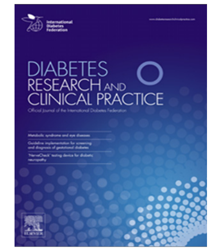
DIABETES RESEARCH AND CLINICAL PRACTICE 158 (2019) 107905

Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation



Risk factors for major amputation in hospitalized diabetic patients with forefoot ulcers

Kyung-Chul Moon, Soo-Byn Kim, Seung-Kyu Han, Seong-Ho Jeong, Eun-Sang Dhong*

Department of Plastic Surgery, Korea University Guro Hospital, Seoul, South Korea

ARTICLE INFO

Article history:
Received 29 June 2019
Received in revised form
4 October 2019
Accepted 25 October 2019
Available online 29 October 2019

Keywords:
Amputation
Diabetic foot
Foot ulcer
Risk analysis
Risk factors

ABSTRACT

Aims: The purpose of this study was to investigate the risk factors for major amputation in patients hospitalized with diabetic forefoot ulcers.

Methods: Between January 2003 and December 2018, a total of 1792 diabetic patients were admitted to the diabetic wound center for the management of diabetic foot ulcers. Among the patients, 1032 diabetic patients with forefoot ulcers were included in this study. Nine hundred and eighty-three patients (95%) healed without major amputations while 49 patients (5%) healed after major amputations. Data related to 88 potential risk factors including demographics, ulcer condition, vascularity, bioburden, neurology, and serology were collected from the patients in these two groups for comparison.

Results: Among the 88 potential risk factors, 34 showed statistically significant differences between the two groups. In the univariate analysis of 88 risk factors, 33 showed statistically significant differences. In stepwise multiple logistic regression analysis, four of the 33 risk factors remained statistically significant. The multivariate-adjusted odds ratios for gender, magnesium levels, platelet levels, and glycated hemoglobin (HbA1c) levels were 8.216, 2.480, 1.009, and 0.570, respectively.

Conclusion: Risk factors for major amputation in patients hospitalized with diabetic forefoot ulcers include male gender, increased magnesium, increased platelet levels, and low levels of HbA1c.

1. Introduction

Diabetic foot ulcer is a common complication of diabetes. The lifetime prevalance of diabetic foot ulcers has been estimated to between 19 and 34% in diabetic patients [1]. In addition, the annual incidence rates of diabetic foot ulcers in the global population of diabetic patients has been reported to be 6.3 percent [2]. Diabetic foot ulcers frequently lead to lower extremity amputations, approximately 75% of which are performed in diabetic patients due to a combination of peripheral neuropathy, peripheral vascular disease, poor glycemic control, and superimposing infections [3]. Therefore, diabetic foot ulcers are significant health and socioeconomic problems with adverse effects on the quality of life.

In the European Study Group on Diabetes and the Lower Extremity (Eurodiale) study by Pickwell et al. [4], the most frequent diabetic foot ulcer site was the forefoot (56%). Therefore, the number of diabetic patients with forefoot ulcers who undergo major amputation (3%) was far greater than those with midfoot (1%) or hindfoot ulcers (1%) [4]. Accordingly, there is considerable interest in the treatment of diabetic forefoot ulcers. Diabetic foot ulcers involving the forefoot are

* Corresponding author at: Department of Plastic Surgery, Korea University Guro Hospital, 148 Guro-Dong, Guro-Ku, Seoul 152-703, South Korea.

E-mail address: pshan@kumc.or.kr (S.-K. Han).

https://doi.org/10.1016/j.diabres.2019.107905

generally managed via minor amputation, including partial or complete toe amputation, partial or full ray resection, and proximal foot amputation (transmetatarsal, Lisfranc's, Chopart's, and Symes amputations). However, diabetic forefoot ulcers are commonly caused by repetitive stress over an area that is subject to high vertical or shear stress in the presence of peripheral neuropathy [5]. Therefore, recurrence is common and recurred ulcers may increase the risk resulting in infection and osteomyelitis. Consequently, the contiguous spread of infection and osteomyelitis proximal to the ankle may result in major amputation.

