Comorbidities associated with Egyptian diabetic foot disease subtypes

Mary N. Rizk[a] and Ashraf I. Ameen[b]

[a]Department of Internal Medicine, Cairo University, Cairo and [b]Department of Clinical Pathology, Egypt

Correspondence to Mary N. Rizk, MD, Department of Internal Medicine, Cairo University, 26, Street 18 from street 9, Mokattam, Cairo, Egypt
Tel: +20 122 398 0137;
e-mail: mnriz1970@hotmail.com

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Introduction
Diabetic foot problems are highly prevalent, responsible for almost 50% of all diabetes-related hospital admissions and a 10-year reduction in life expectancy. The main factors involved in the pathology of diabetic foot are neuropathy, ischemia, and infection. The comorbidities of diabetes are hypertension, obesity, and dyslipidemia. Because of the huge premature morbidity and mortality associated with diabetes, prevention of complications is a key issue and, therefore, it is essential to understand the basic mechanisms that lead to tissue damage.

Aim of the work
The aim of our study was to detect the association between patient comorbidities, chronic complications, and different diabetic foot types for the early detection and management of these conditions.

Patients
We carried out a cross-sectional study of 80 consecutive outpatient Egyptian patients with diabetic foot disease in the National Institute of Diabetes and Endocrinology.

Results
Sixty-three percent were purely neuropathic, followed by 19% that were neuroischemic, whereas 18% were of the ischemic type. Hypertension is the most common comorbid condition and coronary artery disease is highly prevalent in the ischemic and neuroischemic types. The coexistence of hypercholesterolemia, smoking, diabetes, and male sex appears to significantly increase the incidence of ischemic diabetic foot. Nephropathy and retinopathy are significantly associated with neuropathic foot ulcers. Hypertriglyceridemia correlates positively to ischemic and neuroischemic ulcers whereas low HDL and proteinuria correlate positively to both neuropathic and neuroischemic ulcers.

Conclusion
Special attention should be paid toward the identification of patients who are at risk of foot ulceration to help prevent foot problems. Comorbid conditions must also be identified early and managed aggressively.

Keywords:
comorbidities, diabetic foot, diabetes mellitus

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Introduction

Because of the huge premature morbidity and mortality associated with diabetes, prevention of complications is a key issue. Diabetic foot problems are highly prevalent, responsible for almost 50% of all diabetes-related hospital admissions [1]. Patients with diabetes and lower extremity arterial disease (LEAD) have an ~10-year reduction in life expectancy and a two-fold increase in mortality compared with patients without LEAD [2]. There are three main factors involved in the pathology of the diabetic foot: neuropathy, ischemia, and infection. The relative role played by each element can vary. Comorbidity, defined as the occurrence of one or more chronic conditions in the same individual with an index disease, occurs frequently among patients with diabetes [3]. Because of the huge premature morbidity and mortality associated with diabetes, special attention should be paid toward the early detection and evaluation of comorbities and hence prevention of progression as a key issue in the control of this disease.

Aim of the work

We attempted to detect the correlation between patient comorbidities, chronic complications, and different diabetic foot types in Egyptian patients. We aimed at early detection and management of these conditions, thus preventing the occurrence or progression to foot ulcers.

Materials and methods

This is a cross-sectional study of 80 consecutive Egyptian diabetic foot patients attending the outpatient diabetes and diabetic foot clinics of the National Institute of Diabetes

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and Endocrinology. We divided the patients into three groups according to the type of foot ulcer, namely, neuropathic, neuroischemic, and ischemic ulcer. Inclusion criteria involved patients with diabetic foot ulcers because of peripheral neuropathy, ischemia, and infection. Exclusion criteria included patients with ulcers because of other causes as trauma, burn, and venous ulcers.

All patients signed a consent form and were subjected to assessment of full history including diabetic history, its duration, control, and family history of peripheral vascular diseases. Full clinical examination was performed, especially for associated manifestations of hypertension, peripheral vascular disease, and full examination of diabetic foot including arterial pulsation, ulcer grading, signs of peripheral neuropathy and inflammation, and associated clinical abnormalities. Investigations included HbA1c, lipid profile, ECG, fundus examination, urinary A/C ratio for proteinuria, and arterial duplex on lower limb in selected cases (when arterial pulse is not felt).

