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Risk factors for the development of diabetic foot

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Abstract: Objective: To determine the risk factors for the development of diabetic foot in patients of the Endocrinology Unit of the Autonomous Institute University Hospital of Los Andes, Mérida,Venezuela. Methods: One hundred type 2 diabetic patients were selected and divided into two groups: 50 patients with diabetic foot (cases) and 50 without diabetic foot (controls), of both sexes, over 18 years of age, matched by age, sex and duration of diabetes. Socio-demographic variables, antecedents, anthropometric measures, disease characteristics, metabolic control, comorbidities and clinical characteristics of the foot were evaluated. Results: There was no association of marital status, education level, psychobiological habits, nutritional status, and presence of arterial hypertension or dyslipidemia, with the presentation of diabetic foot. The predominant lesion in the cases was Wagner grade 2, and according to the Texas classification, it was IIB. There was a significant association of diabetic foot with poor metabolic control (p=0.003; OR:3.451; 95%CI:1.517-7.852), presence of neuropathy (p=0.0001; OR:5.670; 95%CI:2.144-14.997), alteration of the ankle arm index (p=0.004; OR:3.545; IC05%:1.487-8.454) and the personal history of diabetic foot (p=0.0001; OR:8.609; 95%CI:3.110-23.832). In the multivariate logistic regression analysis,the presence of neuropathy, the alteration of the ankle arm index and the personal history of diabetic foot remained as independent predictive factors. Conclusion: The risk factors associated with diabetic foot found in this study are similar to those reported in the world literature. It is very important to maintain adequate metabolic control to avoid neuropathic and angiopathic damage that favor the development of diabetic foot.

Key words: diabetic foot; risk factors; diabetic neuropathy; diabetic angiopathy

1 Introduction

Diabetes is a group of metabolic disorders characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia associated with diabetes is linked to long-term damage, dysfunction, and failure of various organs, particularly the eyes, kidneys, nerves, heart, and blood vessels [1]. The World Health Organization (WHO) currently considers diabetes an "epidemic." It is estimated that the number of people with diabetes worldwide ranges from 194 to 246 million, and could rise to 333 to 380 million by 2025, potentially becoming the seventh leading cause of death by 2030 [2]. In Venezuela, according to reports from the Ministry of Popular Power for Health, diabetes ranks fourth in mortality, accounting for 6.89% of total deaths [3].

Diabetes mellitus (DM) can lead to both acute and chronic complications. Acute complications can be life-threatening, such as diabetic ketoacidosis and hyperosmolar state, while chronic complications can have devastating consequences, including retinopathy, nephropathy, macroangiopathy, and peripheral neuropathy, the latter being the leading cause of ulceration of the lower extremities, Charcot joints, and amputations [4].

Foot ulceration is one of the major health problems for people with diabetes mellitus. It is estimated to affect 15% to 25% of people with diabetes at some point in their lives [4]. Foot ulceration can result in significant physical disability and reduced quality of life, leading to limb loss and death [5,6]. According to the WHO, diabetic foot is defined as the presence of ulceration, infection, and/or gangrene in the foot, associated with diabetic neuropathy and varying degrees of peripheral vascular disease, all of which result from the complex interaction of various factors induced by sustained hyperglycemia [7].

The diabetic foot is the most common cause of complications and hospitalizations among the diabetic population. In 85% of cases, limb amputation is preceded by an ulcer and accounts for 40% to 60% of non-traumatic amputations in hospitals [8]. A person with diabetes is 25 times more likely to develop a foot ulcer than a person without diabetes, and it is estimated that a lower limb amputation is performed somewhere in the world every 30 seconds as a result of diabetes [9,10].

The 3-year survival rate following a major amputation is only 50%, and the 5-year survival rate is 40%. Mortality associated with diabetic foot syndrome is similar to that of breast, prostate, or colon cancer [8]. This complication has not only medical implications, but also social and economic ones [11]. In high-income countries, the treatment of diabetic foot complications accounts for 15 to 25% of the health budget. It is estimated that basic diabetes treatment and care could prevent up to 80% of foot amputations in diabetic patients [2].

This topic has been extensively studied worldwide. In 2012, Shahi et al., in India, studied 581 patients and demonstrated a strong association between diabetic foot and living in a rural area, being over 50 years of age, having had diabetes for more than 8 years, and tobacco use [11]. Similar results were found by Gohel et al.[12]. In another context, Booya et al., in Iran in 2005, found that the predominant risk factors for developing diabetic neuropathy were dyslipidemia, type 2 diabetes rather than type 1, female gender, and sensory abnormalities [13]. Furthermore, from an epidemiological perspective, Shariful et al. reported a high incidence of readmissions due to diabetic foot, either for the same injury or a different one [14]. In another study, 54.7% of patients reported not having received education on foot self-care [15].

