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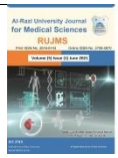

Associated Factors for Lower Extremity Amputation in Patients Admitted with Diabetic Foot Ulcers: A Retrospective Single Center Audit

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Abstract:

Background: Diabetes foot ulcer (DFU) is a serious and much feared complication of diabetes. Ulcerations of diabetes foot which developed gangrene can take weeks or months to heal and can sometimes not heal at all so that amputation for non-traumatic causes is a frequent outcome in the diabetic foot. Notwithstanding this, apparently, there is no systematic research has so far been conducted to assess associated factors for lower extremity amputation in patients admitted with DFU in Yemen. **Aims**: We aimed to determine associated factors for lower extremity amputation in patients who were admitted with DFU to Al-Thawra Modern General Hospital, Sana'a city, Yemen. **Patients and Methods**: Between November 2021 and April 2022, a retrospective observational study of patients was conducted at Al-Thawra Modern General Hospital, Sana'a city, Yemen. We included patients 20 years of age and over with a confirmed diagnosis of either type 1 or type 2 diabetes and coexisting DFU. Participants under the age of 20 years, pregnant women, patients who receiving immunosuppressive therapy or radiotherapy, infected at or above the ankle joint, and those with non-diabetic foot ulcers were excluded from analysis. Participants who attended the Hospital for other management purposes (e.g., podiatry reviews, nail pathology, and education about prevention) were also excluded. All related data about the clinical characteristics and health status of patients were collected from medical records. The main outcome factor in our study was amputation. **Results**: A total of 53 diabetic patients were enrolled in this study. All participants had type 2 diabetes mellitus. The period prevalence of amputation within the study sample was 54.7%. Almost half (47.2%) of the participants were in the age group 51-60 years with mean age 58.92 ± 11.1 years. Males were predominant (73.6 %). When compared with DFU patients without amputation, patients with amputation had increased rates of hypertension (HTN), history of peripheral artery diseases (PAD), osteomyelitis, Wagner Grade 4, foot necrosis or gangrene as well as increased levels of glycosylated hemoglobin (HbA1c) and first fasting plasma glucose (FPG) post admission. **Conclusion**: Foot ulcer is one of the major health problems among Yemeni diabetic patients. Our study has shown that independent risk factors for diabetic foot-related amputations in Sana'a city, Yemen included HTN, history of PAD, osteomyelitis, Wagner Grade 4, foot necrosis or gangrene as well as increased levels of HbA1c and FPG. Every effort should be made to avoid it particularly with limited resources for rehabilitation in developing countries.

Keywords: Diabetes, Diabetic Foot Ulcers, Lower Extremity Amputation, Sana'a, Yemen.

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Introduction

Diabetes mellitus (DM), which is among the most common endocrine diseases, severely deteriorates patients' quality of life; even worse, this condition shortens their life expectancy. More than 415 million people worldwide suffer from diabetes. More seriously, the prevalence of diabetes is still rising, and it is expected that the number of people affected will surge to 640 million by 2040 [1, 2]. Currently, up to 1/4 of diabetic patients can develop diabetic foot ulcers (DFU), and at least one quarter of these ulcers do not heal [3]. DFU may cause significant morbidity and lower extremity amputation (LEA) due to diabetic foot problems can occur more often compared to the general population [4].

Among diabetes patients, the prevalence of foot ulcers ranges from 4 to 10%, and the lifetime incidence of foot ulcers may be as high as 25% [5]. Foot ulceration poses a distinct hurdle to conservative therapies attributed to the challenge of effectively unloading the wounds, inability to provide daily foot hygiene, and compromised distal vascular flow in diabetes [4]. DFU are difficult to treat, frequently get infected, and become a leading cause of diabetes-related hospital admission [6]. Compared to healthy individuals, DM holds a 15- to 20-fold increased risk of LEA and the majority of diabetes amputation are reported to be preceded (up to 85%) by a poor healing ulcer [7]. Given the continuously expanding diabetes population globally and the high incidence of DFU, diabetes-related LEA will continue to be a substantial cause of morbidity and mortality in the future [8]. Global Lower Extremity Study Group defined LEA as "a complete loss of any part of the lower extremity irrespective of the causes" [9]. Approximately 82% of LEAs are performed on diabetic patients, most of which follows ulceration of foot [10]. The pathway to ulceration and finally LEA may include essential contribution from underlying diabetes-related pathophysiology (peripheral arterial disease (PAD), neuropathy, limited joint mobility and foot deformity), initiating environments (trauma), subsequent infection, and healing complications [11]. LEA is performed for various indications including severe soft-tissue infection, osteomyelitis, peripheral arterial occlusion, and gangrene. Following a surgery of LEA, the impact of this procedure on an individual patient is very tremendous so that amputation is always considered as the last resort of any unsalvageable limb [12]. Regardless of its causes, all efforts should be made to avoid amputation once DFU has developed or presents itself in the hospital [4, 7, 8].

