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Risk factors for diabetic foot ulcers: an Albanian retrospective study of inpatients with type 2 diabetes

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Abstract. – OBJECTIVE: The aim of this study was to assess the impact of glucose control, diabetes-related complications and cardiometabolic risk factors on the risk of diabetic foot ulcers (DFUs) and DFU complications in Albanian adult inpatients with T2D.

PATIENTS AND METHODS: We conducted a retrospective case-control study on 482 Albanian adult inpatients with T2D. DFU was defined as a full-thickness skin lesion requiring ≥14 days for healing and was classified at the time of hospital admission. Demographic and biochemical parameters of the study participants, the presence of comorbidities and diabetes-related complications at the time of hospital admission were evaluated through a retrospective chart review.

RESULTS: Mean age of study participants was 54.8±10.7 years. Participants (284 males and 198 females) were divided into two groups: DFU (cases; n=104) and non-DFU (controls; n=378). Multivariate analysis (performed by a logistic regression model) revealed that the most relevant independent variables associated with DFU were BMI [OR=0.62; *p*=0.007], HDL-cholesterol [OR=0.00; *p*<0.0001], triglycerides [OR=7.48; *p*=0.0004], cigarette smoking [OR=26.46; *p*=0.005], duration of diabetes [OR=1.53; *p*<0.0001], fasting plasma glucose (FPG) [OR=1.06; *p*<0.0001], systolic blood pressure (SBP) [OR=1.13; *p*=0.0004] and insulin therapy alone [OR=0.11; *p*=0.02]. ROC curve analysis showed that FPG (AUC=0.83), glycated hemoglobin (HbA1c) (AUC=0.75), triglycerides (AUC=0.78) and HDL-cholesterol (AUC=0.82) were the most reliable biomarkers able to detect DFU. In the DFU group, the most relevant independent variables associated with previous minor lower-extremity amputations (LEAs) were represented by HbA1c [OR=1.47; *p*=0.03], age <55 years [OR=0.12; *p*=0.05] and female sex [OR=4.18; *p*=0.03]; whereas the most relevant independent variables associated with diabetic peripheral neuropathy (DPN) were HbA1c [OR=1.70; *p*=0.006], SBP [OR=1.08; *p*=0.05], BMI [OR=1.20; *p*=0.03] and lack of cigarette smoking [OR=0.07; *p*=0.01]. Correlation analysis (performed through the nonparametric Spearman's rank correlation test or through the parametric Pearson test, as appropriate) revealed a significant positive relationship between HbA1c and FPG (r=0.58; *p*<0.0001), ulcer surface area (r=0.50; *p*<0.0001), ulcer grade (r=0.23; *p*=0.02), minor LEAs (r=0.20; *p*=0.04), DPN (r=0.41; *p*<0.0001), and metformin therapy alone (r=0.72; *p*<0.0001). There was a significant inverse correlation between HbA1c and insulin therapy alone (r=-0.31; *p*=0.01) and combined metformin and insulin therapy (r=-0.60; *p*<0.0001). Both DFU and non-DFU groups exhibited suboptimal mean LDL-cholesterol levels (>100 mg/dl) and mean HbA1c values >7.5%. Moreover, in DFU group HbA1c values were markedly elevated (≥10%) particularly in patients with a grade 3 ulcer and an ulcer surface area ≥4 cm², as well as in patients with history of minor LEAs and in patients affected by DPN.

CONCLUSIONS: The present study suggested that longer duration of diabetes, cigarette smoking, lower HDL-cholesterol levels, poor glucose control, and elevated triglyceride and SBP val-

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ues may all represent major risk factors for the development of DFU in Albanian patients with T2D. Thus, community interventions and health policies aimed to improve the management of diabetes and related cardiometabolic risk factors should be urgently implemented in Albania, in order to prevent DFUs and other diabetes complications in patients with T2D.

Key Words:

Diabetic foot ulcers, Diabetic foot, Albanian inpatients, Type 2 diabetes, T2D, Diabetic peripheral neuropathy, Lower-extremity amputations, Glucose control, Therapeutic adherence.

Introduction

Type 2 diabetes (T2D) is a chronic disease characterized by impaired glucose homeostasis due to a gradual loss of adequate pancreatic β-cell insulin secretion, frequently on the background of peripheral insulin resistance[1]. Family history of T2D, physical inactivity, older age, prediabetes, overweight, obesity and other clinical conditions associated with insulin resistance represent major risk factors for T2D[1]. According to the 9th International Diabetes Federation (IDF) Diabetes Atlas, the global prevalence of diabetes in 2019 is estimated to be 9.3% (463 million people) and it is projected to reach 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045[2]. It has been reported that diabetes prevalence is higher in high-income (10.4%) than low-income countries (4.0%), and in urban (10.8%) than rural (7.2%) areas. Yet, diabetes prevalence is projected to increase over the next decades even in low-income countries[2]. T2D accounts for approximately 90% of all types of diabetes and the rising trend in its global prevalence can be attributed to several factors, such as the increasing ageing population and the rapid increase in obesogenic environments and urbanization[2,3].

Albania is a Western Balkan developing country that faced an escalating burden of diabetes since the 1980s, in line with the trend observed in other countries undergoing rapid modernization and adoption of a westernized lifestyle. Over the last decades, diabetes prevalence doubled in Albanians older than 50 years of age[4]. The prevalence of T2D in rural areas of Albania has been reported as 4.17%[5], whereas the prevalence in urban areas amounts to approximately 6.3% in the age group older than 25 years of age[4]. According to recent IDF estimates, trends in T2D prevalence in Albania are in line with those observed on a global scale: the age-adjusted comparative prevalence of diabetes was 9.0% in 2019; this percentage is expected to increase to 10.2% by 2030 and to 10.9% by 2045[6]. This rising trend has also deleterious implications in terms of diabetes-related health expenditure and mortality[6], which are primarily linked to microvascular and macrovascular diabetes complications such as nephropathy, retinopathy, neuropathy, ischemic heart disease, cerebrovascular disease, peripheral arterial disease (PAD), foot ulcers, and lower-extremity amputations (LEAs)[7,8].

Diabetic foot ulcers (DFUs) affect up to 15% of diabetic subjects throughout their lives and represent the most common lower-extremity complication in diabetic patients, which results in an increased risk for hospitalization and significant morbidity and mortality[9-12]. Mortality rates associated with the development of DFU amount to approximately 5% during the first 12 months, whereas the 5-year mortality rates have been estimated at 42%[10]. About one-third of the total costs of diabetes care has been related to the treatment of DFU[13], the majority being associated with inpatient hospital admissions[14] and with the treatment of infected foot ulcers[12]. The term "diabetic foot syndrome" (DFS) encompasses all diabetic foot complications and is defined as an ulceration of the foot (distally from the ankle and including the ankle) associated with neuropathy and different grades of ischemia and infection[15]. DFS is regarded as the most severe consequence of diabetes-related long-term complications, PAD and diabetic peripheral neuropathy (DPN)[9]. Of note, up to one-third of DFUs may have a mixed ischemic and neuropathic etiology[16]. Diabetic foot infection represents a common complication of DFUs, which can involve deeper soft tissue (cellulitis) and bone tissue (osteomyelitis), thereby increasing the morbidity and the subsequent risk of LEAs related to DFUs[17,18].

