Predictors for Amputation in Patients with Diabetic Foot Wound

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Purpose: Diabetic foot wound (DFW) is known as a major contributor of nontraumatic lower extremity amputation. We aimed to evaluate overall amputation rates and risk factors for amputation in patients with DFW.

Materials and Methods: From January 2014 to December 2017, 141 patients with DFW were enrolled. We determined rates and risk factors of major amputation in DFW and in DFW with peripheral arterial occlusive disease (PAOD). In addition, we investigated rates and predictors for amputation in diabetic foot ulcer (DFU).

Results: The overall rate of major amputation was 26.2% in patients with DFW. Among 141 DFWs, 76 patients (53.9%) had PAOD and 29 patients (38.2%) of 76 DFWs with PAOD underwent major amputation. Wound state according to Wagner classification, congestive heart failure, leukocytosis, dementia, and PAOD were the significant risk factors for major amputation. In DFW with PAOD, Wagner classification grades and leukocytosis were the predictors for major amputation. In addition, amputation was performed for 28 patients (38.4%) while major amputation was performed for 5 patients (6.8%) of 73 DFUs. Only the presence of osteomyelitis (OM) showed significant difference for amputation in DFU.

Conclusion: This study represented that approximately a quarter of DFWs underwent major amputation. Moreover, over half of DFW patients had PAOD and about 38.2% of them underwent major amputation. Wound state and PAOD was major predictors for major amputation in DFW. Systemic factors, such as CHF, leukocytosis, and dementia were identified as risk factors for major amputation. In terms of DFU, 38.4% underwent amputation and the presence of OM was a determinant for amputation.

Key Words: Diabetic foot wound, Amputation, Peripheral arterial occlusive disease, Risk factors

INTRODUCTION

Diabetic foot wound (DFW), including diabetic foot ulcer (DFU) and diabetic foot gangrene (DFG), is a relatively common complication of diabetic mellitus (DM). It has known

to be the main cause of non-traumatic lower extremity amputation. Several studies have reported that diabetic patients have a 10-15 times risk of lower extremity amputation compared to patients without DM [1,2]. It has been estimated that approximately 15% of all diabetic patients

develop DFU during their lifetime and 5% to 8% of DFU will require major amputation within one year despite of aggressive wound management treatment and recent advanced revascularization techniques, especially in patients with peripheral arterial occlusive disease (PAOD) [3-6]. DFG is also one of critical limb manifestations of DFW. It can be caused by PAOD or bacterial infections. In clinical practice, most DFGs require major amputation, such as below-knee amputation or above-knee amputation with poor functional prognosis because proper antibiotic treatment and aggressive wound management may not be effective. DFU is at increased risk of DFG mainly due to PAOD and foot infections [7,8]. Although most DFW patients have diabetic polyneuropathy, PAOD is also present in one-half of all DFU patients. It is considered an important predictor of overall outcomes [9-11].

DFW is not only a serious health problem, but also poses socioeconomic burden to the patient and the county because of prolonged hospitalization and rehabilitation time [12]. Therefore, early recognition and proper management of risk factors for amputation in DFW patients may reduce major amputations and prevent adverse outcome.

However, despite well-defined risk factors for the development of DFW, there are little data on overall amputation rates or predictors of DFW. Therefore, the objective of the present study was to evaluate overall amputation rates and risk factors of major amputation in DFW patients and in DFW with PAOD patients. In addition, in patients with DFU, overall rates of amputation and major amputation were investigated and potential predictors for amputation were also determined.

