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An evaluation of risk factors affecting amputation in patients with diabetic foot infection

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ABSTRACT

Introduction: Diabetic foot infections are one of the most common complications of diabetes and generally result in lower extremity amputations.

Aim: The purpose of this study is to investigate risk factors affecting amputation in patients diagnosed with diabetic foot ulcer.

Material and Method: This prospective cohort study involved 137 patients diagnosed with diabetic foot infection in a university hospital diabetic foot clinic.

Results: The mean age of the participants was 60.5±10.1 years, and 70.8% (n=97) were men. The majority of patients (62.0%) were educated to elementary or middle school level, while 26.3% were illiterate. Mean duration of diabetes was 13.3±6.2 years. Hypertension was present in 48.2% of patients, hypercholesterolemia in 31.4%, cardiovascular disease (CVD) in 38%, peripheral artery disease (PAD) in 21.2%, peripheral venous insufficiency in 10.2%, and polyneuropathy in 70.1%, and 9.5% were receiving hemodialysis. According to the PEDIS classification, moderate foot ulcers were present in 60.6% of patients, mild ulcers in 34.3%, and severe ulcers in 5.1%. Forty-six percent of patients were diagnosed with osteomyelitis during follow-up. Amputation was present in 28.5% (n=39) of the patients followed-up due to foot ulcers. PAD increased the risk of amputation 2.7-fold (95% CI: 1.02-7.14), osteomyelitis 2.6-fold (95% CI: 1.10-6.16), and repeated hospitalizations 5.9-fold (95% CI: 2.25-15.33). Growth was observed in 72.6% of patients without amputation, 76.5% were polymicrobial, and 65.9% of antibiogram results were multidrug resistant. No significant difference was observed among the patients in terms of multidrug resistance (p=0.468).

Conclusion: PAD, osteomyelitis, and history of repeated hospitalizations are separate risk factors for amputation in patients with diabetic foot ulcers.

Keywords: Diabetic foot, amputation, risk factors, infection, multidrug resistance

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disease affecting approximately 425 million individuals worldwide. Hyperglycemia is a condition caused by a problem in the effect and/or production of insulin (1). Diabetic foot ulcer (DFU) is one of the most common diabetic complications. The lifetime prevalence of DFU in diabetic patients is estimated at 19-34% (2). DFU arising from peripheral neuropathy (PNP), peripheral vascular disease, and poor glycemic control results in lower extremity amputations (3). DFU causes amputation at different levels at a rate of approximately 20% (4). DFU therefore has an adverse impact on patients' quality of life and increases treatment costs. Several factors causing increased morbidity and mortality in diabetic patients have been identified. These include the duration of the disease, coronary artery disease, smoking, male gender, diabetic nephropathy, and peripheral artery disease (PAD) (5). Diabetic foot infections are also associated with increased amputations rates, morbidity, and mortality (6,7).

Polymicrobial infections can make healing of the ulcer less likely and can lead to amputation and death (8). The purpose of this study was to evaluate risk factors affecting amputation in the light of data obtained prospectively in patients under follow-up in our clinic with diagnoses of diabetic foot infection.

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MATERIAL AND METHOD

The study was carried out with the permission of Atarürk University Clinical Researches Ethics Committee (Permission granted: 07.05.2020, Decision no: 04-04, Ethics approval certificate: B.30.2.ATA.0.01.00/200). One hundred thirty-seven patients aged 18 or over, with type 2 DM and hospitalized for treatment of foot ulcer in our clinic were included in this study that commenced in May 2019. This is a prospective study with a sample of 137 patients with DFU and infected. Patients were followed-up for one year. Repeat hospitalizations during the follow-up process were disregarded and considered as a single case.

Demographic data including age, sex, place of residence, and education level, and duration of disease, treatment received and presence of amputation, and comorbid conditions including hemodialysis, cardiovascular disease (CVD), hypercholesterolemia, hypertension (HT), PAD, peripheral venous insufficiency (PVI), peripheral neuropathy (PNP), smoking, and osteomyelitis, tissue culture results, polymicrobial growth, and multidrug resistance (MDR) of growing agents were evaluated.

