DOI: 10.7860/JCDR/2023/62070.17645

Original Article

Surgery Section

Characteristics of Neuropathic, Ischaemic and Neuroischaemic Diabetic Foot Ulcers- A Prospective Cohort Study

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ABSTRACT

Introduction: Diabetic Foot Ulcers (DFU) can be divided into neuropathic, ischaemic and neuroischaemic types. Since the pathophysiology is different, it is important to ascertain the outcome data on the three subgroups of DFU.

Aim: To compare and assess the differences in the characteristics and healing process of the three types (Neuropathic, Ischaemic, and Neuroischaemic) of DFU.

Materials and Methods: A prospective cohort study was conducted from April 2019 to July 2021 in the Department of Surgery, Regional Institute of Medical Sciences (RIMS) Hospital, Imphal, Manipur, India. Age, gender, duration of diabetes mellitus, smoking, hypertension, Glycosylated Haemoglobin (HbA1c), aetiology of DFU, osteomyelitis, gangrene, estimated Glomerular Filtration Rate (eGFR), and presence of multiple ulcer were recorded. Healing time and outcome (healed, non healed and amputation) of ulcer were the dependent variable. Data collected were analysed using SPSS-version-21. Fisher's-exact test was used for proportions. Analysis of the time needed for healing was performed using the Kaplan-Meier method. A p-value of <0.05 was taken as significant.

Results: A total of 42 patients were recruited for the study and 29 (69%) were males. Patients in neuropathic, ischaemic and neuroischaemic DFUs were 18,14 and 10, respectively. Hypertension (100%) and smoking history (100%) were present in the ischaemic group. Maximum healing (88.9%) was seen in patient with neuropathic ulcers and maximum non healing (28.6%) and amputation (21.4%) occurred in ischaemic group. Mean (SD) heal time in days were 165.5 (4.62), 141.1 (9.17) and 86.4 (8.02) for ischaemic, neuroischaemic and neuropathic, respectively (p<0.001). The average time in which 50% of patients (median) had healed wounds was 75, 136, and 171 days for neuropathic, ischaemic, and neuroischaemic ulcers, respectively.

Conclusion: Neuropathic DFU has better healing than the other DFUs. Ischaemic DFU have maximum non heal ulcers and amputation.

Keywords: Aetiology, Diabetes mellitus, Duration, Kaplan-meier method

INTRODUCTION

Diabetes mellitus refers to a group of common metabolic disorders that share the phenotype of hyperglycaemia. Depending on the aetiology, the factors contributing to hyperglycaemia include reduced insulin secretion, decreased glucose utilisation, and increased glucose production [1]. According to WHO, an estimated 422 million adults were living with diabetes in 2014. The prevalence of diabetes nearly doubled since 1980, rising from 4.7%-8.5% in the adult population in 2014 [2]. In India, there were 77 million cases of diabetes according to IDF in 2019 [3].

The DFU is a foot affected by ulceration that can be associated with neuropathy and/or Peripheral Arterial Disease (PAD) of the lower limb [4]. The prevalence of DFU among diabetic patients is reported to be between 4%-10% with an estimated lifetime incidence of almost 25% [5]. DFU puts a huge financial burden on the patient and healthcare services. Amputation of the lower limb is 10-20 times more common in diabetic patients and it is estimated that every 30 seconds, a lower limb or a part of the lower limb is lost somewhere in the world as a consequence of diabetes [6].

The DFUs can be divided into neuropathic, ischaemic and neuroischaemic types. Neuropathic DFU form as a result of loss of peripheral sensations. Damage to the motor and sensory nerves leads to muscle wasting and eventually foot deformities. This then provides additional pressure points which are prone to ulceration. The wound margins are undermined and the surrounding skin is calloused. Foot temperature is warm and foot pulses palpable. Ulcers are typically painless [7]. On the other hand, ischaemic ulcers develop due to PAD, which typically involves tibial and peroneal arteries but spares the dorsalis pedis artery. These ulcers occur spontaneously and are associated with pain. It occurs at the edges of the foot, toes, and heels, and they often present with gangrene. Their foot temperature is cold and their pulses are palpable. Neuroischaemic ulcers appear the same as ischaemic ulceration but they are painless due to neuropathy [8].