Table 1. Clinical characteristics and risk factors for major amputation in DFW

Risk factor	DFW (n=141)	Major amputation (n=37, 26.2%)	Univariate P-value	Multivariate P-value	Multivariate OR (95% CI)
Age (y) ≥60	86 (61.0)	27 (31.4)	0.082	0.485	0.653 (0.198-2.156)
Male	71 (50.4)	16 (22.5)	0.314	0.227	1.870 (0.677-5.167)
Site, right	68 (48.2)	19 (27.9)	0.658	0.787	0.879 (0.346-2.236)
Wagner classification			0.001	0.001	12.155 (3.427-43.106)
Wagner grade 0	3 (2.1)	0 (0.0)			
Wagner grade 1	19 (13.5)	0 (0.0)			
Wagner grade 2	1 (0.7)	0 (0.0)			
Wagner grade 3	50 (35.5)	5 (10.0)			
Wagner grade 4	45 (31.9)	9 (20.0)			
Wagner grade 5	23 (16.3)	23 (100.0)			
Wound infection	102 (72.3)	29 (28.4)	0.339	0.476	1.516 (0.483-4.752)
Hypertension	92 (65.2)	25 (27.2)	0.730	0.839	1.114 (0.395-3.139)
DM control			0.525	0.690	0.807 (0.282-2.313)
Insulin	40 (28.4)	9 (22.5)			
Coronary artery disease	36 (25.5)	14 (38.9)	0.046	0.322	1.707 (0.593-4.911)
Congestive heart failure	18 (12.8)	10 (55.6)	0.002	0.028	4.486 (1.180-17.061)
Cerebrovascular disease	35 (24.8)	11 (31.4)	0.421	0.706	1.227 (0.424-3.555)
Chronic kidney disease[a]	31 (22.0)	11 (35.5)	0.185	0.754	1.198 (0.389-3.691)
COPD	41 (29.1)	13 (31.7)	0.345	0.667	1.256 (0.445-3.539)
Leukocytosis	68 (48.2)	25 (36.8)	0.006	0.047	2.661 (1.012-6.995)
HbA1c >9	40 (28.4)	10 (25.0)	0.833	0.894	1.074 (0.376-3.069)
Smoking	81 (57.4)	21 (25.9)	0.921	0.319	1.774 (0.575-5.471)
Dementia	23 (16.3)	10 (43.5)	0.040	0.071	3.340 (0.900-12.391)
Economic state	79 (56.0)	24 (30.4)	0.207	0.140	2.166 (0.775-6.049)
PAOD	76 (53.9)	29 (38.2)	0.001	0.034	3.727 (1.101-12.615)

Values are presented as number (%).
DFW, diabetic foot wound; OR, odds ratio; CI, confidence interval; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; PAOD, peripheral arterial occlusive disease.
[a]Glomerular filtration rate <30.

MATERIALS AND METHODS

From January 2014 to December 2017, a total of 141 DFW patients who underwent lower extremity computed tomography (CT) angiography for assessing PAOD were enrolled in this study. First, all DFWs were classified into DFU group and DFG group based on clinical findings and its symptoms presented for the first time within six months. Next, we reclassified all DFWs according to Wagner classification [13] system based on clinical and radiologic findings. All DFW patients had aggressive wound dressing and/or debridement. They received initially empirical broad-spectrum antibiotics with specific antibiotics thereafter based on culture and sensitivity results if wound infection or concomitant osteomyelitis (OM) was suspected. In this study, the presence of PAOD was determined by findings of lower extremity CT angiography that indicated at least one severe stenotic or occlusive lesion of iliac arteries, femoropopliteal arteries, and tibioperoneal arteries. All CT angiography results were assessed by two board-certified radiologists specializing in vascular imaging. Based on findings of CT angiography, patients with PAOD were divided into three groups based on PAOD location: 1) proximal location defined as the iliac or femoropopliteal arteries involved, 2) distal location when tibioperonal arteries were involved and 3) multiple (proximal and distal) locations. PAODs were also classified into single arterial stenotic/occlusive lesion and multiple arterial stenotic/occlusive lesions. Basically, revascularization procedures were performed for proximal location of PAOD or when all run-off vessels showed significant stenosis or occlusion in patients with DFW and PAOD. In addition, demographic features and potential risk factors were investigated to predict major amputation in DFW group and amputation in DFU group, including age, gender, hypertension, coronary artery disease (CAD), congestive heart failure (CHF), cerebrovascular disease, chronic kidney disease (CKD), hemodialysis (HD), HbA1c, DM medication, concomitant OM, smoking status, and dementia. OM was confirmed based on the findings of magnetic resonance imaging and 3-phase bone scan in DFW patients with an ulcer when the tract extended to the bone and the presence of bony destruction and the involvement of periosteal and bone surface in foot X-ray.