Major risk factors for DFUs or DFU-associated LEAs include poor glucose control, peripheral neuropathy with loss of protective sensation (LOPS), PAD, cigarette smoking, foot deformities, pre-ulcerative callus or corn, history of foot ulcer, previous amputation, visual impairment and chronic kidney disease (particularly end-stage renal disease requiring dialysis)[7]. In turn, the presence of other diabetes-related complications (such as ischemic heart disease and chronic kidney disease) can further deteriorate and negatively affect the clinical outcomes of patients with established DFS[9].

A recent study conducted on Albanian T2D patients found that poor glucose control was significantly associated with higher rates of diabetes complications such as PAD[19]. Moreover, glycated hemoglobin (HbA1c) values were significantly and positively correlated with length of in-hospital stay[19]. These findings are in line with those from another study that examined 7259 medical records of Albanian diabetic patients over a 2-year follow-up period, where more than two-thirds of patients exhibited a progressive deterioration of glucose and metabolic control as well as poor management of cardiovascular risk factors[20].

However, the impact of diabetes complications and markers of glucose and metabolic control on the risk of DFUs and LEAs in the Albanian diabetic population is still unclear due to the scarcity of epidemiological data. Given the high-risk profile of Albanian diabetic population (defined according to the currently available epidemiological data), we conducted a case-control retrospective study aimed to assess whether markers of glucose and metabolic control, diabetes-related complications and cardiometabolic risk factors can affect the risk of DFUs and/or LEAs.

Patients and Methods

This case-control retrospective study was conducted on a total of 482 adult inpatients (mean age: 54.8 ±10.7) with T2D who were consecutively admitted to "Mother Teresa" University Hospital (Tirana, Albania) between June 2014 and January 2018. The main causes of hospital admission were DFU infection and hyperglycemic crisis in patients with DFUs and in patients without DFUs, respectively. Inclusion criteria were i) age ≥18 years; and ii) T2D diagnosis based on the use of any oral antihyperglycemic agent and/or according to the American Diabetes Association classification, namely: fasting plasma glucose (FPG) value ≥126 mg/dl and/or 2-h plasma glucose value during a 75-g oral glucose tolerance test ≥200 mg/dl and/or HbA1c value ≥6.5% and/or random plasma glucose value of ≥200 mg/dl accompanied by classic symptoms of hyperglycemia (polyuria, polydipsia, polyphagia, recent weight loss) and/or hyperglycemic crisis, in combination with absence of islet autoantibodies[1]. Exclusion criteria were the following: i) pregnancy and lactation; ii) malignancy; iii) cognitive and neurodegenerative diseases; iv) positive HIV, HBV and HCV serology testing; v) current use of corticosteroids and/or immunosuppressive drugs.

We evaluated, through a retrospective chart review, demographic parameters and the presence of comorbidities and diabetes-related microvascular complications at the time of hospital admission, namely: i) presence of hypertension; ii) diabetic nephropathy (based on the presence of microalbuminuria or macroalbuminuria)[21]; iii) DPN (diagnosed through medical history and clinical tests)[22]; iv) diabetic retinopathy; and v) DFU.

DFU was defined as a full-thickness skin lesion requiring ≥14 days for healing and was classified at the time of hospital admission according to the Wagner Diabetic Foot Ulcer Grade Classification System as follows: grade 1 (superficial ulcer of the skin and/or subcutaneous tissue that does not extend into tendon, capsule and/or bone); grade 2 (ulcer that extends into the tendon and/or capsule); and grade 3 (ulcer that extends into the bone and/or joint)[23]. The ulcer surface area was determined through mechanical planimetry by multiplying the two maximal perpendicular diameters of the ulcer, and it was expressed in square centimetres (cm^2), as it has been previously described[24]. We also evaluated history of previous LEAs as well as the presence of foot ulcer infections based on clinical signs and symptoms of local inflammation and/or purulence, such as swelling, wound exudate, surrounding cellulitis, wound odor, tissue necrosis, "crackling" sensation on palpation, and fever[10,17]. Minor LEA was defined as the complete loss in the transverse anatomical plane of a part of the lower limb that still allows bipodalic standing, which is an amputation performed through and/or distal to the ankle joint. Major LEA was defined as the amputation above the ankle.

For each patient, we evaluated the following variables at the time of hospital admission: age, sex, body mass index (BMI), cigarette smoking habit (smokers *vs.* non-smokers), FPG, HbA1c, serum creatinine, markers of lipid metabolism such as triglycerides (TG), high-density lipoprotein (HDL)-cholesterol, total cholesterol (TC), and low-density lipoprotein (LDL)-cholesterol (the latter calculated through the Friedewald equation)[25]. BMI was calculated as body weight (in kilograms) divided by height expressed in meters squared (Kg/m^2). We also evaluated duration of diabetes (years), systolic blood pressure (SBP), diastolic blood pressure (DBP), presence of hypertension (defined as SBP ≥140 mmHg and DBP

≥90 mmHg that is confirmed during separate clinic visits)[26], presence of microvascular complications (diabetic retinopathy, neuropathy and nephropathy), and type of antidiabetic therapy (insulin therapy alone, metformin therapy alone and/or both).

At the time of hospital admission, all participants and/ or their legal guardians provided written informed consent to anonymous data collection, analysis and publication for research purposes. Demographic, clinical and laboratory data were recorded in an anonymous database containing unambiguous and alphanumeric codes. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the local Ethics Committee (Catholic University Our Lady of Good Counsel, Tirana, Albania; registration number: M-FP3:125/17; 2017).

Statistical Analysis

Descriptive statistics is composed of the mean ± standard deviation (SD) for parameters with Gaussian distribution such as continuous variables, or frequencies (%) for categorical variables. Distribution of data was confirmed by the Kolmogorov–Smirnov test. Comparison between groups - diabetic foot (DFU) *vs*. non-diabetic foot (non-DFU controls) - was performed through unpaired t-test for continuous variables and through Fisher's exact test for categorical variables. Receiver-operating characteristic (ROC) curve analysis was used to retrieve the best estimated area under the curve (AUC), in order to determine the diagnostic ability of blood markers to predict DFU. Univariate and multivariate analyses of independent predictors associated with DFU were performed by a logistic regression model. The risk of ulcer development was estimated by the odds ratio (OR) with the 95% confidence interval (CI). Multiple correlation analysis was performed through the nonparametric Spearman's rank correlation test or through the parametric Pearson test, as appropriate, to evaluate the correlation of HbA1c (expressed as percentage) with clinical and biochemical parameters in the DFU group. The mean value of HbA1c (%) in the DFU group was put in relation to the ulcer surface area, to the ulcer grade (defined according to the Wagner Diabetic Foot Ulcer Grade Classification System), minor LEA and DPN. Comparison was performed by unpaired t-test or by one-way analysis of variance (one-way ANOVA), as appropriate. A p-value of less than 0.05 was considered statistically significant in all statistical analyses. All statistical analyses were performed by using GraphPad Prism 9.2.0 (GraphPad Software Inc., San Diego, CA, USA).