Major amputations, including above- and below-knee amputations, often lead to significant functional disability, with high rates of post-operative mortality. They are also associated with increased cardiovascular demand in a subset of patients who already have an increased prevalence of cardiovascular disease [6]. While there is evidence that mortality is improving with the adoption of an aggressive cardiovascular risk management policy [7], the overall survival after major amputation still ranges from 81% at one year, and 69% at three years, to 29% at five years [8]. The 5-year mortality after diabetes-related amputation is worse than that of many common cancers [9]. Therefore, limb salvage is essential for the overall stabilization of diabetic foot ulcer patients and the prevention of life-threatening outcomes.

Several risk factors for major amputation among patients with diabetic foot ulcers have been reported in the literatures [10–12]. However, a large-scale study to determine the risk factors for major amputation in diabetic forefoot ulcer patients treated with identical management protocols has yet to be reported. Therefore, the purpose of this study was to determine predictors for major amputation in patients with diabetic foot ulcers involving the forefoot following standard treatment at a referral center for diabetic foot ulcers in Korea.

2. Materials and methods

2.1. *Management protocol in brief*

We hospitalized patients diagnosed with diabetic foot ulcers whose general condition was so poor that outpatient clinic-based treatments were not possible, patients with severely infected ulcers requiring surgical debridement with systemic intravenous antibiotic therapy, and patients with severe vasculopathy that required immediate angioplasty.

A complete patient medical history was obtained upon admission. General serological tests, including serum blood glucose and inflammatory markers, were performed. The vascularity of the diabetic foot was measured based on the transcutaneous partial oxygen tension ($TcPO_2$), toe pressure, Doppler wave, and computed tomography angiography (CTA). Patients with peripheral arterial disease underwent percutaneous transluminal angioplasty by interventional cardiologists. Hyperbaric or normobaric oxygen therapy was used as an adjunct to treatment for several clinical conditions associated with tissue hypoxia. Deep tissue culture was performed for the management of wound bioburden. When necessary, intravenous antibiotics were administered empirically and changed according to the results of the culture and sensitivity tests. Serial surgical debridements were performed as needed at the bedside or in the operating room according to wound conditions. Patients with osteomyelitis were treated with systemic antibiotic therapy for at least three to six weeks. Osteomyelitis was diagnosed via magnetic resonance imaging (MRI) and bone culture. Neuropathy was evaluated via the Semmes-Weinstein monofilament test on a decimal scale, electromyography (EMG), and nerve conduction velocity (NCV) tests. Patients indicated for off-loading received specific individual therapeutic footwear. Moreover, we used folded polyurethane foam or felted foam, which were fixed proximal to the wounds, in combination with appropriate footwear worn consistently, for wound healing and the prevention of ulcer recurrence.

If wound conditions worsened despite treatments based on our protocol and minor amputation for at least six weeks, major amputation was considered to prevent the deterioration of their general condition. We also made every effort, including flap surgery, to save the limb. Major amputation was the last resort. Life-threatening conditions associated with severely infected ischemic limbs with a risk of systemic sepsis were also indications for major amputation.

2.2. *Patients*

This retrospective study was approved by the Institutional Review Board of our institution (#2015GR0181). This study was performed in accordance with the Declaration of Helsinki.

This study included the data of 1792 consecutive patients, who were hospitalized for the management of diabetic foot ulcers at the diabetic wound center of Korea University Guro Hospital between January 2003 and December 2018. The diabetic wound center of Korea University Guro Hospital is a referral center for patients with diabetic foot ulcers. Among the 1792 patients, those who met the following inclusion criteria were included in this study: duration of diagnosed type 1 or 2 diabetes >5 years, ulcer lesion localized at the forefoot, patients without missing data, and patients who were successfully monitored until complete healing was achieved. Complete healing was defined as a completely epithelialized state without discharge or open lesions. Patients were excluded if they had multiple ulcers or ulcers localized at the midfoot or hindfoot (Fig. 1). In total, 1371 patients (922 males, 449 females) were successfully monitored until complete healing was achieved. Of these 1371 patients, 1032 met the inclusion criteria. Nine hundred and eighty-three (95%) of the 1032 patients healed without major amputations, and 49 (5%) patients healed following major amputations (Table 1). The mean age of the patients was 63.2 ± 12.2 years (range, 27–96 years). The mean duration of the diabetic foot ulcers was 14.0 ± 24.1 months and the mean hospitalization period was 23.1 ± 11.9 days.