All open lesions on the feet of patients with diabetes were defined as ulcers and we hospitalized patients diagnosed with DFUs whose general condition was so poor that outpatient clinic-based treatments were not possible. All ulcers were analyzed according to the severity of infection using the PEDIS (Perfusion, Extent/size, Depth/tissue loss, Infection) classification (9). According to this classification, absence of signs and findings of infection is defined as "Grade 1". Local infection involving only the skin and subcutaneous tissue (rim of erythema around the ulcer of 0.5-2 cm) is defined as "Grade 2". Involvement of structures extending deeper than the skin and subcutaneous tissue (abscess, osteomyelitis, septic arthritis, fasciitis) without systemic infection findings, and with a rim of erythema around the ulcer >2 cm is defined as "Grade 3". The presence, in addition to local infection, of at least two inflammatory response syndrome markers (body temperature >38°C or <36°C, heart rate >90 beats/min, respiratory rate >20/min or $PaCO_2$ <32 mmHg, or white cell count >12,000 or 4000 cell/uL or ≥10% band formation) is defined as "Grade 4".

Osteomyelitis was diagnosed via magnetic resonance imaging. Presence of PNP was evaluated on electromyography (EMG) test. Vascular evaluations were made by means of palpation of distal pulses, and using Doppler ultrasound. Cultures in which there was no bacterial growth were considered negative. Cultures that grew two or more different bacteria were considered polymicrobial. The fact that the factors isolated from patients were resistant to at least one of three or more antibiotic groups was defined as MDR (10). Amputations were defined as under-ankle amputations as minor, and above-ankle amputations as major amputations. HbA_{1c} levels were employed to assess patients' diabetic control. Laboratory values at time of presentation to the clinical were employed at statistical analysis

Statistical Analysis

Data analysis was performed on SPSS for Windows version 22 software (Statistical Package for the Social Sciences). Categorical variables were expressed as number and percentage, and numerical variables as mean plus standard deviation. Normality of distribution of numerical variables was investigated using the Kolmogorov Smirnov test, z values calculated for skewness and kurtosis, and charts/tables. The t test was used to compare normally distributed numerical variables between the groups, the Mann Whitney U test to compare non-normally distributed numerical variables between the groups, and the χ^2 test to compare the distribution of categorical variables in the groups. Binary logistic regression analysis was applied to identify risk factors affecting amputation. Independent variables identified as significant at univariate regression analysis were included in the regression model. The backward LR method was used at regression analysis. p levels <0.05 were regarded as significant for all analyses.

RESULTS

The mean age of the 137 cases included in the study was 60.5±10.1 years, and 70.8% (n=97) were men. Mean ages were 62.5±11.9 years for women and 59.6±9.2 men, and the difference was not statistically significant (p=0.132). The majority of patients (62.0%) were educated to elementary or middle school level, and 26.3% were illiterate.

Mean duration of diabetes was 13.3±6.2 years. While 48.9% (n=67) of patients were using insulin alone for DM, 37.2% were using insulin together with oral hypoglycemic drugs. A history of smoking was present in 36.5% of patients, and 20.4% were still smokers.

Mean blood leukocyte count (WBC) at time of admission to the clinic was 9982.9±4172.8, C-reactive protein (CRP) 64.6±65.4 mg/L, sedimentation rate 55.7±29.5 mm/h, HbA_{1c} 9.5±2.6 mg/dL, and creatinine 1.4±1.5 mg/dL.

HT was present in 48.2% of patients, hypercholesterolemia in 31.4%, CVD in 38%, PAD in 21.2%, PVI in 10.2%, and PNP in 70.1%, and 9.5% were receiving hemodialysis. According to the PEDIS classification, "grade 3" foot ulcers were present in 60.6% of patients, "grade 2" ulcers in 34.3%, and "grade 4" ulcers in 5.1%. Forty-six percent

of patients were diagnosed with osteomyelitis during follow-up. Amputation was present in 28.5% (n=39) of patients followed-up due to foot ulcers. 34 of the cases were minor and 5 were major amputation. No mortality occurred during the follow-up period.

