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ORIGINAL ARTICLE

Risk factors for major amputation in hospitalised diabetic foot patients

Sik Namgoong, Suyoung Jung, Seung-Kyu Han, Seong-Ho Jeong, Eun-Sang Dhong & Woo-Kyung Kim

Department of Plastic Surgery, Korea University College of Medicine, Seoul, South Korea

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Correspondence to
S-K Han, MD, PhD
Department of Plastic Surgery
Korea University Guro Hospital
148 Guro-Dong
Guro-Ku
Seoul 152-703
South Korea
E-mail: pshan@kumc.or.kr

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Abstract

Diabetic foot ulcers are the main cause of non-traumatic lower extremity amputation. The objective of this study was to evaluate the risk factors for major amputation in diabetic foot patients. Eight hundred and sixty diabetic patients were admitted to the diabetic wound centre of the Korea University Guro Hospital for foot ulcers between January 2010 and December 2013. Among them, 837 patients were successfully monitored until complete healing. Ulcers in 809 patients (96·7%) healed without major amputation and those in 28 patients (3·3%) healed with major amputation. Data of 88 potential risk factors including demographics, ulcer condition, vascularity, bioburden, neurology and serology were collected from patients in the two groups and compared. Among the 88 potential risk factors, statistically significant differences between the two groups were observed in 26 risk factors. In the univariate analysis, which was carried out for these 26 risk factors, statistically significant differences were observed in 22 risk factors. In a stepwise multiple logistic analysis, six of the 22 risk factors remained statistically significant. Multivariate-adjusted odds ratios were 11·673 for ulcers penetrating into the bone, 8·683 for dialysis, 6·740 for gastrointestinal (GI) disorders, 6·158 for hind foot ulcers, 0·641 for haemoglobin levels and 1·007 for fasting blood sugar levels. The risk factors for major amputation in diabetic foot patients were bony invasions, dialysis, GI disorders, hind foot locations, low levels of haemoglobin and elevated fasting blood sugar levels.

Introduction

The worldwide prevalence of diabetes was estimated to be 2·8% in 2000 with a projected rate of 4·4% in the year 2030. Epidemiological studies suggest that 2·5% of diabetic patients develop diabetic foot ulcers each year, and 15% develop diabetic foot ulcers during their lifetime (1). Diabetic foot lesions are significant health and socioeconomic problems with adverse effects on the quality of life. Diabetic foot is the main cause of non-traumatic lower extremity amputation (2). Approximately 75% of foot amputations are performed in patients with diabetes mellitus. For the purpose of preventing serious complications like generalised infection or sepsis, diabetic foot ulcers have been commonly treated with minor or major amputation. Minor amputations include partial toe amputation, complete toe amputation, partial or full ray resection and proximal foot amputation (transmetatarsal, Lisfranc's, Chopart's and Symes amputations). Below-the-knee and above-the-knee amputations are considered major amputations.

Major amputations were associated with high rates of post-operative mortality and morbidity as they have been associated

Key Messages

- previous studies to determine the risk factors for major amputation in patients with diabetic foot ulcers were mainly conducted on a multi-centre basis; hence management protocols for diabetic foot ulcers might vary widely according to hospitals
- this study was designed to determine the risk factors in patients who were treated using the identical management protocol for this subject
- the risk factors for major amputation in diabetic foot patients were bony invasions, dialysis, gastrointestinal disorders, hind foot locations, low levels of haemoglobin and elevated fasting blood sugar levels

with increased cardiovascular demand in a subset of patients who already have an increased prevalence of cardiovascular disease (3). A retrospective study by Aulivola *et al.* revealed a mortality rate of 8·6% at 30 days and overall survival of 69·7% at 1 year and 34·7% at 5 years after major amputation (4).

