original article

Diabetic neuropathy, foot ulceration, peripheral vascular disease and potential risk factors among patients with diabetes in Bahrain: a nationwide primary care diabetes clinic-based study

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BACKGROUND: Although epidemiological studies have persistently shown a high prevalence of diabetes in Arabs, the control of diabetes is still poor and complications of diabetes are common. We examined the prevalence of diabetic peripheral neuropathy (DN), neuropathic foot ulceration (FU) and peripheral vascular disease (PVD), and potential risk factors for these complications among patients attending primary care diabetes clinics in Bahrain.

PATIENTS AND METHODS: We studied 1477 diabetic patients (Type 2 diabetes 93%); to, including 635 men and 842 women, with ages ranging from 18-75 years in a cross-sectional study. The main predictor variables were demographic and clinical data, including assessment of foot and blood parameters.

RESULTS: Mean age of the patients and duration of diabetes were 57.3±6.32 and 9.5±8.4 years, respectively. DN was present in 36.6% of the population, FU in 5.9%, and PVD in 11.8%. Diabetic patients with neuropathy were older than patients without neuropathy (P=0.001) and had had diabetes longer (P=0.002). Diabetic patients with foot ulcers had more severe neuropathy and higher vibration perception thresholds values than patients without foot ulcers (P<0.05). Older age, poor glycemic control, longer duration of diabetes, elevated cholesterol levels, current smoking, obesity defined by body mass index, large waist circumference, elevated triglycerides levels and hypertension but not gender, were significant risk factors for DN in both the univariate and the multivariate analyses (P< 0.05). DN and PVD also remained significant risk factors for foot ulceration in the multiple logistic regression analysis.

CONCLUSION: Rates of DN and PVD are high among diabetic patients in Bahrain. Implementation of strategies for prevention, early detection, and appropriate treatment at the primary health care level are urgently needed.

Diabetes mellitus leads to several recognizable clinicopathologic neuropathic syndromes.[1] Diabetic foot complication is the most common cause of nontraumatic lower extremity amputations in the industrialized world. The risk of lower limb amputations is 15 to 46 times higher in diabetic patients than in normal persons.[2,3] In addition, foot complications are the most frequent reason for hospitalization in patients with diabetes, accounting for up to 25 percent of all diabetic admissions to hospitals in the Western world.[4-6] The vast majority of diabetic foot complications resulting in amputations start with the formation of skin ulcers. Early detection and appropriate treatment of diabetic foot ulcers could prevent up to 85 percent of amputations.[7,8] Careful inspection of the diabetic foot on a regular basis along with health education for patients is one of the easiest, least expensive, but most effective measures for preventing future foot complications.

Family physicians have a leading role in ensuring that patients with diabetes receive early and optimal care for skin ulcers. However, several studies have found that foot examinations are infrequently performed by primary care physicians on diabetic patients[9,10] and the feet of hospitalized diabetics are also inadequately evaluated.[11] Diabetes is extremely common among Bahrainis, with prevalence rates of about 25% among adults.[12] The objectives of this study were to determine the prevalence

of diabetic neuropathy, peripheral vascular disease and foot ulceration among diabetic patients attending primary care diabetic clinics so as to identify the risk factors associated with diabetic neuropathy among these patients.

PATIENTS AND METHODS

In Bahrain, there are 21 primary health care centers; 6 have diabetes clinics. A cross-sectional study was carried out on diabetic patients on routine visits to these six specialized clinics, which represented all districts of Bahrain during the period 1 January to 30 June 2005. Patients aged 18 to 75 years, who had already been diagnosed with diabetes, were enrolled in the study. Exclusion criteria included patients with other diseases known to cause neuropathy, such as pernicious anemia and alcoholism.

All patients were interviewed by trained diabetic nurses and the clinical examinations were performed by the investigators. The clinical evaluation included a thorough history and physical examination, measurements of blood pressure levels at supine and standing positions, height, weight and a neurological, vascular and foot examination. Laboratory investigations included fasting blood glucose, electrolytes, blood urea nitrogen, creatinine, total cholesterol, triglycerides and glycated hemoglobin.

