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Risk Factors Associated with Lower Extremity Amputation in Diabetic Patients with Neuropathic Ulcerations of the Foot Treated with Human Recombinant Epidermal Growth Factor (Heberprot P)

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Abstract

Introduction: Early recognition and management of risk factors for amputations and the opportune solution of them may prevent this dramatic outcome, especially the major level of amputation. The present study was assumed to identify and quantify the risk factors for lower extremity amputation in diabetic patients with neuropathic ulcerations of the foot treated with Heberprot P.

Methods: Prospective study with 331 patients with diabetes and neuropathic ulcerations of the foot referred to the Matanzas Province Vascular Surgery Service of the Matanzas Province Clinic Surgical Hospital from January 2009 to May 2019 and followed through December 2021.

Results: The bad prognosis factors identified in this population were increase in the mean age of the amputated population 67.8 years old, smokers and high frequency of alcohol intake 63.2%. Rendering to the Diabetes Mellitus behaviour was finding a long-time of evolution of the disease 19.7 years; the presence of insulin treatment at the admission time in 63.2%; high prevalence of another diabetic's complications like renal disease and ischemic heart disease in the 89.5%, also severe visual impairment in the 63.2%. According to the diabetic foot evaluation includes a Wagner 4 gradation patient 78.9%; the worse topography was associated with the middle segment 52.6%, and PEDIS gradation level 3 moderate infection in 89.5% (n=17). All the amputee had presence of osteomyelitis at the beginning of the treatment, the vascular status mark an ankle brachial index (ABI) lower than 0.6 63.2% and absent of both pedal pulses 78.9%, associated with a big Size more than 10 cm2 89.5% and time of evolution of the current ulcer of 14.9 weeks.

Conclusion: There are Risk factors Associated with lower extremity amputation in diabetic patients with neuropathic ulcerations of the foot treated with human recombinant Epidermal Growth factor.

Keywords: Diabetic foot; Diabetic foot amputation; Risk factors; Lower limb amputation

Introduction

Diabetes Mellitus (DM) is a serious health problem; several factors are contributing to the high prevalence of this chronic condition that increase steadily each year [1,2]. Added to this are an unknown number of persons with undiagnosed diabetes; also the prevalence of many costly and complex complications that have wide spread effects in human, economic and social terms, are growing [3].

Patients with diabetes are at greater risk of complications, one of the most important of them is the Diabetic foot (DF), consider like a foot that exhibits any pathology that results directly from diabetes mellitus or any long-term complication of diabetes mellitus [4,5].

The decisive factors for the aetiology of the diabetic foot ulcers are diabetic neuropathy, macroangiopathy and the combination of neuropathy with macroangiopathy [6]. Diabetic foot can present several types of presentation such neuropathic alone, mixed neuropathic-ischemic, or ischemic with infection [7,8].

Furthermore, diabetic foot is one of the most common complication associated with diabetes. It is estimated that approximately from 15 to 25% of diabetes patients develop diabetic foot ulcers in the course of their disease, it means that in every six people with diabetes will have an ulcer during their lifetime. The annual incidence of diabetic foot ulcers in developed countries, up to 5% of people with diabetes have foot ulcers, fluctuating from 1.0 to 5.0% [9].

Foot ulcers are the principal cause of severe complications and hospitalization among patients with diabetes, substantially increasing the costs with this disease. Adding to the costs of managing infection, patients with diabetes are confronted with the risk of limb amputation, with rates 30 to 40 times higher than in individuals without the disease [1,5,8]. Its cited that 85% of the lower limb non traumatic amputation are related with diabetes chronic complications; most amputations relating to diabetes begin with a foot ulcer and amputations could be prevented [4,6].

More recently, some factors have been identified that are believed to increase the risk of amputation in patients with DFU, including: smoking, gender, renal impairment, ischemia, diabetic neuropathy, and high levels of glucose and triglycerides have been reported as

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importantly associated with the risk of foot amputation [8,10,11].

Early recognition and management of risk factors for amputations and the opportune solution of them may prevent this dramatic ending procedure, especially of the major type and prevent other adverse outcomes [7].