In this study, we firstly determined overall rates of major amputation in patients with DFW and DFW with PAOD. Moreover, additional risk factors as independent predictors for major amputation were analyzed in DFW group and DFW with PAOD group using logistic regression model. Major amputation-free survival was also calculated in DFW and DFW with PAOD by Kaplan-Meier survival curves. Next, for DFU only group, we investigated rates of amputation and major amputation and then analyzed potential predictors that showed statistically significant correlations with amputation by univariate and multivariate analyses. Multivariate analysis was used to evaluate odds ratio (OR) for statistically significant correlation between potential risk factors and amputation or major amputation with 95% confidence interval (CI). A P-value of less than 0.005 was considered to indicate statistical significance. All statistical analyses were performed with IBM SPSS Statistics ver. 20.0 software (IBM Co., Armonk, NY, USA).

RESULTS

1) Major amputation in DFW

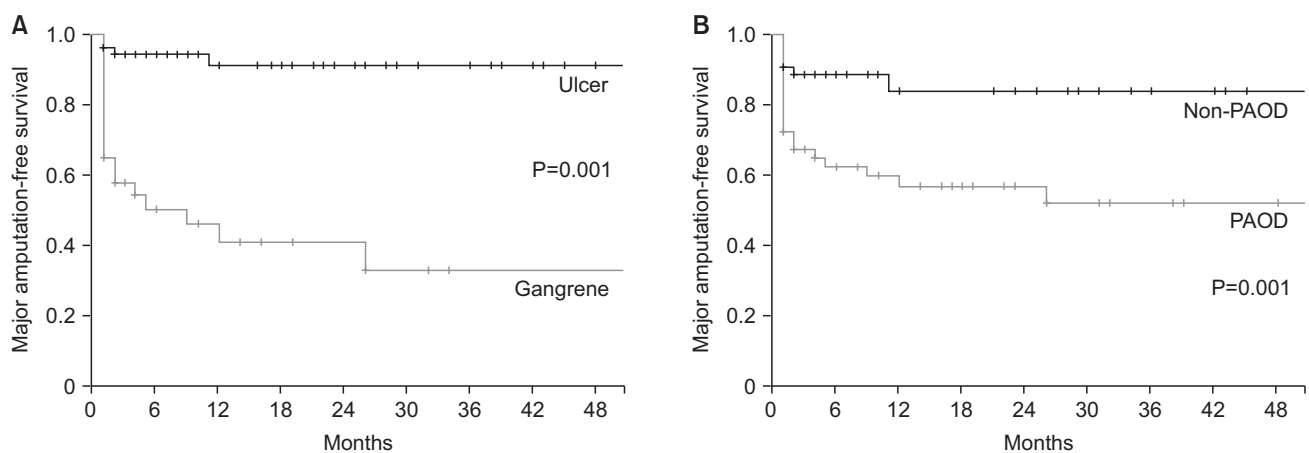In this study, major amputation in patients with DFW

Fig. 1. Major amputation-free survival rates for diabetic foot wound (DFW). (A) Kaplan–Meier survival curves howing major amputation-free survival rate for DFW; DFW patients are divided into two groups as diabetic foot ulcer and diabetic foot gangrene. (B) Kaplan–Meier survival curves demonstrating major amputation-free survival rate in DFW with and without peripheral arterial occlusive disease (PAOD).

was performed for 37 of 141 patients (26.2%). Moreover, the rates of major amputation in were 6.8% in DFU group and 47.1% in DFG group. Wound state according to Wagner classification grade, CAD, CHF, leukocytosis, dementia, and PAOD showed statistically significant differences between the non-major amputation group and the major amputation group (Table 1). Our multivariate analysis indicated that wound state (OR, 12.155; 95% CI, 3.427-43.106; P=0.001), CHF (OR, 4.486; 95% CI, 1.180-17.061; P=0.028), leukocytosis (OR, 2.661; 95% CI, 1.012-6.995; P=0.047), and PAOD (OR, 3.727; 95% CI, 1.101-12.615; P=0.034) were significant risk factors for major amputation in patients with DFW (Table 1). Major amputation-free survival was 83.9% at 1 year in DFW group and 56.7% at 1 year in DFW with PAOD group and showed statistically significant difference (P=0.001) (Fig. 1).