Foot ulceration requires long and intensive treatment and has important effects on quality of life of patient and is associated with major healthcare costs [9]. Although recently much effort is made to develop international guidelines in order to deliver uniform and structured care, prospective data on outcomes in patients with DFU is limited in the northeast part of India. Moreover, the population of diabetic patients who present with foot ulceration is heterogeneous. Although, most patients have peripheral neuropathy, there are several other characteristics that may vary among patients, such as the presence of peripheral artery disease, infection, and comorbidities. So it is important to ascertain the outcome data on the three subgroups of DFU [10].

Hence, the present study was designed to compare and assess the differences in the characteristics and healing process of these three types of DFU namely neuropathic, ischaemic, and neuroischaemic. This study information may be helpful for the health planners and clinicians of this state and our country for effective and better clinical decision-making in both the prevention and management of DFUs.

MATERIALS AND METHODS

A prospective cohort study was conducted from April, 2019 to July, 2021 in Manipur at the Department of Surgery, RIMS. Ethical approval was obtained from the institutional Research

Ethics Board before the commencement of the study {No.A/206/REB-Comm(SP)/RIMS/2015/615/2019}.

Inclusion criteria: All the patients of both sexes aged 35 years and above who were diagnosed as DFU during the study period were included.

Exclusion criteria: Those who refused to participate, those with severe hepatic dysfunction, and those with auto-immune disease and malignancy were excluded from the study.

Study Procedure

After the patient and their relatives were explained about the study and those who were willing and giving valid informed written consent, were enrolled for the study. The patient's socio-demographic data and relevant clinical history was recorded in preformed proforma and thorough clinical examination was carried out. All the patients were divided into three groups-ischaemic, neuroischaemic and neuropathic type of DFU. Laboratory investigations like lipid profile, blood sugar test, HbA1c, kidney function test were done. The healing time of the three types of DFUs were compared.

All patients were given standard ulcer wound care including the use of appropriate footwear, non weight-bearing limb support, debridement of slough and dead tissue, and daily monitoring of the ulcer. When there were clinical signs of soft tissue infection, appropriate antibiotics according to the predominant bacterial flora in the gram staining were given i.e., quinolones, aminopenicillins, first or second-generation cephalosporins. All patients were given insulin therapy with the goal to keep fasting serum glucose levels below 6 mmol/L. Patients were followed-up to six months. At the end of the observation period, the results were analysed.

Operational definition

1. DFU with only features of PAD was considered as ischaemic ulcer. PAD was defined as ankle brachial index <0.9 [11].
2. DFU with only features of peripheral neuropathy was considered as neuropathic ulcer. Peripheral neuropathy was defined as more than one insensate areas of the three sites (plantar aspect of hallux, metatarsophalangeal joint 1 and 5) tested per foot based on the Semmes Weinstein 10-g monofilament. Presence of paraesthesia, tingling, numbness, absence of Achilles tendon reflex, loss of vibration sensation (by 128 Hz tuning fork) was taken into account [10-12].
3. DFU with features of both PAD and peripheral neuropathy were considered as neuroischaemic.

Study variables: Socio-demographic characteristics like age, sex, other variables like duration of diabetes mellitus, smoking history, HbA1c, hypertension, gangrene, osteomyelitis, eGFR, presence of multiple ulcer, healing time, outcome of the ulcers were recorded.

STATISTICAL ANALYSIS

The collected data were entered and analysed in Statistical Package for Social Sciences (SPSS) (IBM) version 21. Summarisation of data was carried out by using descriptive statistics such as mean, median, standard deviation and percentages. Fisher's-exact test were used for categorical variables. Analysis for time needed for healing was performed using the Kaplan-Meier method [13]. Healing time of the three DFU types were compared using the log rank test. The p-value <0.05 was taken as statistically significant.

RESULTS

Out of a total of 72 patients with DFU only 42 patients were recruited in the study and others were excluded by exclusion criteria. Out of 42 patients, 29 patients were male, distributed among neuropathic, ischaemic and neuroischaemic as 12,10 and 7, respectively. The mean age (in years) of the patients among neuropathic, ischaemic and neuroischaemic were 45.44±8.94, 59.29±8.77, and 57.2±7.98, respectively as shown in [Table/Fig-1].

