Diabetes & Metabolic Syndrome: Clinical Research & Reviews 11S (2017) S583–S587

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

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

Original Article

Diabetic foot ulcer carries high amputation and mortality rates, particularly in the presence of advanced age, peripheral artery disease and anemia

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ARTICLE INFO

Keywords:
Diabetic foot
Foot ulcer
Amputation
Death

ABSTRACT

Introduction: Foot ulcer is also a clinical marker for limb amputation and for death in diabetic patients. The purpose of this study was to determine amputation and mortality rates and its associated factors in patients with diabetic foot ulcerations in a tertiary hospital in Brazil.
Methods: Retrospective medical records from 654 diabetic foot patients were reviewed. The risk factors were determined using the conditional logistic regression model analysis.
Results: The mean patient age was 63.1 years (SD 12.20). Peripheral arterial disease was present in 160 patients (24.5%). Major amputations were performed in 135 (21%). The in-hospital mortality rate was 12% and the mortality rate of the amputees was 22.2%. The lowest hemoglobin level, the median value was 9.50 g/dL, (4.0–17.0). Anemia was detected in 89.6% of patients submitted to amputation and in 82,1% of those who died. Hemoglobin <11 g/dL was the most significant risk factor for major amputation (odds ratio 5.57, $p < 0.0001$). The presence of peripheral arterial disease and old age were also a risk for major amputation (odds ratio 1.84, $p = 0.007$ and 1.02, $p = 0.028$, respectively). Factors associated with increased risk for death were hemoglobin <11 g/dL (odds ratio 4.04, $p < 0.001$), major amputation (1.79, $p = 0.03$) and old age (1.05, $p < 0,001$).
Conclusions: Diabetic foot ulcer is associated with high amputation and mortality rates. Old age, peripheral arterial disease and low hemoglobin level are risk factor for major amputation. Old age, major amputation and low hemoglobin level are risk factors for death.

1. Introduction

The impact of the global diabetes burden is evidenced by the growing morbidity and mortality rates, and by permanent disabilities such as blindness, diabetic retinopathy, end-stage renal failure and lower extremity amputations [1]. The diabetic foot is one of the major complications of this disease, with an estimated 10% to 25% of diabetic patients developing a diabetic foot ulcer in their lifetimes [2]. Foot ulcers, the leading cause of hospitalization in diabetic patients, are among the most common, serious and costly complications of diabetes mellitus, resulting in major medical, financial, and social consequences for patients, their families and society in general [3,4]. Foot ulcer is also a clinical marker for limb amputation and for death in these patients [5,6].

The etiology of diabetic foot ulcers is complex and risk factors include peripheral vascular disease, peripheral neuropathy, foot deformities and local foot trauma [7]. The coexistence of neuropathy, ischemia and immunosuppression in diabetic patients, favors development of severe ascending infections emanating from the ulcer and is associated with a poor prognosis as these infections frequently lead to amputation and even death [8]. In the literature, the amputation rates associated with diabetic

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http://dx.doi.org/10.1016/j.dsx.2017.04.008
1871-4021/

foot disease range from 4.7 in Germany [9] to 47.7% in a study carried out in Brazil [10]. The in-hospital mortality rate from diabetic foot ulcer can reach 40,5% in a prospective study conducted in Nigeria[11].

Therefore, the early recognition and management of risk factors for foot complications may prevent amputations and deaths [12]. The present study was undertaken to determine amputation and mortality rates and its associated factors in patients with diabetic foot ulcerations in a tertiary hospital in Brazil.

2. Methods

This retrospective study was conducted in the Vascular Surgery Unit of Hospital Risoleta Toletino Neves, a tertiary university hospital in Belo Horizonte, Brazil. The records of 654 consecutive patients admitted to the vascular surgery service with diabetic foot lesions between January 2007 and December 2012 were reviewed. All patients presented with deep ulceration, gangrene, infection and/or deep tissue injury in the foot below the ankle, e.g. Wagner wound classification equal or greater than 3. All patients had diabetes and neuropathy, independent of the presence or absence of peripheral arterial disease (PAD), and were classified according to the International Consensus on the Diabetic Foot and Practical Guidelines [13].

