulcers tend to have a higher grade of ulcer severity as well as a higher rate of infection due to continued weight bearing on insensate feet compared to ulcers occurring in feet with intact sensations.[17] On the other hand, among ischemic ulcers, delayed ulcer healing has been observed compared to non-ischemic ulcers.[20]

Clinical characterization of diabetic foot ulcers, including assessment of ulcer severity, presence of infection and an assessment of the underlying etiology is essential for risk stratification, optimizing management, and reducing debilitating complications. This prospective study aimed to determine the risk of non-healing of diabetic foot ulcers in relation to its grade, stage of infection and treatment protocol while comparing ischemic versus neuropathic ulcers and to correlate these with ulcer severity, grading, presence of infection and short term outcomes (complete healing,

non-healing ulcers, amputation and/or death).

METHODS

This prospective, non-interventional study was conducted at a tertiary care teaching hospital of Lahore city in Pakistan. Ethical approval for this study was granted by institutional review board Services Institute of Medical Sciences (SIMS) Lahore (IRB/ 2019/562/SIMS). Participants were recruited between July 2019 and December 2020 and then followed up to June 2021. Sample size of 132 was found to be suitable to detect the effect size. This sample size was calculated using WinPEPI software, taking prevalence of diabetic foot ulcer as 5 % and at 5 % precision around the prevalence, using formula:$n=z^2pq/d^2$ (Where z = 1.96, p=5% and d=5%). Recruitment was consecutive with non-probability convenient sampling technique. Those adult patients with DFU and with serious co-morbid conditions requiring emergency treatment and those unwilling to participate were excluded. Only patients presenting in out-patient department were included in sample. After taking informed consent, patients were clinically evaluated for diabetes status, complications and their management as per departmental guidelines. Peripheral neuropathy was diagnosed based on pain in the feet, legs or hands, decreased or loss of sensation and/or degree of numbness; and confirmed by 10g mono-filament test and 128 Hz Tuning Fork test. Assessment for vascular insufficiency included palpation of arterial pulses in the popliteal, posterior tibial and dorsalis pedis arteries of both limbs, followed by measurement of Ankle brachial index (ABI) using a hand-held Doppler (Vascular Doppler HI DOP – NSL – BT-200V BISTOS (KOREA) with a frequency of 8 mHz on both sides. ABI>0.9 was taken as normal, while ABI<0.9 was considered to indicate peripheral arterial disease (PAD). PAD was further sub classified into mild to moderate PAD, (ABI 0.4 to 0.9), and severe PAD (ABI <0.4). Ankle brachial pressure index of the patient was measured on both sides, using a handheld Doppler probe and aneroid sphygmomanometer gauge. Biochemical tests like HbA1c, complete blood count, renal function tests, fasting lipid profile were done. A sterile swab was used for wound cultures, taken to confirm infection. Stratification of wound infection was done with Wagner's grade and Taxas grading system (Table 1).[21] Patients were managed according to standard guidelines based upon the type of wound and presence of infection. Modified proforma from the Model of Care for the Diabetic foot was used.22 Considering COVID-19 restrictions, we switched our plan of regular physical follow up for measuring outcomes to interviewing participants on telephone using a structured questionnaire, and using WhatsApp to visually inspect the ulcer site. Non-healing status of neuropathic and ischemic types of ulcers during follow up follow-up time was the primary outcome. SPSS 25.0 version was used to manage data and its coding. Age of participants was examined both as a quantitative and qualitative variable. Sex, type of diabetes mellitus (DM), duration of DM, macrovascular complications, smoking status, status of wound, nephropathic stage (eGFR) were stratified and its comparison was carried out between neuropathic and ischaemic ulcers. Pathophysiological characterization and severity grading of diabetic foot ulcers were also analyzed based on Wagner's and Texas staging and grading system. Statistical significance for difference in proportions and difference in means were calculated using Pearson's Chi-Squared test and Student's t-test respectively. Fisher's Exact test was used when cell values were less than five. P-value less than 0.05 was considered statistically significant.

