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Evaluation of major and minor lower extremity amputation in diabetic foot patients

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Background/aim: We evaluated the existing risk factors with clinical results in patients who underwent major and minor amputation of the lower extremity as a result of diabetic foot ulcers (DFUs).

Materials and methods: We retrospectively studied 107 patients who had undergone lower extremity amputation. The patients were divided into minor (Group 1, n = 75) and major (Group 2, n = 32) amputation groups. On clinical evaluation, the type of surgery performed, smoking history, comorbidities, duration of diabetes mellitus (DM) diagnosis, duration of DFU presence, peripheral neuropathy, peripheral arterial disease, results of deep tissue culture, length of hospitalization, and blood parameters were investigated.

Results: In Group 2, mean hospitalization time was significantly longer than in Group 1 ($P < 0.05$). The proportion of patients with Wagner Grade 4 was significantly higher in Group 2 than in Group 1 ($P < 0.05$). The duration of DM and DFU was significantly longer in Group 2 ($P < 0.05$). The number of polymicrobial agents was significantly higher in Group 1 ($P < 0.05$).

Conclusion: In our study, the most important risk factors that led to major amputation in patients with DFU were age, Wagner classification, duration of DM, duration of DFU, and C-reactive protein level.

Key words: Diabetic foot, foot ulcer, amputation, infection, Wagner classification, surgery

1. Introduction

Diabetes mellitus (DM) is a major public health problem and diabetic foot incidence increases with the prevalence of DM (1–3). Diabetic foot ulcer (DFU) is one of the major complications of DM and occurs at an estimated rate of 10%–25% in diabetic patients in their lifetime (1–5). In addition, 40%–85% of nontraumatic amputations consist of diabetic foot amputations (6,7).

DFU causes increased morbidity and decreased quality of life, incurs high treatment costs, and leads to high rates of lower extremity amputation (LEA) (3,4,8). Death rates 5 years after a major amputation can be as high as 78% (8).

The diabetic foot is a multifactorial disorder (2,4,5). DM causes a range of complications such as nephropathy, retinopathy, neuropathy, DFUs, and cardiovascular disease. The incidence of complications is expected to increase with the rising number of diabetic patients (1,3,6,9). In particular, diabetic neuropathy and peripheral arterial disease that causes angiopathy are two major risk factors that play a role in the development of DFUs (1,3,6,9). Regardless of DM, we can list smoking, comorbidities, alcoholism, use of steroids or toxic drugs, congenital wound healing problems, malnutrition, and old age as additional risk factors for foot ulcers (9).

Despite the well-defined risk factors in the development of DFU, there are factors that predict major or minor amputation related to the diabetic foot. Age, sex, ulcer depth, severity of infection, ischemia, osteomyelitis, duration of diabetes, neuropathy, and glycemic control are considered as potential predictors of amputation in DFU (6,10).

In this study, we tried to determine the risk factors that may cause amputation type by comparing the existing clinical results of patients with major or minor amputation of a lower extremity due to diabetic foot. Our hypothesis is that risk factors in diabetic foot are effective in determining the level of amputation.

2. Materials and methods

We retrospectively studied 268 patients. After the first evaluation, patients who were treated without amputation or those with Grade 0, 1, 2, or 5 lesions according to the Wagner classification were excluded. The remaining 107 patients (56 males, 51 females; 64 right side, 43 left side;

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mean age, 60.08 years; range, 43–88 years) who underwent LEA due to DFU between March 2011 and November 2015 were evaluated. The patients were divided into minor (Group 1, n = 75) and major (Group 2, n = 32) amputation groups. A minor LEA was defined as any amputation distal to the ankle joint, whereas a major LEA was any amputation through or proximal to the ankle joint (11). The general state of the patients and their extremities, such as peripheral vascular status, neuropathy, and intraoperative tissues, were considered as the criteria of the amputation levels. Foot lesions of the patients were classified according to the Wagner system: Grade 0- skin lesions absent, hyperkeratosis below or above bony prominences; Grade 1- skin and immediate subcutaneous tissue are ulcerated; Grade 2- lesions are deeper and may penetrate to tendon, bone, or joint capsule; Grade 3- deep tissues are always involved, osteomyelitis may be present; Grade 4- gangrene of some portion of the toes or forefoot; Grade 5- the entire foot is gangrenous (12).