Data recorded included age, sex, smoking status and comorbidities such as hypertension and PAD. An admission ankle-brachial index (ABI) ≤ 0.9 was considered as presence of PAD [14]. Serum lower hemoglobin and higher creatinine levels during the admission, number of previous surgical procedures, level of lower limb amputation, intra-hospital mortality and number of readmissions were also collected. Lower limb amputation above the ankle was considered as major amputation. Digit, ray and transmetatarsal were considered as minor amputations.

Analyses were carried out using the Statistical Package for the Social Science (SPSS) 17.0 Windows version (SPSS Inc., Chicago, IL, USA). Descriptive analysis was done for demographic characteristics. Categorical data were analyzed using the chi-squared ($\chi 2$) test. Continuous data were expressed as means and standard deviation, and were analyzed using Student's *t*-test. Predictors of lower limb amputation and death were determined using conditional logistic regression. Multivariable analysis was performed by including variables selected through univariable analysis ($p < 0.10$) that were eliminated with backward selection.

This study was approved by the Federal University of Minas Gerais Ethics Committee (ETIC number 15638113.5.0000.5149).

3. Results

Demographic and clinical characteristics of 654 consecutive patients with diabetic foot ulcers are summarized in Table 1. The mean patient age was 63.1 years (SD 12.20), 441 (67%) were male. The most common co-morbidities were hypertension (60.55%) and active smoking (32.72%). Peripheral arterial disease was present in 160 patients (24.5%). The mean ABI was 0.41, with the majority of ischemic patients having an ABI lower than 0.4. On the other hand, only eleven subjects had incompressible ABIs, as shown in Table 1. In the amputees subgroup the mean ABI was 0.33, and within the patients that eventually died the median was 0.42; there was no statistically difference between these groups. The median serum level of the highest creatinine during any admission was 1.29 mg/dL (range 0.47-11.73). For the lowest hemoglobin level, the median value was 9.50 g/dL, ranging from 4.0 to 17.0.

From the total sample, 487 participants (74%) required only a single surgical procedure. Eighty patients (12%) required two procedures, while 24 patients (4%) required three procedures and less than 2% required four or more procedures (Fig. 1). Fifty-five patients (8%) were treated with conservative management of antibiotics and wound care without any intervention.

Revascularization via conventional bypass and/or endovascular therapy were performed in 150 patients (23%).

Amputations were performed in 449 patients (69%). 314 (48%) were minor amputations (214 toe amputation and 100 transmetatarsal) and 135 (21%) were major amputation (56 below the knee, 75 above the knee and 4 hip disarticulation). The overall limb salvage rate was 79%. The mortality rate of the amputees was 22.2%.

Sixty-one percent of the patients were admitted only once, while 134 patients (20%) had to be readmitted only once, and 124 patients (19%) were readmitted twice or more times. The total rate of readmissions at the same hospital was 39% through the period of the study.

The in-hospital mortality rate was 12%. Analysis of mortality rate by age (Table 3), showed an increase of mortality as the groups got older. For patients younger than 30 years, there was no death. The mortality rate for patients with 31 to 60 years was 6.1%, with 61 to 80 years was 13.4%, and older than 80 years was 38.1%.

Table 1
Demographics, comorbidities, creatinine serum level, hemoglobin serum level and number of surgical procedures.

	General (%) (n = 654)	Amputees (n = 135)[a]	Deceased (n = 78)
Age, mean (SD)	63.08 (12.19)	65.97 (12.17)	70.04 (10.77)
Sex (male) n (%)	441 (67.4)	91 (67.4)	48 (61.5)
Hypertension n (%)	258 (39.4)	73 (54.7)	42 (53.8)
Active Smoking n (%)	214 (32.7)	43 (31.8)	24 (30.7)
PAD n (%)	160 (24.5)	50 (37.0)	23 (29.4)
ABI[b]			
<0.4	63 (43)	26 (52)	10 (43.5)
0.4–0.59	53 (33)	12 (24)	8 (34.8)
0.6–0.9	28 (17)	6 (12)	4 (17.4)
Incompressible	11 (7)	6 (12)	1 (4.3)
Highest serum creatinine, median (min-max)[c]	1.29 (0.47–11.73)	1.34 (0.47–9.39)	1.40 (0.54–11.73)
Lowest serum hemoglobin, median (min-max)[c]	9.50 (4.0–17.0)	7.50 (4.1–14.0)	7.05 (4.1–16.2)
Number of surgical procedures per patient, mean (SD)	1.15 (0.69)	1.32 (0.76)	1.04 (0.74)
Amputation n (%)	135 (20.6)	135 (100)	30 (38.4)
Mortality n (%)	78 (11.9)	30 (22.2)	78 (100)