The present study assumed to identify the risk factors for lower extremity amputation in diabetic patients with neuropathic ulcerations of the foot treated with human recombinant Epidermal Growth factor (Heberprot P).

Materials and Methods

Patients and methods

This prospective study included a cohort of 331 patients with diabetes and neuropathic ulcerations of the foot, referred to the Matanzas Province Vascular Surgery Service of the Matanzas Province Clinic Surgical Hospital from January 2009 to May 2019 and followed through December 2021.

Recorded data included

- Age;
- Gender;
- Ethnicity;
- Toxic habits;
- Type of diabetes mellitus (1 or 2);
- Time of evolution of the diabetes mellitus (in years);
- Current treatment for the diabetes (oral hypoglycaemic drugs or insulin);
- Deformities in the Foot;
- Stage according to the Wagner Gradation; topography according to Garcia Herrera Topographic taxonomy;
- To scales the Diabetic Foot Infections with (PEDIS) classification;
- Presence of osteomyelitis;
- Stage according to the perfusion,
- The assessment included the presence of pedal pulses and measurement of the ankle brachial index (ABI) using a hand-held Doppler device, peripheral arterial disease (PAD) was considered present if the ABI was lower than 0.8 and/or both dorsalis pedis and posterior tibial pulses were absent,
- The size was determined by using digital photography and the Image J system;
- Time of evolution of the current ulcer (in weeks);
- Patient's comorbidities included the presence of severe visual impairment (i.e. cataract, retinopathy), presence of renal disease (haemodialysis, peritoneal dialysis, renal transplant), and ischemic heart disease and major amputation in the follow up

The ulcer management included a protocol of multidisciplinary approach with metabolic control, management of the ischemia situation, wound bed preparation (according to TIME concept includes: wound cleansing, debridement, dressing, adjuvants and periwound treatment), antibiotic therapy according to our local guidelines, functional reconstruction surgery of the foot if is necessary, adjuvant therapy with intralesional human recombinant Epidermal Growth factor and off-loading and pain Management. The treatment protocol was consistent throughout the study period.

Statistical Analysis

Data were collected using a pre-designed data collection sheet after getting informed consent from all patients. Data analysis was carried out using the statistical package for social sciences (SPSS v19) to compare healed versus non-healed DFU. Differences were tested by Chi-squared test and statistical significance was defined as 0.05.

Ethics

The institutional review board of the Matanzas Province Clinic Surgical Hospital, Matanzas City, Cuba, approved the protocol. The institutional review board of the University of Matanzas Medical Sciences, Matanzas City, Cuba, also approved the protocol. Patients were fully informed about the aim of the study and they were told that their participation was optional. Written informed consent was obtained from each participant.

Results

Basic Characteristics

Three hundred thirty-one subjects with diabetes and neuropathic ulcerations where follow up for the period of the study. According to Table 1 the mean age of participants was 61.7 years; there was a predominance of women with the 57.1% (n=189), the ethnicity was mixed with 72.8% of mestizo (n=241) , the smoke habit present in the 44.4% (n=147), others toxic habits fundamentally alcohol intake was present in the 20.8% (n=69); and most of them had type 2 diabetes 93.4% (n=309) with a median time of evolution of the diabetes mellitus (in years) of 13.7, the current treatment for the diabetes used at the admission time was the oral anti-diabetic drugs in the 44.1% (n=156) and the prevalence of the most frequent patient's comorbidities detected were advance renal disease in the 8.8% (n=29), previous diagnosis of

Table 1: Demographic characteristics and Diabetes baseline clinical findings. 2009-2021.