Logistic regression modelling was used with scores 1 and A in the Texas stage were used as reference category (OR=1). Model estimates were adjusted for age, sex, type of DM, duration of DM, Control of DM based on HBA1c, and smoking status. Kaplan-Meier survival analysis was used to estimate median healing times and a log-rank test was used to compare healing times for different levels of grade or stage. Hazard ratios with 95% Confidence intervals were estimated using Cox's proportional hazard regression model. Model estimates were adjusted for age, sex, type of DM, duration of DM, Control of DM based on HBA1c, and

smoking status. The proportional hazard assumption was examined and there was no significant violation of this assumption. Non-healing was coded 1 as our primary outcome and P value < 0.05 was considered significant.

RESULTS

The aim of this prospective study was to determine risk of non- healing of diabetic foot ulcers in relation to its grade, stage of infection and treatment protocol while comparing ischemic against neuropathic ulcers. Table 2 describes the baseline characteristic of participants with DFU. Of 132 participants 97(73%) patients had neuropathic ulcers and 35(27%) were diagnosed with ischemic ulcers respectively. Most participants were males with average age of those with ischemic ulcers was two years higher than those with neuropathic ulcers; with majority were between aged 40-59 years; yet no statistically significant difference was observed in these individuals. About 68% patients with neuropathic ulcers were males compared to 74% with ischemic ulcers. As regards smoking status, no statistically significant difference was observed among those with neuropathic versus ischemic ulcers patients (p=0.66). Most participants had type 2 Diabetes Mellitus and more than fifty percent patients had DM for ten years or less (Table 2). Regarding diabetic control of these patients, we found that more than 90% of both neuropathic and ischemic ulcer patients have poor diabetic control with HBAIc level more than 7%. Both neuropathic and ischemic ulcers patients did not give history of myocardial infarction or cardiovascular accidents, however, the difference of reporting myocardial infarction between those with neuropathic ulcer and ischemic ulcers was statistically significant (p=0.007). We found that a total of 33 patients (34%) with neuropathic ulcers and 18 patients (51.4%) with ischemic ulcers had infected wound, but this difference was not found to be statistically significant (p=0.07). Regarding the ulcer outcome in terms of healing, 82 (85%) of the patients with neuropathic ulcers and 26 (74%) patients with ischemic ulcers reported complete healing of ulcer, but there was no significant difference in healing versus non-healing found among these two types of ulcers (p=0.18).

Table 1: *Wagner's and Texas ulcer grading and staging System* [21]

Wagner's ulcer score

Score	Description
1	Superficial ulcer –not infected
2	Deep ulcer, with or without cellulitis, no abscess or bone involvement
3	Deep ulcer with bone involvement or abscess formation
4	Localized gangrene (toe, forefoot, heel)
5	Gangrene of whole foot
Texas's ulcer grading	
1	Superficial wound that does not penetrate tendon, capsule or bone
2	Wound that penetrate tendon or capsule
3	Wound that penetrate bone or joint
Texas's ulcer stage	
A	Clean wound
B	Non-Ischemic infected wound
C	Ischemic non-infected wound
D	Ischemic infected wound

Table 3 represents Pathophysiological characterization and severity/grading of diabetic foot ulcers based on Wagner and Texas classification systems. Using Wagner's ulcer score, categorizing the ulcer based on its depth and presence of gangrene, it was found that 55 patients with neuropathic ulcers (56.7%) where having superficial ulcers without infection (Score 1), whereas 23 patients (24%) having deep ulcer with or without infection (score 2). Likelihood of healing DFU based on Wagner ulcer score, it was observed that patient with score 2 had three times more likely to have their ulcer healed compared to those with score 1 and 3; OR =3.09 (95% CI:0.62-15.38, P= 0.17) (Table 4). Comparatively, of 35 patients with ischemic ulcers, 13 (37%) were categorized as score-1 and 10 (28.6%) were given score 3 (deep ulcer with bone involvement). The likelihood of healing of ischemic ulcers of those patients with score 3 and above was higher [OR =1.09 (95% CI 0.12 -9.58, P=0.94)] compared to patients at score 1 and 2 (Table 4).