S. No.	Characteristics	No. of patients, N (%)		
		Neuropathic (n=18)	Ischaemic (n=14)	Neuroischaemic (n=10)
1.	Male gender	12 (66.6)	10 (71.4)	7 (70)
2.	Mean age+SD in years	45.44±8.94	59.29±8.77	57.2±7.98
3.	Duration of DM (Mean±SD) in years	10.94±3.10	19.29±3.45	22.0±3.43
4.	Hypertension	10 (55.56)	14 (100)	8 (80)
5.	Smoking history	10 (55.56)	14 (100)	5 (50)

[Table/Fig-1]: Distribution of the patients by type of ulcers with socio-demographic variables (N=42).

Out of 42 patients, maximum patients were having neuropathic ulcer (42.9%) followed by ischaemic ulcers (33.3%) and neuroischaemic ulcers (23.8%).

Patient with HbA1c value more than 6.5 is well-distributed among the three groups with ischaemic group having the highest (92.9%). Similarly, lowest eGFR values were observed in the ischaemic group (42.74±4.31) as shown in [Table/Fig-2].

S. No.	Characteristics	No. of patients, N (%)		
		Neuropathic DFU (n=18)	Ischaemic DFU (n=14)	Neuroischaemic DFU (n=10)
1.	HbA1c value >6.5%	16 (88.9%)	13 (92.9%)	9 (90%)
2.	eGFR (Mean±SD) in mL/min/1.73m^2	67.23±7.05	42.74±4.31	50.8±7.46

[Table/Fig-2]: Distribution of the patients by type of ulcers with laboratory findings (N=42).

As shown in [Table/Fig-3], gangrene appeared more prevalent in ischaemic (50%) and neuroischaemic (50%) group than patients in neuropathic (11.1%) group of patients.

As shown in [Table/Fig-4], healing occurred more in patient with neuropathic ulcers (88.9%) than in patient with ischaemic ulcers (50%) and neuroischaemic ulcers (70%) but it was not statistically significant.

S. No.	Complications	No. of patients, N (%)		
		Neuropathic DFU (n=18)	Ischaemic DFU (n=14)	Neuroischaemic DFU (n=10)
1.	Gangrene	2 (11.1%)	7 (50%)	5 (50%)
2.	Multiple Ulcers	1 (5%)	11 (78.6%)	7 (70%)
3.	Osteomyelitis	2 (11.1%)	5 (35.7%)	3 (30%)

[Table/Fig-3]: Complication of the patients by type of ulcers (N=42).

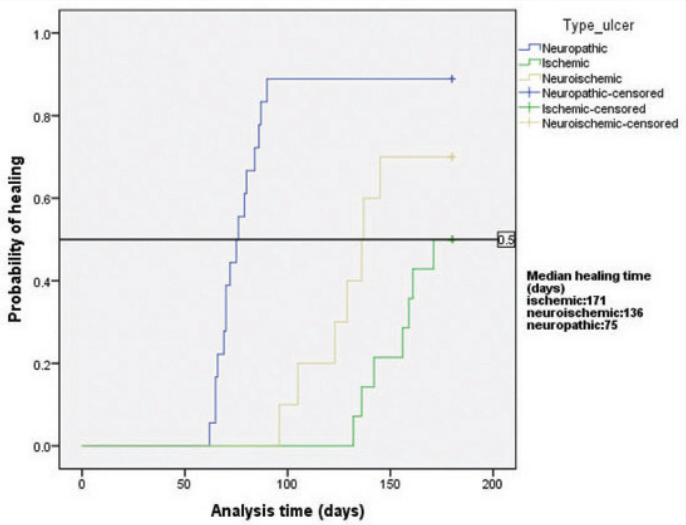
Patient outcome	No. of patients, N (%)			p-value
	Neuropathic (n=18)	Ischaemic (n=14)	Neuroischaemic (n=10)	
Healed	16 (88.9%)	7 (50%)	7 (70%)	0.397
Amputation	1 (5.55%)	3 (21.4%)	2 (20%)	0.057
Non heal	1 (5.55%)	4 (28.6%)	1 (10%)	0.201