Results

In this study, we enrolled a total of 482 patients with T2D (284 males and 198 females). Participant demographics and clinical features are shown in Table I. Mean age of study participants was 54.8±10.7 years. Participants were divided into two groups according to the presence or absence of DFU. These two groups were referred to as: i) DFU group, including 104 participants with DFU (cases); and ii) non-DFU group, including 378 participants without DFU (controls). In the DFU group, 64 subjects were males and 40 were females, with a mean age of 53 years. In the non-DFU group, 220 subjects were males and 158 were females, with a mean age of 55 years. There was no statistically significant difference in mean age and in percentage of males and females between the two groups (Table I). Mean BMI was slightly - but significantly - greater in the DFU group compared to the non-DFU group (26.6±4.95 Kg/m^2 *vs*. 25.2±4.04 Kg/m^2; p=0.002). In the DFU group, there was a significantly higher proportion of smokers compared to the non-DFU group (88.5% *vs*. 55.3%; p<0.0001). DFU group also showed significantly greater mean FPG (247.5±54.14 mg/dl *vs*. 184.7±15.45 mg/dl; p<0.0001) and HbA1c values compared to the non-DFU group (9.7±2.33% *vs*. 7.8±0.9%; p<0.0001). Mean serum creatinine was significantly greater in the DFU group compared to the non-DFU group (1.4±0.4 mg/dl *vs*. 1.2±0.5 mg/dl; p=0.002). Conversely, non-DFU group exhibited significantly higher mean TG value compared to the DFU group (118.3±17.7 mg/dl *vs*. 99.1±17.4 mg/dl; p<0.0001). On the other hand, DFU group exhibited significantly lower mean HDL-cholesterol values compared to non-DFU group (41.2±3.2 mg/dl *vs*. 45.1±2.9 mg/dl; p<0.0001), while no significant difference was reported in mean LDL-cholesterol values between the two groups (Table I). However, both groups exhibited suboptimal mean LDL-cholesterol levels (108.4 mg/dl in the DFU group; 110.51 mg/dl in the non-DFU group), which were above the target LDL-cholesterol levels established for patients with diabetes and atherosclerotic cardiovascular disease (<70 mg/dl)[27].

Table I. Participant demographics and clinical features.

Variables	DFU group (cases) n = 104	Non-DFU group (controls) n = 378	*p*-value
Age (years)*	53 ± 12.4 (30-93)	55 ± 10.2 (29-87)	0.32
Gender (M/F)	64/40	220/158	0.57
BMI (Kg/m2)	26.6±4.95	25.2±4.04	**0.002**
Cigarette smokers (n, %)	92 (88.5%)	209 (55.3%)	**< 0.0001**
FPG (mg/dl)	247.5±54.14	184.7±15.45	**< 0.0001**
HbA1c (%)	9.7±2.33	7.8±0.9	**< 0.0001**
Serum creatinine (mg/dl)	1.4±0.4	1.2±0.5	**0.002**
TG (mg/dl)	99.1±17.4	118.3±17.7	**< 0.0001**
LDL-C (mg/dl)	108.4±18.7	110.51±17.4	0.28
HDL-C (mg/dl)	41.2±3.2	45.1±2.9	**< 0.0001**
TC (mg/dl)	169.4±25.3	179.3±23.9	**0.0003**
Duration of diabetes (years)	10.3±7.6	9.4±6.9	0.29
Hypertension (n, %)	55 (53%)	117 (31%)	**< 0.0001**
SBP (mmHg)	136.3±15.8	130±15.7	**0.0004**
DBP (mmHg)	77.1±10.8	75.97±11.9	0.73
Microvascular complications			
Diabetic retinopathy (n, %)	64 (61.5%)	102 (27%)	**< 0.0001**
DPN (n, %)	76 (73%)	96 (25.4%)	**< 0.0001**
Diabetic nephropathy (n, %)	47 (45.2%)	118 (31.2%)	**0.006**
Antidiabetic therapy			
Metformin therapy alone (n, %)**	58 (55.8%)	67 (17.7%)	**< 0.0001**
Insulin therapy alone (n, %)***	30 (28.9%)	228 (60.3%)	**< 0.0001**
Combined metformin and insulin therapy (n, %)	16 (15.4%)	83 (22%)	0.17

Data are expressed as mean ± standard deviation (SD) or absolute numbers (with accompanying percentages shown in brackets). Comparison between DFU group (cases) and non-DFU group (controls) was performed by unpaired t-test or Fischer's exact test, as appropriate. A *p*-value < 0.05 was considered statistically significant. Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; DFU, diabetic foot ulcer; DPN, diabetic peripheral neuropathy; F, females; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; M, males; ns, not significant; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides. *Age range is shown in brackets. **Metformin dose ranged from 500 mg/day to 2000 mg/day. ***Basal-bolus insulin therapy.

DFU group exhibited significantly lower mean total cholesterol (TC) values compared to the non-DFU group (169.4±25.3 mg/dl *vs.* 179.3±23.9 mg/dl; p=0.0003). There was no statistically significant difference in mean duration of diabetes between the two groups. DFU group showed a significantly higher proportion of patients with hypertension (53% *vs.* 31%; p<0.0001) as well as significantly higher mean SBP values compared to the non-DFU group (136.3±15.8 mmHg *vs.* 130±15.7 mmHg; p=0.0004). However, there was no statistically significant difference in mean DBP values between the two groups (Table I).

With regard to the presence of chronic diabetes complications, DFU group showed a significant higher frequency of microvascular complications compared to the non-DFU group, namely: diabetic retinopathy (61.5% *vs.* 27%; p<0.0001), DPN (73% *vs.* 25.4%; p<0.0001), and diabetic nephropathy (45.2% *vs.* 31.2%; p=0.006). Participants belonging to the DFU group were more frequently treated with metformin monotherapy than participants in the non-DFU group (55.8% *vs.* 17.7%; p<0.0001). Metformin dose ranged from 500 mg/day to 2000 mg/day. Conversely, DFU group included a significantly lower proportion of participants on insulin therapy alone (basal-bolus insulin therapy) compared to the non-DFU group (28.9% *vs.* 60.3%; p<0.0001). Moreover, non-DFU group showed a more frequent use of combined metformin and insulin therapy compared to the DFU group (22% *vs.* 15.4%), although this difference was not statistically significant (Table I).