Patients' medical histories were reviewed with particular attention to previous coronary artery disease (CAD) [myocardial infarction, stable angina, revascularization procedures at the coronary arteries, or diagnosed stenosis (>50%) at the coronary arteries] and ECG was performed to confirm the diagnosis. Patients were considered to have cerebrovascular disease when they reported a history of stroke, transient ischemic attack, revascularization procedures at the carotid arteries, or carotid artery stenosis (>50%). LEAD was diagnosed when one of the following was present: (a) history of intermittent claudication, (b) absence of at least two of four peripheral pulses in the feet, (c) ischemic rest pain, (d) gangrene, (e) history of revascularization procedures at the aorta or the lower leg arteries, or (f) arterial duplex with ankle peak systolic velocity (APSV) less than 75. Peripheral neuropathy was diagnosed when at least two of the following four tests were abnormal: Modified Neuropathy Symptom Score and a Neuropathy Disability Score, vibration perception threshold, and cutaneous pressure perception threshold [4]. Ulcers in patients with neuropathy but without LEAD were classified as purely neuropathic, whereas ulcers in patients with both neuropathy and LEAD were classified as neuroischemic. Patients were considered to have an infected diabetic foot ulcer when they reported a history of purulent secretions and fever.

BMI was calculated in all patients. Hypertension was defined when systolic and/or diastolic pressure exceeded 140/90 mmHg, respectively, in three observations or when patients were treated with antihypertensive agents. Patients with hypertension were assigned a score (0, 1, 2, 3) depending on the number of drugs taken for hypertension treatment. The smoking index was calculated in all patients. Retinopathy was diagnosed as background or proliferative by direct fundoscopy.

Dyslipidemia was diagnosed when low-density lipoprotein (LDL) cholesterol levels were higher than 100 mg/dl and/or LDL or high-density lipoprotein (HDL) levels were less than 40 and 50 mg/dl for men and women, respectively, and/or fasting plasma triglyceride (TG) levels were higher than 150 mg/dl, according to the American Diabetes Association guidelines, or when patients had been treated with statins or fibrates. Serum lipids, creatinine, and HbA1c values were obtained from the medical records. Microalbuminuria was diagnosed in a morning urine sample when the albumin/creatinine ratio was in the range of 2.5–30 mg/mmol for the men and 3.5–30 mg/mmol for the women in at least two urine samples over a 6-month period; values higher than 30 mg/mmol were diagnostic for microalbuminuria.

Statistical analysis

Analyses were carried out using the SPSS 15.0 (SPSS Inc., Chicago, Illinois, USA) statistical package. All variables were tested for normal distribution of data. Data are shown as mean ± SD or median (interquartile range) as appropriate. Differences between the studied groups were examined using student's unpaired *t*-test or the Mann–Whitney *U*-test for parametric and nonparametric data, respectively, whereas a χ^2-test was used for categorical data. *P* value less than 0.05 (two tailed) was considered statistically significant.

Results

The patients were divided into three groups according to the type of diabetic foot ulcer, namely, neuropathic, neuroischemic, and ischemic ulcer, using the University of Texas Classification System [5].

Of the 80 patients, 52 were men and 28 women (65 and 35%, respectively, $P = 0.029$). Their ages ranged between 28 and 66 years. There were 13 (16.25%) type 1 diabetic patients and 67 (83.75%) type 2 diabetic patients ($P = 0.080$). Table 1 shows the distribution of the variable comorbidities among the different ulcer group subtypes.

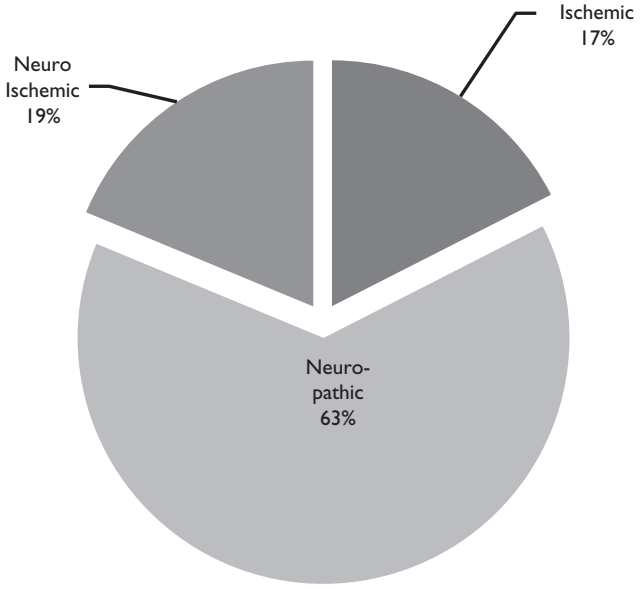
Fifty-one patients presented with a neuropathic foot ulcer (63%), 15 with neuroischemic (19%) and 14 with ischemic foot (18%). There was a significantly higher incidence of neuropathic ulcers than neuroischemic and ischemic ulcers (Fig. 1).