The risk of non-healing of DFU, hazard ratios comparing healing of DFU among patients with neuropathic against ischemic ulcers, in relation to Wagner

Table 2: *Baseline characteristics of participants with diabetic foot ulcers attending Diabetic Centre of Services Hospital Lahore (n=132)*

Characteristics	Patients with Neuropathic ulcers (n=97)		Patients with Ischemic ulcers (n=35)		*P**
	Numbers	Percentage	Numbers	Percentage	
Age (in groups)					
Less than 40 years	10	10.3	02	5.7	0.71
40-59 years	54	55.7	20	57.1	
60 years and above	33	34.0	13	37.1	
Sex					
Males	66	68.0	26	74.3	0.49
Females	31	32.0	09	25.7	
Smoking Status					
Smoker	20	20.6	06	17.1	0.66
Non-Smoker	77	79.4	29	82.9	
Type of Diabetes Mellitus					
Type I DM	23	23.7	08	22.9	0.91
Type II DM	74	76.3	27	77.1	
Duration of Diabetes Mellitus					
10 years or less	54	55.7	18	51.4	0.67
More than 10 years	43	44.3	17	48.6	
Diabetic Control (based on HbA1c)					
Reasonable control (HbA1c <7 %)	05	5.2	01	2.9	0.49
Poor control (HbA1c ⩾7 %)	92	94.8	34	97.1	
Ever had Myocardial Infarction					
Yes	13	13.4	12	34.3	**0.007**
No	84	86.6	23	65.7	
Ever had Cardiovascular accident					
Yes	07	7.2	01	2.9	0.32
No	90	92.8	34	97.1	
Had Macrovascular complications					
Yes	14	14.4	12	34.3	**0.01**
No	83	85.6	23	65.7	
Had Intermittent Claudication					
Yes	03	3.1	07	20.0	**0.004**
No	94	96.9	28	80.0	
Have Diabetic Retinopathy					
Yes	14	14.4	04	11.4	0.45
No	83	85.6	31	88.6	
Nephropathy Stage (based on eGFR)					
eGFR 59 or less	15	15.5	06	17.1	0.87
eGFR 60-90	41	42.3	16	45.7	
eGFR>90	41	42.3	13	37.1	
Whether ulcer wound infected?					
Yes	33	34.0	18	51.4	0.07
No	64	66.0	17	48.6	
Ulcer healing outcome					
Healed	82	84.5	26	74.3	0.18
Not Healed	15	15.5	09	25.7	

ulcer scoring, we found that superficial ulcers (Score 2) had higher chance of healing compared to deep ulcers or ulcers with gangrene [HR:0.82 (95% CI: 0.47- 1.43, p=0.48].(Table 5). On the other hand, the estimates for patients with ischemic ulcers for healing pattern using Wagner's ulcer scoring were insignificant and unremarkable (p=0.68). (Table 5).

Figure 1 depicts Kaplan-Meier survival curves

Table 3: *Patho-physiological characterization and severity grading of diabetic foot ulcers based on Wagner and Texas classification, among patients attending Diabetic Centre of Services Hospital Lahore (n=132)*

	Classification system	Patients with Neuropathic ulcers (n=97)		Patients with Ischemic ulcers (n=35)	
Score		**Numbers**	**Percentage**	**Number**	**Percentage**
Wagner's ulcer score					
1	Superficial ulcer –not infected	55	56.7	13	37.1
2	Deep ulcer, with or without cellulitis, no abscess or bone involvement	23	23.7	09	25.7
3	Deep ulcer with bone involvement or abscess formation	15	15.5	10	28.6
4	Localized gangrene (toe, forefoot, heel)	04	4.1	03	8.6
5	Gangrene of whole foot	0	0	0	0
Texas's ulcer grading					
1	Superficial wound that does not penetrate tendon, capsule or bone	78	80.4	28	80.0
2	Wound that penetrate tendon or capsule	16	16.5	06	17.1
3	Wound that penetrate bone or joint	03	3.1	01	2.9
Texas's ulcer stage					
A	Clean wound	59	60.8	11	31.4
B	Non-Ischemic infected wound	28	28.9	08	22.9
C	Ischemic non-infected wound	05	5.2	06	17.1
D	Ischemic infected wound	05	5.2	10	28.6

Table 4: *Likelihood of healing of diabetic foot ulcers in relation to its stage and grades using Wagner and Texas scoring system in patients attending Diabetic Centre of Services Hospital Lahore (n=132)*