2) Major amputation in DFW with PAOD

Among a total of 141 DFW patients, 76 patients (53.9%) had PAOD and 29 of 76 PAOD patients (38.2%) underwent

Table 2. Risk factors for major amputation in DFW with PAOD

Risk factor	DFW with PAOD (n=76)	Major amputation (n=29, 38.2%)	Univariate P-value	Multivariate P-value	OR (95% CI)
Age (y)			0.708	0.092	0.110 (0.008–1.435)
≥60	64 (84.2)	25 (39.1)			
Male	38 (50.0)	12 (31.6)	0.238	0.080	6.096 (0.806–46.079)
Site, right	32 (42.1)	14 (43.8)	0.392	0.595	1.557 (0.304–7.966)
Wound infection	57 (75.0)	23 (40.4)	0.495	0.375	0.363 (0.039–3.410)
Hypertension	52 (68.4)	19 (36.5)	0.669	0.957	0.952 (0.154–5.885)
DM control			0.771	0.126	5.436 (0.623–47.428)
Insulin	17 (22.4)	7 (41.2)			
Coronary artery disease	26 (34.2)	13 (50.0)	0.125	0.074	5.502 (0.849–35.672)
Congestive heart failure	15 (19.7)	9 (60.0)	0.052	0.171	4.259 (0.534–33.962)
Cerebrovascular disease	20 (26.3)	10 (50.0)	0.204	0.398	2.402 (0.315–18.382)
Chronic kidney disease[a]	20 (26.3)	10 (50.0)	0.204	0.467	0.500 (0.077–3.240)
COPD	24 (31.6)	9 (37.5)	0.936	0.589	1.681 (0.256–11.052)
Leukocytosis	42 (55.3)	22 (52.4)	0.005	0.019	8.457 (1.410–50.716)
HbA1c >9	18 (23.7)	7 (38.9)	0.942	0.855	1.231 (0.133–11.368)
Smoking	36 (47.4)	14 (38.9)	0.901	0.884	0.867 (0.127–5.902)
Dementia	20 (26.3)	10 (50.0)	0.204	0.167	3.859 (0.569–26.162)
Economic state	37 (48.7)	17 (45.9)	0.173	0.247	2.847 (0.484–16.749)
PAOD location				0.802	0.705 (0.046–10.812)
Proximal	7 (9.2)	3 (42.9)			
Distal	27 (35.5)	9 (33.3)			
Proximal & distal	42 (55.3)	5 (26.3)			
Arterial stenotic/occlusive lesion			0.668	0.802	0.705 (0.046–10812)
Multiple lesions	61 (80.3)	24 (39.3)			
Revascularization	16 (21.1)	4 (25.0)	0.223	0.156	4.415 (0.566–34.431)
Wagner classification			0.001	0.003	97.257 (4.807–1,967.729)
Wagner grade 0	1 (1.3)	0 (0.0)			
Wagner grade 1	6 (7.9)	0 (0.0)			
Wagner grade 2	0 (0.0)	0 (0.0)			
Wagner grade 3	17 (22.4)	2 (11.8)			
Wagner grade 4	34 (44.7)	9 (26.5)			
Wagner grade 5	18 (23.7)	18 (100.0)			

Values are presented as number (%).
DFW, diabetic foot wound; PAOD, peripheral arterial occlusive disease; OR, odds ratio; CI, confidence interval; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease.
[a]Glomerular filtration rate <30.

major amputation. Wound state according to Wagner classification grades (OR, 97.257; 95% CI, 4.807-1,967.729, P=0.003) and leukocytosis (OR, 8.457; 95% CI, 1.410-50.716; P=0.019) were found to be statistically significant predictors for major amputation in patients with DFW with PAOD by univariate and multivariate analyses (Table 2). In terms of PAOD location, proximal location in 7 patients (9.2%), distal location in 27 patients (35.5%), and multiple locations in 42 patients (55.3%) were found. Among 42 patients with multiple locations, 17 patients (40.5%) underwent major amputation. However, these findings did not show statistically significant relationship according to PAOD location. In this study, two-thirds of DFW patients with PAOD had multiple stenotic/occlusive lesions. Although the presence of multiple arterial stenotic/occlusive lesions showed higher rate of major amputation (33.3% in single arterial lesion vs. 39.3% in multiple arterial lesion), there was no statistically significant difference between two groups (P=0.668). Moreover, vascular/endovascular procedure was performed in 16 of 76 DFW patients (21.1%) with PAOD and all procedures were clinically and radiologically successful. Rates of major amputation were 41.7% in non-vascular/endovascular procedure group and 25.0% in vascular/endovascular procedure group. In addition, we performed a subgroup analysis of PAOD patients except Wagner classification 5 (n=18) and bedridden state (n=3) to assess the effect of vascular/endovascular procedure on major amputation. Among 55 patients with DFW and PAOD, revascularization procedures were performed in 13 patients (23.6%) and major amputations were done in 9 patients (16.4%). The rates of major amputation were 16.7% in non-vascular/endovascular procedure group and 15.4% in vascular/endovascular procedure group. We did not find any statistical significances among two groups by univariate

(P=1.000) and multivariate (P=0.999) analyses.