2.3. *Evaluation*

The patient data were linked to hospital electronic records. Linked data were obtained from the Korea University Guro Hospital Admitted Data Collection which was regularly

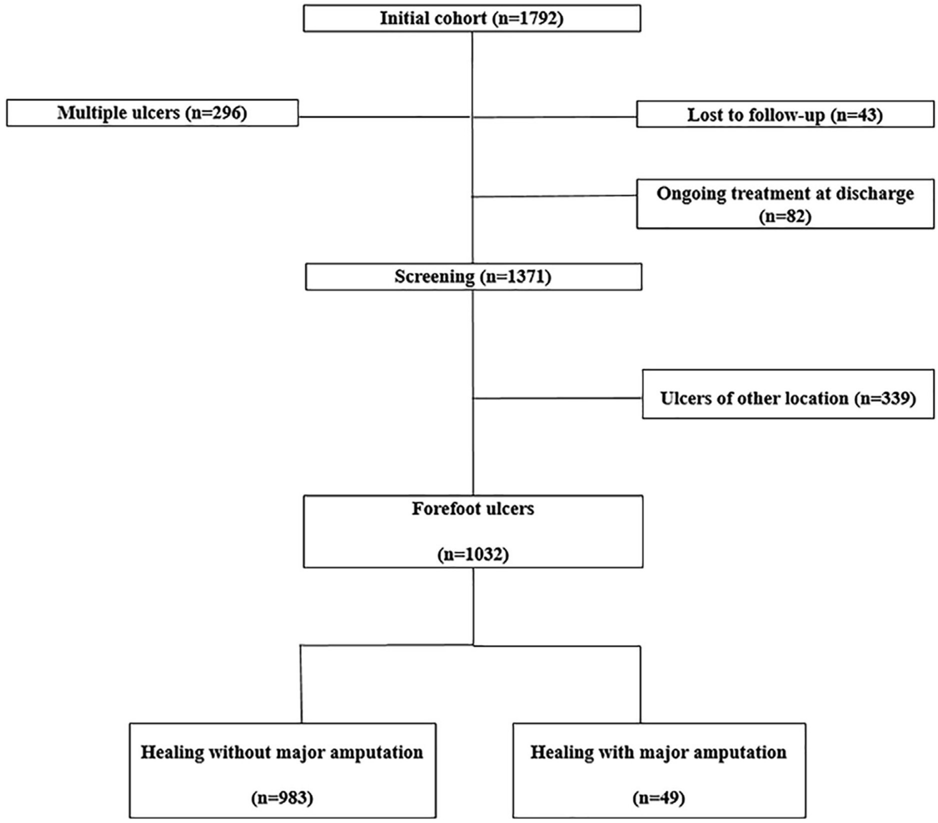


Fig. 1 – A flow diagram of patients included in the study (n = number of patients).

Table 1 – Rate of major amputations according to ulcer locations.

	Total patients	Major amputation (%)
Forefoot	1032	49 (4.7)
Midfoot	162	15 (9.3)
Hindfoot	177	17 (9.6)
Total	1371	81 (5.9)

audited to minimize data inaccuracy. During the admission process, we collected a total of 88 different forms of patient data representing potential risk factors including demographics, ulcer characteristics, baseline vascularity, wound bioburden, neurology, and serology of all hospitalized patients. To compare the demographic and clinical characteristics, 28 variables, such as gender, age, dialysis, and duration of the ulcer, were investigated. The ulcer characteristics, including 16 variables, such as location, size, and depth of the ulcer in the major amputation and non-amputation groups, were compared. The results of the $TcPO_2$, toe pressure, Doppler wave test, and CTA were used to compare the vascularity. In addition, 11 variables associated with wound bioburden, two variables suggesting neuropathy, and 26 variables of general serology, such as glycated hemoglobin (HbA1c), albumin, and glucose, were compared between the two groups (Table 2).

All patients showed unilateral involvement except for 92 individuals. Among the patients with bilateral involvement, the foot with the larger ulcer was selected for the analysis. Among the patients who were admitted multiple times for different episodes, only the first admission was included in this study.