The demographic data of the patients were recorded. On clinical evaluation, the education level of the patient, smoking history, history of foot trauma, comorbidities, presence of improper foot care, duration of DM diagnosis, duration of DFU presence, peripheral neuropathy, and peripheral arterial disease (PAD) were investigated.

The peripheral vascular status was assessed by palpation of the dorsalis pedis and posterior tibial pulses on both feet. The presence of two or fewer of the four pedal pulses indicated PAD. In addition, to determine peripheral vascular history, the patients were asked whether they had undergone any previous peripheral bypass surgery or peripheral angioplasty (1,7).

Diabetic peripheral sensory neuropathy was defined as the inability to perceive pressure with an amount of 10 g using a nylon monofilament test (5). The test was performed at three sites (two plantar, one dorsal) of each foot while the patient's eyes were closed (2,13). The presence of associated comorbidities, including renal diseases and cardiac/pulmonary/endocrinological conditions, was examined.

Blood parameters were investigated, such as glycated hemoglobin (HbA1c), preoperative leukocyte count (WBC), sedimentation, C-reactive protein (CRP), and serum albumin levels. Blood sugar was similarly investigated, as to whether it was regulated or not. Blood sugar regulation was assessed according to patients' blood sugar and HbA1c levels. In addition, we recorded the type of surgical interventions performed, the results of deep tissue culture received intraoperatively, and the length of hospitalization.

2.1. Statistical analysis

Statistical analysis was performed using IBM SPSS 21.0 (IBM, Armonk, NY, USA). Frequency analysis was performed for categorical variables. The data were expressed as numbers and percentages. Paired Student's t-tests and Pearson's chi-square tests were used to compare categorical data. $P < 0.05$ was considered as statistically significant.

3. Results

Baseline characteristics are given in Table 1. Mean follow-up time was 23.7 months (range, 10–32). According to the Wagner classification, Grades 3 and 4 disease was noted in 36 (48%) and 39 (52%) patients, respectively, in Group 1 and 2 (6.2%) and 30 (93.8%) in Group 2 ($\chi^2 = 0.018$, $P = 0.046$).

In this study, 18 (16.8%) patients had below-knee, 14 (13%) had Syme's, 9 (8.4%) had metatarsal, 61 (57%) had ray, and 5 (4.6%) had toe amputations (Table 2) (Figures 1a–1c). The mean length of hospitalization was 16.2 ± 7.35 days in Group 1 and 31.8 ± 13.6 days in Group 2 ($P = 0.0001$). There was no blood sugar regulation in 50 (66.6%) and 22 (68%) patients, respectively ($\chi^2 = 0.194$, $P = 0.66$). Regarding the preoperative blood parameters, the average WBC count was 18.837 ± 2909.67/mm^3 in Group 1 and 16.235 ± 6188.02/mm^3 in Group 2 ($P = 0.676$), whereas the mean sedimentation level was 56.3 ± 32.68 and 56.81 ± 39.76 mm/h, respectively ($P = 0.19$). Mean CRP level was 31.3 ± 14.61 and 37.1 ± 18.38 mg/dL, respectively ($P = 0.03$), and mean serum albumin level was 3.6 ± 0.72 and 3.64 ± 0.82 g/dL, respectively ($P = 0.239$).

Mean diabetes duration was 8.49 ± 4.4 years in Group 1 and 9.5 ± 4.32 years in Group 2 ($P = 0.045$); mean HbA1c was 10.27 ± 2.44% and 11.01 ± 2.71%, respectively ($P = 0.675$); and a low level of education was noted in 54.6% and 65.6%, respectively ($\chi^2 = 0.046$, $P = 0.830$).