Classification system	Patients with Neuropathic ulcers (n=97)			Patients with Ischemic ulcers (n=35)		
Wegener's ulcer score*						
	Odds ratio	95% CI	*p*	**Odds Ratio**	95% CI	*p*
Score 1	**Reference**	**Reference**		**Reference**	**Reference**	
Score 2	3.09	0.62- 15.38	**0.17**	0.37	0.04 - 3.65	**0.39**
Score 3 and above	1.65	0.30 - 8.96	**0.56**	1.09	0.12-9.58	**0.94**
Texas's ulcer grading**						
Grade 1	**Reference**	**Reference**		**Reference**	**Reference**	
Grade 2 and above	5.72	1.09 - 29.87	**0.04**	0.92	0.13 -6.61	**0.93**
Texas's ulcer stage***						
Stage A	**Reference**	**Reference**		**Reference**	**Reference**	
Stage B	2.87	0.34- 24.22	**0.33**	0.41	0.05 - 3.46	**0.42**
Stage C and above	2.02	0.22 - 18.20	**0.53**	0.42	0.03 - 5.49	**0.51**

Footnotes: Logistic regression modelling was used. with score 1 & A in Texas stage were used as reference category (OR=1). Model estimates are adjusted for age, sex, type of DM, duration of DM, Control of DM based on HBA1c, smoking status

* **Wegener's ulcer Score:** Score 1: Superficial ulcer –not infected;Score 2. Deep ulcer, with or without cellulitis, no abscess or bone involvement; Score 3=Deep ulcer with bone involvement or abscess formation; score 4= Localized gangrene (toe, forefoot, heel); score 5= Gangrene of whole foot

** **Texas's ulcer Grading:** Grade 1= Superficial wound that does not penetrate tendon, capsule or bone; Grade 2= Wound that penetrate tendon or capsule; Grade 3= Wound that penetrate bone or joint.

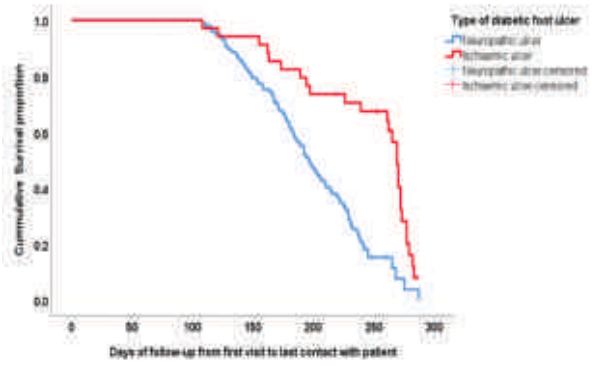
*** **Texas's ulcer stage:** Stage A= Clean wound; Stage B= Non-Ischemic infected wound; Stage C= Ischemic non-infected wound; Stage D= Ischemic infected wound

Table 5: *Hazard Ratio with 95% confidence intervals comparing healing of diabetic foot ulcers (neuropathic versus ischemic) in relation to its stage and grades using Wagner and Texas scoring system in patients attending Diabetic Centre of Services Hospital Lahore (n=132)*

Classification system	Patients with Neuropathic ulcers (n=97)			Patients with Ischemic ulcers (n=35)		
	Hazard Ratio	95% CI	*p*	Hazard Ratio	95% CI	*p*
Wagner's ulcer score						
Score 1	**Reference**	**Reference**		**Reference**	**Reference**	
Score 2	0.82	0.47- 1.43	0.48	1.06	0.32- 3.48	0.92
Score 3 and above	0.73	0.35- 1.51	0.39	1.22	0.45- 3.30	0.68
Texas's ulcer grading						
Grade 1	**Reference**	**Reference**		**Reference**	**Reference**	
Grade 2 and above	0.28	0.12- 0.63	0.002	1.54	0.52-4.53	0.43
Texas's ulcer stage						
Stage A	**Reference**	**Reference**		**Reference**	**Reference**	
Stage B	1.43	0.84- 2.42	0.17	0.97	0.22-4.33	0.97
Stage C and above	0.98	0.45- 2.13	0.96	0.52	0.15-1.77	0.29

Abbreviations: HR, Hazard ratio; CI, confidence interval; DM, Diabetes Mellitus
Footnotes: Cox's proportional hazard regression modelling was used. Model estimates are adjusted for age, sex, type of DM, duration of DM, Control of DM based on HBA1c, smoking status.