The reviewed literature also revealed a strong association between the development of diabetic foot and poor metabolic control, as reported by Al-Rubeaan et al.[16], who demonstrated that HbA1c levels were higher in the group with diabetic foot compared to those without, and were directly proportional to structural foot abnormalities; these results are also comparable to those of Pinilla et al.[17] . In their characterization and classification of diabetic foot, Alcántara et al.[18] reported in their study that the most common type of ulcer in the studied population was Wagner IV-V, accounting for 64.08%.

Based on this evidence found in the global literature, and considering that the state of Mérida has a high prevalence rate of diabetic patients (810.5 per 100,000 inhabitants) [19], it was considered of great importance to answer the following question: What risk factors are associated with the development of diabetic foot in patients consulting the Endocrinology Service at the Instituto Autónomo Hospital Universitario de Los Andes (IAHULA), Mérida, Venezuela?

2 Materials and methods

2.1 Subjects

An observational, analytical, retrospective case-control study was conducted, selecting a group of patients with diabetic foot (cases) and a group of diabetic patients without diabetic foot (controls), both over the age of 18. A patient was considered to have diabetic foot if they presented with any type of ulceration at the time of the study. To calculate the sample size, the study by Chiwanga and Njelekela [20] was used as a reference, in which diabetic neuropathy—the risk factor most closely associated with diabetic foot—was present in 94% of patients with diabetic ulcers and in 44% of those

without diabetic ulcers; A type α error of 0.05 and a β value of 0.2 were established; this resulted in a sample of at least 30 diabetic patients with diabetic foot and 30 without diabetic foot. This sample size was exceeded by including 50 patients in each group; they were selected from the Specialized Diabetes Clinic of the Endocrinology Service at IAHULA, and the controls were matched to the cases by age, sex, and duration of diabetes. Patients with type 1 diabetes were excluded.

2.2 Procedures

The participants signed the informed consent form, and the researcher administered the data collection instrument in accordance with the guidelines of the Declaration of Helsinki on research. Data were collected on identification and sociocultural characteristics, personal history of hypertension (HTN), dyslipidemia, heart disease, history of diabetic foot, smoking and drinking habits (whether current, past, or never), years since diabetes diagnosis, and treatment received.

To assess metabolic control, the targets established by the ADA [1] were used, which include fasting blood glucose between 80 and 130 mg/dL, postprandial: < 180 mg/dL, and HbA1c < 7% in patients without comorbidities, with a recent diagnosis, increased life expectancy, no cardiovascular risks, and no history of severe hypoglycemia; and <8% for patients with a history of severe hypoglycemia, limited life expectancy, or heart or kidney disease. Dyslipidemia was defined as: triglycerides >150 mg/dL; total cholesterol >200 mg/dL; non-HDL cholesterol: >80 mg/dL in patients with extremely high cardiovascular risk, > 100 mg/dL in patients at very high and moderate risk and >160 mg/dL in those at low risk; LDL cholesterol >100 mg/dL in people without cardiovascular disease and >70 mg/dL if there was a history of cardiovascular disease; HDL cholesterol <40 mg/dL in men and <50 mg/dL in women [21,22].

Anthropometric variables were measured according to the standards and techniques described by the National Health and Nutrition Examination Survey [23]. Body mass index (BMI) was calculated using the formula BMI = Weight (kg)/Height [2] (m), and based on this, participants were classified as underweight <18.49 kg/m², normal weight: 18.5–24.99 kg/m², overweight: 25–29.99 kg/m², and obese: >30 kg/m². Regarding blood pressure, values above 140 mmHg for systolic blood pressure (SBP) and 90 mmHg for diastolic blood pressure (DBP) were considered hypertension (HTN) [1].