The mean duration of DFU was 4.24 ± 2.41 and 6.31 ± 2.49 months, respectively, in Groups 1 and 2 ($P = 0.001$), whereas peripheral neuropathy was present in 38 (50.6%) and 9 (28.1%), respectively ($\chi^2 = 0.025$, $P = 0.874$). Peripheral vascular disease (PVD) was present in 40 (53.3%) and 20 (62.5%), respectively ($\chi^2 = 0.009$, $P = 0.926$). Although the power analysis was calculated, the mean duration of DFU of both groups was used. The statistical power of the study was calculated as 97.8%. A smoking history was noted in 37 (49.3%) and 22 (68.7%) patients, respectively ($\chi^2 = 3.334$, $P = 0.068$), whereas 26 (34.6%) and 15 (46.8%) patients, respectively, had a Charcot foot deformity ($\chi^2 = 1.663$, $P = 0.197$).

The main direct cause was inadequate foot care in 39 patients (52%) in Group 1 and 17 (53.1%) in Group 2, followed by direct trauma in 9 (12%) and 17 (53.1%), respectively ($\chi^2 = 1.890$, $P = 0.169$; $\chi^2 = 1.103$, $P = 0.294$).

There was no significant difference among the groups in terms of the number of comorbidities ($\chi^2 = 12.998$, $P = 0.369$). Six patients had no additional disease (4 in

Table 1. Patient demographic characteristics and clinical outcomes.

Patient characteristics	Group 1 (n = 75)	Group 2 (n = 32)	P-value
Age (years), mean (range)	58.8 ± 8.74	62.8 ± 9.35	P = 0.002
Sex, n (%)			
Female Male	40 (53.3) 35 (46.7)	11 (34.4) 21 (65.6)	χ^2 = 1.332, P = 0.248
Duration of diabetic foot ulcer (months)	4.24 ± 2.41	6.31 ± 2.49	P = 0.001
Duration of DM (years)	8.49 ± 4.40	9.5 ± 4.32	P = 0.045
HbA1c (%)	10.27 ± 2.44	11.01 ± 2.71	P = 0.675
WBC count	18,837 ± 2909.67	16,235 ± 6188.02	P = 0.676
Sedimentation	56.3 ± 32.68	56.8 ± 39.76	P = 0.19
CRP	31.3 ± 14.61	37.1 ± 18.38	P = 0.03
Albumin	3.60 ± 0.72	3.64 ± 0.82	P = 0.239
Mean length of hospitalization, days	16.2 ± 7.35	31.8 ± 13.6	P = 0.0001
Wagner, n (%)			
Grade 3 Grade 4	36 (48) 39 (52)	2 (6.2) 30 (93.8)	χ^2 = 0.018, P = 0.046
Number of comorbidities, n (%)			
0 1 2 ≥3	4 (14.1) 33 (33.3) 34 (32.1) 4 (20.5)	2 12 13 (25) 5 (75)	χ^2 = 12.998, P = 0.369
Blood sugar regulation, n (%)			
Absent Present	50 (66.6) 22 (29.4)	22 (68.7) 10 (31.3)	χ^2 = 0.194, P = 0.66
Inadequate foot care, n (%)			
Absent Present	36 (48) 39 (52)	15 (46.8) 17 (53.1)	χ^2 = 1.890, P = 0.169
Peripheral neuropathy, n (%)			
Absent Present	37 (49.4) 38 (50.6)	23 (71.9) 9 (28.1)	χ^2 = 0.025, P = 0.874
Peripheral arterial disease, n (%)			
Absent Present	35 (46.7) 40 (53.3)	12 (37.5) 20 (62.5)	χ^2 = 0.009, P = 0.926
Peripheral arterial disease, n (%)			
Absent Present	38 (50.6) 37 (49.3)	10 (31.2) 22 (68.7)	χ^2 = 3.334, P = 0.068
Charcot foot, n (%)			
Absent Present	49 (65.3) 26 (34.6)	17 (53.1) 15 (46.8)	χ^2 = 1.663, P = 0.197

DM: Diabetes mellitus; WBC: white blood cell; CRP: C-reactive protein.

Table 2. Operation method.

Therapies	Number of cases
Minor amputation, n (%) Metatarsal amputation Ray amputation Toe amputation	9 (8.4) 61 (57) 5 (4.6)
Major amputation, n (%) Below-the-knee amputation Syme's amputation	 18 (16.8) 14 (13)

Group 1, 2 in Group 2). Renal disease was identified in 15 patients (9 in Group 1, 6 in Group 2). Pulmonary disease was detected in 52 patients (33 in Group 1, 19 in Group 2), while 21 had endocrinological disease (16 in Group 1, 5 in Group 2) and 77 had cardiac disease (54 patients in Group 1, 23 in Group 2; Table 3).