The common course taken by the diabetic foot starts with a minor ulcer or small surgical incision. The majority of DFU (60-80 percent) will heal, whilst only 10-15 percent will stay active and up to 24 percent of them will ultimately result in LEA [7, 11]. The matter at hand is why some DFU patients required LEA while others did not. Previous studies have shown that poor glycemic control [13-15], duration of DM [16, 17], previous foot ulceration or amputation [13, 14, 16, 18], dyslipidemia [17, 19, 20], hypertension (HTN) [19, 20], presence of PAD [13, 15, 17, 18, 21], osteomyelitis [19, 22], as well as peripheral neuropathy [14, 18, 21], and severity of wound [23, 24] are independent predictors for LEA. Other additional factors involve older age [15, 23], history of smoking [23, 24], hypoalbuminemia [21, 24], leukocytosis [15, 19, 23], anemia [15], as well as presence of other macrovascular [14, 20, 23] and microvascular comorbidities [14, 16-20, 22]. However, the results of the studies are conflicting, and apparently there is no previous study has so far been conducted in Yemen. In addition, the associated factors of LEA have not been made clear in our hospital so that the understanding scope the reasons for reduction of LEA risk is restricted. The initial step in the process for developing preventative and/or therapeutic programs to lower LEA rates at institutional levels using local resources is to identify variables and recommend modifiable factors. Furthermore, patients with DFU may benefit from prompt and appropriate medical care and a reduction in the risk of amputation by having a better awareness of the associated risk factors for amputation in Yemen.

Patients and Methods

Between November 2021 and April 2022, a retrospective observational study of patients was conducted at Al-Thawra Modern General Hospital, Sana'a city, Yemen. All procedures were performed by high-volume surgeons [25, 26]. We included patients 20 years of age and over with a confirmed diagnosis of either type 1 or

type 2 diabetes and coexisting DFU. Participants under the age of 20 years, pregnant women, patients who receiving immunosuppressive therapy or radiotherapy, infected at or above the ankle joint, and those with non-diabetic foot ulcers (e.g., trauma related, vasculitic, and neoplastic ulcers) were excluded from analysis. Participants who attended the Hospital for other management purposes (e.g., podiatry reviews, nail pathology, and education about prevention) were also excluded.

Data Collection

A structured questionnaire about participants' sociodemographic status, history of comorbidities, and about diabetes regarding type, duration, follow up, and treatment was used. Data on the clinical characteristics and health status of patients were collected from medical records. Baseline investigations including hemoglobin (Hb), Glycosylated hemoglobin (HbA1c), total leucocyte count (TLC), percent of neutrophils, serum creatinine, serum albumin, lipid profile, and fasting blood sugar levels were collected. Venous blood sample (3 mL) was drawn from each patient in the morning after an overnight fast of eight to ten hours into gel separator tubes. The gel separator tubes were centrifuged at 3000 revolutions per minute for ten minutes and the serum separated and kept in plain separator tubes at a temperature of -20°C till it was time for analysis. The Automated Flexor Junior Chemistry Analyzer was used to analyze the samples. X-ray of foot was done to assess features of osteomyelitis. PAD was evaluated using a hand held Doppler. Peripheral neuropathy was assessed by physical examination. Characteristics of ulcers were assessed regarding its type, side, site, width, and depth. All foot ulcers were graded according to Wagner criteria. Grade 1 ulcers are superficial, involving full skin thickness. Grade 2 ulcers are deeper, penetrating down to ligaments and joint capsule. Those of Grade 3 are deep lesions, with abscesses or osteomyelitis. Grade 4 ulcers exhibit localized gangrene. Grade 5 includes extensive gangrene, compromising more than two-thirds of foot.