All studied patients had established diabetes mellitus according to WHO criteria.[13] Hypertension was defined as previous treatment for hypertension or blood pressure measurement in the clinic equal to 160/95 mm Hg or higher on at least two successive visits.[14] Foot ulcer was defined according to the Wagner classification and associated pathogens.[15] Peripheral neuropathy was defined as nerve damage characterized by sensory loss, pain, muscle weakness and wasting of muscle in the hands or legs and feet.[16] Peripheral vascular disease was defined as arteriosclerosis of the extremities, a disease of the blood vessels characterized by narrowing and hardening of the arteries that supply the legs and feet.[17]

Painful symptoms of neuropathy were assessed using the modified Neuropathy Symptom Score (NSS) based on the original system proposed by Dyck.[18] Patients were asked if they had experienced at any time the following symptoms: pins and needles, abnormal cold or hot sensations in their feet, aching pain, burning pain, and irritation in their feet and legs by the bedclothes at night (paresthesia). One point for the presence of each of these symptoms was assigned. For the first five symptoms one extra point was added if nocturnal exacerbation was present.

The Neuropathy Disability Score (NDS) was used to quantify the severity of diabetic neuropathy on clinical examination conducted by the authors. The sensations of pain, touch, cold, and vibration were tested in both legs and were scored according to the level up to which the sensation was impaired (from 1 for the toe up to 5 just below the knee). Reflexes were scored in every leg as normal (0), present with reinforcement (1), and absent (2). If the NDS was greater than 5 (maximum, 28) it was considered abnormal.[14] The vibration perception threshold (VPT) was measured at the great toe of the dominant side using a Bio-Thesiometer (Biomedical Instrument, Newbury, Ohio, USA). The mean value after three readings was recorded according to the methods of Bloom et al.[19]

Peripheral neuropathy was diagnosed when at least two of the three quantitative measurements (NSS, NDS, and VPT) were abnormal. Foot pulses were recorded as either present or absent. The absence of one or more pulse, the presence of claudication, and/or a history of previous revascularization was regarded as diagnostic for peripheral vascular disease (PVD). Information on the existence of a foot ulcer or history of foot ulceration was also obtained from the diabetic patients.

For the univariate analysis, the chi-square test and Student t-test were used. Multivariate analysis was done considering that nerves are affected simultaneously by all the potential risk factors. All the significant predictors of diabetic neuropathy and foot ulcers in the univariate analysis were included in the logistic regression model. The 95% confidence interval (CI) was calculated when appropriate, and statistical significance was defined as a P value <0.05. Statistical analysis was performed using SPSS for Windows, version 13.0 (SPSS, Chicago).

RESULTS

The study sample included 1477 diabetic patients (635 men, 842 women), of whom 93% had type 2 diabetes. The mean age was 57.3±6.32 years and the mean known duration of diabetes was 9.5±8.4 years. The prevalence of neuropathy was significantly different between current smokers and never smokers (57% vs. 16%, P=0.05). The overall prevalence rate of diabetic neuropathy was 32.3% in men and 38.1% in women, the rates of foot ulceration were 4.9% in men and 6.6% in women, and the rates of peripheral vascular disease were 12.1% in men and 11.6% in women (Table 1).

Table 2 compares demographic and risk factors variables among diabetic patients according to the presence of diabetic neuropathy, foot ulceration, and peripheral vascular disease. Not surprisingly, the mean values of the risk factors were higher in those with diabetic neu-

Table 1. Prevalence of diabetic neuropathy, foot ulceration, and peripheral vascular disease (PVD) by sex and age.