Deep tissue culture was negative in 4 (3.7%) patients (3 in Group 1, 1 in Group 2). The most frequently isolated pathogen was *Staphylococcus aureus* in both groups. According to deep tissue culture results, polymicrobial agents were found in 16 (21.3%) patients in Group 1 and 11 (34.3%) in Group 2 ($\chi^2 = 5.453$, P = 0.02; Table 4).

4. Discussion

We determined risk factors and clinical outcomes of major and minor LEA in 107 patients treated for diabetic foot disease. The main findings showed that age, duration of DM, duration of DFU, CRP count, Wagner classification, and length of hospitalization of major LEA were significantly different compered to minor LEA.

DFU and amputations are acute health and socioeconomic problems that negatively affect the quality of life for diabetic patients and additionally create a high economic burden for patients and society (3,5,14). DM is the leading cause of amputations with an accounted rate of 40% of total amputations (15).

In our study, the proportion of patients with Wagner Grade 4 was higher in the major LEA group than in the minor LEA group. Sun et al. (16) showed that the risk of amputation was strongly associated with high Wagner grade classifications. Similarly, in other studies, Wagner classification was reported to be a predictor of LEA (6,10,17).

Low serum albumin and high HbA1c levels have been reported to be risk factors for limb loss in cases of diabetic foot (10,18). Serum albumin is used as a measure to evaluate the nutritional status of the human body. Therefore, a low serum albumin level implies poor nutrition, which causes delayed wound healing (10). The mean HbA1c value is used to indicate the level of diabetic control. HbA1c is a risk factor for major amputation, which underlines the importance of controlling the underlying diabetes from the point of view of functional prognosis, as well. Lehto et al. (19) reported that plasma glucose levels and the risk of amputation increase in a largely linear fashion. In our study, we found no significant differences between the major and minor amputation groups in terms of serum albumin and HbA1c levels.

Baseline levels of acute phase reactants were associated with increased amputation risk (6,20). In recent studies, baseline CRP and sedimentation levels were reported to be independent predictors of major amputations (6). Lipsky et al. (20) showed that increased baseline levels of acute phase reactants (WBC, CRP, and sedimentation) were associated with clinical failure in diabetic foot infections treated with broad-spectrum antibiotics. In our study, CRP levels were significantly different in the major compared to the minor amputation group.

Foot problems are common in diabetic patients over 40 years of age and are thought to increase with age (2,6,10). Amputations associated with diabetic foot have been reported to be more common in men than women. In our study, the mean age of patients in the major amputation group was significantly higher than that of the minor amputation group. Most patients were male, concordant with the literature. In contrast, decreasing age has been reported to be an independent predictor of increased ulcer risk (2). Although the reason for this finding is unclear, it may be because older patients are probably less mobile than younger patients and less exposed to potentially traumatic situations for the foot at risk (2).

A relationship between the development of diabetic foot and duration of DM has been reported (21). The proportion of cases of diabetic foot leading to major amputation significantly increases with increasing duration of DM (18,21). In our study, the duration of DM is at least 5 years in 91.5% of the patients with diabetic foot. However, the duration of DM and DFU was significantly higher in patients undergoing major amputation.

Clinical studies have reported that the measure of peripheral neuropathy was the main predicting factor for DFU (22). Other associations with DFU are PVD, limited