SD = Standard deviation – PAD = Peripheral arterial disease – ABI = Ankle-brachial index.
[a] Amputees: patients who underwent major amputation.
[b] n = 155.
[c] n = 629

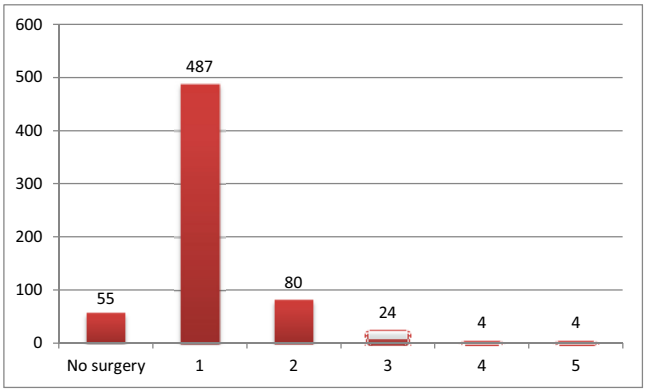

Fig. 1. Number of procedures per patient.

Thirty-six percent of the patients (n = 234) were discharged home in good conditions. Forty-seven percent of the patients required special home care after discharge, including the need for parenteral antibiotics, wound care, and/or physical rehabilitation.

The association of amputation and mortality rates with age and serum hemoglobin level is shown in Table 2. Anemia, meaning hemoglobin level <11 g/dL was detected in 89.6% of patients submitted to amputation and in 82,1% of those who died. Risk factors that predicted major amputation are shown in Table 3. Univariable analysis showed that hemoglobin <11 g/dL was the most significant risk factor for major amputation (odds ratio 5.93, $p < 0.0001$). This relationship was also confirmed by multivariable logistic regression. The presence of peripheral arterial disease and old age were also a risk for major amputation.

Factors associated with increased risk for death were hemoglobin <11 g/dL, old age and major amputation, as confirmed by both univariate and multivariable logistic regression (Table 4).

4. Discussion

Our findings showed high rates of amputation and mortality related to diabetic foot ulcers. Old age, peripheral arterial disease (ABI ≤ 0.9) and an hemoglobin level lower than 11 g/dL were independent predictors for major amputation. Old age, major amputation during any admission and hemoglobin lower than 11 g/dL were identified as risk factors for death.

The major amputation rate was 21% in the studied sample. In the literature, there is a wide range of amputation rates due to the heterogeneity of patients sample, if they were treated as outpatients or in hospital, if patients had diabetic foot ulcers or diabetic foot infections and if the area have or not a structured health program. Sereday et al., in a study over 11 hospitals of different regions of Argentina found a major amputation rate of 32,5% in diabetic patients. Infection was the most frequent immediate cause of amputation and PAD the underlying cause [15]. In Brazil, amputation rate may be as high as 47.7% [10]. In Guiana, close to Brazil, prior to the development of a structured national program for diabetic patients, the amputation rate was 42%. After the implementation of the program, it was lowered in two thirds [16]. In Portugal, the outpatient amputation rate reported was 5.8%, but we can assume that as outpatients, they had less severe disease [6]. In Germany, the amputation rate ranged from 4.7% inside a structured health program to 21.7% outside the program [9]. Amputation rates of 42.3% were also surprisingly found in the US (NYC) in a series in three hospitals (private, public and VA), with the lowest rate in private hospital and the highest rate at the VA [17]. In Turkey, the amputation rate found was 36.7% [18]. In papers that included only diabetic foot infections, the major amputation rate ranged from 19.9% to 39% [19–22]. Lavery et al., 2009 [23], estimated that the risk of amputation increases 154 times with the infection of a diabetic foot ulcer. Therefore, considering that we have no structured health system and that our diabetic patients had deep infected foot ulcers (Wagner ≥ 3), a major amputation rate of 21% is quite acceptable, once we had 79% limb salvage rate.