Age group (years)		Without complications	Diabetic neuropathy	Foot ulceration	PVD
Men	N	N (%)	n (%)	n (%)	n (%)
18-29	14	12 (85.7)	2 (14.3)	0	0
30-39	43	22 (51.2)	12 (27.9)	3 (6.9)	6 (13.9)
40-49	178	118 (66.3)	45 (25.3)	4 (2.2)	11 (6.2)
50-59	252	126 (50.0)	92 (36.5)	7 (2.8)	27 (10.7)
60-69	90	22 (24.4)	34 (43.6)	11 (12.2)	23 (25.5)
70+	58	22 (37.9)	20 (34.5)	6 (10.3)	10 (17.2)
Total	635	322 (50.7)	205 (32.3)	31 (4.9)	77 (12.1)
Women	N	N (%)	n (%)	n (%)	n (%)
18-29	11	8 (72.7)	3 (27.3)	0	0
30-39	58	36 (62.1)	18 (31.0)	2 (3.4)	2 (3.4)
40-49	209	112 (53.6)	70 (33.5)	7 (3.3)	20 (9.6)
50-59	382	177 (46.3)	152 (39.8)	14 (3.7)	39 (10.2)
60-69	124	28 (22.6)	50 (40.3)	19 (15.3)	27 (21.8)
70+	58	6 (10.3)	28 (48.3)	14 (24.1)	10 (17.2)
Total	842	367 (43.6)	321 (38.1)	56 (6.6)	98 (11.6)
Total	1477	689 (46.4)	526 (36.6)	87 (5.9)	175 (11.8)

Table 2. Demographic and risk factors variables in diabetic patients by presence of diabetic neuropathy (DN), foot ulceration (FU), and peripheral vascular disease (PVD).

Variables	Without complications (n = 689)	Diabetic neuropathy (n =526)	Foot ulceration (n =87)	PVD (n=175)	*P* value
Gender (M/F) (%)	51/44	32/38	5/7	12/12	0.05
Age (years and range)	52 (18-75)	54 (18-77)	56 (18-77)	58 (18-77)	<0.05
Glycated hemoglobin (%)	8.2 (2.1)	8.7 (2.6)	9.8 (3.1)	9.2 (2.8)	<0.01
Body mass index (kg/m2)	27.3 (5.2)	28.2 (5.4)	29.3 (5.1)	28.4 (5.6)	<0.05
Waist (cm)	98.0 (11.0)	98.7 (12.2)	99.1 (11.4)	99.0 (11.6)	<0.05
Systolic blood pressure (mm Hg)	142 (20)	145 (21)	156 (27)	152 (23)	<0.05
Diastolic blood pressure (mm Hg)	86 (11)	87 (12)	89 (11)	88 (13)	0.10
Serum total cholesterol (mmol/L)	5.7 (1.5)	6.2 (1.5)	7.5 (2.8)	7.9 (2.7)	<0.01

Values are means (SD) unless stated otherwise.

Table 3. Relationship of neuropathy to duration since diagnosis of diabetes.

Years since diagnosis	Prevalence of diabetic neuropathy (%)	Cases/Total	Age-adjusted odds ratio (95% CI)
<1	5	13/248	1*
1-5	34	68/202	2.8 (1.4-3.6)
6-10	35	127/363	2.1 (1.8-4.3)
11-15	48	139/287	1.8 (2.1-2.8)
16-20	53	99/187	2.4 (1.6-4.7)
≥21	45	86/190	1.8 (1.1-2.6)

*Reference group

Table 4. Logistic regression of diabetic neuropathy with glycated hemoglobin as a categorical variable.

Level of glycated hemoglobin (%)	Number of patients	Odds ratio for diabetic neuropathy	95% CI	*P* value
<7	141	0 (reference group)		
7-9	375	3.15	1.06-5.23	0.03
9.1-11	557	3.29	1.18- 5.39	0.002
>11	404	2.55	1.30-4.80	0.02

Table 5. Univariate logistic regression analysis for risk factors associated with diabetic neuropathy.