2.4. *Statistical analyses*

The data of all 88 variables in patients treated with major amputations were compared with those without major amputations and the statistical significance was examined. Mann-Whitney *U* tests were used to compare the quantitative variables between the two groups after Shapiro-Wilk tests confirmed that the variables were not normally distributed. Chi-square tests were used for categorical variables, except for the variables of gastrointestinal disorders, hepatobiliary disorders, arthritis, musculoskeletal disorders, genitourinary disorders, metabolic disorders, malignant tumors, the cause and depth of the ulcer, Doppler wave tests, MRI, and EMG findings. Fisher's exact tests were used to analyze these variables where sample sizes were small and more than 20% of the cells had expected frequencies below five.

Univariate logistic regression analysis and odds ratios (OR) with 95% confidence interval (CI) were used to analyze the association between the risk of major amputation and the aforementioned 88 variables. Statistically significant variables identified in univariate regression analysis were used to perform stepwise multivariate logistic regression. A p-value of less than 0.05 was considered statistically significant. The data were analyzed using the IBM SPSS version 21 software package (SPSS, Chicago, IL).

Table 2 – Risk factors analyzed in this study.

Risk factor (p-value)			
Demographics	Gender (0.041)*	Foot deformity	Comorbidities (continued)
	Age (0.433)	Charcot deformity (0.569)	GI disorder (0.004)*
	DM duration (0.005)*	Claw toe (0.921)	Hepatobiliary disorder (0.363)
	Ambulation (<0.001)*	Hammer/Mallet toe (0.354)	Ophthalmic disorder (0.272)
	Neuropathic Sx. (0.063)	Hallux valgus (0.752)	CNS disorder (0.260)
	Dialysis (<0.001)*	High arch foot (0.263)	Arthritis (1.000)
	Dialysis duration (0.627)	Comorbidities	Musculoskeletal disorder (1.000)
	Smoking (0.132)	Cardiac disorder (0.083)	Genitourinary disorder (0.067)
	Previous history of DM foot treatment (0.137)	Hypertension (0.008)*	Metabolic disorder (0.069)
		Pulmonary disorder (<0.001)*	Malignant tumor (0.214)
		Renal disorder (<0.001)*	Other comorbidities (0.763)
Ulcer characteristics	Cause	Depth	Location
	Trauma (0.578)	Dermis (0.104)	Dorsal foot (0.452)
	Burn (1.000)	Subcutaneous tissue (0.073)	Plantar foot (0.089)
	Pressure (0.195)	Tendon/Joint (0.162)	Border (0.240)
	Spontaneous (0.012)*	Bone (0.002)*	
	Duration (0.558)	Inflammatory sign (0.003)*	
	Side (0.160)		
	Size (<0.001)*		
	Previous treatment at other hospital (0.301)		
Vascularity	$TcPO_2$ (<0.001)*	Toe pressure (1.000)	Doppler (0.762)
	CT angiography		
	ATA stenosis (0.003)*		
	PTA stenosis (<0.001)*		
Wound bioburden	Serology	MRI	Tissue culture
	WBC (<0.001)*	No infection (0.639)	No growth (0.457)
	ESR (<0.001)*	Cellulitis (<0.001)*	Growth, soft tissue (0.102)
	CRP (<0.001)*	Bone marrow edema (0.062)	Growth, bone (0.475)
	Procalcitonin (0.192)	Osteomyelitis (0.118)	
Neurology	Monofilament test (0.012)*	EMG and NCV (0.398)	
General serology	HbA1c (0.010)*	Cholesterol (0.759)	HDL (<0.001)*
	LDL (0.641)	Hemoglobin (<0.001)*	Glucose (0.270)
	Albumin (<0.001)*	Protein (0.510)	BUN (<0.001)*
	Creatinine (<0.001)*	ALT (0.047)*	AST (0.368)
	FBS (0.191)	Vitamin A (0.034)*	Vitamin C (0.236)
	Vitamin Eα (0.676)	Vitamin Eβ (0.026)*	Vitamin Eγ (0.155)
	Fe (0.001)*	Mg (0.044)*	Zn (0.008)*
	Cu (0.101)	Platelet (0.064)	Ferritin (<0.001)*
	TIBC (<0.001)*	2-hour postprandial blood sugar (0.293)	