Freedom form major amputation was 62.2% at 1 year in no procedure group and 58.2% at 1 year in procedure group (P=0.321) (Fig. 2). However, univariate or multivariate analysis for major amputation did not identify any statistical significance between the two groups (P=0.156) (Table 2).

3) Amputation in DFU

Of 73 patients with DFU, amputation was performed for 28 patients (38.4%) while major amputation was performed for 5 patients (6.8%). Age (P=0.044) and OM (P=0.021) showed statistically significant differences between the non-amputation group and the amputation group (Table 3). Amputation-free survival rate was 68.3% at 1 year in non-OM group and 41.6% at 1 year in OM group (P=0.010). The presence of PAOD of DFU patients showed similar rate in the amputation group (33.3% in non-amputation vs. 32.1% in amputation) and there was no significant difference between the presence of PAOD and amputation (P=0.916).

DISCUSSION

DM is known to increase the risk of major amputation by 20 times [14]. However, few studies have evaluated amputation rates or predictors in overall DFW patients. Miyajima et al. [15] have reported that 45 of 210 patients (21.4%) with diabetic foot lesion require major amputation and atherosclerosis obliterans with multiple stenosis, HD, and HbA1C are risk factors for major amputation. In the present study, the overall rate of major amputation in patients with DFW was 26.4% with wound state according to Wagner classification grade, CHF, leukocytosis, dementia, and
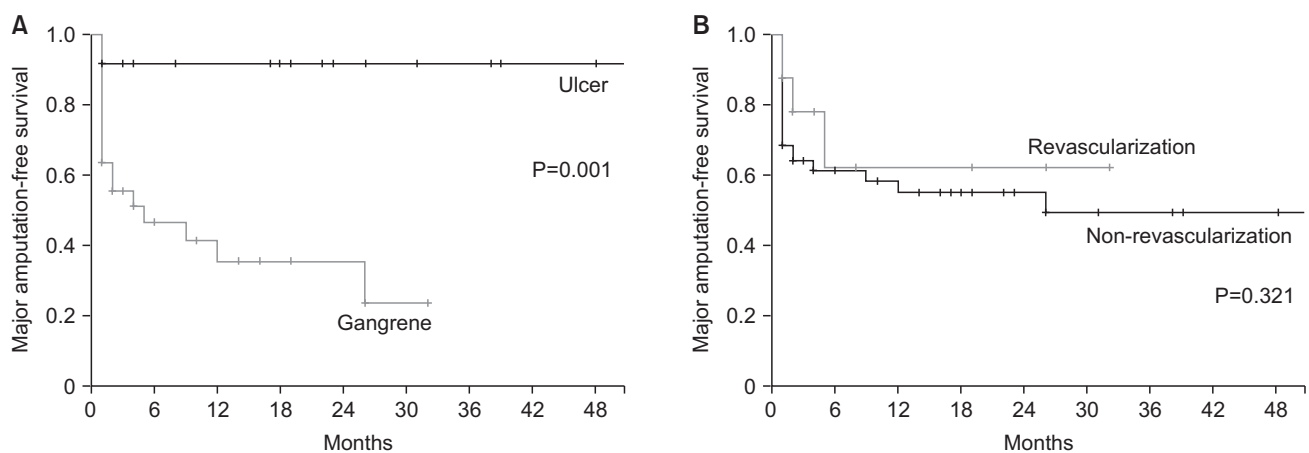

Fig. 2. Major amputation-free survival rates for diabetic foot wound with peripheral arterial occlusive disease (PAOD). (A) Kaplan-Meier survival curves demonstrating major amputation-free survival rate in patients with PAOD as the presence of diabetic foot ulcer or diabetic foot gangrene. (B) Kaplan-Meier survival curves illustrating major amputation free survival rate in PAOD patients with and without revascularization.