To characterize neuropathy, the Michigan Neuropathy Program (a tool designed to detect diabetic neuropathy) was used; this program was validated and published in Diabetes Care in 1994 [24], and it assesses, on the one hand, subjective factors, which are neuropathic symptoms reported by the patient through 15 questions, in which each positive response is worth one point; and, secondly, a clinical evaluation of the foot through visual inspection of its appearance, looking for characteristics such as deformity, skin hydration, presence of infection, fissures, and ulceration, with one point assigned to each characteristic if present; Another aspect considered by the scale is the Achilles reflex, which is assessed using a Taylor reflex hammer, held between the thumb and index finger; the limb must be relaxed, and a direct, rapid tap must be applied to the Achilles tendon of the foot being evaluated. If the reflex is present, no points are awarded; if it is not present, the maneuver is repeated to enhance the response, as this allows for isometric contraction of other muscles that increase reflex activity; if the reflex appears with this technique, it is scored as 0.5 points, but if it remains absent, 1 point is added to the total. To assess vibratory perception, a 128 Hz tuning fork was used, which must be held by the handle and struck across its prongs with the palm of the opposite hand; it should be placed on the big toe or on the bony prominence of the head of the first metatarsal, and the patient must note the vibration and report whether they feel it or not; if they do not perceive it, the test is repeated in a more proximal area (malleoli or tibial tuberosity); if not felt, 1 point is added; if diminished, 0.5 points; and if present, no points are added to the scale [25]. Finally, the points from the questionnaire and the physical examination are added together; a score of >6 points is classified as neuropathy, categorized as: mild neuropathy (7-12 points), moderate neuropathy (13-29 points), and severe: 30 to 46 points.

For the classification of foot lesions, the University of Texas scale was used. Designed by Lavery and Armstrong in

1996 and subsequently validated in 1998, it is a classification system in which lesions are reported based on two main criteria: depth and the presence of infection/ischemia. Thus, the longitudinal axis of the matrix addresses the parameter depth, assigning four grades (from grade 0 to grade 3), while the vertical axis represents the infection/ischemia parameter, classified using four letters (A — no infection or ischemia, B — presence of infection, C — presence of ischemia, D — presence of both infection and ischemia) [26]. The Maggitt – Wagner classification, first described in 1976 by Maggitt [27] but popularized by Wagner in 1981, was also used to categorize ulcers. This system consists of five categories or grades. Each grade describes a type of lesion. The first three grades use depth as the primary descriptor; the fourth includes infection as an additional descriptor; and the last two include vascular disease. In addition, the classification includes a series of characteristics for each grade to assist the clinician in staging. Grade 1 ulcers are superficial, involving the full thickness of the skin; Grade 2 ulcers are deeper, penetrating ligaments and the joint capsule; Grade 3 are deep lesions, with abscesses or osteomyelitis; Grade 4 ulcers present localized gangrene; and Grade 5 includes extensive gangrene, affecting more than two-thirds of the feet [28].

Finally, vascular assessment was performed using the ankle-brachial index. To determine this, the patient was placed in a warm environment; the sphygmomanometer cuff was placed above the malleoli; the posterior tibial or dorsal foot artery was located by palpating the pulses; acoustic gel was applied; the Doppler transducer was positioned at an angle of approximately 45° in the direction opposite to blood flow; the area with the most audible sound was identified, and the cuff pressure was increased to at least 20 mm Hg above the previously measured systolic blood pressure in the arm; the pressure was then decreased until the wave with the greatest intensity reappeared, which corresponded to the systolic pressure; once both values were obtained, the systolic blood pressure at the ankle was divided by the systolic blood pressure in the arm, yielding the right and left ABI. Based on this value, the results were classified according to the European Society for Vascular and Endovascular Surgery as: normal 0.91-1.30, minimal occlusion: 0.70-0.90, moderate occlusion: 0.40-0.69, severe occlusion: <0.40, and calcifications: >1.30 [29].

2.3 Statistical analysis

Quantitative variables were presented as means and standard deviations, and categorical variables as counts and percentages. The association between categorical variables was assessed using the chi-square test and by calculating the odds ratio when appropriate. The statistical difference between quantitative variables was determined using Student's t-test for unpaired samples for those with a normal distribution, and the Mann-Whitney test for those with a non-normal distribution (blood glucose, triglycerides, and blood pressure). A Pearson correlation matrix was performed between the quantitative variables. A logistic regression analysis was performed with the presence or absence of diabetic foot as the dependent variable and with the variables that showed a significant association as independent variables. A p-value of ≤ 0.05 was considered significant. The data obtained were processed using the SPSS statistical software, version 20.

3 Results

This study included 100 patients with type 2 diabetes, 50 with diabetic foot (cases) and 50 without diabetic foot (controls). The demographic characteristics of the study sample are presented in Table 1. The gender distribution was similar between cases (50% female and 50% male) and controls (46% female and 54% male). The mean age was 64.70 ± 11.47 years for the case group and 65.12 ± 11.96 years for the control patients, with no significant differences. No difference was found regarding the presence or absence of a current partner or marital status, with "married" being the most common status in both the cases (44%) and the controls (38%). When analyzing educational level, there was no difference between the two groups; however, it is important to note that the most common educational level among our patients was primary school (cases: 42%; controls: 30%), which demonstrates the low level of education among these patients.