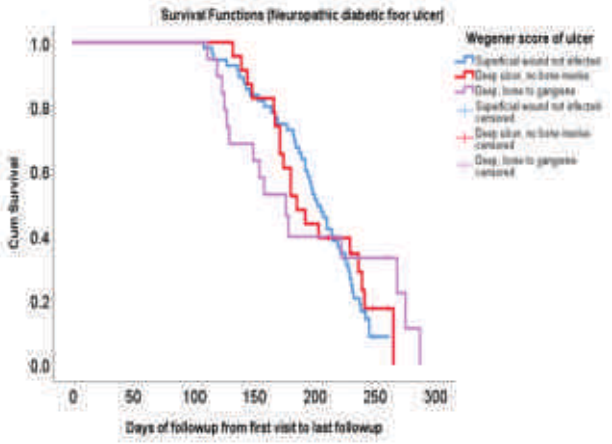
showing healing through time of neuropathic versus ischemic diabetic foot ulcers among patients. We observed that the healing pattern among ischemic ulcer is considerably better compared to neuropathic ulcers and there is strong evidence against the hypothesis of equal healing of ulcers in time (Log-rank (Mantel Cox) test= p<0.001.



Footnote: *Log-rank (Mantel Cox) p<0.001 (Rejecting null hypothesis of equal survivor)*

Figure 1: *Kaplan-Meier survival curves showing healing trend (through time) of neuropathic diabetic foot versus ischemic diabetic foot ulcers among patients attending Diabetic Centre of Services Hospital Lahore Pakistan (n=132)*

Figures 2 depicts the survival pattern (healing) of diabetic neuropathic ulcers (Mantel Cox p =0.86) and diabetic ischemic ulcers (Mantel Cox p =0.07) based on Wagner ulcer scores respectively. We found no statistically significant difference in healing pattern through time across the scoring categories. Finally, we did not find any statistically significant difference in healing through time using Texas staging and grading (data not shown).



Footnote: *Log-rank test (Mantel Cox) p=0.86 (no statistical significant difference in healing)*

Figure 2: *Kaplan-Meier survival curves showing healing trend of diabetic neuropathic ulcers based on Wegener's ulcer score, among patients attending Diabetic Centre of Services Hospital Lahore Pakistan (n=132)*

DISCUSSION

Worldwide, diabetic foot problems have become most prevalent issues which lead to severe economic crises for the patients, their families, and society.[7] The main underlying reasons of diabetic foot ulcers are diabetic peripheral sensory neuropathies, peripheral vascular diseases, and resulting deformities. Additionally, callus formation, edema, and trauma are commonly identified as the factors that precede the development of diabetic foot ulcers.

Our study showed that there are certain risk factors that are associated with foot ulcers, including having diabetes for a longer period of time and having higher HbA1C levels. Males had a higher frequency of foot ulcers, and several studies have shown that advancing age is also a contributing factor to foot ulceration in diabetic patients.[22] We also found that the frequency of foot ulcers was particularly high among those over the age of 50 which is consistent with the findings of a previous study by Khan et al.[25]

Neuropathy plays a significant role in the development of diabetic foot ulcers (DFU) because it causes the feet to become insensitive and lose their position sense. As a result, patients may injure their feet without realizing it and are unable to take steps to prevent further damage, which impairs the healing process.[25] A decrease in foot pulses has been linked to an increased risk of foot ulcers, and this may be a practical clinical alternative to more complex peripheral vascular assessments. However, the ankle/brachial pressure index has also been identified as an independent risk factor.[26]

Younis et al. found that 74% of ulcers were neuropathic, 19% were neuro-ischemic, and 7% were ischemic.[19] Our study also found that 73.48% of ulcers were neuropathic, and 26.51% were ischemic, which is similar to study by Younis et al. Other studies have reported that around 45-60% of diabetic foot ulcers are purely neuropathic, while approximately 45% have both neuropathic and ischemic components.[27] Similarly, Shahbazian et al.[28] found that 33.3% of the patients suffering from grade 1 or higher DFU had co-morbidities. In our study, we found that 57% of cases had co-morbidities, including 13.6% with retinopathy, 15.9% with an eGFR of 59 ml/min or lower, and 19.7% with macrovascular complications. These co-morbidities contribute to the development of foot ulcers probably due to factors like generalized ischemia, chronic eczema, oozing ulcers in edematous feet as well as immobility.[25]

