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Cardiovascular risk profile and morbidity in subjects affected by type 2 diabetes mellitus with and without diabetic foot

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Abstract

Diabetic foot syndrome (DFS) is the most frequent cause of hospitalization of diabetic patients and one of the most economically demanding complications of diabetes. People with diabetes have been shown to have higher mortality than people without diabetes. On this basis, the aim of our study was to evaluate the possible role of diabetic foot as a cardiovascular risk marker in patients with type 2 diabetes mellitus. We enrolled 102 consecutive patients with type 2 diabetes mellitus with diabetic foot and 123 patients with type 2 diabetes mellitus without limb lesions to compare the prevalence of main cardiovascular risk factors, subclinical cardiovascular disease, previous cardiovascular morbidity, and incidence of new vascular events on a 5-year follow-up. Diabetic patients with diabetic foot were more likely to have a higher prevalence of cardiovascular risk factors such as hypercholesterolemia, hypertriglyceridemia, hyperuricemia, and microalbuminuria or proteinuria, a higher prevalence of a previous cardiovascular morbidity (coronary artery disease, transient ischemic attack/ischemic stroke, diabetic retinopathy), and a higher prevalence of subclinical cardiovascular disease. Furthermore, diabetic patients with foot ulceration showed, on a 5-year follow-up, a higher incidence of new-onset vascular events (coronary artery disease, transient ischemic attack/ischemic stroke, diabetic retinopathy). At multivariate analysis, duration of diabetes, age, hemoglobin A_{1c}, and DFS maintained a significant association with cardiovascular morbidity; but DFS presence showed the highest hazard ratio.

1. Introduction

Diabetic foot syndrome (DFS) is defined, according to the World health Organization, as "ulceration of the foot (distally from the ankle and including the ankle) associated with neuropathy and different grades of ischemia and infection" [1]. Diabetic foot syndrome is a major complication of diabetes and consumes most of the resources allocated for the treatment of diabetes [2]. It is estimated that foot ulceration may occur in up to 15% of diabetic patients during their lifetime [3].

Several studies have indicated that mortality and morbidity rates of cardiovascular diseases (CVDs) are 2 to 4 times higher among patients with type 2 diabetes mellitus than in nondiabetic subjects [4]. Boyko et al [5] affirmed that foot ulcer and lower extremity vascular disease are related to a higher risk of death in diabetic subjects, but the reasons for this higher mortality require further investigation.

Diabetic foot represents an important cause of morbidity in diabetic patients [6], and the mortality rate is approximately twice that of patients without foot ulcerations [7-9].

Despite the magnitude of the problem of diabetic foot ulcer and its consequences, little research has been performed to investigate the epidemiologic and the prognostic pattern of the subjects with type 2 diabetes mellitus complicated with diabetic foot compared with diabetic patients without foot ulcerations. We hypothesize that patients with type 2 diabetes mellitus with diabetic foot could have a worse prognosis in terms of faster progression of cardiovascular damage and higher cardiovascular morbidity. On this basis, our study was designed with the aim of assessing the following in subjects with type 2 diabetes mellitus with and without diabetic foot: (1) cardiovascular risk factor distribution, (2) prevalence of cardiovascular

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morbidity on a retrospective evaluation, (3) prevalence of markers of subclinical cardiovascular damage at the time of recruitment, and (4) incidence of new-onset cardiovascular events on a prospective evaluation.

2. Subjects, materials, and methods

Between 1995 and 2002, subjects with type 2 diabetes mellitus and foot ulceration hospitalized for every condition related to diabetic disease (decompensated diabetes, hypoglycemia, clinical revaluation for foot ulceration), but not for new vascular events, at the Internal and Specialist Medicine Department of the *Policlinico P. Giaccone* Hospital of Palermo were recruited. All the patients enrolled underwent a 5-year follow-up and were monitored after discharge until April 2006. We also recruited patients with type 2 diabetes mellitus without foot ulceration admitted to our department for other causes between 1995 and 2001. The study was carried out in accordance with the principles of the Declaration of Helsinki as revised in 2001.