Regarding place of origin, no difference was found between rural and urban areas.

With regard to the psychobiological habits of diabetic patients, there were no significant differences. Among the cases, the majority (48%) had a history of smoking, while currently only 6% do so; among the controls, the majority have never smoked (56%), and currently only 6% do so. Alcohol consumption follows a similar pattern: currently, only 6% of the cases and 10% of the controls consume alcohol, and the majority had consumed alcohol in the past (cases: 52% and controls: 58%) (Data not shown).

Table 1. Demographic characteristics of diabetic patients according to cases (with diabetic foot) and controls (without diabetic foot)

Variables	Cases n=50	Controls n=50
Sex M/F	25 (50.0) / 25 (50.0)	23 (46.0) / 27 (54.0)
Age (years)	64.70 ± 11.47	65.12 ± 11.96
Marital Status		
Married	22 (44.0)	19 (38.0)
Common-law marriage	7 (14.0)	4 (8.0)
Divorced	4 (8.0)	12 (24.0)
Widowed	10 (20.0)	7 (14.0)
Single	7 (14.0)	8 (16.0)
Current Partner		
Yes	29 (58.0)	23 (46.0)
No	21 (42.0)	27 (54.0)
Education Level		
No schooling	13 (26.0)	11 (22.0)
Primary school	21 (42.0)	15 (30.0)
Secondary school	8 (16.0)	11 (22.0)
University	8 (16.0)	13 (26.0)
Origin		
Rural	26 (52.0)	22 (44.0)
Urban	24 (48.0)	28 (56.0)

Data presented as N (%) and mean ± SD.

The results regarding personal history, duration of diabetes, nutritional status, blood glucose and glycated hemoglobin levels, and data on hypertension and dyslipidemia are presented in Table 2. With regard to the personal history of the patients studied, no association was found between diabetic foot and hypertension, dyslipidemia, or a history of heart disease; however, it was observed that 54% of the cases had a previous history of diabetic foot, compared to 12% of the controls, which represents a statistically highly significant association (p=0.0001) and an 8.609-fold higher risk of diabetic foot if this history was present (95% CI: 3.110–23.832). The duration of diabetes did not differ between cases (19.86 ± 10.57 years) and controls (17.62 ± 9.25 years). In the assessment of nutritional status, there was no difference between the groups, although there was a slight predominance of patients with normal weight in the cases (54% vs. 30% in the controls) and of overweight patients in the controls (48% vs. 26% in the cases). Hypertension was found to be significantly more common in the control group (68%) compared to the cases (42%) (p=0.009). The mean fasting blood glucose level was

higher in the cases (187.49 ± 62.83) than in the controls (152.49 ± 50.22), corresponding to the glycated hemoglobin values (cases: 8.0 ± 1.56; controls: 7.16 ± 1.37), with both variables showing statistical significance (p =0.003). Thus, upon examining the patients' metabolic control, it was observed that poor control predominated in the cases (64%), while in the controls it was 34%; the opposite was true for good control, where the highest prevalence was observed in the control group (66%), while in the case group it was 36%; this was a statistically significant association (p=0.003) and was associated with a 3.451-fold increased risk of diabetic foot if metabolic control was poor (95% CI: 1.517 – 7.852). The prevalence of dyslipidemia was similar, at 84% for the case group and 86% for the control group. There were no differences regarding treatment; the majority received subcutaneous insulin, 52% of cases and 46% of controls.

Table 2. Nutritional status, blood pressure, and lipid profile of diabetic patients according to cases (with diabetic foot) and controls (without diabetic foot)

Variables	Cases n=50	Controls n=50
Previous Diabetic Foot	27 (54.0)	6 (12.0)***
Diabetes Duration (years)	19.86 ± 10.57	17.62 ± 9.25
Nutritional Status:		
Underweight	3 (6.0)	3 (6.0)
Normal weight	27 (54.0)	15 (30.0)
Overweight	13 (26.0)	24 (48.0)
Obesity	7 (14.0)	8 (16.0)
Presence of Hypertension (HTN)	21 (42.0)	34 (68.0)*
Fasting Glucose (mg/dL)	187.49 ± 62.83	152.49 ± 50.22*
Glycosylated Hemoglobin (g%)	8.08 ± 1.56	7.16 ± 1.37**
Metabolic Control		
Good control	18 (36.0)	33 (66.0)**
Poor control	32 (64.0)	17 (34.0)
Presence of Dyslipidemia	42 (84.0)	43 (86.0)
Treatment		
Oral hypoglycemic agent	19 (38.0)	7 (34.0)
Insulin	26 (52.0)	23 (46.0)
Combination	5 (10.0)	10 (20.0)