Table 3. Demographic features and predictors for amputation in DFU

Risk factor	DFU (n=73)	Amputation (n=28, 38.4%)	Univariate P-value	Multivariate P-value	Multivariate OR (95% CI)
Age (y)			0.044	0.274	0.487 (0.134–1.768)
≥60	37 (50.7)	10 (27.0)			
Male	33 (45.2)	12 (36.4)	0.750	0.258	2.230 (0.555–8.965)
Site, right	36 (49.3)	10 (27.8)	0.067	0.083	3.063 (0.864–10.853)
Hypertension	47 (64.4)	15 (31.9)	0.128	0.531	0.644 (0.163–2.551)
DM control			0.542	0.165	2.997 (0.636–14.132)
Insulin	23 (31.5)	10 (43.5)			
Coronary artery disease	15 (20.5)	7 (46.7)	0.458	0.278	2.661 (0.454–15.607)
Cerebrovascular disease	16 (21.9)	7 (43.8)	0.616	0.230	2.360 (0.581–9.581)
Chronic kidney disease[a]	10 (13.7)	3 (30.0)	0.732	0.336	0.384 (0.054–2.700)
COPD	19 (26.0)	8 (42.1)	0.696	0.789	1.212 (0.296–4.956)
HbA1c >9	19 (26.0)	7 (36.8)	0.875	0.785	0.816 (0.189–3.530)
Smoking	41 (56.2)	18 (43.9)	0.270	0.523	1.622 (0.368–7.150)
Dementia	7 (9.6)	1 (14.3)	0.239	0.391	0.280 (0.015–5.125)
Bed ridden state	6 (8.2)	3 (50.0)	0.669	0.599	0.500 (0.038–6.651)
Economic state	43 (58.9)	17 (39.5)	0.804	0.913	0.928 (0.243–3.550)
PAOD	24 (32.9)	9 (37.5)	0.916	0.682	1.354 (0.317–5.787)
Osteomyelitis	27 (37.0)	15 (55.6)	0.021	0.116	3.321 (0.743–14.838)
Leukocytosis	28 (38.4)	13 (46.4)	0.263	0.287	1.975 (0.565–6.909)

Values are presented as number (%).
DFU, diabetic foot ulcer; OR, odds ratio; CI, confidence interval; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; PAOD, peripheral arterial occlusive disease.
[a]Glomerular filtration rate <30.

PAOD being identified as significant risk factors for major amputation. These findings indicated that systemic factors such as CHF, leukocytosis, and dementia might affect major amputation in patients with DFW rather than local wound factors. Huang et al. [16] have also reported a major amputation rate of 57.3% in patients with infectious DFG. Our results showed similar rate of 47.1% in DFG (32 of 68 DFG patients). In addition, we also identified that wound state according to Wagner classification grades was a major predictor for major amputation in all DFW and DFW with PAOD, as previous studies reported that Wagner classification system was significantly correlated to the amputation in DFW [17,18]. Our current study demonstrated that about half of DFW patients (76 of 141 DFWs) had PAOD and 38.2% of all PAOD patients needed major amputation. Several studies have established that PAOD is a significant risk factor in diabetic foot lesions [15,16,19]. Our analyses also supported that the presence of PAOD was the predictor for major amputation in patients with DFW. In terms of PAOD severity, the major amputation group had higher rates of multiple locations and multiple arterial stenotic/occlusive lesions of PAOD. However, the present study failed to prove statistically significant relationship between major amputa-

tion and PAOD severity. Furthermore, current guideline recommends revascularization procedures with either bypass surgery or endovascular treatment for functional limb salvage in patients with diabetes and lower extremity wounds [20]. On the contrary, Claesson et al. [21] have reported that there is no difference in major amputation between conservative management and endovascular treatment or in unreconstructable patients. In our study, the rate of major amputation in DFW patients was lower in the vascular/endovascular procedure group (25.0% in procedure group vs. 41.7% in non-procedure group). However, subgroup analysis except extensive foot necrosis and bedridden state showed similar rate of major amputation between non-procedure group (16.7%) and procedure group (15.4%).