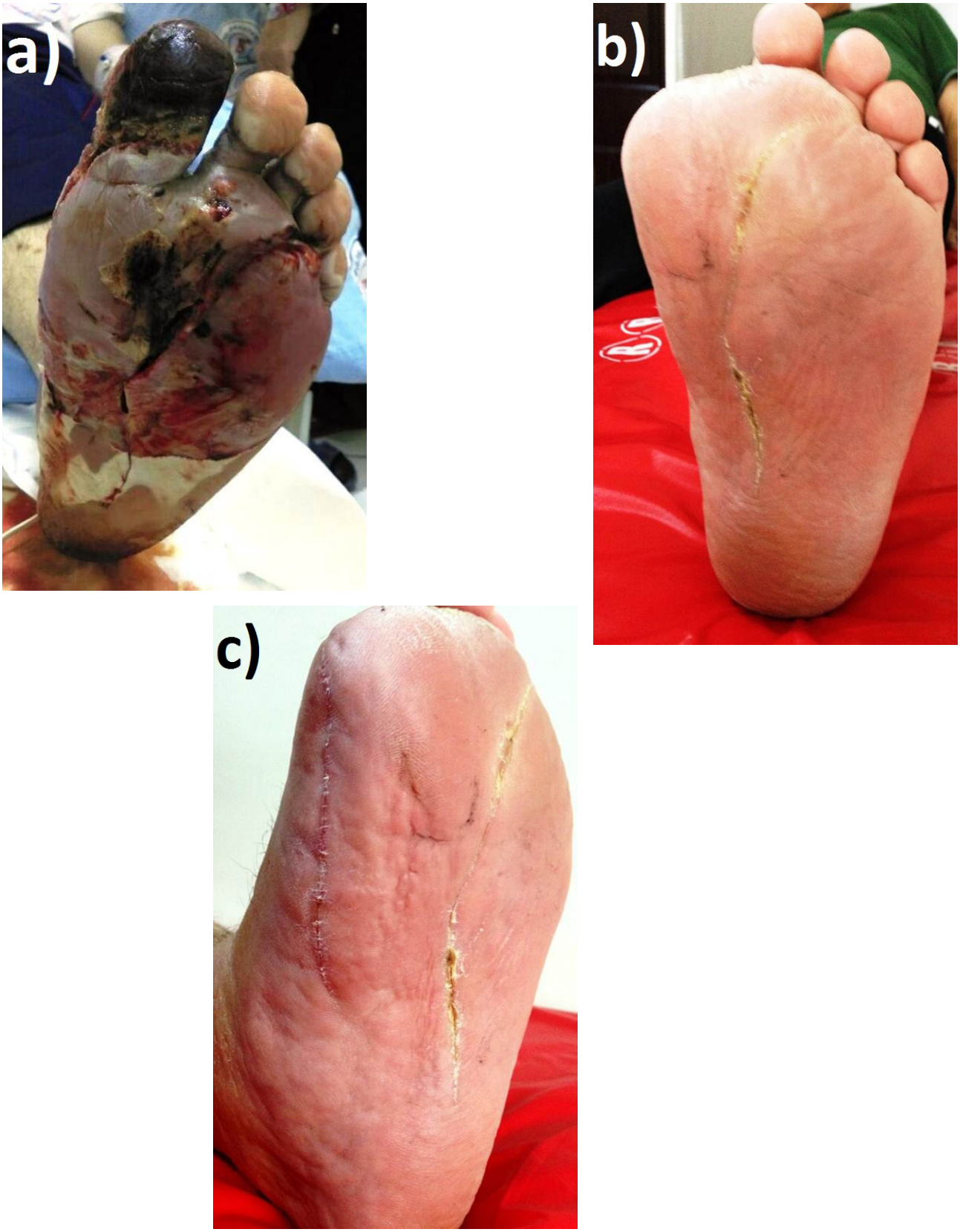

Figure 1. a, b, c) Appearance before and after surgical interventions of Wagner's Grade 4 disease in a diabetic foot patient.

Table 3. Comparison of comorbidities.

	Group 1 n (%)	Group 2 n (%)	p
Cardiac diseases	54 (72)	23 (71.8)	0.489
Pulmonary diseases	33 (44)	19 (59.3)	0.821
Endocrinological diseases	16 (21.3)	5 (6.6)	0.295
Renal diseases	9 (12)	6 (8)	0.451

Table 4. Isolated microorganisms and their characteristics.