Risk factor	Odds ratio	95% CI for odds ratio	*P* value
Age	1.22	1.98-2.06	0.00175
Gender (male/female)	1.02	0.68-1.06	0.175
Body Mass Index (≥30)	2.12	1.34-1.16	0.001
Height (cm >162)	1.84	1.77-2.14	0.001
Waist circumference (>40 inch)	2.42	1.22-1.48	0.001
Glycated hemoglobin (>7%)	1.24	1.02-2.93	0.02
Diabetes duration (>5 years)	1.32	1.24-3.66	0.001
Total cholesterol (>5.2 mmol/L)	1.98	1.52-2.37	0.02
Triglycerides (>1.8 mmol/L)	1.64	1.43-1.88	0.006
Hypertension (yes/no)	1.75	1.04-2.97	0.03
Smoking (yes/no)	2.18	1.16-1.77	0.002

ropathy, foot ulceration, and peripheral vascular disease than in diabetic patients without such complications. Diabetic patients with neuropathy were older (mean age, 59.46±16.37 years) than patients without neuropathy (mean age 49.3±17.17 years, P=0.001). Duration of diabetes ranged from less than 1 year to 30 years and longer (mean, 8.4 years). Analysis of diabetic neuropathy rates by duration time in years since diagnosis revealed a stepwise increase in prevalence rates of diabetic neuropathy that ranged from 5% at 1 year after initial diagnosis to 48% at more than 11 years since diagnosis of diabetes (Table 3).

In a multivariate regression analysis using logistic regression with glycated hemoglobin as a categorical variable, a significant positive association of the glycated hemoglobin level and diabetic neuropathy was found (Table 4), which indicates the role of poor glycemic control in the development of diabetic neuropathy. Tables 5 and 6 show the results of univariate and multivariate regression analyses with age, sex, hypertension, body mass index, glycated hemoglobin, duration of diabetes, smoking, total cholesterol and triglycerides as dependent variables. The mean± standard deviation duration of smoking in current smokers versus nonsmokers was 11.6±12 years (P=0.001). All the risk factors in the model were significantly associated with increased severity of neuropathy except for gender. A multiple logistic regression analysis of the prevalence of neuropathy was performed using all the significant risk factors. This analysis showed that age, hypertension, body mass index, glycated hemoglobin, duration of diabetes, smoking, total cholesterol and triglycerides were significant independent predictors of prevalence of neuropathy (P<0.05 for all) (Table 6). A similar analysis showed that diabetic neuropathy and peripheral vascular disease were significant risk factors for foot ulceration (P<0.05) .

DISCUSSION

Prevalence rates of neuropathic complications in patients diagnosed with diabetes in Bahrain were higher than those reported for European and USA patients, which probably reflects the better management and diabetes care in Western countries from that currently practiced in Bahrain.[20-22] Hospital-based studies do not reflect the true prevalence of disease, and usually involve mainly type 1 diabetic patients since the majority of type 2 patients are traditionally cared for by general practitioners in the community. A major strength in the design of this study was clinic-based in primary health care.

While the prevalence of peripheral neuropathy among diabetics has been established in many Western populations, little information is available for Arab populations for meaningful comparisons. For example, some studies in the UK reported low rates of peripheral neuropathy,[23] which was in sharp contrast to data reported here for Bahrainis. This may be related to the less rigorous criteria for diagnosis of peripheral neuropathy used in the UK study, which may have underestimated the disease. On the other hand, a population-based study in the UK found a high prevalence rate (41.6%) of neuropathy.[22] This rate is similar to the prevalence rate (36.6%) of neuropathy in diabetic patients attending primary health care centers in Bahrain and in line with the Oxford community-based study findings.[24]

We found that development of neuropathy was related to the level of glycemic control. This confirms the need for optimal care of diabetic patients in preventing complications.[25] The risk of neuropathy and peripheral vascular disease increased steadily with elevated glycated hemoglobin. The increased risk of neuropathy associated with hyperglycemia is likely to account for the high proportion of cases of foot ulcerations in diabetic patients in Bahrain. The strong association of the presence of diabetic neuropathy with high levels of glycated hemoglobin suggests that poor glycemic control is an important risk factor for diabetic neuropathy and foot ulcerations among Bahrainis (and likely other Arabian Gulf communities).[26]