Table 2
Amputation and mortality rates according with age and serum hemoglobin level.

Variable	Major amputation rate n (%)	Mortality rate n (%)
Age		
Younger than 30 years	0 (0)	0 (0)
31–60 years	40 (15.4)	16 (6.2)
61–80 years	79 (22.7)	46 (13.2)
Older than 80 years	16 (38.1)	16 (38.1)
Serum Hemoglobin Level		
<11 g/dL	121 (89.60)	64 (82.10)
≥11 g/dL	14 (10.40)	14 (17.90)

In-hospital mortality was 12% in the present study. This rate was higher in the subgroup of patients submitted to major amputation (22,2%), showing that major amputation is related to mortality. Probably, the patients requiring major amputation may have more severe infection, more tissue loss and less systemic organ functional reserve. Similar results were also found in another area of Brazil [10]. It is in accordance to the literature, which shows results ranging from 8.4% to 17% for diabetic patients with foot ulcers [10,15,22,24,25]. The main causes of death were cardiovascular events and septicemia [26].

In our sample, the mean age was 63 years, similar to other studies where the age ranged from a mean of 56.1 to 76.0 years [11,19,20,22,24,25,27–29]. Ageing has been considered as a potential predictor for lower limb amputation in diabetic patients presenting foot ulcers [29,30] and an establish risk factor for in-hospital mortality [24,29]. This old aged people usually have more peripheral neuropathy, progressive atherosclerosis with PAD, carotid and coronary artery disease, and chronic renal failure [24,30,31].

PAD is an independent risk factor for subsequent ulceration and limb loss in diabetic patient. In our study, the prevalence of PAD was 25.1%. In the literature, this prevalence ranged from 8% to 56% [27,28,32,33]. A consensus of the Italian societies of diabetes reports a prevalence up to 50% of subjects with diabetic foot ulcer [31]. In our study, patients with PAD had 2.28 times higher risk for limb loss. Won at al [32], in a retrospective study with 173 subjects, found a 2.64 times increased risk of limb loss in diabetic patients with PAD. In addition, other authors have found similar results [21,23,29–31,34]. This important relation between PAD and major amputation reinforces the importance of vascular assessment and treatment for diabetic foot patients, focused on evidence-based strategies to promote healing and preserve life and limb.

In this study, we identified the association of lower hemoglobin levels with worse outcomes. More than 80% of patients who underwent major amputation and those who died had hemoglobin levels <11 g/dL, indicating anemia. The high prevalence of anemia is well recognized in patients with diabetes and is a common problem related to adverse outcomes in diabetic foot ulcer patients [11,35–38]. An inverse correlation was found between hemoglobin level and diabetic foot disease progression in the study of Richards et al., [39]. Desormais et al., [40], found a risk 1.44× higher for amputation and death in patients with anemia. It is probably due to diminished delivery of oxygen to the tissues and the impairment in the compensatory response to reduced circulating hemoglobin levels found in patients with diabetes [39], leading to impairment in healing and poor infection control. Kengne et al., in an

Table 3
– Risk Factors associated with major amputation.

	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	p-value*	OR	95% CI	p-value
Age, per year	1.026	1.009–1.043	0.002**	1.020	1.002–1.038	0.028
Gender, Male	1.001	0.669–1.500	0.995			
Hypertension	0.714	0.488–1.047	0.085	0.667	0.445–1.002	0.051
Active Smoking	0.951	0.634– 1.427	0.809			
PAD	2.187	1.455–3.289	<0.0001	1.841	1.183–2.866	0.007
Multiple surgical procedures (3 or more)	2.104	0.988–4.478	0.054	1.480	0.675–3.245	0.328
Multiple Readmissions (2 or more)	0.964	0.593–1.568	0.883			
Creatinine >1.8md/dL	0.989	0.642–1.524	0.960			
Hemoglobin <11 g/dL	5.936	3.118–11.299	<0.0001	5.574	2.906–10.691	<0.0001

PAD = Peripheral arterial disease.

Table 4
Risk Factors associated with mortality.