Data presented as mean ± SD and N (%). HTN: Hypertension. *p = 0.009, **p = 0.003, ***p = 0.0001

Previous Diabetic Foot: OR: 8.609; 95% CI: 3.110–23.832

Poor Metabolic Control: OR: 3.451; 95% CI: 1.517–7.852

Table 3 presents the assessment of neuropathy in the studied patients according to cases (diabetic foot) and controls (no diabetic foot); neuropathy was higher in the cases (86%) than in the controls (52%) (p<0.0001), and this neuropathy was determined by the score on the Michigan scale, which had a higher mean in the cases (12.53 ± 5.26) compared to the controls (7.02 ± 2.89; p < 0.0001); when classified by type of neuropathy, mild neuropathy predominated in the controls (80.8% vs. 39.5%), while moderate neuropathy predominated in the cases (60.5% vs. 19.2%); this difference in neuropathy severity was significant (p = 0.001); there were no cases with severe neuropathy. The presence of Neuropathy is associated with a 5.670-fold increased risk of diabetic foot (95% CI: 2.144-14.997).

Table 4 presents the assessment of angiopathy; it shows that the right and left ITB values were significantly lower in the cases (0.73 ± 0.38 vs. 0.93 ± 0.24 on the right and 0.72 ± 0.36 vs. 0.91 ± 0.24 on the left; p<0.004 for both), and therefore, the presence of angiopathy as determined by the ITB was higher in the case group (78%) compared with the control group (50%; p<0.004), with this change in the ITB being a significantly determinative factor in the development of diabetic foot (odds ratio: 3.545; 95% CI: 1.487-8.454). In the classification based on ITB values, the predominant abnormality in the cases was moderate vascular occlusion, 36% in the right limb and 34% in the left, whereas in the controls, the most common finding was normality, 56% in the right and 52% in the left.

Table 3. Evaluation of neuropathy in diabetic patients according to cases (with diabetic foot) and controls (without diabetic foot)

Variables	Cases n=50	Controls n=50
Michigan Scale Score	12.53 ± 5.26	7.02 ± 2.89**
Presence of Neuropathy	43 (86.0)	26 (52.0)**
Type of Neuropathy		
Mild	17 (39.5)	21 (80.8)*
Moderate	26 (60.5)	5 (19.2)

Data presented as mean ± SD and N (%). *p < 0.001 ** p < 0.0001

Presence of neuropathy: Odds ratio: 5.670; 95% CI: 2.144–14.997

Table 4. Evaluation of angiopathy in diabetic patients according to cases (with diabetic foot) and controls (without diabetic foot)

Variables	Cases n=50	Controls n=50
Right ABI	0.73 ± 0.38	0.93 ± 0.24*
Left ABI	0.72 ± 0.36	0.91 ± 0.24*
ABI Alteration	39 (78.0)	25 (50.0)*
Right ABI Classification		
Normal	14 (28.0)	28 (56.0)*
Mild Occlusion	6 (12.0)	10 (20.0)
Moderate Occlusion	18 (36.0)	10 (20.0)
Severe Occlusion	8 (16.0)	1 (2.0)
Calcifications	4 (8.0)	1 (2.0)
Left ABI Classification		
Normal	12 (24.0)	26 (52.0)**
Mild Occlusion	6 (12.0)	11 (22.0)
Moderate Occlusion	17 (34.0)	12 (24.0)
Severe Occlusion	11 (22.0)	0 (0.0)
Calcifications	4 (8.0)	1 (2.0)

Data presented as mean ± SD and N (%). ABI: Ankle-brachial index *p < 0.004 ** p < 0.0001

ABI Alteration: Odds ratio: 3.545; 95% CI: 1.487–8.454

In the correlation analysis, it was found that the Michigan Neuropathy Scale score showed a statistically significant positive correlation with HbA1c values (r=0.217; p=0.029) and blood glucose levels (r=0.209; p=0.037) (Figure 1, upper

panel), as well as with right ITB (r=0.328; p=0.001) and left ITB (r=0.355; p=0.0001) (lower panel). There was no correlation between HbA1c or blood glucose and the right or left ABI.