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ATA, anterior tibial artery; BUN, blood urea nitrogen; CNS, central nervous system; CRP, C-reactive protein; CT, computed tomography; Cu, copper; DM, diabetes mellitus; EMG, electromyography; ESR, erythrocyte sedimentation rate; FBS, fasting blood sugar; Fe, iron; GI, gastrointestinal; HbA1c, glycated hemoglobin; HDL, high density lipoprotein; LDL, low density lipoprotein; Mg, magnesium; MRI, magnetic resonance imaging; NCV, nerve conduction velocity; PTA, posterior tibial artery; $TcPO_2$, transcutaneous partial oxygen tension; TIBC, total iron-binding capacity; WBC, white blood cell; Zn, zinc. *$p < 0.05$.

3. Results

In comparative analysis of the major amputation and the other groups, 34 of the 88 risk factors for major amputation showed statistically significant differences (Table 2). In univariate analysis, significant differences were observed for 33 of the 88 risk factors. In stepwise multiple logistic analysis, four factors remained statistically significant among the 33 risk factors. The multivariate-adjusted ORs in the stepwise logistic regression model for gender, magnesium levels, platelet levels, and HbA1c levels were 8.216 (95% CI: 1.429–47.241, $p = 0.018$), 2.480 (95% CI: 1.027–5.986, $p = 0.043$), 1.009 (95% CI: 1.004–1.013, $p < 0.001$), and 0.570 (95% CI: 0.376–0.864, $p = 0.008$), respectively (Table 3).

Table 3 – Results of univariate and stepwise multiple logistic analyses.

	Univariate analysis			Stepwise logistic regression		
Factors	OR	95% CI	p-value	OR	95% CI	p-value
Demographics						
Gender	2.207	1.014–4.801	0.046	8.216	1.429–47.241	0.018
DM duration	1.034	1.005–1.063	0.019			
Ambulation	0.355	0.193–0.652	<0.001			
Dialysis	12.777	6.212–26.283	<0.001			
Comorbidities						
Hypertension	2.742	1.262–5.961	0.011			
Pulmonary disorder	3.449	1.747–6.806	<0.001			
Renal disorder	3.984	2.128–7.456	<0.001			
GI disorder	4.162	1.742–9.943	0.001			
Ulcer characteristics						
Size	1.012	1.007–1.018	<0.001			
Cause						
Spontaneous	2.144	1.173–3.921	0.013			
Depth						
Bone	4.612	1.636–13.006	0.004			
Inflammatory sign	0.092	0.013–0.670	0.019			
Vascularity						
$TcPO_2$	0.954	0.930–0.979	<0.001			
CT angiography						
ATA stenosis	0.256	0.099–0.662	0.005			
PTA stenosis	0.197	0.069–0.561	0.002			
Wound bioburden						
Serology (Standard value)						
WBC (7100–11000/μl)	1.151	1.097–1.208	<0.001			
ESR (0–10 mm/hour)	1.023	1.012–1.034	0.004			
CRP (0–5 mg/L)	1.009	1.006–1.011	<0.001			
MRI						
Cellulitis	4.112	1.857–9.106	<0.001			
General serology						
HbA1c (4.0–5.6% (20–39 mmol/mol))	0.747	0.612–0.914	0.005	0.570	0.376–0.864	0.008
HDL (35–70 mg/dl)	0.930	0.901–0.960	<0.001			
Hemoglobin (13.5–17.5 g/dl)	0.597	0.501–0.712	<0.001			
Albumin (3.3–5.1 g/dl)	0.266	0.131–0.540	<0.001			
BUN (8–23 mg/dl)	1.026	1.012–1.040	<0.001			
Creatinine (0.6–1.3 mg/dl)	1.282	1.196–1.375	<0.001			
FBS (74–106 mg/dl)	1.006	1.002–1.010	0.001			
Vitamin A (1.05–2.45 μg/dl)	0.528	0.295–0.942	0.031			
Vitamin Eβ (5.5–17 μg/ml)	0.042	0.002–0.965	0.047			
Mg (1.7–2.2 mg/dl)	2.848	1.516–5.352	0.001	2.480	1.027–5.986	0.043
Zn (66–110 μg/dl)	0.981	0.966–0.995	0.009			
Platelet (150–440 × 10^3/μl)	1.003	1.000–1.005	0.022	1.009	1.004–1.013	<0.001
Ferritin (30–400 ng/ml)	1.002	1.001–1.002	<0.001			
TIBC (250–450 μg/dl)	0.976	0.969–0.983	<0.001			