Table 1 Distribution of comorbid conditions stratified by type of diabetic foot ulcer

	Ischemic (%)	Neuroischemic (%)	Neuropathic (%)	*P*
IHD	85	36	12	<0.01
Proteinuria	92	78	74	<0.015
Retinopathy	35	31	44	<0.036
HTN	93	52	25	<0.01
Smoker	57	52	49	<0.039
Obesity	28	36	42	<0.032
High T cholesterol	28	26	36	0.368
High TG	28	26	23	<0.01
Low HDL	0	16	34	<0.01
High LDL	7	5	6	>0.05
High V LDL	7	5	6	>0.05
Infected ulcer	36	47	45	>0.05
Ischemia	100	100	2	<0.01
A1c>7	100	95	91	>0.05

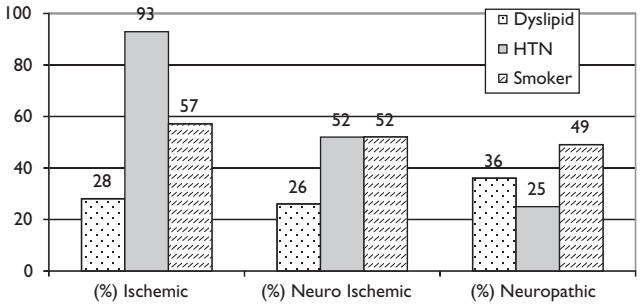
HDL, high-density lipoprotein; HTN, hypertension; IHD, ischemic heart disease; LDL, low-density lipoprotein; TG, triglyceride.

Figure 1



Foot ulcer types.

Figure 2



Prevalence rates of dyslipidemia, hypertension (HTN), and smokers (%).

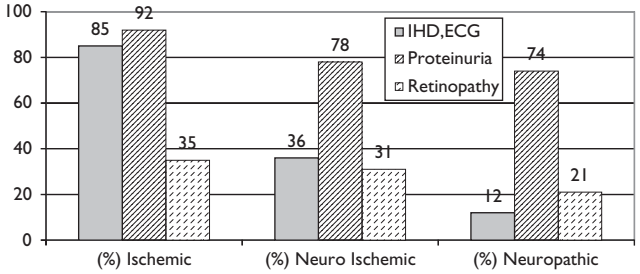
In terms of hypertension, 35 patients were hypertensive (43.75%) and 45 patients were not hypertensive (56.25%). Hypertension ($P<0.01$) was significantly associated with ischemic and neuroischemic types than the neuropathic type (Table 1 and Fig. 2).

Twenty-five patients presented with ischemic heart disease (31%) and 55 were not ischemic (68%). Ischemic heart disease ($P<0.01$) was highly significantly associated with ischemic and neuroischemic types than the neuropathic type. In terms of proteinuria, 63 patients had proteinuria (78.75%) and 17 patients did not have proteinuria (21.25%, $P<0.015$) mainly in the neuropathic type.

Retinopathy was present in 31 patients (38.75%) and 49 patients did not have retinopathy (61.25%, $P=0.036$), with higher prevalence in neuropathic foot (Table 1 and Fig. 3).

In terms of smoking status, 41 patients were smokers (51.25%) and 39 patients were nonsmokers (48.75%, $P=0.039$). In terms of dyslipidemia and diabetic foot

Figure 3



Prevalence rates of ischemic heart disease (IHD), proteinuria, and retinopathy (%).

Table 2 Correlation between the severity of hypertension vs. critical limb ischemia

	Spearman's ρ	P
Neuropathic ($n=47$)	0.086	0.567
Neuroischemic ($n=19$)	0.172	0.481
Ischemic ($n=14$)	0.379	0.181

ulcer, 26 patients had an abnormal lipid profile (32.5%) and 54 patients were normal (67.5%, $P=0.368$). Furthermore, we found that low HDL levels and high TG levels were highly associated with ischemic and neuroischemic types than with the neuropathic type ($P<0.01$).