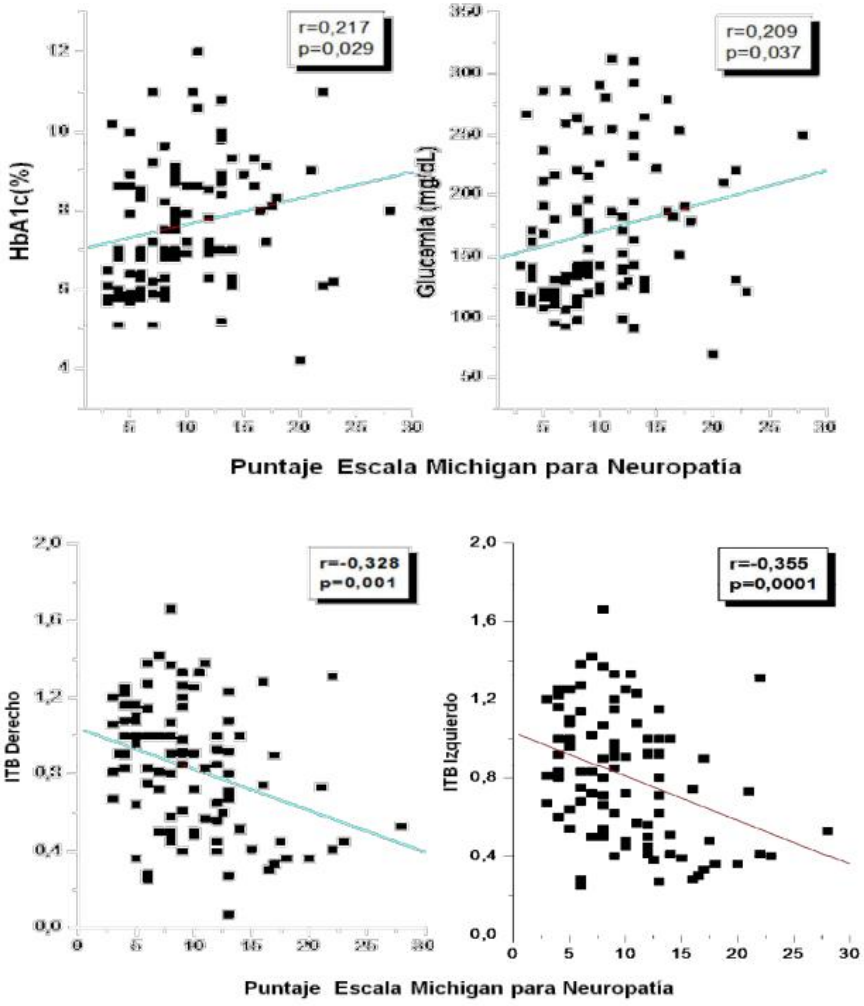

Figure 1. Correlations of the Michigan Neuropathy Screening Scale score with glycosylated hemoglobin (HbA1c) and mean blood glucose (upper panel), and with right and left ankle-brachial index (ABI) (lower panel), including all studied patients (cases and controls)

Table 5 presents the clinical characteristics of patients in the diabetic foot case group; the most commonly affected foot was the right foot (60%). According to the Wagner classification, Grade 2 ulcers—that is, deep ulcers without bone involvement—were the most common (32% of cases), followed by Grade 3 and 4 ulcers (24% each). Meanwhile, when classified according to the University of Texas system and evaluating depth, the most common grade was Grade II (40%), that is, a wound involving a tendon or capsule, followed by grade III (34%—a wound penetrating to bone or joint) and finally grade I (26%); when evaluating the presence or absence of infection or ischemia, stage B was the most prevalent (40%), that is, an ulcer infected, followed by stage D (34%)—that is, infection plus ischemia—then stage C (22%), and least frequently stage A (4%).

In Table 6, when performing the multivariate logistic regression analysis, taking into account the presence or absence of diabetic foot as the dependent variable, and the identified risk factors—namely, poor versus good metabolic control, the presence versus absence of neuropathy, abnormal versus normal ABI, and a personal history of diabetic foot—as

independent variables, it is observed that the statistical significance of metabolic control is lost, and the presence of neuropathy, abnormal ABI, and a personal history of diabetic foot remain as independent risk factors predicting diabetic foot, with an R-squared of 0.461, meaning that the presence of these three risk factors explains 46% of the cases of diabetic foot in the study sample.