We performed ROC curve analysis to further explore the applicability of different biochemical parameters as potential predictive biomarkers for DFU. ROC curve analysis showed that FPG (AUC=0.83; Figure 1, panel A), HbA1c (AUC=0.75; Figure 1, panel B), TG (AUC=0.78; Figure 1, panel D) and HDL-cholesterol (AUC=0.82; Figure 1, panel F) were the most reliable biomarkers able to detect DFU. Table II shows ROC curve characteristics, including sensitivity and specificity for all biochemical biomarkers that were analysed.

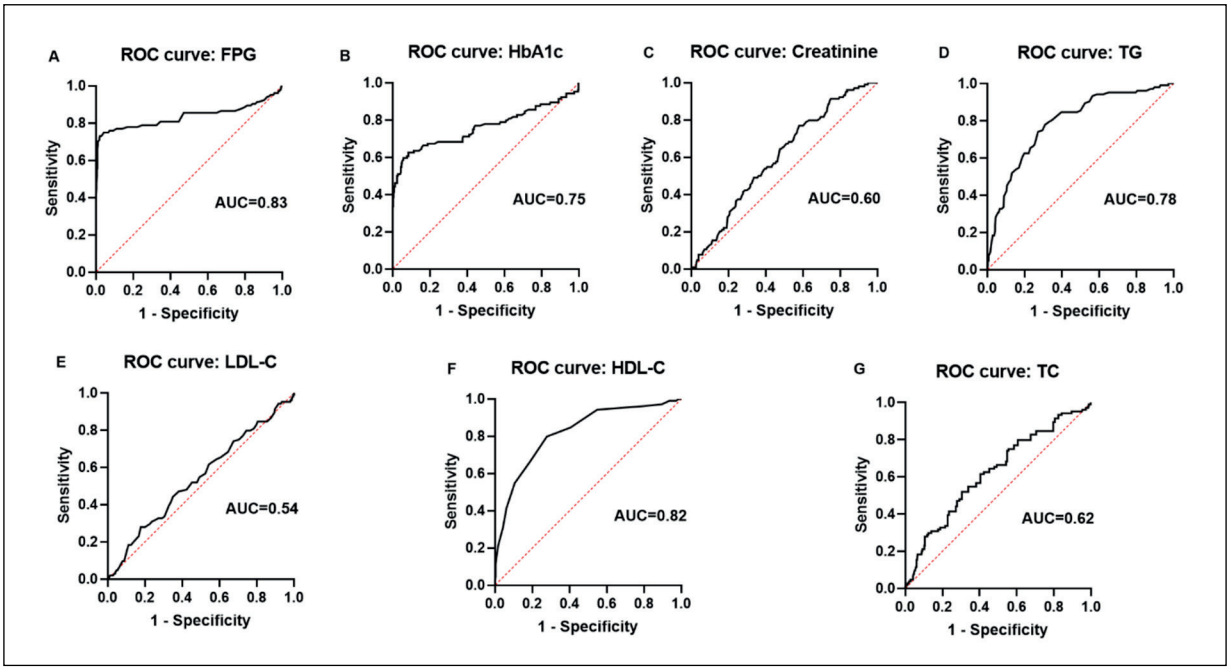


Figure 1. Receiver-operating characteristic (ROC) curve analysis performed for different biochemical parameters (FPG, HbA1c, creatinine, TG, LDL-C, HDL-C, TC) in relation to the clinical outcomes "DFU" vs. "non-DFU". Abbreviations: AUC, area under the curve; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; TC, total cholesterol; TG, triglycerides.

According to the Wagner Diabetic Foot Ulcer Grade Classification System, in the DFU group only 17 patients (16.4%) had a grade 1 ulcer, whereas 67 patients (64.4%) had a grade 2 ulcer, and 20 patients (19.2%) had a grade 3 ulcer (Table III). With regard to the ulcer surface area (expressed in cm^2), 73 patients (70.2%) had an ulcer surface area ≤4 cm^2, whereas 31 patients (29.8%) had an ulcer surface area >4 cm^2 (Table III). All patients in the DFU group

Table II. Receiver-operating characteristic (ROC) curve analysis characteristics, including sensitivity and specificity for all the analysed variables.

Biochemical biomarker	Cut-off	Sensitivity	Specificity	AUC	*p*-value
FPG (mg/dl)	> 194.5	0.78 (95% CI: 0.70; 0.85)	0.77 (95% CI: 0.73; 0.81)	0.83 (95% CI: 0.77; 0.89)	**< 0.0001**
HbA1c (%)	> 8.2	0.70 (95% CI: 0.60; 0.78)	0.62 (95% CI: 0.57; 0.67)	0.75 (95% CI: 0.69; 0.82)	**< 0.0001**
Creatinine (mg/dl)	> 1.2	0.57 (95% CI: 0.48; 0.66)	0.54 (95% CI: 0.48; 0.58)	0.60 (95% CI: 0.54; 0.66)	**0.001**
TG (mg/dl)	< 108.5	0.74 (95% CI: 0.65; 0.82)	0.72 (95% CI: 0.68; 0.76)	0.78 (95% CI: 0.73; 0.83)	**< 0.0001**
LDL-C (mg/dl)	< 108.5	0.51 (95% CI: 0.42; 0.61)	0.54 (95% CI: 0.49; 0.59)	0.54 (95% CI: 0.47; 0.60)	0.18
HDL-C (mg/dl)	< 43.5	0.79 (95% CI: 0.71; 0.86)	0.72 (95% CI: 0.67; 0.76)	0.82 (95% CI: 0.77; 0.86)	**< 0.0001**
TC (mg/dl)	< 174.8	0.61 (95% CI: 0.51; 0.70)	0.59 (95% CI: 0.54; 0.64)	0.62 (95% CI: 0.58; 0.60)	**0.0001**

A *p*-value < 0.05 was considered statistically significant. *Abbreviations:* 95% CI, 95% confidence interval; AUC, area under the curve; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; TC, total cholesterol; TG, triglycerides.

Table III. Clinical characteristics of diabetic foot ulcers in the DFU group (cases).

Ulcer grade (Wagner Diabetic Foot Ulcer Grade Classification System)	
Grade 1	17 (16.4%)
Grade 2	67 (64.4%)
Grade 3	20 (19.2%)
Ulcer surface area (cm^2)	
≤ 4 cm^2	73 (70.2%)
> 4 cm^2	31 (29.8%)
DFU complications	
Superficial infection	17 (16.4%)
Subcutaneous infection	67 (64.4%)
Osteomyelitis	20 (19.2%)
Major LEAs	0 (0%)
Minor LEAs	39 (37.5%)

Data are expressed as absolute numbers (with accompanying percentages shown in brackets). *Abbreviations:* LEAs, lower-extremity amputations.

exhibited clinical signs of DFU infection: 17 patients (16.4%) had a superficial infection, 67 patients (64.4%) had a subcutaneous infection, and the remaining 20 patients (19.2%) had osteomyelitis. None of the patients had previously underwent major LEAs, whereas 39 patients (37.5%) had previously underwent minor LEAs (Table III).