Severe CKD and dialysis are known to be independent risk factors for major amputation in DFW [15,22,23]. Our results showed that DFW patients with severe CKD and HD had higher rate of major amputation (35.5% in severe CKD and HD vs. 23.6% in non-severe CKD and HD). In addition, high HbA1c is a potential risk factor for non-healing and amputation in DFU. Good glycemic control is also important to reduce amputation risk [18,24,25]. We analyzed HbA1c >9% as a risk factor for amputation and found that HbA1c >9%

showed slightly higher rate of amputation in DFU patients (42.9% in HbA1c >9% vs. 39.7% in HbA1c ≤9%), although there was no statistical significance between the two groups.

The EURODIALE study reported that 77% of DFU patients healed and 5% underwent major amputation [5]. However, among DFU patients healed, 17% underwent minor amputation. They also found that patients with PAOD and major amputation had worse wound rates with higher mortality rates in PAOD patients. Another large cohort study stated that overall amputation rate in patients with DFU was 37.1% with limb ischemia, OM, presence of gangrene, and ulcer depth being identified as major predictors of overall and major amputation [25]. Our present study showed that overall amputation and major amputation rates were 38.4% and 6.8%, respectively, in DFU patients, similar to the amputation rates reported in previous studies. Twenty-four of 79 DFU patients (32.9%) had PAOD. Our results revealed that DFU patients with the presence of PAOD had similar rate of amputation (amputation rate of 33.3%) compared to DFU patients without PAOD (amputation rate of 32.1%). In addition, more than half of DFU patients with OM underwent amputation and showed statistically significant difference between DFU with OM and DFU without OM. Previous studies have reported a significant association of OM with overall and major amputations although our multivariate analysis failed to be identified that OM was a major predictor for amputation in DFU patients. These findings indicated that the presence of deep infection involving the bone is a major risk factor for amputation in patients with DFU despite aggressive surgical debridement to control deep infection.

This present study has several potential limitations. First, the number of patients with DFW was small. Therefore, we found a relatively higher rate of major amputation. However, we failed to prove PAOD severity as a risk factor for major amputation, although the presence of PAOD was identified as a predictor for major amputation in patients with DFW. Second, it had a retrospective study design to investigate predictors for major amputation in DFW and amputation in DFU. Especially, the classification system for detailed local wound state including WIFI grading classification could not be applied to analyze risk factors for amputation. The presence of wound infection or OM was analyzed as potential predictors for amputation. Another limitation of this study was a relatively lower rate of vascular/endovascular procedure in patients with DFW and PAOD. Although the procedure group showed lower rate of major amputation, our analyses did not show statistically significant correlation between vascular/endovascular procedure and major amputation. This result might be caused by the small number of patients and the lower late of vascular/endovascular procedure in DFW patients with PAOD.

In conclusion, our findings showed that 37 of 141 DFW patients (26.2%) underwent major amputation with wound state by Wagner classification system, CHF, leukocytosis, dementia, and PAOD as significant risk factors for major amputation. Moreover, over half of DFW patients had PAOD and about 38.2% of them underwent major amputation. Higher grade of Wagner classification and leukocytosis were found to be significant predictors for major amputation in patients with DFW with PAOD. In addition, among DFU patients, 38.4% underwent amputation. The presence of OM showed significant difference for amputation in DFU patients. In summary, our present study indicates that wound state and the presence of PAOD are major predictors for major amputation in patients with DFW. Moreover, systemic factors such as CHF, leukocytosis, and dementia can affect major amputation in DFW. In terms of DFU, local wound state, such as OM rather than systemic factors is a determinant for amputation.

REFERENCES

1) Most RS, Sinnock P. The epidemiology of lower extremity amputations in diabetic individuals. Diabetes Care 1983;6:87-91.

2) Fylling CP, Knighton DR. Amputation in the diabetic population: incidence, causes, cost, treatment, and prevention. J Enterostomal Ther 1989;16:247-255.

3) Reiber GE, Lipsky BA, Gibbons GW. The burden of diabetic foot ulcers. Am J Surg 1998;176(2A Suppl):5S-10S.

4) Apelqvist J, Larsson J, Agardh CD. Long-term prognosis for diabetic patients with foot ulcers. J Intern Med 1993;233:485-491.

5) Prompers L, Schaper N, Apelqvist J, Edmonds M, Jude E, Mauricio D, et al. Prediction of outcome in individuals with diabetic foot ulcers: focus on the differences between individuals with and without peripheral arterial disease. The EURODIALE study. Diabetologia 2008;51:747-755.