Patients with amputation were compared with those without amputation. PAD was present in 21.2% (n=29) of cases, and the distribution of amputations was significantly higher these patients than in those without PAD (p=0.037). Osteomyelitis developed in 46.0% (n=63) of patients, and the distribution of amputation was also higher among these patients (p=0.004).

Growth was observed in 27.4% of tissue cultures in amputated patients and in 72.6% among non-amputated patients, of which 23.5% and 76.5%, respectively, were polymicrobial. Growth in culture and polymicrobial culture results were similar among the amputated and non-amputated patients (p=0.518, and p=0.462, respectively). However, antibiogram results of 34.1% of amputated patients and 65.9% of non-amputated patients were reported as MDR (+), and no significant difference in MDR distributions was observed among the patients (p=0.468). The agents most commonly isolated from cultures were *Staphylococcus spp*. (36.7%) in amputated patients and *Escherichia spp*. (35.3%) in non-amputated patients.

Demographic characteristics of the patients with and without amputation, comorbid characteristics, a comparison of various laboratory parameters, and distributions of foot ulcers according to the PEDIS classification are shown in **Table 1**.

Logistic regression analysis was applied in order to evaluate risk factors for amputation. Major and minor amputations were included in the regression model as a dependent variable. Risk factors identified as significant at univariate analysis were added to the multivariate regression model. PAD, osteomyelitis, and history of repeated hospitalizations were found to make a significant contribution to the final model obtained using the backward elimination method with presence of amputation as the dependent variable. PAD increased the risk of amputation 2.7-fold (95% CI: 1.02-7.14), osteomyelitis 2.6-fold (95% CI: 1.10-6.16), and repeated hospitalizations 5.9-fold (95% CI: 2.25-15.33) (**Table 2**).

Table 2. Logistic regression analysis results

Variable	Wald	OR	95% CI	p value
Hemodialysis	3.113	3.394	0.873-13.193	0.078
PAD	3.977	2.695	1.017-7.142	0.046
Osteomyelitis	4.800	2.611	1.106-6.163	0.028
Repeated hospitalization	13.128	5.881	2.255-15.335	<0.001

R2= 0.28 (Nagelkerke). χ^2 (5)= 1.12 (Hosmer&Lemeshow)

DISCUSSION

Diabetic foot ulcer is a complication involving severe outcomes, such as psychosocial problems, the need for prolonged hospitalization for treatment, and amputation. Some recent studies have reported that DFU is an important independent predictor of mortality and frequently leads to lower extremity amputation (11,12). It is of great importance to identify risk factors in order to prevent extremity losses in patients with DFUs. In the present study, PAD, osteomyelitis, and a history of repeated hospitalizations were identified as independent risk factors for amputation at logistic regression analysis.

The mean age of the patients undergoing amputation was 61. One population-based study reported an approximate mean age of 65 (13). While some studies have reported a significant effect of age on amputations others, including the present research, have reported no such effect (14,15).

Sex was reported as a risk factor in Moon et al.'s study of risk factors for major amputation in DFU patients (16). Studies have also shown that major amputation rates in DFUs are significantly higher among men than in women (17,18). In the present study, although the amputation rate was higher among male DFU patients, sex was not identified as a risk factor at regression analysis. Men are generally taller, and PNP is more common among men. In addition, joint mobility and the pressure to which the feet are exposed are also greater in men (19,20). In contrast, women pay more attention to personal care, and engage in more active wound care (21). These factors may account for the higher prevalences of DFU and amputation among men.

Orneholm et al. reported a significant association between age and wound healing in patients with DFUs (22). Studies have also reported that advanced age and duration of diabetes exceeding 10 years increase the risk of mortality (23). On the other hand, it is also possible to encounter studies reporting that age is not a risk factor for amputation (16). The findings of the present study suggest that patient age and duration of diabetes are not risk factors for amputation (p>0.05).