Table IV shows the univariate and multivariate analyses of different independent variables associated with DFU. In the multivariate analysis, the most relevant independent variables associated with DFU were BMI [OR=0.62; p=0.007], HDL-cholesterol [OR=0.00; p<0.0001], TG [OR=7.48; p=0.0004], cigarette smoking [OR=26.46; p=0.005], duration of diabetes [OR=1.53; p<0.0001], FPG [OR=1.06; p<0.0001], SBP [OR=1.13; p=0.0004], insulin therapy alone [OR=0.11; p=0.02] (Table IV). The combination of these independent variables reached a 99% concordance rate in predicting DFU.

A multivariate analysis was also performed in the DFU group to identify the best predictors for minor LEAs and DPN (Table V). The most relevant independent variables associated with minor LEAs were represented by age <55 years [OR=0.12; p=0.05], HbA1c [OR=1.47; p=0.03] and

Table IV. Univariate and multivariate analyses of different independent variables associated with diabetic foot ulcer (DFU).

	Univariate analysis			Multivariate analysis		
Independent variable	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Age (years)	1.01	0.99-1.32	0.31	-	-	-
Female sex	1.14	0.73-1.80	0.54	-	-	-
BMI (Kg/m^2)	1.08	1.01-1.37	**0.002**	0.62	0.47-0.83	**0.007**
Duration of diabetes (years)	0.92	0.95-1.01	0.28	1.53	1.25-1.86	**< 0.0001**
FPG (mg/dl)	1.06	1.04-1.07	**0.0001**	1.06	1.03-1.08	**< 0.0001**
Hb1Ac (%)	2.41	1.96-2.95	**< 0.0001**	-	-	-
Creatinine (mg/dl)	2.10	1.32-3.34	**0.001**	-	-	-
TG (mg/dl)	1.06	1.04-1.08	**< 0.0001**	7.48	2.47-22.45	**0.0004**
LDL-C (mg/dl)	1.00	0.99-1.01	0.28	-	-	-
HDL-C (mg/dl)	0.65	0.59-0.71	**< 0.0001**	0.00	0.00-0.001	**< 0.0001**
TC (mg/dl)	0.98	0.97-0.99	**0.003**	-	-	-
Hypertension (%)	2.50	1.60-3.89	**< 0.0001**	-	-	-
SBP (mmHg)	1.03	1.01-1.04	**0.0005**	1.13	1.05-1.21	**0.0004**
DBP (mmHg)	0.99	0.97-1.01	0.37	-	-	-
Cigarette smoking	6.19	3.28-11.69	**< 0.0001**	26.46	2.66-263.0	**0.005**
Diabetic retinopathy	4.32	2.75-6.87	**< 0.0001**	-	-	-
DPN	7.97	4.87-13.0	**< 0.0001**	-	-	-
Diabetic nephropathy	1.82	1.16-2.83	**0.008**	-	-	-
Insulin therapy alone*	0.15	0.09-0.25	**< 0.0001**	0.11	0.01-0.78	**0.02**
Metformin therapy alone	4.17	2.58-6.74	**< 0.0001**	-	-	-
Combined metformin and insulin therapy	1.54	0.88-2.86	0.14	-	-	-

A p-value < 0.05 was considered as statistically significant. *Abbreviations:* 95% CI, 95% confidence interval; BMI, body mass index; DBP, diastolic blood pressure; DPN, diabetic peripheral neuropathy; F: female, FPG, fasting plasma glucose; Hb1Ac, glycated haemoglobin; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides. The symbol "-" Refers to variables excluded from the final model by the calculation algorithm. *Basal-bolus insulin therapy.

Table V. Multivariate analysis of different independent variables associated with minor LEAs and DPN in the diabetic foot ulcer (DFU) group

Independent variable	Minor LEAs			DPN		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Age (< 55 years)	0.12	0.01-0.87	**0.05**	1.05	0.81-1.57	0.87
Female sex	4.18	1.20-16.44	**0.03**	0.87	0.21-3.62	0.85
BMI (Kg/m^2)	1.00	0.87-1.16	0.93	1.20	1.03-1.45	**0.03**
Lack of cigarette smoking habit	0.74	0.04-10.72	0.82	0.07	0.00-0.50	**0.01**
FPG (mg/dl)	1.00	0.99-1.01	0.89	1.02	0.99-1.03	0.08
HbA1c (%)	1.47	1.07-2.16	**0.03**	1.70	1.20-2.60	**0.006**
SBP (mmHg)	1.02	0.96-1.09	0.43	1.08	1.00-1.18	**0.05**
DBP (mmHg)	1.09	0.99-1.21	0.06	1.04	0.96-1.14	0.34
Creatinine(mg/dl)	0.55	0.10-2.67	0.46	0.34	0.06-1.80	0.21
TG (mg/dl)	2.45	0.44-15.18	0.31	0.42	0.05-3.11	0.40
LDL-C (mg/dl)	1.80	0.41-8.35	0.43	2.47	0.42-16.86	0.33
HDL-C (mg/dl)	2.21	0.24-22.66	0.48	0.48	0.04-4.70	0.53

A *p*-value < 0.05 was considered statistically significant. Abbreviations: 95% CI, 95% confidence interval; BMI, body mass index; DBP, diastolic blood pressure; DPN, diabetic peripheral neuropathy; FPG, fasting plasma glucose; F, female; Hb1Ac, glycated hemoglobin; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; LEAs, lower-extremity amputations; SBP, systolic blood pressure; TG, triglycerides. Total cholesterol was excluded from the final model by the calculation algorithm.

female sex [OR=4.18; *p*=0.03]. On the other hand, the most relevant independent variables associated with DPN were HbA1c [OR=1.70; *p*=0.006], SBP [OR=1.08; *p*=0.05], BMI [OR=1.20; *p*=0.03] and lack of cigarette smoking [OR=0.07; *p*=0.01], (Table V).