The development of a diabetic foot ulcer is traditionally considered to result from a combination of peripheral vascular disease, peripheral neuropathy and infection (5). Several risk factors for major amputation among patients with diabetes have been cited in the literature, including age (6), male sex (7,8), size of the ulcer (9), hypertension (7,8), neuropathy (8), nephropathy (6,8,10), poor glycemic control (6), white blood cell count (11,12) and lipid abnormalities (13,14). However, there are inconsistencies in the results of the studies. As previous studies were mainly conducted on a multi-centre basis, management protocols for diabetic foot ulcers might vary widely according to hospitals. So far, there has been no large-scale study in patients who were treated using the identical management protocol for this subject. Moreover, there are few reports on the risk factors for major amputation in Korean patients. Therefore, the objective of this study was to determine the risk factors for major amputation in patients with diabetic foot ulcers who received standard treatment at a referral centre for diabetic foot ulcers in Korea.

Patients and methods

Management protocol in brief

We hospitalised patients with diabetic foot ulcers whose general condition was so poor that outpatient clinic-based treatments were not possible and patients with severely infected ulcers that required surgical debridement with systemic intravenous antibiotic therapy, including septic diabetic foot. Other criteria for admission included the finding of severe vasculopathy that required immediate angioplasty and situations where outpatient clinic-based debridement was not possible.

Complete medical history of the patients was obtained on admission. General serological tests, including those for blood glucose and other inflammatory markers, were performed. To evaluate the vascularity of the diabetic foot, transcutaneous partial oxygen tension ($TcpO_2$), Doppler wave and toe pressure were measured. Patients with peripheral arterial disease underwent percutaneous transluminal angioplasty (PTA) by an interventional cardiologist. For the management of wound bioburden, a deep tissue culture was performed. When necessary, intravenous antibiotics were administered empirically, and they were changed according to the results of the culture and sensitivity tests. Serial surgical debridement was performed whenever necessary at the bedside or in the operating room according to the wound condition. In patients with osteomyelitis, systemic antibiotic therapy was given for at least 3–6 weeks. Osteomyelitis was diagnosed by magnetic resonance imaging (MRI) and bone biopsy cultures. To evaluate neuropathy, a Semmes–Weinstein monofilament test, pin prick test, temperature test, electromyography (EMG) and nerve conduction velocity (NCV) test were conducted. Appropriate off-loadings were provided according to the ulcer locations. Patients were discharged when outpatient treatment was possible. Before discharge, patients received definitive individual therapeutic footwear.

If the wound condition worsened despite appropriate treatments based on our protocol for at least one month and if the wound could not be closed by a minor amputation, we considered major amputation to prevent deterioration of the general condition. Life-threatening conditions with severely infected ischaemic limbs that could lead to systemic sepsis were also indications for major amputation.

Patients

Eight hundred and sixty diabetic patients were admitted to the diabetic wound centre of the Korea University Guro Hospital because of foot ulcers between January 2010 and December 2013. Among them, 837 patients were successfully monitored until complete healing. The diabetic wound centre of the Korea University Guro Hospital is a referral centre for patients with diabetic foot ulcers. Ulcers in 809 patients (96·7%) healed without major amputation and those in 28 patients (3·3%) healed with major amputation. Data of 88 potential risk factors including demographics, ulcer characteristics, vascularity, wound bioburden, neurology and serology were collected from patients in the two groups. For comparison of the demographic and clinical characteristics, 28 variables such as gender, age, dialysis and duration were investigated. For ulcer characteristics, 20 variables such as location, size and depth of the ulcer were compared. The $TcpO_2$ level was used for comparison of vascularity. In addition, 11 variables for wound bioburden, 2 variables for neuropathy and 26 variables for general serology such as HbA1c, albumin and glucose were compared between the two groups (Table 1).

All the patients except for 37 individuals had unilateral involvement. In patients with bilateral involvement, the foot with the larger ulcer was chosen for the analysis. For patients who were admitted several times for different episodes, only the first admission period was included in this study.

Statistical analyses

Mann–Whitney *U*-tests were used to compare quantitative variables between the two groups. With regard to categorical variables, Chi-square tests were used except for ambulation status, smoking status, neuropathic symptoms, location and depth of ulcer, MRI findings and EMG findings. For these seven variables, Fisher's exact tests were used due to the statistically small amount of data for these variables. Odds ratios with 95% confidence interval (CI) were calculated as estimates of relative risk when a statistically significant difference was observed in the frequency of the variable between the two groups. Predictors for major amputation were determined using univariate and stepwise multiple logistic regression analyses. SAS 9·3 statistical software (SAS Institute, Cary, NC) was used for statistical analysis. A P-value $< 0{\cdot}05$ was considered statistically significant.