Risk factors for diabetic neuropathy were comparable among male and female patients. While this was not consistent with findings from studies in other populations that identified male gender as a risk factor,[22,27] the finding that age and duration of diabetes are risk factors for glycated hemoglobin[22,27] together with tall stature were in agreement with previous studies.[23] While speculative at this stage, it is possible that longer nerve fibers in taller people are more vulnerable to the toxic effects of hyperglycemia, and reduced endoneurial blood flow resulting from microvascular damage.[28,29]

In another cross-sectional study that involved newly diagnosed type 2 diabetic patients, diabetic neuropathy was not related to levels of glycemic control defined by glycated hemoglobin.[30] Among Bahrainis, glycated hemoglobin remained a significant risk factor for diabetic neuropathy, even after adjustment for all other risk factors in the multivariate model. In addition, the mean values for the duration of diabetes since diagnosis correlated with glycated hemoglobin level, which is in agreement with studies in Western populations that identified glycemic control as an established risk factor for diabetic neuropathy.[31-32]

Current smoking was positively related to neuro-

Table 6. Multivariate logistic regression analysis for risk factors associated with diabetic neuropathy.

Risk Factor	Odds ratio	95% CI for odds ratio	*P* value
Age	1.04	0.99-1.09	0.100
Gender (male/female)	1.04	0.33-1.26	0.075
Hypertension (yes/no)	2.02	1.77-2.24	<0.01
Body Mass Index (≥ 30)	1.04	1.01-1.09	<0.04
Waist circumference (>40 inch)	1.88	1.12-1.32	0.01
Glycated hemoglobin (>7%)	1.10	1.33-2.15	<0.05
Diabetes duration (>5 years)	1.33	1.56-1.67	<0.01
Smoking (yes/no)	1.24	1.01-1.31	<0.02
Total cholesterol (>5.2 mmol/L)	1.56	1.75-2.16	<0.02
Triglycerides (> 1.8 mmol/1)	1.98	1.08-3.64	<0.02

pathic rates in this population, which provides further evidence that current smoking is a risk factor for diabetic neuropathy in diabetic patients[30] and emphasizes the need for patients to quit smoking. The presence of neuropathy was also related to dyslipidemia, hypertension and obesity. Earlier studies have reported that high blood pressure is a significant risk factor for diabetic neuropathy, both in type 1 and type 2 diabetic patients.[20] However, the role of hypertension in the pathogenesis of neuropathy remains controversial, and most experts consider high blood pressure as a risk marker for neuropathy rather than a risk factor.[32]

The observed prevalence rates of foot ulceration (5.9%) and peripheral vascular disease (11.8%) were high, but are in line with those reported from the UK[32] and in a population-based study on type 2 diabetic patients.[22] In addition, a Swedish community-based study found that 2% of the diabetic population currently had foot ulcers and 10% had a history of ulceration.[21] Our findings provide further proof that the severity of the neuropathy (as shown by the NDS and VPT values) is associated with the development of foot ulceration. This association remained significant in the multivariate analysis. Similar results were reported by Young and colleagues.[33]

We used clinical criteria to diagnose peripheral vascular disease, which was based mainly on the presence of claudication, the absence of foot pulses, or a history of revascularization. Epidemiological studies have shown that the sensitivity of such diagnostic approach is high (93%) with Doppler-proven diagnosis of peripheral vascular disease.[34] Furthermore, peripheral vascular disease was found to be a significant risk factor for the development of foot ulceration.

In summary, the present primary clinic-based study on Bahraini diabetics showed that a large proportion of the diabetic patients have neuropathic complications and are therefore, at substantial risk of developing foot ulceration. The study also identified some important risk factors for diabetic neuropathy, including poor glycemic control, older age, long duration of diabetes, tall stature, smoking and high cholesterol levels. Strategies to reduce the risk of neuropathy among diabetic patients in Arab populations must be implemented. In addition, better diabetic care including foot care, screening programmes for early diagnosis and health education for diabetic patients are urgently needed to reduce the risk of foot ulceration and potentially preventable lower limb amputations.

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