Outcome measures and Operational definitions

The International Consensus on Diabetic Foot defined foot ulcer as "a full-thickness wound below the ankle in a diabetic patient, irrespective of duration" [27]. The main outcome factor in our study was amputation, which was defined as "the resection of a segment of a lower limb through a bone" [28]. High blood pressure (HBP) was defined as systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg or known hypertensive on treatment. eGFR < 60 mL/min/1 73 m^2 shows renal dysfunction (Presence of nephropathy) [28].

Statistical analysis

Stata® 17.0 software was used for statistical analysis. Categorical variables were analyzed with Pearson's x2, Fisher's exact test, and the two-sample test of proportions. Kolmogorov–Smirnov test was used to test normality of continuous variables. Normally distributed data were presented as means ± standard deviation (SD). The rates and proportions of discrete variables were determined using the chi-squared test and Fisher's exact test. The median with data range (minimum to maximum) was used for non-normally distributed data. The independent samples t test was used for parametric groups, while Mann–Whitney U test was used for nonparametric groups. The p-value < 0.05 was considered significant.

Ethics

The study was approved by the administration of Al Thawra Modern General Hospital. We carried out this study according to the Declaration of Helsinki. In addition, all patients signed a consent form before surgery.

Results

Participants characteristics

A total of 53 diabetic patients were enrolled in this study. All participants had type 2 diabetes mellitus. The period prevalence of amputation within the study sample was 54.7%. The sociodemographic characteristics of the participants are presented in Table 1. Almost half (47.2%) of the participants were in the age group 51-60 years with mean age 58.92 ± 11.1

years. Males were predominant (73.6 %). The majority of the participants (66%) were rural residents. Only 11.3% of participants had university education. More than half (54.7%) of the participants were unemployed. Regarding the personal habits of participants, 17 (32.1), 31 (58.5) and 3 (5.7) were Smokers, Khat chewers and Shamma users respectively.

Table 1: characteristics of Participants

Variable	Value
Age in Years, Mean (SD)	58.92 ± 11.1
Gender, n (%)	
Males	39 (73.6)
Females	14 (26.4)
Residence, n (%)	
Urban	18 (34.0)
Rural	35 (66.0)
Educational level, n (%)	
Illiterate	11 (20.7)
Basic	24 (45.3)
Secondary	12 (22.7)
≥ University	6 (11.3)
Occupation, n (%)	
Farmer/worker	5 (9.4)
Employee	9 (17.0)
Unemployed	29 (54.7)
Others	10 (18.9)
Personal habits	
Smokers	17 (32.1)
Khat chewers	31 (58.5)
Shamma users	3 (5.7)

Associated Comorbidities

As shown in figure1, the most common associated comorbidities were HTN (53%), followed by PAD (47%) and peripheral neuropathy (34%).

Management of Diabetes Mellitus

The mean value of diabetes duration was 5 ± 0.9 years. As for management of DM, more than half of patients (53%) were on oral hypoglycemic agents. Ten percent of the cases were just diagnosed with DM at hospital admission. Figure 2 shows DM management before admission.