ATA, anterior tibial artery; BUN, blood urea nitrogen; CI, confidence interval; CRP, C-reactive protein; CT, computed tomography; DM, diabetes mellitus; ESR, erythrocyte sedimentation rate; FBS, fasting blood sugar; GI, gastrointestinal; HbA1c, glycated hemoglobin; HDL, high density lipoprotein; Mg, magnesium; MRI, magnetic resonance imaging; PTA, posterior tibial artery; OR, odds ratio; $TcPO_2$, transcutaneous partial oxygen tension; TIBC, total iron-binding capacity; WBC, white blood cell; Zn, zinc. *$p < 0.05$.

4. Discussion

In the Eurodiale study [4], 5.1% of diabetic patients with forefoot ulcers were resolved by major amputations. Although hospitalized patients with relatively severe ulcers included in this study, the percentage of patients with major amputations (4.7%) in our study was lower than the Eurodiale study. The relatively low major amputation rate may be because of the aggressive limb salvage policy in which major amputations are performed only when there is no option for saving the foot. In addition to adequate treatment for successful limb salvage, identification and understanding of the risk factors for major amputations in diabetic forefoot ulcers are essential.

In our study, univariate and multivariate stepwise logistic regression analyses showed that 33 and four items, respectively, were predictors for major amputation in patients with diabetic foot ulcers involving the forefoot. Risk factors for major amputation in patients hospitalized with diabetic forefoot ulcers include male gender, increased magnesium, increased platelet levels, and low levels of HbA1c.

Gender (OR = 8.216, p = 0.018) was a risk factor for major amputation in the stepwise multivariate analysis. Previous studies have shown that major amputation rates in diabetic foot ulcers was significantly higher in males than females [13,14]. Males are known to have limited joint mobility and higher foot pressure. Higher mean height and peripheral insensate neuropathy found more frequently in males [15,16]. In contrast, females may be more self-caring and have a positive mood in terms of being active with wound care, while males may express fear, negative attitudes, and behavior in an uncooperative manner [17,18]. These issues may cause diabetic foot ulcers to delay wound healing in males, being more likely to terminate in major amputation.

Serum magnesium levels (OR = 2.480, p = 0.043) were also found to be a risk factor for major amputation in the stepwise multivariate analysis. Previous studies have suggested that chronic kidney disease (CKD) in diabetic patients play an important role in hypermagnesemia [19,20]. In CKD patients, magnesium urinary fractional excretion can compensate for the decline in magnesium ultrafiltration due to the decreased glomerular filtration rate (GFR) [20]. However, a severe decline in GFR, especially a GFR < 30 mL/min, cannot be compensated by fractional excretion. Therefore, there is a high prevalence of hypermagnesemia in stages 4 and 5 CKD patients [19]. Renal disorders (OR = 3.984, p < 0.001) and dialysis (OR = 12.777, p < 0.001) were found to be risk factors for major amputation in our univariate analysis. Previous studies have also shown that CKD and current dialysis for end-stage renal disease were independent risk factors for major amputations in diabetic patients [21–23].

Serum platelet levels (OR = 1.009, p < 0.001) were a significant risk factor in the stepwise logistic regression. Diabetes is known to lead to significant changes in blood platelets, including increased mean platelet volumes and greater numbers of reticulated platelets [24]. Thus, a high reticulated platelet count has been proposed to contribute to the high risk for thrombotic events [25]. Thrombocytosis may lead to the development of atherosclerotic plaques (atheroprogression) and the thrombotic complications associated with plaque rupture (atherothrombosis) [26]. Furthermore, circulating platelets in diabetic patients are hyperreactive to agonist stimulation and are more likely to form aggregates with circulating leukocytes, thereby increasing inflammation [27]. A combination of atherosclerotic plaques and inflammation may increase the risk for peripheral vascular disease. Peripheral vascular disease has been cited by many authors as a risk factor for amputations in diabetic patients [3,7,21,28,29].