Thirty-one patients were obese (BMI >25) (38.5%) and 49 patients were not obese (61.5%), with no significant difference between the two groups ($P=0.03$).

Correlation was assessed using Spearman's ρ coefficient between hypertension and critical limb ischemia. Hypertensive patients were assigned a score (0, 1, 2, 3) depending on the number of drugs taken for hypertension treatment. Critical limb ischemia scores were assigned according to decrease in the APSV value (0 for >76, 1 for 25–75, and 2 for <25). Table 2 shows no significant correlation between the severity of hypertension and degree of limb ischemia.

Discussion

Recent data have shown higher mortality rates in patients with foot ulcers [6]. The key players include neuropathy, ischemia, and infection. The role played by these different participating factors can vary [7]. The reason for the high mortality among patients with neuropathic foot ulcers is not known. An increased prevalence of comorbid conditions could be a possible explanation. However, this hypothesis has not been examined [2]. Hence, assessment of the comorbid conditions and their association with diabetic foot ulcers is highly needed.

We found that the majority of our diabetic foot patients were purely neuropathic (63%), followed by neuroischemic (19%) and ischemic type (18%). This agrees with the study of Doupis *et al.* [2] as they estimated the prevalence of different types of foot ulcers in diabetics and they also

reported a higher prevalence of neuropathic ulcer than ischemic and neuroischemic types.

In our study, we found a positive correlation between smoking and diabetic foot ulcer, mainly the ischemic and neuroischemic types more than the neuropathic type. This is in agreement with the study of Selby and Zhang [8], who reported that lifetime quantity smoked is predictive of amputation in diabetic patients mainly presenting with LEAD than with peripheral neuropathy.

Cigarette smoking is a positive risk factor for peripheral vascular disease in diabetic patients. Furthermore, smoking is known to enhance diabetic peripheral neuropathy even up to 2–12 times more than that in nonsmokers [9].

Patients with ischemic ulcers have the highest mortality, followed by those with neuroischemic and neuropathic ulcers. Furthermore, it is expected that patients with peripheral vascular disease will probably develop other macrovascular complications such as coronary and carotid artery disease.

The prevalence of diabetic foot ulcer in our study was higher in men (52%) than women (28%). Gershater *et al.* [6] also found a higher prevalence in men than women in developing foot ulcers. Doupis *et al.* [2] reported that men may have more risk factors and risk for trauma and infection. In contrast, Edmonds and Foster [10] found no difference between sexes in the prevalence of ulcers.

We found the prevalence of comorbid conditions such as nephropathy and retinopathy to be more common in patients with neuropathic foot ulcers. This is in agreement with the study of Doupis *et al.* [2], who found that nephropathy and retinopathy were much more prevalent in neuropathic foot than in the ischemic type.

Furthermore, we found a higher incidence of dyslipidemia, hypertension, and smoking in patients with ischemic or neuroischemic ulcers compared with patients with neuropathic ulcers.

Diabetic dyslipidemia plays an important role in the progression of vascular complications of diabetes. It involves all classes of lipoproteins, but most commonly consists of elevated TG, near-normal LDL levels, and low HDL [11]. There is an elevated oxidized LDL form that has a decreased metabolic clearance and an increased toxicity to endothelial cells; hence, the quality of LDL rather than its level is discriminating in the pathogenesis of diabetic foot ulcer [12]. This could explain our findings. We found no correlation between LDL cholesterol level and diabetic foot. This is also in agreement with the study of Doupis *et al.* [2] and Tseng *et al.* [12], who found near-normal LDL levels in neuropathic, ischemic, and neuroischemic types.

In our study, we found a positive correlation between high TG level and diabetic foot ulcer, mainly ischemic and neuroischemic types. This is in agreement with the study of Laakso and Pyorala [13], who reported that a high TG level is associated with peripheral vascular disease in diabetes and is also a strong risk factor for lower limb amputation. We found no correlation between total cholesterol level and diabetic foot, which is also in agreement with Doupis' work [2]. We also found a positive correlation between low HDL level and diabetic foot, mainly neuropathic and neuroischemic types. Some studies have reported results that are in agreement with ours [2], whereas others [14] have found no correlation between low HDL level and diabetic foot disease.