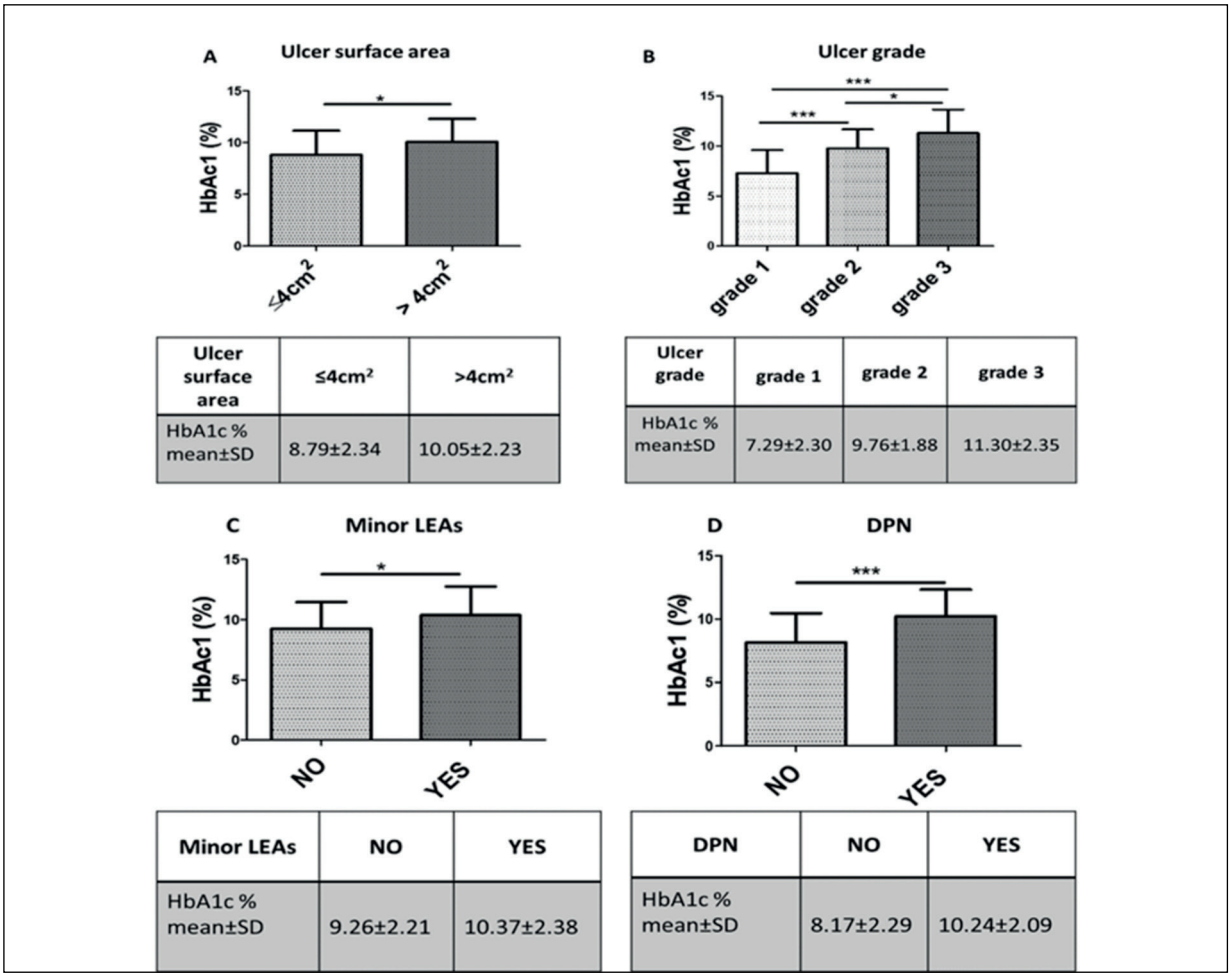
Furthermore, we performed a correlation analysis through the nonparametric Spearman's rank correlation test or through the parametric Pearson test, as appropriate, to evaluate the correlation of HbA1c (expressed as percentage) with clinical and biochemical variables in the DFU group. We found a significant positive correlation between HbA1c and FPG (r=0.58; *p*<0.0001), ulcer surface area (r=0.50; *p*<0.0001), ulcer grade (r=0.23; *p*=0.02), minor LEAs (r=0.20; *p*=0.04), DPN (r=0.41; *p*<0.0001), and metformin therapy alone (r=0.72; *p*<0.0001). There was a significant inverse correlation between HbA1c and insulin therapy alone (r=-0.31; *p*=0.01) and combined metformin and insulin therapy (r=-0.60; *p*<0.0001) (Table VI). Conversely, no significant correlation was found between HbA1c and TG, LDL-cholesterol, HDL-cholesterol, TC, creatinine, hypertension, diabetic retinopathy, diabetic nephropathy, SBP and DBP (Table VI).

Figure 2 shows mean HbA1c values (%) in different subgroups of patients with DFU stratified based on ulcer surface area, ulcer grade, minor LEAs and DPN. Mean HbA1c values were >7% in all subgroups. Mean HbA1c values were significantly higher in patients with an ulcer surface

Table VI. Correlation analysis between HbA1c (expressed as percentage) and clinical and biochemical variables in patients with diabetic foot ulcer (DFU).

Independent variable	Correlation coefficient	*p*-value
FPG (mg/dl)	0.58	**< 0.0001**
TG (mg/dl)	0.09	0.32
LDL-C (mg/dl)	0.10	0.30
HDL-C (mg/dl)	0.10	0.30
TC (mg/dl)	0.10	0.30
Creatinine (mg/dl)	0.08	0.35
Hypertension#	0.15	0.13
SBP (mmHg)	0.08	0.41
DBP (mmHg)	-0.09	0.35
Ulcer surface area (cm^2)#	0.50	**< 0.0001**
Ulcer grade#	0.23	**0.02**
Minor LEAs#	0.20	**0.04**
Diabetic retinopathy#	0.12	0.23
DPN#	0.41	**< 0.0001**
Diabetic nephropathy#	0.13	0.18
Insulin therapy alone#*	-0.31	**0.01**
Metformin therapy alone#	0.72	**< 0.0001**
Combined metformin and insulin therapy#	-0.60	**< 0.0001**

Multiple correlation analysis was performed through the nonparametric Spearman's rank correlation test (variables indicated by the symbol#) or through the parametric Pearson test, as appropriate. A *p*-value < 0.05 was considered statistically significant. Ulcer grade was defined according to the Wagner Diabetic Foot Ulcer Grade Classification System. Abbreviations: DBP, diastolic blood pressure; DPN, diabetic peripheral neuropathy; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; LEAs, lower-extremity amputations; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides. *Basal-bolus insulin therapy.