Table 5. Characteristics of diabetic foot in affected patients according to the Wagner and Texas classifications

Variables	Cases n=50
Affected Foot	
Right	30 (60.0)
Left	20 (40.0)
Wagner Grade	
1 (Superficial ulcer)	10 (20.0)
2 (Deep ulcer without bone involvement)	16 (32.0)
3 (Deep ulcer with bone involvement)	12 (24.0)
4 (Localized gangrene)	12 (24.0)
5 (Extensive gangrene)	--
Texas Grade	
I (Superficial wound)	13 (26.0)
II (Wound involving tendon or capsule)	20 (40.0)
III (Wound penetrating to bone or joint)	17 (34.0)
Texas Stage	
A (No infection or ischemia)	2 (4.0)
B (Infection)	20 (40.0)
C (Ischemia)	11 (22.0)
D (Infection + ischemia)	17 (34.0)

Data presented as N (%).

Table 6. Multivariate logistic regression analysis of the presence or absence of diabetic foot as the dependent variable and associated risk factors as independent variables

Risk Factor	Univariate p-value	Multivariate p-value	Odds Ratio; 95% CI
Poor Metabolic Control	0.003	0.098	
			R-squared: 0.461
Presence of Neuropathy	0.0001	0.033	OR: 3.671; CI: 1.113–12.106
ABI Alteration	0.004	0.007	OR: 4.848; CI: 1.525–15.413
Previous Diabetic Foot	0.0001	0.0001	OR: 9.710; CI: 2.945–32.008

4 Discussion

The findings of this study identified the main risk factors for the development of diabetic foot in the study sample, namely: 1) history of diabetic foot, 2) poor metabolic control, 3) presence of neuropathy, and 4) Altered ABI. Regarding personal history, 54% of the patients studied had a previous ulcer; a similar finding has been described by multiple authors, such as in the observational study by Hurley et al. [30], where 56% of patients reported a previous foot ulcer (p=0.001),

while Al-Rubeaan et al. [16] found such a history in 39.3% (p=0.0001) and Wu et al. [31] reported 35.1%, which also proved to be significant; the opposite is true when compared to the research by Asaad-Khalil et al. [32], where, upon studying 2,000 patients in a case-control study, the presence of this history was only 8%.

When characterizing the metabolic control of the patients studied, poor control prevailed in 64% of cases, with this variable being statistically significant (p=0.003) compared to controls, and yielding an odds ratio of 3.451 for diabetic foot. In this regard, Booya et al. [13] compared risk factors to identify diabetic foot in a case-control study of 110 patients, and it was found that among the most significant factors was poor glycemic control ($p < 0.001$), with a mean baseline blood glucose level of 143.6 ± 60.2 in the case group and 130.8 ± 63.5 in the control group, and HbA1c values of 8.2 ± 2.5 in the case group versus 7.9 ± 2.7 in the control group; similar results were reported in the study by Hurley [30] , in which HbA1c was higher in patients with diabetic foot (7.3%) compared to those without (6.9%) (p=0.0001). Reinforcing these findings, in a study conducted in Saudi Arabia involving 65,534 patients [16] , poor metabolic control was prevalent when comparing cases (with diabetic foot) to controls (without diabetic foot) (p=0.0001). In our country, Castellano [33] in 2011 assessed the risk of developing diabetic foot in Zulia State, finding results similar to the previous ones with a baseline blood glucose level of 173 ± 78.6 in female patients and 188.9 ± 32.5 in male patients, demonstrating poor metabolic control as an influential factor; these results are similar to ours and consistent worldwide, with poor control predominating in patients with diabetic foot.

Our study found a strong association between the presence of neuropathy and diabetic foot; 86% of the cases and 52% of the controls had neuropathy. A review of the global literature indicates that this is the most common factor and the one with the greatest statistical significance for diabetic foot, as shown by Rosales et al.[34] in Colombia, in their case-control study (100 patients in each group), found that the presence of neuropathy was more frequent in the case group, a finding that was statistically significant ($p \leqslant 0.001$; OR: 10.14); similar results were reported in China by Wu et al.[31] in a prospective analysis of a cohort of 296 patients, where diabetic neuropathy was present in 66.2%, making it the most prevalent risk factor among those studied (p=0.0001). Meanwhile, Chiwanga et al.[20] conducted a cross-sectional study in 2015 involving 404 patients, concluding that those with neuropathy were 8 times more likely to develop an ulcer ($p<0.001$); in line with these results, Al-Rubeaan et al.[16] highlight neuropathy as a predictor of diabetic foot complications, affecting 61.98% of cases with diabetic foot, which contributed to one-third of the ulcer cases in the studied cohort ($p<0.001$); similar to these results, agreement was found with other studies [18,25,32,34,35].