Variable		Values
Age (years)		**61.7** (4.2)
gender	Female	**189** (57.1%)
	Male	142 (42.9%)
ethnicity	White	40 (12.1%)
	African descent	39 (11.8%)
	Mestizo	**241** (72.8%)
	Asian descent	11 (3.3%)
toxic habits	Smoke	**147** (44.4%)
	Others	69 (20.8%)
type of diabetes mellitus	1	22 (6.6%)
	2	**309** (93.4%)
time of evolution of the diabetes mellitus (in years)		**13.7** (2.3)
current treatment for the diabetes at the admission time	oral antidiabetic drugs	**156** (44.1%)
	insulin	102 (30.8%)
	Combination of treatment	73 (22.1%)
patient's comorbidities	severe visual impairment	**21** (6.4%)
	advance renal disease	29 (8.8%)
	Previous diagnosis of ischemic heart disease.	27 (8.2%)

Others include alcohol consumption. n Values for age, time of evolution of diabetes mellitus. Other values are present like n (%). Values in bold face type are significant at $P < 0.05$, based on χ^2 test.

ischemic heart disease 8.2% (n=27) and severe visual impairment 6.4% (n=21)

The Diabetic foot evaluation and clinical findings shows the characteristics of the wound (Table 2). Deformities of the Foot were present in the 57.1% of the population (n=189) and the Gradation according to Wagner reveals a predominance of grade 3 with 66.2% of the total (n=219). The topography agreeing to Garcia Herrera Topographic taxonomy exhibit that predominates the forefoot ulcers located in the anterior segment with 69.8% (n=231). In the evaluation of the Diabetic Foot Infections by PEDIS classification was considered Grade 2 in 53.8% (n=178), the osteomyelitis wasn´t present in the 72.2% of DFU includes in the study (n=239). The analysis of the vascular status express an ankle brachial index (ABI) between 0.9-1.3 in the 60.7% (n=201), the evaluation of both Pedal pulses distinguish the most established situation the presence of both in the 61.4% (n=203). The time of evolution of the current ulcer (in weeks) was 8.7, and the outcome in the follow-up was a major amputation only in the 6% (n=19).

For to identify and quantify the risk factors for lower extremity amputation in diabetic patients with neuropathic ulcerations of the foot treated with Heberprot P, we star with the analysis of the demographic characteristics and Diabetes baseline clinical findings of the patients amputated in the follow up. 2009-2021 (Table 3), and the main findings were and increase in the mean age of the amputated population 67.8

Versus 61.7 in non-amputated patients; smoke like toxic habits in all the amputated patients and alcohol intake in the 63.2% (n=12); a longer time of evolution of the diabetes mellitus (in years) 19.7 vs. 13.7. In reference with the current treatment for diabetes at the admission time insulin was used in 63.2% (n=12), and a high prevalence of another diabetes complications like advance renal disease and previous diagnosis of ischemic heart disease; both with the 89.5% (n=17) and severe visual impairment in the 63.2% (n=12).

Table 2: Diabetic Foot evaluation and clinical findings. 2009-2021.

Variable		Values
deformities of the Foot	Yes	**189** (57.1%)
	No	142 (42.9%)
stage according to the Wagner Gradation	2	79 (23.9%)
	3	**219** (66.2%)
	4	33 (9.9%)
topography according to Garcia Herrera Topographic taxonomy	Anterior segment	**231**(69.8%)
	Middle segment	29 (8.8%)
	Posterior segment	40 (12.1%)
	Combined wounds	31 (9.3%)
Diabetic Foot Infections with (PEDIS)	1	119 (35.9%)
	2	**178** (53.8%)
	3	32 (9.7%)
	4	2 (0.6%)
Osteomyelitis	Yes	92 (27.8%)
	No	**239** (72.2%)
ankle brachial index (ABI)	>1.3	39 (11.9%)
	0.9-1.3	**201** (60.7%)
	0.6-0.9	69 (20.8%)
	<0.6	22 (6.6%)
Both Pedal pulses	Present	**203**(61.4%)
	Absent	12 (3.6%)
	Tibial posterior absent	37 (11.2%)
	Dorsal pedal absent	79 (23.8%)
Size	> 10 cm^2	68 (21.2%)
	5-10 cm^2	**174** (52.6%)
	<5 cm^2	89 (26.2%)
time of evolution of the current ulcer(in weeks)		**8.7** (2.5)
Major amputation in the follow up	Yes	19 (6%)
	No	**312**(94%)

n Values for time of the current ulcer (in weeks) are presented as mean (SD). Other values presented as n (%). Values in bold face type are significant at P < 0.05, based on χ^2 test.

Table 3: Demographic characteristics and Diabetes baseline clinical findings of the patients amputated in the follow up. 2009-2021.