Serum HbA1c levels (OR = 0.570, p = 0.008) were another risk factor for major amputation in our study. Previous studies showed that poor glycemic control was a risk factor for limb loss in diabetic patients [28,30]. Regarding the influence of the HbA1c level, previous researches has reported conflicting results. Pscherer et al. [31] found that patients with a mean HbA1c level above 7.5% (59 mmol/mol) had a 20% higher risk of amputation compared to patients with a level below 7.5 percent (59 mmol/mol). Selvin et al. [32] also showed that an increase in HbA1c increased the risk of major amputation. In contrast, Won et al. [23] showed that patients with a mean HbA1c level below 7.5% (59 mmol/mol) had a 52% higher risk of amputation compared to patients with a mean HbA1c level above 7.5 percent (59 mmol/mol). A 13-year retrospective analysis conducted by Al-Thani et al. [33] showed that the mortality of patients with lower extremity amputations was higher in the group with HbA1c levels below 6.5% (48 mmol/mol) compared to other groups with HbA1c levels above 6.5 percent (48 mmol/mol). In our study, low HbA1c levels were associated with major amputations in diabetic forefoot ulcer patients. This was counterintuitive because chronic hyperglycemia is known to disrupt wound healing in diabetic patients. One possible reason for this unexpected association may be that unrecognized hypoglycemia could contribute to a stress response which impairs wound healing via immune dysregulation [34,35].

Although Orneholm et al. [36] reported that age ≥67 years was associated with healing without major amputation in diabetic patients with plantar forefoot ulcers, our data revealed that age was not a risk factor for major amputation in diabetic patients with forefoot ulcers (p = 0.433). Age may be related to survival rates rather than major amputation rates [37]. Furthermore, diabetic foot ulcers at old ages may delay wound healing due to cellular senescence, such as in keratinocytes and fibroblasts. Therefore, we believe that the old ages might not be a predictor for wound healing without major amputation in diabetic patients with forefoot ulcers.

Based on the results of the study, we suggest proper intervention and preventive strategies that may be helpful in reducing the risk for major amputation in diabetic patients with forefoot ulcers. Gender differences should be taken into consideration for patients with diabetic forefoot ulcers and physicians should pay more special attention to male patients. Maintaining magnesium or platelets, and HbA1c levels within normal limits is a therapeutic strategy to prevent major amputations. In particular, frequent monitoring of patients with high magnesium, platelet, or low HbA1c levels is necessary for a timely response. The prevention of hypermagnesemia and low HbA1c requires ongoing professional nephrologist and endocrinologist care for the management of poor renal function and glycemic control. In addition, current strategies to prevent atherothrombosis following thrombocytosis include the use of inhibitors of cyclooxygenase-1 (aspirin) and inhibitors of the platelet adenosine diphosphate receptor P2Y12 such as clopidogrel, prasugrel, or ticagrelor [25].

Our study had limitations inherent to all retrospective studies. For example, patient compliance, which could affect the outcomes, was not considered. Our patient population was entirely Korean. A selection bias may exist because our hospital is a tertiary referral center for complex diabetic foot ulcers. Therefore, the results of this study might not be applicable to the general population or primary care centers. This study focused only on baseline data at the time of admission. Therefore, our databases lacked information associated with the mortality rate of patients without complete healing after major amputation. Furthermore, this study only included the larger ulcer for analysis when patients had bilateral ulcers. Further studies investigating the mortality rate and the risk of bilateral ulceration for major amputation may be needed.

Although general knowledge is not comprehensive enough to ensure the prevention of major amputations in high-risk diabetic patients, this study might be the first large-scale cohort study to specifically investigate the risk factors for major amputation in diabetic patients with forefoot ulcers. These factors may facilitate physicians engaged in the assessment of patients requiring hospitalization and prompt treatment.

Acknowledgements

None.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Contribution statement

Seung-Kyu Han coordinated the work. Kyung-Chul Moon and Seung-Kyu Han interpreted the data, made concept, designed the study, and wrote the final version of the manuscript. Seung-Kyu Han, Kyung-Chul Moon, Soo-Byn Kim, Eun-Sang Dhong, and Seong-Ho Jeong contributed to data analyses and data handling. All authors had direct access to original data, critically revised the draft, and approved the final manuscript.

Declaration of Competing Interest

The authors declare no conflict of interest.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.107905.

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