Several studies have described weak glycemic control as a risk factor for amputation in diabetic patients (16, 24,25). In contrast to Selvin et al.'s study describing an increase in HbA_{1c} levels as increasing the risk of major amputation, Winkley et al. reported that low HbA_{1c} levels were associated with higher mortality (26,27). HbA_{1c} was also not reported as a predictive factor for amputation in Cardoso et al.'s study (28). Serum HbA_{1c} levels were also not identified as a risk factor for amputation in the present study.

Table 1. Demographic characteristics, diabetic treatment, comorbid characteristics, a comparison of various laboratory parameters, and distributions of foot ulcers according to the PEDIS classification of the patients with and without amputation

Variables		Amputated (n=39)	Non-amputated (n=98)	p value
Age (years)		60.7±11.6	60.4±9.5	0.845
Sex [n (%)]	Female	13 (32.5)	27 (67.5)	0.502
	Male	26 (26.8)	71 (73.2)	
Education [n (%)]	Not literate	15 (41.7)	21 (58.3)	0.068
	Elementary/middle school	22 (25.9)	63 (74.1)	
	High school/university	2 (12.5)	14 (87.5)	
	Duration of diagnosis (years)	13.2±6.5	13.3±6.2	0.914
Diabetes treatment [n (%)]	Insulin	18 (26.9)	73.1	0.253
	Oral hypoglycemic drugs	3 (15.8)	84.2	
	Insulin and oral hypoglycemic drugs	18 (35.3)	64.7	
Smoking history [n (%)]	Yes	14 (28.0)	36 (72.0)	0.815
	No	26 (29.9)	61 (70.1)	
Hypertension [n (%)]	Yes	21 (31.8)	45 (68.2)	0.515
	No	19 (26.8)	52 (73.2)	
Hypercholesterolemia [n (%)]	Yes	10 (23.3)	33 (76.7)	0.301
	No	30 (31.9)	64 (68.1)	
Cardiovascular disease [n (%)]	Yes	15 (28.8)	37 (71.2)	0.944
	No	25 (29.4)	60 (70.6)	
Peripheral artery disease [n (%)]	Yes	13 (44.8)	16 (55.2)	0.037
	No	27 (25.0)	81 (75.0)	
Peripheral venous insufficiency [n (%)]	Yes	4 (28.6)	10 (71.4)	0.957
	No	36 (29.3)	87 (70.7)	
Peripheral neuropathy [n (%)]	Yes	31 (32.3)	65 (67.7)	0.233
	No	9 (22.0)	32 (78.0)	
Hemodialysis [n (%)]	Yes	7 (53.3)	6 (46.2)	0.054
	No	33 (26.6)	91 (73.4)	
Osteomyelitis [n (%)]	Yes	26 (41.3)	37 (58.7)	0.004
	No	14 (18.9)	60 (81.1)	
PEDIS classification [n (%)]	Grade 2	7 (14.9)	40 (85.1)	0.056
	Grade 3	29 (34.9)	54 (65.1)	
	Grade 4	3 (42.9)	4 (57.1)	
	WBC	10345.4±4299.1	9838.6±4135.1	0.523
	Sedimentation (mm/h)	62.7±22.3	52.9±31.6	0.043
	CRP	75.5±74.4	60.3±61.4	0.317
	Creatinine (mg/dL)	1.8±2.2	1.3±1.1	0.588
	HbA1c1 (mg/dL)	9.7±2.8	9.4±2.5	0.901
Growth in culture [n (%)*]	Yes	34 (87.2)	90 (91.8)	0.518
	No	5 (12.8)	8 (8.2)	
Polymicrobial culture result [n (%)*]	Yes	8 (20.5)	26 (26.5)	0.462
	No	31 (79.5)	72 (73.5)	
Multipl drug resistance [n (%)*]	Yes	14 (48.3)	27 (40.3)	0.468
	No	15 (51.7)	40 (59.7)	
Pathogens growing in culture [n (%)*]	*Enterococcus spp*	2 (5.9)	8 (8.9)	
	Staphylococcus spp	7 (20.6)	33 (36.7)	
	Streptococcus spp	1 (2.9)	5 (5.6)	
	Acinetobacter spp	2 (5.9)	9 (10.0)	
	Citrobacter spp	3 (8.8)	5 (5.6)	
	Escherichia spp	12 (35.3)	17 (18.9)	
	Enterobacter spp	2 (5.9)	3 (3.3)	
	Klebsiella spp	1 (2.9)	6 (6.7)	
	Proteus spp	3 (8.8)	3 (3.3)	
	Pseudomonas spp	1 (2.9)	1 (1.1)	

*: Column percentage

A low level of education can adversely effect patients' possession of adequate information about diabetes and its complications, and also the prevention of such complications (28). No association was determined between patients' education levels and amputation status in the present study, and education did not emerge as a risk factor in progression to amputation.