Variable		Values
Age (years)		**67.8** (3.2)
gender	Female	**11** (57.9%)
	Male	8 (42.1%)
ethnicity	White	3 (15.8%)
	African descent	4 (21%)
	Mestizo	**11** (57.9%)
	Asian descent	1 (5.3%)
toxic habits	Smoke	**19** (100%)
	Others	**12** (63.2%)
type of diabetes mellitus	1	7 (36.8%)
	2	**12** (63.2%)
time of evolution of the diabetes mellitus (in years)		**19.7** (2.3)
current treatment for the diabetes	oral hypoglycaemic drugs	2 (10.5%)
	insulin	**12** (63.2%)
	Combination of treatment	5 (26.3%)
patient's comorbidities	severe visual impairment	**12** (63.2%)
	advance renal disease	**17** (89.5%)
	Previous diagnosis of ischemic heart disease.	**17** (89.5%)

Others includes alcohol consumption. n Values for age, time of evolution of diabetes mellitus presented as mean (SD). Other values offered as n (%). Values in bold face type are significant at P < 0.05, based on χ^2 test.

The second step consists of the analysis of diabetic foot evaluation and clinical findings of the patients amputated in the follow up. 2009-2021. All the DFU patients that suffer an amputation like an outcome had the following findings deformities in the Foot, Gradation Wagner Grade 4 78.9% (n=15). The topographic evaluation according to Garcia Herrera Topographic taxonomy the middle segment includes the 52.6% of the amputee (n=10). The evaluation of the Diabetic Foot Infections by PEDIS, establish the level three (moderate infection), that constitutes the 89.5% (n=17), and the presence of osteomyelitis at the beginning of the treatment in the 100%. The vascular status of the neuropathic ulceration, shows patients with an ankle brachial index (ABI) lower than 0.6 63.2% (n=12) and the absent of both pedal pulses (*dorsal pedis* and *tibial porterior*) constitutes the 78.9% (n=15). Typically a big Size more than 10 cm2 justified the 89.5% (n=17) and the time of evolution of the current ulcer (in weeks) of 14.9 (Table 4).

Discussion

This study makes a unique and fundamental contribution to the global evidence base for the prognosis assessment for diabetes-related neuropathic foot ulcers, treated with human recombinant Epidermal Growth Factor. The rate of major lower limb amputations for diabetic foot problems in the present study (6.0%), with a 14 years follow-up is lower than the rates reported by other studies [11-13].

In the present study, age was found to be a significant predictive factor for major lower limb amputation. The patients who had major lower limb amputations (LLA) were significantly older, with a mean age of 67.8 (3.2) years compared to 61.7 (4.2) years for those who did not have major limb amputations. According to the international research, age above 60 years is a protective factor for major lower limb

Table 4: Diabetic Foot evaluation and clinical findings of the patients amputated in the follow up. 2009-2021.

Variable		Values
deformities in the Foot	Yes	**19** (100%)
	No	-
stage according to the Wagner Gradation	2	-
	3	4 (21.1%)
	4	**15** (78.9%)
topography according to Garcia Herrera Topographic taxonomy	Anterior segment	-
	Middle segment	**10 (52.6%)**
	Posterior segment	5 (26.3%)
	Combined wounds	4 (21.1%)
Diabetic Foot Infections with (PEDIS)	1	-
	2	-
	3	**17**(89.5%)
	4	2 (10.5%)
Osteomyelitis at the beginning of the treatment	Yes	**19** (100%)
	No	-
ankle brachial index (ABI)	>1.3	5 (26.3%)
	0.9-1.3	-
	0.6-0.9	2 (10.5%)
	<0.6	**12** (63.2%)
Both Pedal pulses	Present	-
	Absent	**15** (78.9%)
	Tibial posterior absent	-
	Dorsal pedal absent	4 (21%)
Size	> 10 cm^2	**17** (89.5%)
	5-10 cm^2	2 (10.5%)
	<5 cm^2	-
time of evolution of the current ulcer(in weeks)		**14.9** (3.2)

n Values for time of the current ulcer (in weeks) presented as mean (SD). Other values offered as n (%). Values in bold face type are significant at $P < 0.05$, based on $\chi 2$ test.

amputation in diabetic patients [5,14]. The evaluation of the gender was no significant in the prognosis, there are varied distribution in several studies in some predominate the percentage of men, but in the most of them the female patients [15] age and gender evaluation were similar to the demographic profile of the diabetic population on others studies [6,9].