Jia et al. Found that 37% of cases had neuropathic ulcers, 28.4% had neuro-ischemic ulcers; ischemic ulcers were presented in 6.2%, and the remaining 28.4% reported having other types of ulcers. The overall infection rate of foot ulcers was 40.1% with the highest rate of 42.1% among neuropathic ulcers, 26.4% of these were ischemic ulcers, and 43.8% neuro-ischemic ulcers were infected ($p = 0.11$). Deep ulcers were found in 6.5% of neuropathic ulcers, 3.8% of ischemic ulcers, and 7.5% of neuro-ischemic ulcers ($p = 0.003\%$).[29] Furthermore, past history of amputation was reported in 28.4% of the cases. In our study, we found that 38.6% of patients had wound infections. Neuropathic ulcers accounted for 73% of cases, while ischemic ulcers accounted for 27% of cases. On the other hand, about 34% of the neuropathic ulcers, 51.4% of the ischemic ulcers were infected ($p = 0.07$). Furthermore, 23.7% of neuropathic ulcers and 25.7% of ischemic ulcers had Wagner's grade 2 indicating a deep ulcer without bone involvement.

The most frequent reason for hospitalization related to diabetes is foot ulcer infection, which also remains a significant cause of amputation of the lower limbs. In the presence of neuropathy or peripheral arterial disease, the typical signs of local infection and the local inflammatory response are masked or reduced. Despite appropriate care, diabetic foot ulcers can progress to grave complications like infections, amputations, or even death. Previous studies indicate that peripheral arterial disease (PAD) is a more significant risk factor for diabetic foot ulcers compared to infection, possibly due to the participants from diverse populations. If a diabetic foot ulcer becomes infected, underlying PAD can speed up the infection's progression, leading to greater risk of hospitalization and ultimately amputation.[30] Our study shows that there was a greater infection rate among ischemic type of DFUs; Regarding healing

pattern, it was found that comparing neuropathic diabetic foot with ischemic ulcer, healing pattern among ischemic ulcer is considerably better which may depend upon the level of care such patients are getting over there; lack of diagnostic facilities for neuropathy at primary health care centers can also lead to a delay in diagnosis. Hence, our suggestion is for patients to receive a thorough evaluation, preferably through non-invasive testing methods such as ABI measurements. This will also create an opportunity for conducting larger-scale studies with a more extensive sample size.

Results of this study should be interpreted after considering few limitations. Participants were recruited using convenient sampling and size of sample was relatively small for precise estimates. These issues might limit the generalization of findings. Follow-up was conducted by telephone (due to COVID-19 lockdown) with images of wound were virtually examined. This indirect examination might affect the inconsistency of grading of these wounds. We analyzed the data using both descriptive and inferential statistics especially examined the time to event analysis, which is unique for such data and highlight different aspects of exposure and outcome relationship.

CONCLUSION

Risk of non-healing DFU is significantly higher among those with ischemic diabetic ulcers compared to those with neuropathic ulcers. Infected wound at presentation is an important determinant of its subsequent healing. Early detection of neuropathy and preventive foot care may help prevent ulceration with its resultant disability. In most cases, neuropathy was the primary contributing factor to diabetic foot ulcers rather than peripheral arterial disease.