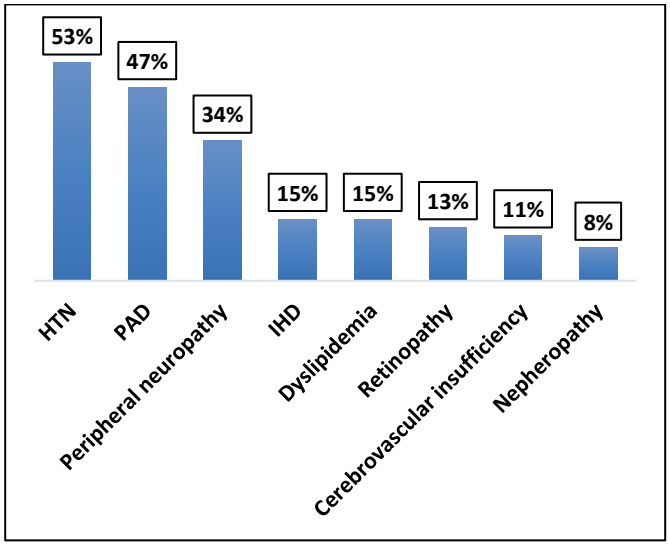

Figure 1: Associated Comorbidities among participants

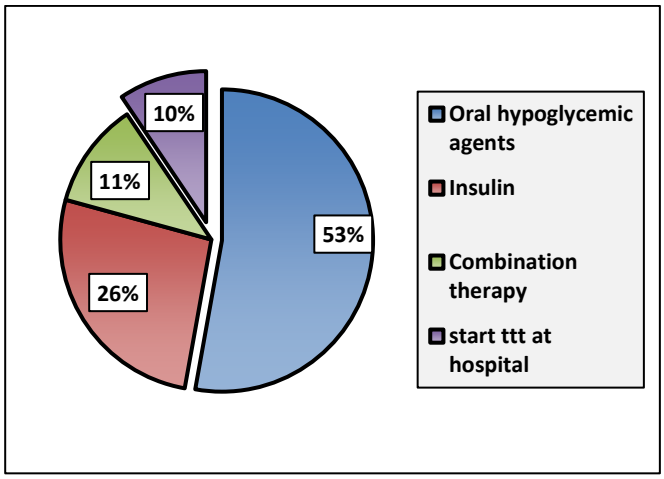

Figure 2: DM management before admission (ttt= treatment).

Wagner classification

Wagner classification showed 13 cases (24%) were grade 1 or 2, 21 (40%) cases were grade 3, and 19 cases (36%) were grade 4. Figure 3.

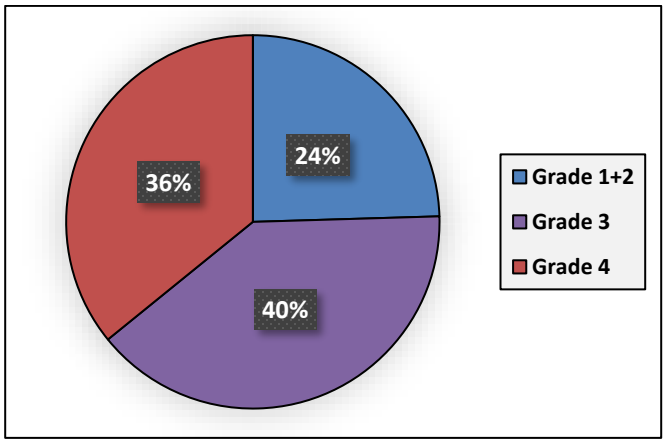

Figure 3: Wagner grading of DFU among cases.

There were no significant differences in the age, gender, smoking, dyslipidemia, history of IHD, history of ICVA, peripheral neuropathy, presence of nephropathy and retinopathy, TLC, S. creatinine, S. albumin, duration of ulcer, previous DFU and LEA, trauma induced ulcer, neuropathic, ischemic and venous ulcers, deep to fascia and tendon, reach to Joint or bone, as well as Wagner Grade 1+2 and Wagner Grade 3 between the amputation and non-amputation groups. When compared with DFU patients without amputation, patients with amputation had increased rates of HTN, history of PAD, osteomyelitis, Wagner Grade 4, foot necrosis or gangrene as well as increased levels of HbA1c and first FPG post admission. (Table 2).

Tables 2. Comparison of amputated and non-amputated groups

Characteristics	Amputation	Non-amputation	P-value
Age, mean (SD)	59.60 (11.12)	58.24 (11.18)	0.513
Male sex, N (%)	21 (72.4)	18 (75.0)	0.621
Smoking, N (%)	10 (34.5)	7 (29.2)	0.543
Dyslipidemia, N (%)	5 (17.2)	3 (12.5)	0.431
HTN, N (%)	17 (58.6)	11 (45.3)	**0.031***
History of IHD, N (%)	5 (17.2)	3 (12.5)	0.301
History of ICVA, N (%)	7 (24.1)	4 (16.7)	0.211
History of PAD, N (%)	18 (62.1)	7 (29.2)	**0.012***
Peripheral neuropathy, N (%)	12 (41.4)	6 (25)	0.061
Presence of nephropathy, N (%)	2 (6.9)	2 (8.3)	0.745
Presence of retinopathy, N (%)	4 (13.8)	3 (12.5)	0.234
TLC > 15000 /ul, N (%)	7 (24.1)	5 (20.8)	0.834