6) Jonasson JM, Ye W, Sparén P, Apelqvist J, Nyrén O, Brismar K. Risks of non-traumatic lower-extremity amputations in patients with type 1 diabetes: a population-based cohort study in Sweden. Diabetes Care 2008;31:1536-1540.

7) American Diabetes Association. Peripheral arterial disease in people with

diabetes. Diabetes Care 2003;26:3333-3341.

8) Gemechu FW, Seemant F, Curley CA. Diabetic foot infections. Am Fam Physician 2013;88:177-184.

9) Prompers L, Huijberts M, Apelqvist J, Jude E, Piaggesi A, Bakker K, et al. High prevalence of ischaemia, infection and serious comorbidity in patients with diabetic foot disease in Europe. Baseline results from the Eurodiale study. Diabetologia 2007;50:18-25.

10) Boulton AJ. The pathogenesis of diabetic foot problems: an overview. Diabet Med 1996;13 Suppl 1:S12-16.

11) Armstrong DG, Lavery LA, Harkless LB. Validation of a diabetic wound classification system. The contribution of depth, infection, and ischemia to risk of amputation. Diabetes Care 1998;21:855-859.

12) Shojaiefard A, Khorgami Z, Larijani B. Independent risk factors for amputation in diabetic foot. Int J Diabetes Dev Tries 2008;28:32-37.

13) Wagner FW. A classification and treatment program for diabetic, neuropathic, and dysvascular foot problems. Am Acad Orthop Surg Instr Course Lect 1979;28:143-165.

14) Moss SE, Klein R, Klein BE. The 14-year incidence of lower extremity amputations in a diabetic population. The Wisconsin epidemiologic study of diabetic retinopathy. Diabetes Care 1999;22:951-959.

15) Miyajima S, Shirai A, Yamamoto S, Okada N, Matsushita T. Risk factors for major limb amputation in diabetic foot gangrene patients. Diabetes Res Clin Pract 2006;71:272-279.

16) Huang YY, Lin CW, Yang HM, Hung SY, Chen IW. Survival and associated risk factors in patients with diabetes and amputations caused by infectious foot gangrene. J Foot Ankle Res 2018. doi: 10.1186/s13047-017-0243-0.

17) Oyibo SO, Jude EB, Tarawneh I, Nguyen HC, Harkless LB, Boulton AJ. A comparison of two diabetic foot ulcer classification systems: the Wagner and the university of Texas wound classification systems. Diabetes Care 2001;24:84-88.

18) Calhoun JH, Cantrell J, Cobos J, Lacy J, Valdez RR, Hokanson J, et al. Treatment of diabetic foot infections: Wagner classification, therapy, and outcome. Foot Ankle 1988;9:101-106.

19) Lenselink E, Holloway S, Eefting D. Outcomes after foot surgery in people with a diabetic foot ulcer and a 12-month follow-up. J Wound Care 2017;26:218-227.

20) Hingorani A, LaMuraglia GM, Henke P, Meissner MH, Loretz L, Zinszer KM, et al. The management of diabetic foot: a clinical practice guideline by the Society for Vascular Surgery in collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine. J Vasc Surg 2016;63(2 Suppl):3S-21S.

21) Claesson K, Kölbel T, Acosta S. Role of endovascular intervention in patients with diabetic foot ulcer and concomitant peripheral arterial disease. Int Angiol 2011;30:349-358.

22) Otte J, van Netten JJ, Woittiez AJ. The association of chronic kidney disease and dialysis treatment with foot ulceration and major amputation. J Vasc Surg 2015;62:406-411.

23) He Y, Qian H, Xu L, Zhang S, Gu X, Gu J, et al. Association between estimated glomerular filtration rate and outcomes in patients with diabetic foot ulcers: a 3-year follow-up study. Eur J Endocrinol 2017;177:41-50.

24) Pemayun TG, Naibaho RM, Novitasari D, Amin N, Minuljo TT. Risk factors for lower extremity amputation in patients with diabetic foot ulcers: a hospital-based case-control study. Diabet Foot Ankle 2015. doi: 10.3402/dfa.v6.29629.

25) Yesil S, Akinci B, Yener S, Bayraktar F, Karabay O, Havitcioglu H, et al. Predictors of amputation in diabetics with foot ulcer: single center experience in a large Turkish cohort. Hormones (Athens) 2009;8:286-295.