[Table/Fig-4]: Association between type of DFUs and outcome of the patients (N=42). *Fishers-exact test

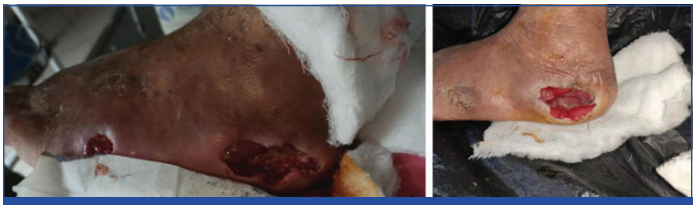
The Kaplan Meier function analysis was performed to estimate mean healing time accounting no-healing as right censored in different type of ulcer, it is estimated the mean heal time in days for ischaemic was 165.5 (Median=171), followed by neuroischaemic 141.1 (Median=136), and neuropathic 86.4 (Median=75) with significant p<0.001 by log rank test [Table/Fig-5]. [Table/Fig-6] presents the time in days until the patient achieve healing according to ulcer type. The average time in which 50% of patients (median) had healed wounds was 75, 136, and 171 days for neuropathic, ischaemic, and neuroischaemic ulcers, respectively. [Table/Fig-7] shows the picture of a neuropathic ulcer. [Table/Fig-8,9] shows clinical pictures of ischaemic and neuroischaemic ulcers respectively, which were followed-up till six months of duration.

S. No.	Type of ulcer	Mean healing time in days (Median)				p-value
		Estimate	SE	Lower CI	Upper CI	
1.	Ischaemic	165.5 (171)	4.62 (-)	156.4 (-)	174.5 (-)	0.001
2.	Neuropathic	86.4 (75)	8.02 (4.24)	70.7 (66.6)	102.1 (83.3)	
3.	Neuroischaemic	141.1 (136)	9.17 (6.32)	123.1 (123.6)	159.1 (148.3)	
4.	Overall	125.8 (132)	6.97 (17.28)	112.1 (98.1)	139.4 (165.8)	

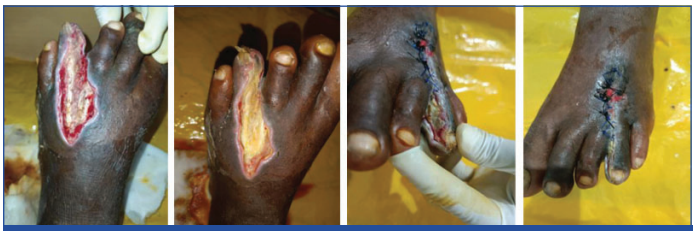
[Table/Fig-5]: The Kaplan Meier function analysis of healing time.



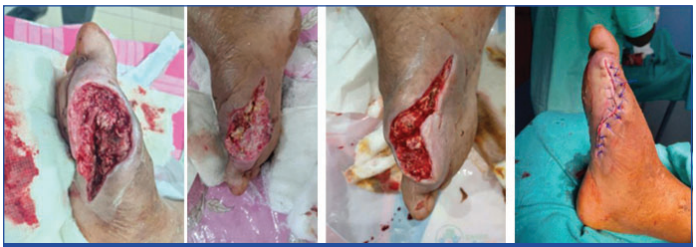
[Table/Fig-6]: Healing time of Diabetic Foot Ulcer (DFU) by type of ulcer (Kaplan Meier healing estimates).



[Table/Fig-7]: Neuropathic ulcers seen at the lateral side of the left foot.



[Table/Fig-8]: Ischaemic ulcers seen over the dorsum of left foot which was followed-up till six months.



[Table/Fig-9]: Neuroischaemic ulcers seen over the medial side of right foot which was followed-up till six months.