Tables 2 (Continued)			
HbA1c > 8%, N (%)	14 (48.3)	8 (33.3)	**0.004***
Admission PG >200 mg/dL, N (%)	13 (44.8)	10 (29.2)	0.122
FPG post admission >126, N (%)	14 (48.3)	11 (45.3)	**0.038***
S. creatinine >1.5g/dL, N (%)	8 (27.6)	7 (29.2)	0.692
S. Albumin < 2.5 g/dL, N (%)	4 (13.8)	3 (12.5)	0.431
Duration of the ulcer (weeks), mean (SD)	3.9 (3.12)	2.8 (4.32)	0.112
Previous DFU, N (%)	7 (24.1)	6 (25)	0.546
Previous LEA, N (%)	5 (17.2)	2 (8.3)	0.215
Trauma induced ulcer, N (%)	13 (44.8)	11 (45.3)	0.793
Neuropathic ulcer, N (%)	7 (24.1)	5 (20.8)	0.643
Ischemic ulcer, N (%)	10 (34.5)	8 (33.3)	0.734
Venous ulcer, N (%)	2 (6.9)	2 (8.3)	0.616
Deep to fascia and tendon, N (%)	12 (41.4)	6 (25)	0.126
Reach to Joint or bone, N (%)	8 (27.6)	1 (4.2)	0.081
Osteomyelitis, N (%)	20 (69)	6 (25)	**0.003***
Wagner Grade 1+2, N (%)	2 (6.9)	11 (45.3)	0.102
Wagner Grade 3, N (%)	13 (44.8)	8 (33.3)	0.122
Wagner Grade 4, N (%)	17 (58.6)	2 (8.3)	**0.001***
Foot necrosis or gangrene, N (%)	17 (58.6)	2 (8.3)	**0.001***

*Indicates significant result

Discussion

Among Yemeni diabetic patients, foot ulcer is one of the major health problems. Our patients had 4 years lower in diabetes duration than their Chinese counterparts [29]. Because metabolic control in diabetic patients tends to deteriorate linearly with time after the diagnosis, the exposure to the harmful effects of hyperglycemia will increase with the longer duration of diabetes [17, 30]. In a study from Finland by ***Lehto et al.*** the duration of diabetes was related to the risk of LEA independently of the degree of hyperglycemia [17]. Our finding for lower in diabetes duration might be reflect the high percentage of uncontrolled diabetic patients in Yemen.

DFU is the most frequent cause of hospitalization among diabetic patients and LEA is the most feared consequence of foot ulceration [5, 6, 10]. Our study reports the results of an extensive subset analysis of the data collected during a period of hospitalization in the treatment of DFU. The samples were limited to 50 patients treated by a diabetic foot team in Al-Thawra Modern General Hospital, Sana'a city, Yemen and the studied populations represented a diabetic population that constituted the highest risk of poor outcome.

The prevalence of amputation in our patients was 54.7%, a figure that is considerably higher in comparison with others' findings of 15.4% in Germany to 34.1% in Australia as showcased in [31, 32] respectively. However, our study conforms to ***Amogne et al.*** and ***Miner and Kirsner*** who report of higher rate of LEA in their respective diabetic foot clinic populations Ethiopia [33, 34]. The high prevalence might be related to inclusion of the population at the highest risk of the disease and its complications [35].

To describe the severity of DFU, we used the diabetic foot classification systems of Wagner grade [36]. In a Turkish cohort, ***Yesil et al.*** reported that Wagner grade (Wagner grade 4 and 5) was a strong predictor for LEA with OR 23.95 [23]. A study from Pakistan also reported that the frequency of amputation increased with the higher grade (Wagner grade ≥ 3) of ulcers [37]. According to Wagner classification, our study revealed that three-quarters of our patients were with the higher grade (Wagner grade ≥ 3). Our hospital was considered as the main referral medical center in Sana'a City, thus hospitalized patients contained complexities and more advanced DFU with an increased risk of extensive surgical management. This fact becomes a relatively common scenario in developing countries while there was a sequential timeline of patients before referred to the hospital and brings considerable delay for optimal management when an amputation surgery was inevitable [4].