Ulcer surface area	≤4cm²	>4cm²
HbA1c % mean±SD	8.79±2.34	10.05±2.23

Ulcer grade	grade 1	grade 2	grade 3
HbA1c % mean±SD	7.29±2.30	9.76±1.88	11.30±2.35

Minor LEAs	NO	YES
HbA1c % mean±SD	9.26±2.21	10.37±2.38

DPN	NO	YES
HbA1c % mean±SD	8.17±2.29	10.24±2.09

Figure 2. Mean HbA1c values (%) (histogram and related data) in different subgroups of patients with DFU stratified based on ulcer surface area (panel **A**), ulcer grade (panel **B**), history of minor LEAs (panel **C**) and presence of DPN (panel **D**). Ulcer grade was defined according to the Wagner Diabetic Foot Ulcer Grade Classification System. Unpaired *t*-test was used in panels **A, C,** and **D,** whereas one-way analysis of variance (one-way ANOVA) was used in panel B. Abbreviations: DPN, diabetic peripheral neuropathy; HbA1c, glycated hemoglobin; LEAs, lower-extremity amputations; SD, standard deviation. Panel A: **p*=0.01; Panel B: ****p*<0.0001 and **p*<0.05; Panel C: **p*=0.017; Panel D; ****p*<0.0001. NO: no history of minor LEAs or absence of DPN; YES: history of minor LEAs or presence of DPN.

area >4 cm^2 (10.05±2.23%) compared to patients with an ulcer surface area ≤4 cm^2 (8.79±2.34%) (p=0.01; Figure 2, panel A). Mean HbA1c values were also significantly higher in patients with a grade 3 ulcer (11.30±2.35%) compared to patients with a grade 1 ulcer (7.29±2.30%) (p<0.0001) or with a grade 2 ulcer (9.76±1.88%) (p<0.05) (Figure 2, panel B). Mean HbA1c values were also significantly higher in patients with previous minor LEAs compared to those with no history of minor LEAs (10.37± 2.38% *vs.* 9.26±2.21%) (p=0.017; Figure 2, panel C), as well as in patients with DPN compared to those without DPN (10.24±2.09% *vs.* 8.17±2.29%) (p<0.0001; Figure 2, panel D).

Discussion

We found that Albanian T2D patients with DFU, as compared to T2D controls without DFU, exhibited significantly higher mean BMI and SBP values (associated with a higher frequency of hypertension) and lower mean HDL-cholesterol levels. DFU group also included a higher proportion of smokers, and patients with DFUs showed worse glucose control (as evidenced by FPG and HbA1c values) compared to patients without DFUs. Of note, the present study reported a significant association between specific cardiometabolic risk factors (low HDL-cholesterol

levels, elevated TG levels, poor glucose control, elevated SBP values, and cigarette smoking) and increased risk of developing DFUs in an Albanian adult population with T2D. These data are of particular interest, as they highlight the main risk factors that could be targeted to prevent the major diabetes complications (including DFUs) in developing countries.

In line with the abovementioned remarks, the present data are in agreement with those from previous studies conducted in other developing countries such as Pakistan, Iran and India, where subjects with DFUs showed significantly higher FPG and HbA1c values (indicative of uncontrolled diabetes), along with significantly greater BMI values and lower HDL-cholesterol levels[28-30]. This evidence is reinforced by the significant association between higher BMI values and risk of DFU found in similar previous analyses[31,32]. Indeed, the correlation between overweight/obesity and altered wound healing has long been established. This correlation appears to be the consequence of several factors, such as inherent anatomic features of adipose tissue, vascular insufficiencies, nutritional deficiencies, dysregulation of collagen turnover, increase in oxidative stress, and alterations in immune mediators and growth factors[33,34]. However, it is interesting to note that multivariate analysis performed in our study showed an inverse significant association between BMI and DFU. The apparent protective effects of higher BMI against DFU development (OR=0.62; p=0.007) could be explained by the so-called "obesity paradox". This phenomenon may be due to the fact that patients with higher BMI values are more likely to receive optimal medications for several clinical conditions, including hypertension, dyslipidemia and T2D. Also, these patients may be more likely to exhibit a good nutritional status, which potentially results in a lower risk of DFU and DFU-related LEAs[35]. Nevertheless, BMI was significantly and positively associated with the presence of DPN in patients with DFUs (OR=1.20; p=0.03). Therefore, the investigation of the exact role of BMI in the development of DFU, DPN and other diabetes-related complications in Albanian T2D population is warranted in future prospective studies.

In our study, lower HDL-cholesterol levels were one of the most significant factors that we found significantly associated with the risk of DFU. This was confirmed by our multivariate analysis, in which HDL-cholesterol appeared to be a protective factor against the DFU development (OR=0.00; p<0.0001). Intriguingly, a longitudinal cohort study conducted on 163 Japanese ambulatory patients with DFU already showed similar findings. This study reported that lower HDL-cholesterol levels were significantly associated with an increased incidence of the primary composite endpoint, which was defined as the worst of the following outcomes for each individual: minor LEA, major LEA, and wound-related death[36]. The exact mechanisms underlying the protective role of HDL-cholesterol against DFU development and progression are still not clearly understood. It has been suggested that such protective role may involve the antiatherogenic and immunomodulatory properties exerted by HDL-cholesterol, resulting in attenuated endothelial adhesion molecule expression, endothelial nitric oxide synthase activation, antioxidant activities, and inhibition of macrophage activation by lipoteichoic acid[37,38].

Additionally, it is not surprising that our multivariate analysis showed a significant positive association between cigarette smoking and presence of DFU (OR=26.46; p=0.005). Cigarette smoking has already been associated with DFU and it is likely to contribute to the development of this diabetes complication[39]. Indeed, cigarette smoking represents a major source of free radicals and oxidative stress in many organs (including nervous system and blood vessels), resulting in cellular damage and apoptosis. Thus, cigarette smoking can contribute to the development or progression of diabetic microangiopathy (including diabetic neuropathy) and to altered wound healing by promoting vascular oxidative stress via increased production of reactive oxygen species (ROS) and inflammatory mediators, augmented lipid peroxidation and decreased antioxidant defenses[39]. In addition, cigarette smoking is a well-established risk factor for atherosclerosis and related cardiovascular mortality[40-42], and it has also been reported as an independent risk factor for diabetic neuropathy[43]. In our study, lack of cigarette smoking habit also represented a protective factor against the development of DPN (OR=0.07; p=0.01), which may partly explain the increased risk of DFU associated with cigarette smoking habit.

Accordingly, the present study also showed that patients with DFU had a significantly higher frequency of microvascular complications of diabetes (diabetic retinopathy, DPN, and diabetic nephropathy) compared to patients without DFU, although there was no significant difference in

the duration of diabetes between the two groups. Besides DPN, which is a well-established contributor to DFU[44], visual impairment due to diabetic retinopathy has also been reported as one of the main risk factors for DFU development, since microvascular alterations are involved in the pathophysiology of both these complications[45,46].

The main explanation for the increased frequency of microvascular diabetes complications observed in patients with DFUs is likely related to poor glucose control and low adherence to antidiabetic therapy in such population. Accordingly, our study showed that patients with DFU had significantly greater FPG and HbA1c values compared to those without DFU. Of note, in DFU group HbA1c values were markedly elevated (≥10%) particularly in patients with a grade 3 ulcer and an ulcer surface area ≥4 cm^2, as well as in patients with history of minor LEAs and in patients affected by DPN. Our correlation analysis also showed that HbA1c values were significantly and positively associated with ulcer grade and ulcer surface area, minor LEAs, and presence of DPN. Moreover, multivariate analysis showed that HbA1c was significantly and positively associated with history of minor LEAs (OR=1.47; p=0.03) and with presence of DPN (OR=1.70; p=0.006) in patients with DFUs. Although previous studies already reported a trend towards a positive correlation between HbA1c values and the onset of DFU, such studies presented various limitations, including the small sample size[47], the ethnic heterogeneity of the study participants as well as some methodological limitations (e.g., amputation rate[48,49] or total time to complete healing[47,49]).