The study protocol was approved by the Institutional Review Board of Korea University Guro Hospital.

Table 1 Risk factors analysed in this study

	Risk factor (*P*-value)		
Demographics	Gender (0·633)	Foot deformity	Comorbidities (continued)
	Age (0·546)	Charcot deformity (0·767)	GI disorder (0·047)*
	DM duration (0·232)	Claw toe (0·786)	Hepatobiliary disorder (0·253)
	Ambulation (0·476)	Hammer/Mallet toe (0·251)	Ophthalmic disorder (0·622)
	Neuropathic Sx. (0·037)*	Hallux valgus (0·670)	CNS disorder (0·791)
	Dialysis (<0·001)*	High arch foot (0·159)	Arthritis (1·000)
	Dialysis duration (0·449)	Comorbidities	Musculoskeletal disorder (1·000)
	Smoking (0·965)	Cardiac disorder (0·082)	Genitourinary disorder (0·410)
	Previous Hx. of DMF Tx. (0·166)	Hypertension (0·688)	Metabolic disorder (1·000)
		Pulmonary disorder (0·028)*	Malignant tumour (0·681)
		Renal disorder (0·013)*	Other comorbidities (1·000)
Ulcer characteristics	Cause	Depth	Location
	Trauma (0·321)	Dermis (0·640)	Dorsal foot (0·017)*
	Burn (0·251)	Subcutaneous tissue (0·037)*	Plantar foot (0·191)
	Pressure (0·559)	Tendon/Joint (0·256)	Border (0·396)
	Spontaneous (0·135)	Bone (0·001)*	Level
	Duration (0·831)	Inflammatory sign (0·119)	Forefoot (0·145)
	Side (0·969)		Midfoot (0·030)*
	Size (< 0·001)*		Hindfoot (0·069)
	Previous Tx. at other hospital (0·333)		Above the ankle (1·000)
Vascularity	$TcpO_2$ (0·135)		
Wound bioburden	Serology	MRI	Tissue culture
	WBC (0·001)*	No infection (0·159)	No growth (1·000)
	ESR (0·038)*	Cellulitis (0·580)	Growth, soft tissue (1·000)
	CRP (<0·001)*	Bone marrow edema (0·518)	Growth, bone (0·554)
	Procalcitonin (0·161)	Osteomyelitis (0·186)	
Neurology	Monofilament test (0·008)*	EMG and NCV (0·892)	
General serology	HbA1c (0·632)	Cholesterol (0·323)	HDL (0·011)*
	LDL (0·287)	Hb (<0·001)*	Glucose (0·940)
	Albumin (<0·001)*	Protein (0·701)	BUN (0·256)
	Creatinine (<0·001)*	ALT (0·033)*	AST (0·127)
	FBS (0·018)*	Vitamin A (0·561)	Vitamin C (0·530)
	Vitamin E α (0·905)	Vitamin E β (0·171)	Vitamin E γ (0·736)
	Fe (0·002)*	Mg (0·908)	Zn (0·001)*
	Cu (0·037)*	Platelet (0·167)	Ferritin (<0·001)*
	TIBC (<0·001)*	2-hour postprandial blood sugar (0·035)*	

ALT, alanine transaminase; DM, diabetes mellitus; EMG, electromyography; ESR, erythrocyte sedimentation rate; FBS, fasting blood sugar; HDL, high density lipoprotein; LDL, low density lipoprotein; MRI, magnetic resonance imaging; NCV, nerve conduction velocity; TIBC, total iron-binding capacity. *$P < 0·05$.