All the enrolled subjects were divided into 2 groups in relation to the presence/absence of foot ulcerations at the time of recruitment; and in both groups, we evaluated the following end points:

- Prevalence of main well-established cardiovascular risk factors.
- Prevalence, on a retrospective evaluation, of previous coronary artery disease (CAD), transient ischemic attack (TIA), ischemic stroke, peripheral artery disease (PAD), diabetic retinopathy, and renal failure.
- Prevalence, at the time of recruitment, of subclinical cardiovascular disease (CVD) (major electrocardiographic [ECG] abnormalities, echocardiographic abnormalities [left ventricular hypertrophy (LVH) and/or abnormal regional wall motion], abnormal intima-media thickness [IMT] [carotid IMT >1 mm], and/or carotid plaque on carotid echo-color Doppler evaluation).
- Incidence, on a 5-year follow-up, of newly diagnosed CAD, TIA, stroke, diabetic retinopathy, and renal failure.

Foot ulcer was defined as a full-thickness skin defect that required >14 days to heal [1]. A physical examination with emphasis on the lower limbs was performed by research operators, who assessed the presence of the following characteristics: hammer/claw toe, Charcot deformity, hallux limitus, prominent metatarsal heads, hallux valgus, bony prominences, and ankle and halluxobility measured with a goniometry. Type 2 diabetes mellitus was determined using a clinically based algorithm that considered age at onset, presenting weight and symptoms, family history, onset of insulin treatment, and history of ketoacidosis.

Hypertension was defined according to the 1993 World Health Organization criteria (systolic blood pressure >140 mm Hg and/or diastolic blood pressure >90 mm Hg in subjects who are not taking antihypertensive medication or antihypertensive treatment yet present on admission) [10,11]. *Hypercholesterolemia* was defined as total serum cholesterol ≥200 mg/dL and *hypertriglyceridemia* as total serum triglyceride ≥150 mg/dL on the basis of the National Cholesterol Education Program–Adult Treatment Panel III reports [12,13] that define this cutoff for optimal total serum cholesterol and triglyceride levels.

All patients had blood pressure, serum glucose, creatinine, serum uric acid, serum cholesterol levels, serum triglyceride levels, and urinary albumin excretion (UAE) values measured on admission to the hospital.

The ankle-brachial index (ABI) was calculated as the ratio of the *ankle systolic pressure* (defined as the higher of the dorsalis pedis or posterior tibialis measurements) divided by the higher brachial systolic pressure. Subjects were classified as having PAD when they had an ABI <0.9 and/or when they had undergone a peripheral arterial bypass or amputation [14].

Coronary artery disease was determined on the basis of a history of physician-diagnosed angina, myocardial infarction, or any previous revascularization procedure assessed by a questionnaire.

Cerebrovascular disease (TIA/ischemic stroke) was assessed by history, specific neurologic examination executed by specialists, and hospital or radiological (brain computed tomography or brain magnetic resonance) records of definite TIA or stroke.

In case of defined ischemic stroke, both for cases and controls, the type of stroke was retrospectively assessed on the basis of clinical history and medical records, with particular attention to instrumental data (brain computed tomography, carotid ultrasound evaluation, and echocardiogram). We used the well-established Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification [15] that divides ischemic strokes into 5 subgroups: (1) large-artery atherosclerosis, (2) cardioembolic infarct, (3) lacunar infarct, (4) stroke of other determined etiology, or (5) stroke of undetermined etiology. Retrospective use of TOAST classification has been validated elsewhere, obtaining accurate and reproducible data [16].

Diabetic retinopathy was diagnosed by a fundus oculi examination in all subjects searching for microaneurysms, exudates, retinal hemorrhage, intraretinal microvascular abnormalities, venous beading, new vessels, pre-retinal or vitreous hemorrhage, fibrous tissue proliferation, or macular edema.

Normal albuminuria was considered to be present if UAE was consistently <20 μg/min. *Microalbuminuria* was defined as a mean UAE between 20 and 200 μg/min and *overt proteinuria* as a mean UAE 200 of μg/min. Renal failure was diagnosed if the patient had a serum creatinine ≥1.5 mg/dL.