Our study has identified the following factors as being associated factors for LEA in patients with DFU: HTN, history of PAD, osteomyelitis, Wagner Grade 4, foot necrosis or gangrene as well as increased levels of HbA1c and first FPG post admission. Our study is the first study that revealed the factors associated with LEA in Yemen, which makes comparison at local level is difficult. However, in other countries many studies have identified various independent risk factors for LEA in diabetics, including a history of foot ulcer [38], limb ischemia, presence of gangrene, deep wounds, advanced age, elevated inflammatory markers [23], poor glycemic control [13], specific ethnicities and geographical regions, and nephropathy [39]. ***Markowitz et al.*** observed that the DFU amputation rate was significantly increased with male gender and the presence of renal disease and peripheral vascular disease in a retrospective case-control study [40]. ***Carlson et al.*** demonstrated that digital deformity, diabetic neuropathy, and ischemia were obvious risk factors for toe amputations, while gender, foot infection, foot abscess, osteomyelitis, diabetic retinopathy, and diabetic nephropathy were less obvious risk factors [22]. ***Chaturvedi et al.*** suggested that elevated levels of glucose and triglyceride and the presence of retinopathy were critical risk factors for amputation [41]. ***Miyajima et al***, in a review of 210 diabetic patients over the past 9 years, showed that atherosclerosis obliterans with multiple stenosis, haemodialysis history, and elevated HbA1c levels were independent risk factors for major amputation [42]. Thus, various risk factors have been identified by different studies. This variability may be because of variations in the study designs, as well as differences in the genetic profiles and cultural or ethnical features of the populations studied.

Although there were inconsistencies among studies regarding risk factors, HbA1c elevation was found to be closely associated with increased risk of amputation in different reports [4, 14, 29, 42-46]. In our study, elevated HbA1c levels also led to a significantly higher rate of amputations, which was compatible with previous studies. According to ***Pemayun et al.***, significant risk factors of LEA in their study included HTN status, presence of PAD , presence of foot necrosis or gangrene , FPG ≥ 126 mg/dL , HbA1c ≥8% , and triglycerides ≥150 mg/dL; thus, good control of blood glucose and lipid levels and management of comorbidities such as PAD and HTN are considered important factors in reducing amputation risk [4]. According to a recent retrospective study by ***Shatnawi et al.,*** higher HbA1c was also significantly associated with increased risk of major amputation, and diabetes duration longer than 15 years, renal dysfunction, and gangrene were also closely associated with increased risk of major amputation [47]. A meta-analysis by ***Zhou et al.*** showed a statistically significant association between HbA1c and LEA risk (χ (2) = 65.51, P < .001), and the OR for LEA incidence was 1.229 (95% CI: 1.169-1.292) for every 1% HbA1c increase in linear model; moreover, for HbA1c between 5% and 9%, the OR of LEA risk increased with HbA1c levels in the spline model [45]. In summary, the strong association of HbA1c with amputations caused by DFU could indicate that long-term hyperglycaemia plays a key role in impaired wound healing, PAD, and increased susceptibility to infection [29].

Limitations

Our study has some limitations that are worth mentioning. It's a single center and a retrospective therefore has an inherent selection bias due to its observational nature. Moreover, the presence of impaired vision was based on self-reported diagnosis and this could have affected the outcome of the study.

Conclusion

Foot ulcer is one of the major health problems among Yemeni diabetic patients. Our study has shown that independent risk factors for diabetic foot-related amputations in Sana'a city, Yemen included HTN, history of PAD, osteomyelitis, Wagner Grade 4, foot necrosis or gangrene as well as increased levels of HbA1c and first FPG post admission. After diagnosis of DFU, intensive monitoring and appropriate medical care may improve the prognosis and reduce the amputation risk of diabetic patients. Emphasizing clinical management and nutritional support are also strongly recommended. Efforts to promote medical treatment and prevent LEAs of diabetics, especially among high-risk individuals, should be supported as a long-term sustainable component of Yemeni's health care system. Every effort should be made to avoid it particularly with limited resources for rehabilitation in developing countries. The results of our study will be useful for the management of diabetic foot ulcers and lower extremity amputations to enhance the quality of life of diabetes patients as well as contribute to further research and to policy formulation and implementation. Large scale multicenter and prospective study is required. We are planning to continue to extend the study prospectively to achieve this endeavour.

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Conflict of Interest

The authors declared no conflicts of interest in this study.

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