When characterizing the clinical variable of vascular impairment by measuring the ABI, a consistent direct association with the development of diabetic foot was observed; this is because, in this study, the degree of impairment was higher in the case group, at 78%; this finding was similar to that described by Alcántara et al. [18] when studying the prevalence of amputation risk in patients with diabetic foot among 206 patients, who reported vascular abnormalities in 71.43% of patients, making this the second most prevalent risk factor (p=0.001), preceded by neuropathy. Supporting and reinforcing the importance of this variable are also Asaad-Khalil et al.[32], who found an association between diabetic foot complications and a history of peripheral vascular disease ($p<0.001$); similar data are reported by Rosales et al.[34], associating vascular abnormalities with a 44.33-fold increased risk (odds ratio) of developing diabetic foot. Similar to these results are those of Won et al.[36] who identified abnormalities vascular patients with impaired ABI in a retrospective study involving 117 patients, which showed that the presence of impaired ABI was positively associated with the risk of major or minor amputation ($p<0.01$).

When performing a multivariate logistic regression analysis, with diabetic foot as the dependent variable, and poor metabolic control, the presence of neuropathy, altered ABI, and a personal history of diabetic foot as independent variables,

it is observed that the statistical significance of metabolic control is lost, while the presence of neuropathy, altered ABI, and a personal history of diabetic foot remain significant—results similar to those of other studies [31,33,36,37]. These factors are confirmed as predictors for the development of diabetic foot in our population, and the prevention of structural abnormalities such as neuropathy or angiopathy is considered very important through maintaining adequate metabolic control, since their presence can lead to diabetic foot even if good metabolic control is achieved at that time.

These findings can be explained from a pathophysiological perspective, since poor metabolic control, characterized by persistent hyperglycemia, activates a series of metabolic pathways that are highly damaging to cells; this is known as glucose neurotoxicity. It is mediated through various molecular mechanisms: the aldose reductase-sorbitol pathway, excessive protein glycation, cellular oxidative stress, altered metabolism of polyunsaturated fatty acids, and the activation of certain cellular signaling pathways, ultimately causing axonal degeneration, segmental demyelination, and, consequently, the characteristic neuropathy, which involves structural nerve damage and facilitates foot ulceration. These mechanisms also explain the vascular alterations, as they increase vascular permeability, resulting in greater procoagulant activity, expression of adhesion molecules, and monocyte entry into the intima, disrupting vascular physiology and promoting atherogenesis. It should be noted that all these factors are perpetuated by poor metabolic control, thus leading to a vicious cycle [25,38].

Based on the characteristics of the diabetic foot in our patients, according to the Wagner classification, grade 2 (deep ulcer without bone involvement) was the most common, accounting for 32%. Similar results were found by Verrone et al. [37], where this grade accounted for 84% of the participants; conversely, Won et al.[36], where grade 2 accounted for only 18% of the 117 patients studied, with grade 1 predominating at 43.4%; conversely, Alcántara et al. [18], in a retrospective study grouping the grades into two categories—Group 1: Wagner 2–3 and Group 2: Wagner 4–5—found that Group 1 accounted for 35.92%, while Group 2 accounted for 64.08% . According to the University of Texas classification, the results of our study showed a higher frequency of Grade II ulcers (34%; wounds involving a tendon or capsule), consistent with the findings of Rakest et al.[39], where this grade accounted for 29.54%; stage B (infected ulcer) in our study accounted for 40%, similar to the study by Saleem et al.[40], which accounted for 46.4% of the ulcers. When comparing these classifications, according to the 2016 publication by Jeon et al.[41], in which they compared five diabetic foot classification systems as predictors of amputation, they concluded that the Wagner and University of Texas systems, although relatively simple to assess, were the best predictors of amputation risk. All of these studies are comparable to ours, demonstrating that the risk factors for diabetic foot in diabetic patients are similar to those in the rest of the global population.

Based on the results obtained, it is concluded that the risk factors associated with diabetic foot identified in this study are similar to those reported in the global literature. A history of diabetic foot was strongly associated with the occurrence of a new episode, and it was demonstrated that poor metabolic control, as well as the presence of impaired blood flow and peripheral neuropathy, are associated with the risk of developing diabetic foot at some point during the course of the disease. It is recommended that healthcare personnel reinforce education on foot self-care and maintaining good disease control, as well as performing an adequate physical examination during patient visits, with the aim of intervening early in the onset of this diabetic foot complication.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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