Subclinical CVD, according to the literature [17,18], was defined as any of the following findings for recruited patients who did not have prevalent clinical disease at baseline: major ECG abnormalities, abnormal IMT or carotid plaques, or

echocardiographic abnormalities. Using a 3-channel Hewlett-Packard (Palo Alto, CA) device type 1516B, a 12-lead ECG lasting an average of 16 seconds was taken in supine position in accordance with classic recommendations. According to the criteria of the pooling project [19], major ECG abnormalities consist of ST-segment depression, T-wave inversion, complete or second-degree atrioventricular block, and complete left bundle-branch block. At baseline, all the patients enrolled underwent a B-mode ultrasonography of both carotid arteries with a 7.5-MHz linear array transducer (ESAOTE SPR 8000, BioMedica, Genova, Italy). In healthy adults, IMT ranges from 0.25 to 1.5 mm; and values >1.0 mm are often regarded as abnormal [17,20]. We defined *plaques* as focal widenings of the vessel wall of ≥50% relative to adjacent segments, with protrusion into the lumen, composed of calcified, noncalcified, and lipidic components (fibrocalcific and fibrolipidic). The left and right common carotid arteries were examined in the anterolateral direction with 3 consecutive measurements. The transducer was placed on the carotid bifurcation with the least possible pressure that did not compress the overlying jugular vein and allowed expansion of the carotid artery in all directions. Measurements were performed in the distal common carotid artery 2 cm proximal to the origin of the carotid bulb.

All subjects underwent routine mono- and 2-dimensional M-mode echocardiography (VINGMED LOGIC 5000, Hørten, Norway). The left ventricular (LV) wall was divided into 14 segments, and asynergy was assessed in each segment to evaluate regional LV wall motion abnormalities by 2-dimensional echocardiography. All measurements were made according to the American Society of Echocardiography guidelines. Three measurements were averaged for each value. The following echocardiographic variables were studied in the present investigation: left atrial dimensions, LV mass, LV wall thickness, LV end-diastolic and end-systolic internal dimensions, and LV wall motion. The LV mass was calculated thus: LV mass = $0.8[1.04(\text{LVIDD} + \text{IVST} + \text{PWT})^3 - (\text{LVIDD})^3] + 0.6$, where LVIDD represents LV end-diastolic internal dimension and IVST and PWT indicate the end-diastolic thicknesses of the interventricular septum and LV posterior wall, respectively. *Left ventricular hypertrophy* was defined as a value of LV mass indexed for height ≥51 g in both sexes [21].

All the enrolled subjects received better drug therapy for diabetes care and, for comorbidities, received adequate dietetic and foot care information. Every 6 months per year, an ambulatory follow-up (for 5 years) was planned (according to the International Working Group on the Diabetic Foot recommendations). During these visits, a complete clinical examination was made; and the new onset of cardiovascular morbidity (CAD, TIA/stroke, diabetic retinopathy, and renal failure) was also assessed. These events were ascertained on the basis of specific questionnaire and clinical documents.

Table 1
Main demographic, clinical, and laboratory characteristics of the study population