Results

Among the 88 potential risk factors compared, the major amputation group had significantly higher incidence in 26 risk factors (Table 1). In the univariate analysis, which was performed for these 26 factors, statistically significant differences were observed in 22 risk factors. In the stepwise multiple logistic analysis, 6 factors remained statistically significant among these 22 factors. Multivariate-adjusted odds ratios in the stepwise logistic regression model were 11·673 for ulcers penetrating into the bone (95% CI: 1·425–95·619; $P = 0·022$), 8·683 for dialysis (95% CI: 2·834–26·601; $P < 0·001$), 6·74 for gastrointestinal (GI) disorders (95% CI: 1·175–38·66; $P = 0·032$), 6·158 for hind foot ulcers (95% CI: 1·808–20·974; $P = 0·004$), 0·641 for haemoglobin levels at admission (95% CI: 0·472–0·871; $P = 0·005$) and 1·007 for fasting blood sugar levels at admission (95% CI: 1·001–1·013; $P = 0·030$). The odds ratios (ORs) and *P* values are shown in Table 2.

Discussion

Various risk factors have been identified in previous studies. Such variability might be due to the variations in the study designs as well as differences in the genetic profile and cultural features of the populations studied. In addition, inequalities in access to health care are also common among different populations. In our study, the multivariate stepwise logistic regression analysis showed that six items were risk factors for major amputation.

Nephropathy (OR = 2·536, $P = 0·016$) and dialysis (OR = 5·738, $P < 0·001$) were found to be predictive factors for limb loss in our univariate analysis. In the stepwise multivariate analysis, dialysis maintained statistical significance (OR = 8·683, $P < 0·001$). Previous studies (14–16) have shown that chronic kidney disease (CKD) and current dialysis for end-stage renal disease (ESRD) were independent risk factors for diabetic foot ulceration and major amputation. Young *et al.* (17) reported that the relative risk of amputation

Table 2 Univariate and stepwise multiple logistic analyses

	Univariate analysis			Stepwise logistic regression		
Factors	OR	95% CI	*P* value	OR	95% CI	*P* value
Demographics						
Neuropathic Sx	0·394	0·176–0·882	0·023	–	–	–
Dialysis	5·738	2·604–12·64	<0·001	8·683	2·834–26·601	<0·001
Comorbidities						
Renal disorder	2·536	1·189–5·408	0·016	–	–	–
GI disorder	3·382	1·117–10·235	0·031	6·740	1·175–38·66	0·032
Pulmonary disorder	2·802	1·158–6·784	0·022	–	–	–
Ulcer characteristics						
Depth						
Subcutaneous tissue	0·241	0·057–1·026	0·054	–	–	–
Bone	7·527	1·774–31·932	0·006	11·673	1·425–95·619	0·022
Location						
Dorsal foot	2·488	1·15–5·381	0·021	–	–	–
Level						
Hindfoot	2·236	0·978–5·112	0·041	6·158	1·808–20·974	0·004
Size	1·013	1·006–1·02	<0·001	–	–	–
Wound bioburden						
Serology (Standard value)						
WBC (7·100–11·000/μl)	1·098	1·034–1·167	0·002	–	–	–
ESR (0–10 mm/hour)	1·014	1·001–1·027	0·038	–	–	–
CRP (0–5 mg/l)	1·006	1·003–1·01	<0·001	–	–	–
Neurology						
Monofilament test	0·984	0·972–0·996	0·011	–	–	–
General serology (Standard value)						
HDL (35–70 mg/dl)	0·95	0·915–0·986	0·008	–	–	–
Hb (13·5–17·5 g/dl)	0·631	0·513–0·776	<0·001	0·641	0·472–0·871	0·005
Albumin (3·3–5·1 g/dl)	0·23	0·098–0·541	0·001	–	–	–
Creatinine (0·6–1·3 mg/dl)	1·188	1·078–1·308	0·001	–	–	–
FBS (74–106 mg/dl)	1·007	1·002–1·011	0·004	1·007	1·001–1·013	0·030
Zn (66–110 μg/dl)	0·978	0·961–0·994	0·008	–	–	–
Ferritin (30–400 ng/ml)	1·001	1·001–1·002	0·0001	–	–	–
TIBC (250–450 μg/dl)	0·982	0·974–0·99	<0·001	–	–	–
2-hour postprandial blood sugar (85–120 mg/dl)	1·005	1–1·01	0·034	–	–	–
ALT (10–44 IU/l)	0·989	0·971–1·007	0·229	–	–	–
Fe (59–158 μg/dl)	1·01	1–1·021	0·059	–	–	–
Cu (75–145 μg/dl)	0·981	0·949–1·013	0·243	–	–	–