Hypertension, in our study, was the most common comorbid condition, mainly in the ischemic and neuroischemic types, among diabetic foot patients. Several studies [2,14,15] generally support the concept that hypertension accelerates the development of peripheral vascular disease in certain populations. The presence of other risk factors such as hypercholesterolemia, smoking, diabetes, and male sex appears to markedly accentuate the effects of hypertension on the development of this process [15].

In our study, we found a positive correlation between high BMI and diabetic foot ulcer. This is in agreement with the study of Doupis *et al.* [2] and Eguchi [16]. Both diabetes mellitus and obesity are related to the risk of cardiovascular disease and sudden death. Obesity is a common comorbid condition among type 2 diabetics. Previous studies concluded that obesity is a major risk factor in the development and progression of macrovascular complications of diabetes such as CAD, peripheral arterial disease, and hypertension [10].

The majority of our patients had proteinuria. We found a strong positive correlation between proteinuria and diabetic foot syndrome in both the neuropathic and the neuroischemic types. This is also in agreement with Doupis *et al.* [2]. Nephropathy reflects wide vascular damage at the glomeruli and also reflects damage at the retina and intimae of the arteries. In addition, nephropathy is associated with the development of hypertension and dyslipidemia, both well-known risk factors for CAD. Moreover, patients at all stages of diabetic nephropathy are at a particularly high risk of foot ulceration as neuropathy is particularly common in the early stages of nephropathy [17]. In addition, diabetes is the most significant risk factor for foot amputation among patients with chronic kidney disease [2]. In our study, we found a high prevalence of CAD and risk factors for macrovascular complications among patients with ischemic and neuroischemic ulcers. These comorbid conditions in patients with foot ulceration may be associated with high cardiovascular mortality. Several studies are in agreement with ours in this aspect [2,14,15]. In fact, CAD is the major cause of death in both ischemic and neuropathic diabetic foot patients [18].

Furthermore, we found that diabetic retinopathy is a common complication in patients with diabetic foot ulcers, mainly the neuropathic type. There is a close relationship between retinopathy and neuropathic foot ulceration. This relationship reflects a widespread microangiopathy, and this is in agreement with the study of Doupis *et al.* [2], who found a positive correlation between progression of peripheral neuropathy and diabetic retinopathy, mainly the background type. We also found a strong positive correlation between the severity of diabetic retinopathy in both the neuropathic and neuroischemic types, which is in agreement with

Fong *et al.* [19]. Moreover, poor vision may interfere with a patient's ability to detect early foot lesions, and hence precipitates its progression.

Our study did not assess quality of life (QOL) in the patients with foot ulcers. Previous studies have shown that patients with diabetes mellitus face multiple emotional issues related to the course of their disease as it requires significant lifestyle changes. It is considered that uncomplicated diabetes mellitus, *per se*, does not affect QOL. However, foot ulceration has a strong detrimental impact on QOL and affects a patient's ability to perform simple daily tasks and leisure activities. Thus, patients with foot ulcers more often have depression and have poorer QOL than those without ulcers [3].

In addition, patients with nonhealing foot ulcers may have infection-related complications, gangrene, or amputation, which are often associated with depression and further compromise QOL. Moreover, QOL is compromised not only by foot ulcers and their complications but, in addition, by the comorbidity, particularly CAD and renal impairment [10].

Finally, our study showed that the higher incidence of comorbid conditions in diabetic Egyptian patients is correlated to a higher incidence of foot ulcers.

Recommendations

As the prevalence of diabetes is increasing, both nationally and globally, a subsequent increase in diabetic foot complications is expected to follow. Hence, it is recommended that physicians should pay special attention toward identification of patients who are at risk for foot ulceration to help prevent foot problems. Early assessment and aggressive treatment of comorbidities is crucial in the prevention of diabetic foot ulcers. Special attention should be paid to assessment of any vascular compromise of lower limbs in diabetics with hypertension, smoking, or CAD. However, special attention is warranted toward assessment of peripheral neuropathy in diabetics with retinopathy or nephropathy. Focusing on the prevention and proper management of the diabetic foot problems will decrease not only amputations but may also preserve and result in longer survival rates among patients with diabetes.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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