	Patients with type 2 diabetes mellitus with diabetic foot	Patients with type 2 diabetes mellitus without diabetic foot	*P*
n	102	123	
Sex: men-women (%)	57:45 (55.8:44.1)	67:56 (54.4:45.5)	NS
Age (y)	66.7 ± 9.8	66.9 ± 13	NS
Diabetes duration (y)	14 ± 8.8	13.9 ± 10.1	NS
Total cholesterolemia (mg/dL)	247.5 ± 20.1	232.6 ± 32.2	.001
LDL cholesterolemia	140 ± 10.8	128.6 ± 15.6	.005
HDL cholesterolemia (mg/dL)	39.6 ± 17.3	41.4 ± 19.9	NS
Triglyceridemia (mg/dL)	189.2 ± 59.7	172.8 ± 83.5	.001
Serum uric acid (mg/dL)	5.9 ± 1.6	5.2 ± 4.2	NS
BMI (kg/m^2)	31.7 ± 6.2	31.1 ± 5.5	NS
ABI	0.72 ± 0.20	0.89 ± 0.41	.05
HbA_{1c} >7 (%)	65 (44.1)	30 (24.3)	.001
Smoking (n/%)	30 (29.4)	37 (30.08)	NS
Comorbidity and medications			
PAD	68 (62.03)	49 (39.8)	.05
Hypertension (n/%)	61 (60.3)	75 (60.9)	NS
Cholesterol plasma levels >200 mg/dL (n/%)	41 (40)	33 (26.8)	.001
Triglyceride plasma levels >150 mg/dL	52 (50.9)	36 (38.2)	.001
LDL plasma levels >130 mg/dL	40 (36.9)	31 (25.2)	.001
Microalbuminuria/proteinuria (mg/dL) (n/%)	64 (62.7)	49 (39.8)	.001
Renal failure (n/%)	6 (5.8)	7 (5.6)	NS
Insulin therapy (n/%)	45 (44.11)	38 (30.89)	.05
Oral antidiabetic treatment	47 (46.07)	64 (52.03)	.05
Statin therapy (n/%)	59 (57.8)	41 (33)	.05
Antiplatelet therapy (n/%)	58 (56.8)	43 (34.9)	.05

Laboratory values are means ± SD. BMI indicates body mass index; HDL, high-density lipoprotein; NS, not significant.

3. Statistical analysis

Continuous variables were represented as mean ± standard deviation (SD). The Student *t* test for nonpaired data was used to compare the means. F test was used to control the variances, and Beherens-Welch test with Satterwaite approximation was applied in case of unequality. The χ^2 test was used to analyze the frequencies by contingence 2 by 2 tables. Yates correction was used if necessary. A *P* value less than .05 was considered statistically significant.

Hazard ratios for the composite end point of cardiovascular morbidity (previous, subclinical, and new-onset cardiovascular morbidity) were determined by univariate and multivariate Cox proportional hazards regression analyses with data presented as hazard ratio with 95% confidence interval. Initial univariate analyses identified demographic and clinical variables that independently predicted cardiovascular morbidity. Furthermore, DFS was entered as a clinical variable to verify its predictive role toward cardiovascular morbidity. Significant variables were entered into subsequent multivariate Cox regression with the variables included in the models using forward stepwise selection, with a probability value of .05 required for entry into the model. A probability value of .05 or less was considered significant.

4. Results

We recruited 102 patients with type 2 diabetes mellitus with diabetic foot (male, 57; female, 43; mean age, 66.7 ± 9.8 years) (group I) and 123 subjects with type 2 diabetes mellitus without diabetic foot (male, 67; female, 56; mean age, 66.9 ± 13 years) (group II) matched for age and sex, body mass index, and mean duration of diabetes (Table 1).

Prevalence of cardiovascular risk factors (Table 1) in the 2 groups was as follows: 61 (60.3%) patients with diabetic foot and 75 (60.9%) without foot lesions had hypertension (not significant); 41 (40%) vs 33 (26.8%) had hypercholesterolemia ($P < .05$); 41 (40%) vs 33 (26.8%) had low-density lipoprotein (LDL) plasma levels >130 mg/dL; 52 (50.9%) vs 36 (38.2%) had hypertriglyceridemia ($P < .05$); 43 (42.15%) vs 39 (31.7%) had a high serum level of uric acid ($P < .05$); and 64 (62.7%) vs 49 (39.8%) had microalbuminuria or proteinuria ($P < .0001$). Moreover, a higher percentage of patients in group I had a hemoglobin A_{1c} (HbA_{1c}) >7. Comorbidity and medications differences between the 2 groups are reported in Table 1. Nonsignificant difference between the 2 groups was observed with regard to duration of diabetes.