ALT, alanine transaminase; CI, confidence interval; ESR, erythrocyte sedimentation rate; GI, gastrointestinal; HDL, high density lipoprotein; OR, odds ratio; WBC, white blood cells.

among the diabetic patients was the highest among those who started dialysis. Factors secondary to dialysis, such as hyperparathyroidism, hyperphosphataemia, hypertriglyceridaemia and platelet dysfunction were cited to be related to dialysis (18,19).

Baseline fasting blood sugar level was another risk factor for major amputation in our study. Previous studies also showed that poor diabetes control was a risk factor for limb loss in diabetic patients (20,21). Regarding the influence of the glycated haemoglobin (HbA1c) level, previous researches reported conflicting results. Pscherer *et al.* (20) found that patients with a mean glycosylated haemoglobin level above 7·5% had a 20% higher risk of amputation compared with patients with a level below 7·5%. Selvin *et al.* had shown that an increase in HbA1c increases the risk of major limb loss (19). On the contrary, Winkley *et al.* (15) showed that a lower HbA1c level was associated with higher mortality. Won *et al.* (16) showed that patients with a mean HbA1c level below 7·5% had a 52% higher risk of amputation compared with patients with a mean HbA1c level above 7·5%. In our study, HbA1c was not found to be a predictive factor. Therefore, we believe that the fasting blood sugar level rather than HbA1c was an important risk factor for limb loss.

In our study, deep ulcers invading the bone were the strongest significant risk factor for major amputation in diabetic patients, which was in accordance with the clinical observation that more extensive wounding was associated with an increased risk of more extensive surgical management such as amputation. Sun *et al.* (22) showed that a high grade of Wagner classification strongly increased the risk of amputation.

Ulcers located on the hind foot area were found to be another predictive factor for major amputation. It is quite reasonable to assume that ulcers located on the forefoot area could be managed with early surgical intervention such as minor amputation. However, hind foot ulcers were more associated with major amputation because of their proximity.

Baseline serum haemoglobin levels were an additional predictive factor for limb loss in the stepwise multivariate analysis. Studies conducted by Aziz *et al.* (23) also found that the haemoglobin level was a significant prognostic factor for major amputation. They found that haemoglobin ≤10·0 g/dl was a highly significant predictive factor for limb loss ($P < 0{\cdot}001$). We have demonstrated a negative association between serum haemoglobin levels and the risk of major amputation in diabetic foot patients. In physiological terms, a higher serum haemoglobin level indicated that more oxygen molecules were delivered to local tissue, and consequently, anabolism and catabolism occurred more effectively. Serum haemoglobin is also used as a measure to evaluate the nutritional status of a human body. Therefore, a low serum haemoglobin level implies poor nutrition, which would delay wound healing. Such a condition will certainly be associated with a higher risk of major amputation in patients with diabetic foot disease.

GI disorders (OR = 3·382, $P = 0{\cdot}031$) were also found to be a predictive factor for limb loss in our study. GI disorders included oesophageal ulcers, ischaemic colitis, rectal ulcers and Barrett's oesophagus. The reason for this is not quite clear and needs further investigation.