DISCUSSION

To predict and manage DFUs, it is essential to assess the presence of risk factors and the severity of peripheral neuropathy and PAD. In this study using the etiological classification system, patients with neuropathic ulcers tended to develop DFUs at a younger age, than those with ischaemic ulcers. Similar finding has been noted in a study by Yotsu RR et al., where neuropathic ulcers were seen in younger DFU patients than those of ischaemic and neuroischaemic [4]. This is further supported in a study by Miyata T et al., where the mean age of patients in neuropathic ulcers group is less than those of other groups [14]. Here, 69% of the patients are males in this study, further in all three groups males are seen to be more in proportion than females, which is supported by other studies Yotsu RR et al., and Miyata T et al., [4,14]. Monteiro-Soares M et al., identified an increased risk of DFU for the male gender [15].

The HbA1C value >6.5 was seen in 92% of the patient in ischaemic group. But in a study by Yotsu RR et al., HbA1c value level was seen highest among the neuropathic DFU group. Gangrene was seen more in ischaemic (50%) and neuroischaemic (50%) group [5]. Multiple ulcers were also seen maximum in ischaemic groups in this study. Similar findings have been shown by Yotsu RR et al., in their study with maximum multiple ulcers in 50% ischaemic group and gangrene were reported in 42.9% neuroischaemic, 40% ischaemic group and 18% neuropathic group [4]. Gershater MA et al., in their study also showed the association between multiple ulcers and ischaemic and neuroischaemic foot ulcers [16]. In this study duration of having diabetes was seen more in the neuroischaemic group followed by ischaemic group, but in a study by Yotsu RR et al., ischaemic (24.2±14.1 years) had the maximum duration of diabetes followed by neuroischaemic (18.2±7.2 years), similarly in another study by Miyata T et al., maximum duration of diabetes was seen in patient with neuroischaemic group (17.42 years) [4,14]. Thus, DFU occurs more frequently among the neuropathic group with a shorter duration of diabetes but it needs further evaluation with the duration of controlled or uncontrolled DM.

Hypertension (100%) and smoking history (100%) were very prevalent among the ischaemic group in this study. Smoking may be a predecessor for hypertension also. Other study also indicated to have more patients with smoking history in ischaemic DFU group [14]. But in another study the patients with smoking history were more common in the neuroischaemic followed by ischaemic group [4]. Sonnaville JJ et al., and Guerrero-Romero F et al., in their study had found that there is a significant relationship between cigarette smoking and DFU which can be attributed to the formation of plaques in blood vessels by cigarette smoking [17,18].

In this study, the lowest eGFR values were noted in the ischaemic group (42.74±4.31 mL/min/1.73 m^2). This compares favourably with the results from the study conducted by Yotsu RR et al., they also found the lowest eGFR among the ischaemic group with 40.5±27 mL/min/1.73 m^2 [4]. Baber U et al., in a study reported that the co-existence of microalbuminuria and reduced eGFR was associated with a high prevalence of PAD and hence ischaemic DFU [19].

The average time in which 50% of patients (median) had healed wounds was 75,136, and 171 days for neuropathic, ischaemic, and neuroischaemic ulcers, respectively. Yotsu RR et al., in their study also compared the healing time of three ulcer types and they found that the average healing time in which 50% of patients had healed wounds was 70,113, and 233 days for neuropathic, ischaemic, and neuroischaemic ulcers, respectively which was similar trend as in this study [4]. Further studies can be done taking into account the duration of controlled or uncontrolled DM and inclusion of larger study population covering multicenter hospitals to confirm our findings.

Limitation(s)

As the sample size was small, the present findings of this study cannot be generalised to the general population.

CONCLUSION(S)

The DFU has strong association with smoking history, thus strict abstinence from smoking among newly diagnosed DM patient may reduce DFU. Ischaemic type of DFU is associated with low eGFR pointing to underlying kidney disease. Therefore, ischaemic type of DFU need through work-up and monitoring for renal dysfunction so as to prevent end-stage renal disease. Ischaemic DFU is also associated with a higher prevalence of multiple ulcers and gangrene

leading to higher incidence of amputation. A robust public health program on DFU may help in reducing amputation in DFU through early detection and appropriate foot care.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Dec 07, 2022
- Manual Googling: Feb 22, 2023
- iThenticate Software: Mar 01, 2023 (15%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. Yes

Date of Submission: **Dec 06, 2022**
Date of Peer Review: **Dec 27, 2022**
Date of Acceptance: **Mar 03, 2023**
Date of Publishing: **Apr 01, 2023**