Concerning previous cardiovascular morbidity prevalence on a retrospective evaluation, diabetic patients with foot ulceration had a higher prevalence of previous CAD, TIA, ischemic stroke, PAD, and diabetic retinopathy compared with diabetic patients without foot ulceration,

Table 2
Prevalence of previous cardiovascular events in patients with and without diabetic foot

	Patients with diabetic foot (n = 102)	Patients without diabetic foot (n = 123)	*P*
CAD (%)	33 (32.3)	24 (19.5)	.0043
TIA (%)	15 (14.7)	9 (7.3)	<.0001
Stroke (%)	18 (17.6)	11 (8.9)	<.0001
Stroke TOAST subtypes			
LAAS	6 (33.3)	a (45.4)	.5
Lacunar	12 (66.6)	6 (54.5)	.5
CEI	0	0	
Diabetic retinopathy (%)	55 (53.9)	47 (38.2)	<.0001
Renal failure (%)	6 (5.8)	7 (5.6)	NS

LAAS indicates large-artery atherosclerotic stroke; CEI, cardioembolic stroke.

Table 3
Prevalence of instrumental markers of subclinical cardiovascular damage at the time of recruitment

	Patients with diabetic foot (n = 102)	Patients without diabetic foot (n = 123)	*P*
Carotid echo-color Doppler findings			
IMT >1 (n/%)	36 (35)	25 (20.3)	<.0001
Asymptomatic carotid plaque (n/%)	45 (44.1%)	31 (25.2)	<.0001
Echocardiographic findings			
LVH (n/%)	18 (17.6)	10 (8.1)	<.0001
Abnormal regional wall motion (n/%)	9 (8.8)	7 (5.6)	<.0001
ECG findings			
Major ECG abnormalities (n/%)	19 (18.6)	14 (11.3)	.05

Table 4
Incidence of new vascular events on a 5-year follow-up in diabetic patients with and without diabetic foot

	Patients with diabetic foot (n = 102)	Patients without diabetic foot (n = 123)	*P*
CAD (n/%)	12 (11.7)	7 (5.6)	<.005
Angina (n/%)	4 (3.9)	3 (2.4)	<.005
Myocardial infarction (n/%)	8 (7.8)	4 (3.5)	<.001
TIA (n/%)	6 (5.8)	4 (3.2)	<.0001
Stroke (n/%)	7 (6.8)	5 (4.0)	<.005
Renal failure (n/%)	4 (3.9)	5 (4)	NS
Deaths (n/%)	14 (13.7%)	10 (8.1%)	<.005
Cardiovascular cause (n/%)	13 (12.7)	9 (7.3)	NS
AMI (n/%)	4 (3.9)	1 (0.81)	
Stroke (n/%)	3 (2.9)	2 (1,6)	
CHF (n/%)	3 (2.9)	3 (2.4)	
Other vascular cause (n/%)	3 (2.9)	3 (2.4)	
Other cause (n/%)	1 (0.9)	1 (0,81)	

AMI indicates acute myocardial infarction; CHF, congestive heart failure.

Table 5
Cox regression analysis of demographic and clinical variables associated with cardiovascular morbidity

	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Age (y)	2.32 (1.78-5.19)	.041	1.60 (1.03-2.69)	.04
Diabetes duration (y)	7.26 (3.80-13.87)	<.001	5.76 (2.97-11.17)	<.001
Hypercholesterolemia	2.03 (1.56-3.64)	<.005	1.11 (1.01-1.76)	.345
LDL plasma levels >130 mg/dL	2.09 (1.59-3.44)	<.005	1.43 (1.31-1.90)	.345
Hypertriglyceridemia (mg/dL)	0.83 (0.40-0.98)	.64		
Hypertension	1.83 (1.50-2.22)	.04	1.13 (1.50-2.22)	.06
Serum uric acid (mg/dL)	0.79 (0.30-0.89)	.77		
HbA_{1c} >7 (%)	2.43 (1.20-4.92)	.014	1.54 (0.70-4.17)	.04
Smoking (%)	1.38 (1.01-1.88)	.044	0.96 (0.89-1.70)	.271
DFS presence	11.40 (5.76-22.59)	<.001	8.67 (4.28-17.56)	<.001
IMT >1	1.80 (1.43-2.27)	<.001	0.98 (0.21-2.03)	.357
LVH	1.48 (0.99-2.19)	.040	0.98 (0.68-3.16)	.423