There has been conflicting data on the role of ethnicity in the outcome of Diabetic Foot Ulcer (DFU) in this investigation seem not associated, is believe that this is due to the historic and strong miscegenation typical of our country's population.

Some variables appeared to have complex relations with lower limb prognosis like Smoking and alcohol consumption [11,16] and its behaviour were heterogeneous across different research, for most studies, around 50% or more of the patients had a history of smoking, and the trends were similar for alcohol consumption [17]. Controversially smoking and alcohol seemed to be protective against ulceration in some studies and predictive of ulceration in others, this may be another expression of the so-called smoker's paradox, is also possible to speculate that both smoking and drinking alcohol could be associated with another variable (acting like confuses) that is genuinely protective against ulceration, for example younger age [14,18].

Like the obtained results, the majority of patients had type 2 diabetes, the proportion ranging in the different studies 61% and 98%, overall, type 1 diabetes accounted for about 9% of recorded types of diabetes [16,17,19].

Insulin treatment accounted mostly for 20-40% of each diabetic population; in the present study, a longer duration of Type 2 of Diabetes Mellitus founded like a significant independent predictive factor for major lower limb amputation. However, another studies observed that the duration of DM do not constitutes a significant factor for major lower limb amputation [20-22].

The comorbidities evaluation suggests according to previous researcher that visual impairment and/or blindness were present with heterogeneous results. Retinopathy was recorded diagnoses ranged from 9% to 49% of the population, not only is consider as a contributing factor, also as the most significant factor leading to amputation amongst DF patients, accentuating the importance of early detection and management of diabetic complications. Renal problems were collected for most studies but in various ways. Nephropathy accounted for 2% and 17% of the population in two studies, stage 3-5 Chronic Kidney Disease accounted for 13-37% of the population in two studies, and end-stage renal failure for 2% and 4% of the population in another two studies [4,8-11,23-25].

The foot deformity was the most frequently collected variable the proportion with any foot deformity ranged from 4% to 80% in different studies. There are a higher proportion of patients with neuropathic disease, with clear predominance of the neuroischemic population, and a smaller number of patients with isolated ischemic disease. Most studies conducted in economically developed nations show a high prevalence of ischemic disease [9,18,26]. Similar findings had been found. Unlike ulcer, patients presenting ischemic disease, either in an isolated form or associated with neuropathy presented the greatest risk for amputation in multivariate analysis. Ischemic disease has frequently been associated with poorer ulcer outcomes, especially when associated with infection [27].

The results of two meta-analyses that evaluated the absent of both pedal pulses were also consistent and show that constitutes and independent predictive of prognosis [28]. This observed effect may be attributable to the underlying vascular pathophysiology of the foot ulcers, because instead that neurological is more frequent that arterial supply disturbance in nature, is more related with prognosis [11,19]. The proportion of patients with abnormal ABI ranged from 25% to 78% [21]. Other recognized risk factors of LLA in subjects with DFU included the Charcot's arthropathy, history of osteomyelitis, severity of foot infection or cellulitis requiring antibiotic treatment [18]. Some authors had linked history of cellulitis and moderate-to-severe foot infection to amputation [7,9,21,29]. There is notably no current evidence suggesting use of antibiotics to prevent infections in subjects with DFU at risk of LLA [28]. The tropical climate of Cuba is a likely contributor to the association, resulting in increased rates of bacterial skin and soft tissue infections requiring on going antimicrobial treatment.

Conclusions

There are Risk factors Associated with lower extremity amputation in diabetic patients with neuropathic ulcerations of the foot treated with human recombinant Epidermal Growth factor, that should be known for the multidisciplinary team approach in the attention and follow-up of the patients treated with human recombinant Epidermal Growth Factor intralesional.

Conflict of Interest Statement

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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