Osteomyelitis was identified as a risk factor increasing progression to amputation 2.6-fold in patients with DFUs (p=0.028). Namgoong et al. reported that ulcers with bone involvement were an important risk factor for major amputation (29). Based on the study findings, the treatment decision being taken in the early period appears to be very important in preventing the progression of DFUs and amputation.

Hypertension, PNP, nephropathy and dyslipidemia also appear among the risk factors for amputation in the literature (29,30,31). However, no significant relationship between amputation and HT, hypercholesterolemia, CVD, PNP, or neuropathy was observed in the present study. The presence of PAD has been described as one of the important risk factors for amputation in diabetics (29,32). In the present study, presence of PAD increased the risk of amputation 2.7-fold (p=0.046).

Diabetic patients are generally hospitalized for treatment due to other comorbid diseases and foot ulcers. In the present study, a history of repeated hospitalization increased the risk of amputation 5.9-fold (p<0.001). While this study was planned as prospective single-center research involving only patients under follow-up by the infectious diseases clinic, the short follow-up period of one year represents its principal limitation. In addition, the effectiveness in terms of progression to amputation of multidisciplinary diabetic foot management could not be evaluated. We think that multi-center and multidisciplinary studies are now needed to assess risk factors for amputation in patients with DFUs.

The type of bacterium isolated from infected ulcers of diabetic feet was not identified as a risk factor for amputation in this study. The most commonly isolated bacteria in the amputated patient group were E. coli (35.39%) and *Staphylococcus spp.* (20.6%). In a study conducted in our country, it was reported that the most common bacteria isolated from diabetic wound infections are Staphyloccus aureus, group B hemolytic streptococci and *Klebsiella spp*. (33). In Cardoso et al.'s study, the most commonly isolated micro-organisms in DFUs in patients with amputation and resulting in mortality were *Acinetobacter spp*. (33.3%), *Morganella spp.* (33.3%) and *Proteus spp*. (27.8%). The type of bacterium isolated was reported not to constitute a risk factor associated with mortality (28). In another, retrospective, study, 65% of cases resulted in amputation, and the most common bacteria were *Staphyloccus spp*. (34).

Polymicrobial cultures may also occur in patients with DFUs, and this can delay the ulcer healing process (8). No polymicrobial culture dominance (23.5%) was observed in amputated patients in this study, and polymicrobial culture was not identified as a risk factor for amputation. Polymicrobial growth is frequently present in patients with severe infection and prolonged DFUs. Knowing the microbiological etiology is an important factor in managing the treatment of DFUs.

Multidrug resistant infections are a significant and growing global problem. Resistant strains prolong patients' hospital stays and increase treatment costs (35). Although the prevalence of MDR was higher in our non-amputated patient group (65.9%), there was no significant difference among the patients in terms of MDR distributions. Prolonged DFUs can result in repeated hospitalizations and multidrug resistant infections. Knowledge of antibiotic susceptibility and multidrug resistance status will be helpful to physicians in prescribing effective medications in the treatment of DFUs.

CONCLUSION

Peripheral artery disease, osteomyelitis, and a history of repeated hospitalizations emerged as risk factors for amputation in patients with DFUs. The identification of risk factors can serve as a useful guide to physicians in the management of such patients. The ability to control diabetic foot and its complications depends on the establishment of a multidisciplinary clinical team and the development of public health-based protection strategies.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Atarürk University Clinical Researches Ethics Committee (Permission granted: 07.05.2020, Decision no: 04-04).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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