Univariate analysis: hazard ratio and *P* value from Cox regression analysis. Multivariate analysis: hazard ratio and *P* value from Cox regression analysis, including age, LVH, IMT >1, diabetes duration, hypercholesterolemia, LDL plasma levels >130 mg/dL, smoking, HbA_{1c}. CI indicates confidence interval.

whereas no significant difference was observed in previous renal failure prevalence between the 2 groups (Table 2).

Regarding clinical subtypes of ischemic stroke, the prevalence of each TOAST subtype is reported in Table 3.

With regard to prevalence of subclinical CVD, patients with diabetic foot were more likely to have major ECG abnormalities, an IMT >0.9, a carotid plaque, LVH, and abnormal regional wall motion compared with patients without foot ulcerations (Table 3).

At the 5-year follow-up, patients with diabetic foot have a higher incidence of new-onset cardiovascular events (Table 4) compared with diabetic patients without limb lesions. Statistically significant differences were found in the incidence of new cases of diabetic retinopathy, but no difference in the incidence of new diagnosis of renal failure. During the 5-year follow-up, 14 (13.7%) deaths were recorded in patients with diabetic foot vs 10 (8.1%) ($P < .05$) in patients without diabetic foot; and most of these deaths in both groups were attributable to cardiovascular cause (Table 4).

To explore if DFS added significant incremental information about risk over and above the normal risk factors, which were not balanced, we evaluated univariate and multivariate Cox proportional hazard regression analyses. On univariate analysis, age, diabetes duration, hypercholesterolemia, LDL plasma levels >130 mg/dL, smoking, hypertension, HbA_{1c}, IMT >1, LVH, and DFS presence were significantly associated with the combined end point of cardiovascular morbidity, whereas on multivariate analysis, only age, duration of diabetes, HbA_{1c}, and DFS maintained a significant association with cardiovascular morbidity, but DFS presence showed the highest hazard ratio (8.67) (Table 5).

5. Discussion

Our study was designed to evaluate in subjects with type 2 diabetes mellitus with and without diabetic foot differences in the following: (1) cardiovascular risk factor profile, (2) cardiovascular morbidity prevalence by a retrospective evaluation, (3) prevalence of markers of subclinical cardiovascular damage at the time of recruitment, and (4) incidence of new-onset vascular events on a prospective analysis.

Our findings show a higher prevalence of major cardiovascular risk factors, of subclinical markers of CVD, and of previous and new-onset cardiovascular and cerebrovascular events in diabetic patients with foot complications.

These findings could explain previous reports of high morbidity and mortality rates in diabetic patients with amputations [22,23].

The main cause of death in patients with diabetes was CAD [23,24]. The risk factor pattern in people with diabetes is complex [25-27]. The basis for excess risk of CAD among diabetic patients has not been completely determined. First, there is a high prevalence of atherosclerosis among diabetic compared with nondiabetic individuals. Second, diabetic patients are at increased risk for thrombosis formation, decreased fibrinolysis, and enhanced inflammatory response [23,28]. Third, glycosylation of proteins may also affect arterial wall physiology and risk of disease [29]. Fourth, there is a high prevalence of subclinical atherosclerosis among older diabetic and nondiabetic individuals [30,31].

In our patients with diabetic foot, we reported a higher prevalence of measures of subclinical CVD such as major ECG abnormalities, echocardiographic abnormalities (LVH and/or abnormal regional wall motion), abnormal IMT, and/or carotid plaque on carotid echo-color Doppler evaluation; and it is well known that subclinical atherosclerosis represents a risk marker of clinical cardiovascular and cerebrovascular morbidity [30,31].