Conflict of interest: *None*

Funding Source: *None*

REFERENCES

1. Vileikyte L. Diabetic foot ulcers: a quality of life issue. Diabetes Metab Res Rev [Internet]. 2001 [cited 2022 Feb 13];17(4):246–9. Available from: https:// pubmed. ncbi.nlm.nih.gov/11544609/
2. Boulton AJM. Diabetic Foot Complications. European Endocrinology [Internet]. 2006 [cited 2022 Feb 13]; (1):51. Available from: http://www. touchendocrinology. com/articles/diabetic-foot-complications-0
3. Riaz M, Miyan Z, Waris N, Zaidi SIH, Tahir B, Fawwad A, et al. Impact of multidisciplinary foot care team on outcome of diabetic foot ulcer in term of lower extremity amputation at a tertiary care unit in Karachi, Pakistan. International Wound Journal [Internet]. 2019 Jun 1 [cited 2022 Feb 13];16(3):768. Available from: /pmc/articles/PMC7948576/
4. Muduli IC, P. P A, Panda C, Behera NC. Diabetic foot Ulcer Complications and Its management -a Medical College-Based Descriptive Study in Odisha, an Eastern State of India. The Indian Journal of Surgery [Internet]. 2015 Dec 1 [cited 2022 Feb 13];77(Suppl 2):270. Available from: /pmc/articles/PMC4692890/
5. Rehman R, Malik FR, Rehman Z. A comparative study on Daibetes foot ulcers leading to amputations. Journal of Postgraduate Medical Institute [Internet]. 2018 Mar 23 [cited 2022 Feb 13];32(1). Available from: https://jpmi.org.pk/index.php/jpmi/article/view/2030
6. Khan A, Junaid N. Prevalence of diabetic foot syndrome amongst population with type 2 diabetes in Pakistan in primary care settings. J Pak Med Assoc. 2017;67(12):1818–24.
7. Raghav A, Khan ZA, Labala RK, Ahmad J, Noor S, Mishra BK. Financial burden of diabetic foot ulcers to world: a progressive topic to discuss always. Therapeutic Advances in Endocrinology and Metabolism [Internet]. 2018 Jan 1 [cited 2022 Feb 13];9(1):29. Available from: /pmc/articles/PMC5761954/
8. Kim CH, Moon JS, Chung SM, Kong EJ, Park CH, Yoon WS, et al. The Changes of Trends in the Diagnosis and Treatment of Diabetic Foot Ulcer over a 10-Year Period: Single Center Study. Diabetes Metab J [Internet]. 2018 Aug 1 [cited 2022 Feb 13]; 42(4): 308–19. Available from: https://pubmed. ncbi.nlm. nih. gov/ 29885115/
9. Yagihashi S, Mizukami H, Sugimoto K. Mechanism of diabetic neuropathy: Where are we now and where to go? Journal of Diabetes Investigation [Internet]. 2011 Feb [cited 2022 Feb 13];2(1):18. Available from: /pmc/articles/PMC4008011/
10. Khalil H, Cullen M, Chambers H, Carroll M, Walker J. Elements affecting wound healing time: An evidence based analysis. Wound Repair Regen [Internet]. 2015 Jul 1 [cited 2022 Feb 13];23(4):550–6. Available from: https://pubmed.ncbi.nlm.nih.gov/25907979/
11. Kafrawy NAEF al, Mustafa EAAEA, Dawood AED-AES, Ebaid OM, Zidane OMA. Study of risk factors

of diabetic foot ulcers. Menoufia Medical Journal [Internet]. 2014 Apr 1 [cited 2022 Feb 13];27(1):28. Available from: http://www.mmj.eg.net/article. asp?issn=1110-2098;year=2014;volume=27;issue=1;spage=28;epage=34;aulast=Al