	Group 1 (n = 75) n (%)	Group 2 (n = 32) n (%)
MSSA	26 (34.8)	16 (50)
MRSA	10 (13.5)	4 (12.6)
Escherichia coli, ESBL+	2 (2.6)	1 (3.1)
Enterococcus faecalis, VRE+	2 (2.6)	2 (6.2)
Enterococcus faecalis, VRE–	2 (2.6)	1 (3.1)
Coagulase-negative staphylococci	4 (5.3)	4 (12.6)
Group B streptococci	10 (13.5)	2 (6.2)
Enterobacter cloacae	1 (1.3)	1 (3.1)
Pseudomonas aeruginosa	3 (4)	2 (6.2)
Acinetobacter baumannii	17 (22.7)	6 (18.8)
Staphylococcus saprophyticus	1 (1.3)	2 (6.2)
Hafnia alvei	1 (1.3)	-
Candida tropicalis	1 (1.3)	-
Proteus vulgaris/penneri	1 (1.3)	-
Klebsiella pneumoniae	2 (2.6)	2 (6.2)
Morganella morganii	1 (1.3)	-
Enterococcus casseliflavus/gallinarum	1 (1.3)	-
Burkholderia species	2 (2.6)	2 (6.2)
Ralstonia species	2 (2.6)	2 (6.2)
Proteus mirabilis	1 (1.3)	1 (3.1)
Citrobacter werkmanii	-	1 (3.1)

MSSA: Methicillin-sensitive *Staphylococcus aureus*; MRSA: methicillin-resistant *Staphylococcus aureus*; ESBL: extended-spectrum β-lactamase; VRE: vancomycin-resistant *Enterococcus faecalis*.

joint mobility, foot deformities, and duration of DM with limited relevance (2,23). Case-control and prospective studies have confirmed that the 10-g monofilament test was one of the strongest independent risk factors for foot ulcers in diabetics (2,5,13,23). The most important risk factor for peripheral neuropathy, diabetic foot syndrome, was 43.9% in our study. Although the PVD rate was not significantly different between the groups, 56% of all cases had PVD.

Furthermore, hemodialysis was an independent risk factor of major limb amputation. Hemodialysis is the final picture of renal microangiopathy and is a growing problem for foot lesions in dialysis patients with diabetic nephropathy. The frequency of amputation is about 10 times higher in patients on dialysis due to diabetes than in those without dialysis (24).

Diabetic foot syndrome is a health problem with high morbidity and mortality rates. Additionally, it creates an economic burden due to lengthy hospital stays and hospital costs (4,5,14). Mean hospital stay for diabetic patients was reported to be two times longer than for nondiabetic patients, and hospital costs for diabetic patients were three times higher than for nondiabetic patients (14). In our study, hospital stay was significantly longer in the major amputation group.

Previous studies suggest that foot infection is a risk factor in major amputation (25). In our study, all deep tissue cultures were positive, except in 4 patients (3 in Group 1, 1 in Group 2). Generally, in severe diabetic foot infections there is more than one microorganism (26). Pathogens are generally gram-positive bacteria; however, very serious life-threatening infections with gram-negative agents can be isolated (27). *S. aureus*, coagulase-negative *Staphylococcus*, and group B *Streptococcus* are the most frequently isolated bacteria (26–28). In our patient group, the four most frequently isolated bacterial agents were methicillin-sensitive *S. aureus* (39.2%), *Acinetobacter baumannii* (21.4%), methicillin-resistant *S. aureus* (13%), and group B *Streptococcus* (12.2%), respectively. However, the number of polymicrobial agents was significantly higher in Group 1.

Empirical antibiotic treatment should be planned according to the severity of diabetic foot infection and possible etiologic agents. It may be sufficient to use antibiotics, which are effective in aerobic gram-positive roots in patients with no history of antibiotic use and with mild–moderate infections. However, in patients with advanced-stage diabetic foot infections, a broader spectrum of antibiotics may be required when selecting empirical antibiotics (26–28).

The present study was limited by its small patient population. Another limitation of our study was its retrospective character.

In conclusion, rigorous control of diabetes as the primary disease is first required to avoid major amputations from foot lesions and a marked reduction in postoperative activity in daily life. For early treatment, early detection of lesions and foot care are also important. Diabetic foot is a disease with high morbidity. Although the differences between minor and major diabetic foot amputations are not marked by sharp boundaries, age, Wagner classification, duration of DM, duration of DFU, and CRP level may be risk factors for major amputation.

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