	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	p-value*	OR	95% CI	p-value
Age, per year	1.061	1.038–1.085	<0.0001**	1.059	1.034–1.084	<0.0001
Gender, Male	1.342	0.823–2.188	0.238			
Hypertension	0.732	0.455–1.177	0.198			
Active Smoking	0.903	0.542–1.506	0.695			
PAD	1.340	0.794–2.261	0.273			
Multiple surgical procedures (3 or more)	0.754	0.224–2.538	0.649			
Multiple Readmissions (2 or more)	1.565	0.902–2.715	0.111			
Creatinine >1.8md/dL	1.166	0.694–1.957	0.562			
Hemoglobin <11 g/dL	4.643	2.092–10.308	<0.0001	4.046	1.776–9.215	<0.0001
Major Amputation	2.804	1.696–4.635	<0.0001	1.797	1.046–3.086	0.034

PAD = Peripheral arterial disease – OR = Odds Ratio – CI = Confidence interval.

epidemiological study, demonstrated that presence of diabetes, anemia and cardiovascular disease doubled the absolute risk of mortality [35]. These results reinforce diabetic patients must be routinely screened and treated for anemia. Considering multiple factors contribute to the presence of anemia in these patients as nutrition and diet, drug therapy, systemic inflammation, renal disease, peripheral arterial disease and cardiovascular disease, a specific protocol treatment of anemia in these patients could potentially reduce the high rate of these devastating events. Although a question exists with regard to the benefits of treatment of anemia in diabetic foot patients.

The presence of hypertension and/or active smoking was not associated with lower limb amputation or death in this diabetic population. Our prevalence of systemic hypertension was 60,5% and 32,7% of the subjects were active smokers. There is a wide range in prevalence of these conditions in diabetic patients with foot lesions. For hypertension, prevalence of 48% to 91% was found, and the proportion of active smokers ranged from 20 to 49% [22,25,27,28]. Although known as important risk factors for cardiovascular disease, these conditions do not appear to have an impact on amputation or mortality rates in our sample [21,25,27,31].

In this study, 92% of patients underwent one or more surgical interventions. Mostly were debridement and minor amputations, which were performed in 48% of the subjects. This express that diabetic foot problems are a surgical condition, therefore requiring an evaluation by a specialized surgeon.

Other important aspect was the high re-admission rate (39%). First, the foot ulcer develops mostly in subjects with peripheral neuropathy. So, even after discharge with good wound care, the foot conditions for a relapse are maintained. Second, once we have no structured heath program, there is a deficiency of adequate primary and secondary medical care in our region [41], which impairs the preventive measures for a new foot lesion. Although this high readmittance rate was not associated with higher amputation and mortality rates, it is important to highlight that it increases morbidity to the patient and is associated with a higher burden.

This study has some limitations. First, missing data was inevitable considering the fact that it was a retrospective study and the data were extracted from the patients' medical records. Second, other variables, such as type of revascularization (if open surgery or endovascular) and C – reactive protein serum levels, were not collected because they were not of interest at the beginning of the studied period. In addition, there was lack of information in the medical records regarding relevant aspects such as heart status, respiratory and previous functional deficit as deambulation and measures of patient's quality of life.

Therefore, we are in need of an aggressive approach to such patients who are referred late in the course of the disease to our hospital. Based on the data collected and identification of ours patients profile, we have made some improvements in the stratification of the patients. We adopted the SVS-WIfI classification system [26], which provides better assessment of the wound, the infection and the ischemia of the limb, allowing us to predict the likelihood of the need for a revascularization procedure and/or major amputation. Alongside this system, we have established a better registry of the patients' heart, lung and renal functions and other regular blood tests through adoption of a standardized protocol, so we will be able to a better categorization of the patients. Finally, we are better assessing the patient's functionality and quality of life through a multidisciplinary protocol designed in conjunction with physical therapists and nurses.

In conclusion, diabetic foot ulcer is associated with high amputation and mortality rates. Risk factors for major amputation were old age, presence of peripheral arterial disease and low hemoglobin level. Old age, major amputation and low hemoglobin level were risk factors for death. The findings from the present

study add evidences on risk factors for major amputation and mortality associated to diabetic foot ulcer patients, with implications for daily practice. Efforts to prevent major amputation should be targeted at elderly patients especially those with PAD and lower hemoglobin levels.

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