Although many previous studies suggest that foot infection is a risk factor for major amputation (24–27), our data did not reveal a significant association ($P = 0{\cdot}165$). This might be because of our management protocol, whereby we treat foot infections relatively aggressively by means of frequent serial surgical debridement and drainage along with systemic antibiotic therapy based on daily assessment of the healing process. The presence of peripheral arterial disease has also been cited by many authors as a risk factor for amputations in diabetics (18,21,25,28–40). We evaluated the vascular status of every patient admitted to our hospital by palpation of the pulses of lower extremities, Doppler wave analysis, computed tomography (CT) angiography in addition to measuring $TcpO_2$. However, in the present study, we only included $TcpO_2$ in the vascular-related evaluation. The level of $TcpO_2$ can be expressed in digits and, hence, can be analysed clearly without the difficulties encountered with assessing tools such as Doppler waves or angiography that cannot be expressed in a digital manner. Furthermore, $TcpO_2$, which represents actual tissue oxygen perfusion, is widely acknowledged as a reliable and objective method for evaluating the wound-healing potential of diabetic patients (41). In our study, the baseline $TcpO_2$ level was higher in the non-amputation group than in the major amputation group (34·6 mmHg versus 26·9 mmHg, respectively). However, the difference was not statistically significant ($P = 0{\cdot}135$). In addition, patients with low $TcpO_2$ at the ulcer site underwent PTA, and the results were favourable in our centre (42). Although baseline $TcpO_2$ was low, the $TcpO_2$ level increased after PTA to a sufficient level for wound healing in most cases. This may be a contributing factor to this study's finding. Therefore, the baseline $TcpO_2$ level was not found to be a predictive factor in our study.

It would be meaningful to evaluate the vascular status of the patients after any vascular intervention is made. However, this was beyond the scope of the current stage of study. As vascular intervention was performed in those with low initial $TcpO_2$ values, the post-procedural data collected may have complicated our current study by adding numerous variables that differ in a time-dependent manner among patients. Thus, we only used the initial $TcpO_2$ data for the current study. However, as the issue is crucial, vascular parameters will be included in further detailed studies.

There are several reports on the major amputation rate in diabetic foot patients. In the EURODIALE (European Study Group on Diabetes and the Lower Extremity) study by Prompers *et al.*, the major amputation rate was 5·1% in 1·229 patients (40). Aziz *et al.* reported an amputation rate of 28% in Singapore in their prospective study on 100 patients with diabetic foot infections treated at the National University Hospital of Singapore in 2011 (23). Riaz *et al.* reported an amputation rate of 11% in Pakistan (43). Nather *et al.* reported a 27·2% major amputation rate, and Zubair *et al.* reported an overall amputation rate of 28·4% in a North Indian tertiary care hospital (44,45). The relatively low amputation rate in our hospital 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. Every effort is made to save the limb by serial debridement, minor amputation, local flap, skin graft or free flap.

In the literature, there are several reports on diabetic wounds that discuss the effect of free flaps in salvaging the extremity. Hong and coworkers reported that diabetic foot reconstruction using free flaps has a high chance for success and significantly increases the 5-year survival rate (46). Ducic and Attinger *et al*. reported that microsurgical free flaps should be considered for larger lower extremity wounds with associated muscle and bone loss, exposed joint and/or neurovascular structure (47). Mun and coworkers also reported that an appropriately thin free flap with thick skin is a valuable option for the reconstruction of skin and soft-tissue defects in the plantar region of the diabetic foot patients (48). Most of these reports suggest that microsurgically transferred tissues enhance the revascularisation of the critically ischaemic extremity through the development of vascular connections at the free-flap-surrounding environmental tissue interface. This surgical technique can be used successfully for large diabetic wound ulcers that are normally unresponsive to conventional therapies and often require amputation. We also made every effort, including free flap surgery, to save the limb. Major amputation was the last resort for patients who experienced life-threatening deteriorations.

Our study had all the limitations inherent to retrospective studies. For example, patient compliance, which can affect the outcomes, was not considered. Our patient population was entirely Korean, and there can be a selection bias because our hospital is a tertiary referral centre for complex diabetic foot ulcers. Therefore, the results of this study might not be applicable to the general population or primary care centres. In addition, this study focused only on baseline data at the time of admission. Responses to treatment for each patient's problem were not considered.

Conclusion

The risk factors for major amputation in hospitalised diabetic foot ulcer patients were bony invasions, dialysis, GI disorders,

hind foot locations, low levels of haemoglobin and elevated fasting blood sugar levels.

Acknowledgements

The authors declare that there are no conflicts of interest.

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