12. Pendsey SP. Understanding diabetic foot. International Journal of Diabetes in Developing Countries [Internet]. 2010 Apr 1 [cited 2022 Feb 13];30(2):75. Available from: /pmc/articles/PMC2878694/
13. Noor S, Zubair M, Ahmad J. Diabetic foot ulcer--A review on pathophysiology, classification and microbial etiology. Diabetes Metab Syndr [Internet]. 2015 Jul 1 [cited 2022 Feb 13];9(3):192–9. Available from: https://pubmed.ncbi.nlm.nih.gov/25982677/
14. Mavrogenis AF, Megaloikonomos PD, Antoniadou T, Igoumenou VG, Panagopoulos GN, Dimopoulos L, et al. Current concepts for the evaluation and management of diabetic foot ulcers. EFORT Open Rev [Internet]. 2018 Sep 1 [cited 2022 Feb 13];3(9):513–25. Available from: https:// pubmed.ncbi.nlm.nih.gov/30305936/
15. del Core MA, Ahn J, Lewis RB, Raspovic KM, Lalli TAJ, Wukich DK. The Evaluation and Treatment of Diabetic Foot Ulcers and Diabetic Foot Infections: https://doi.org/101177/2473011418788864 [Internet]. 2018 Aug 3 [cited 2022 Feb 13];3(3). Available from: https://journals.sagepub.com/doi/full/10.1177/2473011418788864
16. Monteiro-Soares M, Boyko EJ, Jeffcoate W, Mills JL, Russell D, Morbach S, et al. Diabetic foot ulcer classifications: A critical review. Diabetes/ Metabolism Research and Reviews. 2020;36(S1):1–16.
17. Ince P, Game FL, Jeffcoate WJ. Rate of healing of neuropathic ulcers of the foot in diabetes and its relationship to ulcer duration and ulcer area. Diabetes Care [Internet]. 2007 Mar [cited 2022 Feb 13];30(3):660–3. Available from: https://pubmed.ncbi.nlm.nih.gov/17327337/
18. Pourhamidi K, Dahlin LB, Englund E, Rolandsson O. Evaluation of clinical tools and their diagnostic use in distal symmetric polyneuropathy. Prim Care Diabetes [Internet]. 2014 [cited 2022 Feb 13];8(1):77–84. Available from: https://pubmed.ncbi.nlm.nih.gov/23664849/
19. Younis B bin, Shahid A, Arshad R, Khurshid S, Ahmad M, Yousaf H. Frequency of foot ulcers in people with type 2 diabetes, presenting to specialist diabetes clinic at a Tertiary Care Hospital, Lahore, Pakistan. BMC Endocr Disord [Internet]. 2018 Aug 6 [cited 2022 Feb 13];18(1). Available from: https:// pubmed. ncbi.nlm.nih.gov/30081878/
20. Lepäntalo M, Apelqvist J, Setacci C, Ricco JB, de Donato G, Becker F, et al. Chapter V: Diabetic foot. Eur J Vasc Endovasc Surg [Internet]. 2011 Dec [cited 2022 Feb 13];42 Suppl 2(SUPPL. 2). Available from: https://pubmed.ncbi.nlm.nih.gov/22172474/
21. Levin ME. Diabetic foot ulcers: pathogenesis and management. J ET Nurs. 1993;20(5):191–8.
22. Hwang DJ, Lee KM, Park MS, Choi SH, Park JI, Cho JH, et al. Association between diabetic foot ulcer and diabetic retinopathy. PLOS ONE [Internet]. 2017 Apr 1 [cited 2022 Feb 13];12(4):e0175270. Available from: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0175270
23. Oyibo SO, Jude EB, Tarawneh I, Nguyen HC, Harkless LB, Boulton AJM. A Comparison of Two Diabetic Foot Ulcer Classification SystemsThe Wagner and the University of Texas wound classification systems. Diabetes Care [Internet]. 2001 Jan 1 [cited 2022 Feb 13];24(1):84–8. Available from: https:// diabetesjournals.org/care/article/24/1/84/21085/A-Comparison-of-Two-Diabetic-Foot-Ulcer
24. National Diabetes Programme Working Group. National Diabetes Programme Working Group. Model of care for the diabetic foot. Dublin: HSE; 2011. [Internet]. Dublin; Available from: http://hdl.handle.net/ 10147/326403%0AFind
25. Khan H, Khan Z, Khan I, Din J, Rehman S, Khan B. Factors contributing to the development of diabetic foot ulcers and role of health literacy. undefined. 2011;
26. Abbott CA, Carrington AL, Ashe H, Bath S, Every LC, Griffiths J, et al. The North-West Diabetes Foot Care Study: incidence of, and risk factors for, new diabetic foot ulceration in a community-based patient cohort. Diabet Med [Internet]. 2002 [cited 2022 Feb 13]; 19 (5): 377–84. Available from: https://pubmed.ncbi.nlm.nih.gov/12027925/
27. Reiber GE, Smith DG, Vileikyte L, Lavery LA, Boyko EJ, Boulton AJM, et al. Causal pathways for incident lower-extremity ulcers in patients with diabetes from two settings. Diabetes Care [Internet]. 1999 Jan [cited 2022 Feb 13];22(1):157–62. Available from: https://www.researchgate.net/publication/12964651_Causal_pathways_for_incident_lowe-extremity_ulcers_ in _ patients_with_Diabetes_from_two_settings
28. Shahbazian H, Yazdanpanah L, Latifi SM. Risk assessment of patients with diabetes for foot ulcers according to risk classification consensus of International Working Group on Diabetic Foot (IWGDF). Pak J Med Sci [Internet]. 2013 [cited 2022 Feb 13];29(3). Available from: https://pubmed.ncbi.nlm.nih.gov/24353617/
29. Jia L, Parker CN, Parker TJ, Kinnear EM, Derhy PH, Alvarado AM, et al. Incidence and risk factors for developing infection in patients presenting with uninfected diabetic foot ulcers. PLoS ONE [Internet]. 2017 May 1 [cited 2022 Feb 13];12(5). Available from: /pmc/articles/PMC5435321/
30. Richard JL, Sotto A, Lavigne JP. New insights in diabetic foot infection. World Journal of Diabetes [Internet].