In line with the hypothesis of the lower adherence to antidiabetic therapy in DFU group, a significantly lower proportion of patients with DFU were on insulin therapy compared to patients without DFU (28.9% *vs*. 60.3%, respectively; p<0.0001). Conversely, a significantly higher proportion of patients with DFU (and related microvascular diabetes complications) were on metformin monotherapy compared to subjects without DFU (55.8% *vs.* 17.7%, respectively; p<0.0001).

Multivariate analysis also showed that other cardiometabolic factors were significantly and positively associated with DFU, namely: TG (OR=7.48; p=0.0004), SBP (OR=1.13; p=0.0004), FPG (OR=1.06; p<0.0001). ROC curve analysis confirmed that FPG, HbA1c, TG and HDL-cholesterol were the most reliable biomarkers able to detect DFU. Moreover, multivariate analysis revealed that duration of diabetes was another variable significantly and positively associated with DFU (OR=1.53; p<0.0001), suggesting that a longer history of poor glucose control is associated with an increased risk of DFU.

These results seem to indicate that poor adherence to antidiabetic therapy, clinical inertia and inadequate management of diabetes and cardiometabolic risk factors may also have contributed to the worse glucose control and to the development of DFU and microvascular diabetes complications in such patients. In this regard, it is very interesting to note that, in multivariate analysis, insulin therapy alone (basal-bolus insulin therapy) was significantly associated with a reduced DFU risk (OR=0.11; p=0.02). Indeed, correlation analysis revealed a significant inverse association between HbA1c and insulin therapy (alone or in combination with metformin), along with a significant positive association between HbA1c and metformin therapy alone (Table VI). These findings may be explained by the more intensive glucose control achieved with insulin therapy, which may result in a reduced incidence of DFU. This aspect is highly relevant in middle-income and low-income developing countries, particularly in light of the low availability and affordability of newer antidiabetic agents (such as sodium-glucose cotransporter 2 inhibitors and glucagon-like peptide 1 receptor agonists), which are relatively expensive despite conferring significant cardiorenal protection in patients with T2D at high risk of adverse cardiorenal events[50,51]. Interestingly, treatment with the glucagon-like peptide 1 receptor agonist liraglutide in T2D patients at high risk of cardiovascular events enrolled in the LEADER trial did not increase the risk of DFU events and was also associated with a significantly lower risk of DFU-related amputations compared to placebo[52].

In addition, it is worth noting that a previous Albanian study examined 7,259 medical records of adults with previously diagnosed diabetes and reported that only 5.5% of the patients attained the recommended target levels for HbA1c, blood pressure and lipid profile[20]. Similar findings have been reported in our study, where both DFU and non-DFU groups exhibited suboptimal mean LDL-cholesterol levels (>100 mg/dl) and mean HbA1c values >7.5%. These findings indicate a high frequency of inadequate glucose control and poor management of cardiometabolic risk factors in Albanian adult inpatients with T2D, as

a likely consequence of different factors such as poor adherence to antidiabetic therapy, clinical inertia and low availability and affordability of newer antidiabetic agents. Moreover, these data are in line with the fact that fewer than one in ten people with diabetes in low-income and middle-income countries receive coverage of guideline-based comprehensive diabetes treatment[53]. We acknowledge that the present study has different limitations. First, the retrospective design of the study limits the clinical interpretation of our results. Second, we could not retrieve information on macrovascular diabetes complications and ankle-brachial index values. In addition, we could not obtain information on the time of onset of DFU and microvascular diabetes complications. The latter limitation, together with the lack of information on macrovascular diabetes complications and ankle-brachial index values, prevented us from defining a causal relationship between microvascular complications and the development of DFU as well as a possible mixed etiology (micro- and macrovascular) of DFUs.

Conclusions

In the present study we showed that longer duration of diabetes, cigarette smoking, lower HDL-cholesterol levels, poor glucose control, and elevated TG and SBP values may all represent major risk factors for the development of DFU in Albanian adult patients with T2D. As expected, poor glucose control (defined by elevated HbA1c values) was significantly and positively associated with history of minor LEAs and with presence of DPN in patients with DFUs. By contrast, BMI values and insulin therapy alone were significantly and negatively associated with DFU. Our study also suggested that crucial factors contributing to the burden of uncontrolled T2D and related diabetes complications (including DFUs) in Albania may include poor adherence to antidiabetic therapy and clinical inertia. Therefore, community interventions and health policies aimed to improve the management of diabetes and related cardiometabolic risk factors should urgently be implemented, in order to prevent DFU and other diabetes complications, particularly in developing countries[54]. In this regard, proper healthcare diabetes interventions should aim to increase the capacity of health systems to deliver treatments not only to lower glucose values but also to address cardiovascular disease risk factors, such as atherogenic dyslipidemia and hypertension[53]. With regard to DFU, diabetic patients should be educated on a proper knowledge of modifiable risk factors for DFU development (e.g., poor glucose control), as well as on the importance of periodic foot care, which includes foot self-inspection, foot temperature monitoring, proper daily foot hygiene, use of appropriate footwear, as well as rapid recognition and optimal management of newly identified foot lesions. Sophisticated technological devices, such as continuous temperature-monitoring socks[55], may also be useful for preventing DFUs or promoting DFU healing, particularly in patients with uncontrolled T2D and/or DPN and recurrent DFUs. Continuous glucose monitoring through subcutaneous sensors may certainly be an effective means to help diabetic patients to achieve a better glucose control and concurrently prevent chronic diabetes complications (including DFU). All these strategies may have a tremendous impact in terms of reduction of diabetes- and DFU-related hospitalization, morbidity and mortality, especially at the time of coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), since it has been clearly established that diabetic patients are at increased risk for adverse outcomes following SARS-CoV-2 infection[56]. In view of the above, large and long-term prospective longitudinal studies are warranted to better establish which are the major risk factors for the development of DFUs in Albanian adults with T2D.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Data Availability Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Ethics Approval

This research study was conducted retrospectively from data obtained for research purposes. The study was approved by the local Ethics Committee (Catholic University Our Lady of Good Counsel, Tirana, Albania; registration number: M-FP3:125/17; 2017) and was conducted in accordance with the ethical standards of the institutional and national Research Committees and with the Declaration of Helsinki (as revised in 2013). At the time of hospital admission, all participants and/or their legal guardians provided written informed consent to anonymous data collection, analysis and publication for research purposes.

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