In our study, we also reported a higher prevalence of major cardiovascular risk factors such as hypercholesterolemia, LDL plasma levels >130 mg/dL, hypertriglyceridemia, and microalbuminuria/proteinuria in diabetic foot

patients compared with diabetic patients without foot complication; and this finding, probably, could strengthen the hypothesis that DFS in diabetic subjects could represent a possible marker of cardiovascular risk such as subclinical CVD, LVH, and PAD. Nevertheless, higher cholesterol levels should also contribute to the atherosclerotic pathogenesis of DFS syndrome. Indeed, peripheral ischemia resulting from proximal arterial disease was given as a component cause in the pathway to ulceration in 35%; and diabetic patients with diabetic foot seem to also have more distal disease compared with patients without foot ulceration [32,33], which could represent both a macro- and microvascular complication of diabetes.

Interestingly, we do not report either a higher prevalence of hypertension in subjects with diabetic foot in comparison with diabetic controls or a predictive role of hypertension toward cardiovascular morbidity. This finding appears difficult to explain, but probably is related to the clearly high prevalence of hypertension in the diabetic population independently of the presence of foot ulcerations.

In our diabetic patients with diabetic foot, retrospective analysis of prevalence of previous vascular morbidity (CAD, TIA/stroke, retinopathy) showed that patients with foot ulceration are more likely to have a previous cardiovascular morbidity.

On this basis, we explored if DFS added significant incremental information about risk over and above the normal risk factors, which were not balanced between the 2 groups. On multivariate analysis after correction for known cardiovascular predictors such as cholesterol plasma levels, LDL plasma levels >130 mg/dL, hypertension, and HbA_{1c}, DFS presence maintained the highest hazard ratio toward the composite end point of previous, subclinical, and new-onset cardiovascular morbidity; so we can underline the role of DFS to predict cardiovascular morbidity in diabetic patients, even after correction for other well-known cardiovascular risk factors.

Macroangiopathy, diabetic polyneuropathy, and infections are trigger factors for DFS. Recent results imply a pathogenic role of functional and structural microcirculatory changes [34], but the exact role of microangiopathy and the value of microcirculatory diagnostic methods in DFS have not yet been defined. Our findings concerning a higher prevalence of microvascular end points such as diabetic retinopathy, lacunar strokes (microvascular infarcts), and microalbuminuria in patients with diabetic foot appear particularly interesting. A higher prevalence of lacunar subtype of ischemic stroke in diabetic patients in comparison with nondiabetic subjects has been previously reported by our group [35,36] and by some other studies [37,38]. Nevertheless, in this study, patients with foot ulcerations showed a high prevalence of both lacunar and atherosclerotic strokes; and this finding could suggest a role of both microvascular disease and atherosclerotic macroangiopathy as a determinant of vascular morbidity in patients with diabetic foot.

6. Conclusions

Multiple mechanisms contribute to the development of diabetic foot ulcer, which represents a diabetic complication in addition to neuropathy, atherosclerotic macroangiopathy, and diabetic microangiopathy. Because of the interrelatedness of many diabetic complications and associated factors, it may be misleading to consider individual potential risk factors for foot ulcer because many predictors in univariate analysis will not be shown to have independent effects on ulcer risk. Our findings show the worse cardiovascular risk profile of diabetic patients with diabetic foot compared with diabetic subjects without foot ulcerations, with a higher prevalence of cardiovascular risk factors and a higher clinical and subclinical cardiovascular morbidity prevalence. The higher cardiovascular risk associated with diabetic foot could be related to a cumulative effect of the single risk factor linked to neuropathy and PAD, which represent 2 known clinical conditions recently associated with a higher cardiovascular morbidity [8,27]; but another explanation could be recognized in the role of microangiopathy as a global vascular risk determinant. Nevertheless, because the groups evaluated in our study did not start with balanced CV risk factors and CV disease, we cannot exactly correct for so many other powerful indicators especially with small numbers and relatively few events; so our findings can only warn clinicians that diabetic foot has to trigger a vital search for treatable cardiovascular risk factors and diseases. On this basis, it would be particularly interesting to design further larger studies that specifically analyze the role of DFS as a predictor of cardiovascular and cerebrovascular morbidity and mortality independently of other classic predictors.

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