Prevalence and correlates of diabetic peripheral neuropathy in a newly developing country: a cross-sectional study

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Abstract:

The purpose of this cross-sectional study was to assess the prevalence and correlates of diabetic peripheral neuropathy (DPN) in a Qatari population. The study population was comprised of 549 diabetic participants with an average age of 55.2 years; 55.9% were male, and 62.2% were Qatari nationals. The average body mass index (BMI) was 29.4 kg/m^2. DPN was diagnosed using the Michigan Neuropathy Screening Instrument (MNSI) and a neurothesiometer. Information on socio-demographic variables, including smoking status and diabetes history, was obtained from medical records. BMI and clinical markers were assessed using standard procedures. The prevalence of DPN in this population was 21.3% (95% CI, 17.6%-24.8%). Diabetic patients with neuropathy were older than patients without neuropathy (P<0.001), and they had a longer duration of diabetes (P <.001). Similarly, patients with DPN had high fasting blood glucose levels (p=0.003), were more likely to be Qatari nationals (p=0.042), had hypertension (P=0.015), and had high serum creatinine (p=0.040).

Key words: Diabetes, Peripheral Neuropathy, Qatar

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INTRODUCTION

Diabetic peripheral neuropathy (DPN), also known as distal symmetric polyneuropathy (DSP), is the presence of symptoms and/or signs of peripheral nerve dysfunction in patients with diabetes after other causes of dysfunction have been excluded.[1] Diabetes mellitus is the leading cause of peripheral neuropathy, attributing to nearly half of all cases.[2] The neurological consequences of diabetes are estimated to affect approximately 300 million people worldwide, as the incidence of diabetes reaches a global epidemic level.[3] Qatar, a newly developing country, is ranked among the three of the world's top 10 countries with the highest prevalence of diabetes according to the 2003 International Diabetes Federation.[4] This dramatic rise in the prevalence of diabetes is secondary to a very rapid socioeconomic transition coupled with an aging population.

Diabetic neuropathies present with diverse clinical manifestations due to their heterogeneous nature and being either focal or diffuse. Chronic sensorimotor distal symmetric polyneuropathy and autonomic neuropathies are the most common neuropathies among patients with diabetes. DPN is a diagnosis of exclusion. In patients with diabetes, clinicians need to diagnose DPN as early as possible and manage it appropriately for several reasons. First, patients with diabetes may present with non-diabetic neuropathies. Second, symptomatic diabetic neuropathy can be managed by a number of treatment modalities. Third, patients with diabetes are at risk of insensate injury to their feet since up to 50% of DPN may be asymptomatic. Since foot injury or ulcer is the precursor in >80% of amputations, structured education, adequate foot care, and early recognition of at-risk individuals may result in a reduced incidence of ulceration and consequently amputation.[5] This study was conducted to screen patients with Type 2 diabetes for undetected DPN and to identify the determinants of DPN.

DESIGN AND METHODS

The Hamad Medical Corporation Research Ethics Committee (research number #11030) approved this study as part of the (ESD-MCQ study), a comprehensive study assessing diabetes and its epidemiology. Subjects signed a written informed consent, and a verbal consent was obtained from illiterate participants. The sample size was calculated using the Sampsize website. Using a 95% confidence interval, a prevalence of 11%, a precision of 2% with a population size of 2 million, a minimum of 942 participants were required in this study. Therefore, we recruited a total of 942 eligible patients who initially participated in this study. Participants were recruited from Umgwailinah health care center in Qatar. Patient diabetic histories were ascertained from the diagnosis and medical records at the health center. Inclusion criteria were patients over 18 years old with Type 2 diabetes. Exclusion criteria were patients diagnosed with Type 1 diabetes, patients diagnosed with cancer or severe debilitating illness, and documentation of alcohol and or drug abuse. Data were collected from January 2012 to June 2012. However, during the study period 259 participants were re-allocated to different health regions, and 129 participants were excluded due to incomplete data. This resulted in having 549 evaluable subjects at the end of the study.

Data on socio-demographic data, including duration of diabetes, blood pressure, and biochemical values were collected from patient medical records and documented. They are summarized in **Table 1**. Patients' heights, weights, and body mass indices (BMI) were also calculated. Obesity status was defined according to the international classification of an adult's weight, [Normal BMI: 18.5 - 24.99 kg/m2, overweight: 25.00 - 29.99 kg/m^2 and obese ≥ 30.00 kg/m^2]. Biochemical variables included serum fasting glucose, HbA1C level, lipid profile, and serum creatinine and are summarized in **Table 2**. Renal function tests were documented and graded according to the National Kidney Foundation practice guidelines for chronic kidney disease.[6]

Diabetes complications, including micro- and macro-vascular complications and associated conditions, were extracted from medical records.

Statistical Analysis

Median and interquartile ranges represented the distribution of continuous variables. Quantile regression with adjustment for age, sex, and nationality, when applicable, was performed to compare continuous variables between DPN and non-DPN participants.

Numbers and percentages were used to represent all the categorical variables. The distribution of categorical variables between DPN and non-DPN participants was compared using a logistic regression model after adjusting for age, sex, and nationality. Logistic regression models estimated odds ratio (OR) and a 95% confidence interval (CI) for each correlate with adjustment for sex, age (continuous), and nationality (Qatari, non-Qatari). Continuous variables were categorized into quartiles.

Measurement of Peripheral Neuropathy

The Michigan Neuropathy Screening Instrument (MNSI) was used to assess peripheral neuropathy. The MNSI consisted of two parts: a self-administered questionnaire on clinical signs and symptoms of neuropathy and a clinical examination of both feet involving: 1) an examination to detect dry skin, callosities, fissures, ulceration, cellulitis, and osteomyelitis; 2) a grading of ankle reflexes; 3) vibration perception assessing semi-quantitatively by a applying the neurothesiometer at the dorsum of the great toe; and 4) 10-g Semmes Weinstein monofilament testing. In this study we used the clinical examination part of the MNSI, with 10 being the maximum possible score. The presence of peripheral neuropathy was defined as an MNSI score of >2.[7] The MNSI has been validated against quantitative vibration threshold tests, nerve conduction measures, the Michigan Diabetic Neuropathy Score, and the Mayo Clinic Neuropathy Disability Score. The maximum possible score was 8 in these validation studies because the score at that time did not include the 10-g monofilament test.[8]

Measurement of Nerve Dysfunction

We used a neurothesiometer to quantify the vibration perception threshold (VPT), a measure of the severity of nerve dysfunction. The neurothesiometer is a battery-operated diagnostic tool that has been validated against nerve conduction studies. It assesses sensitivity thresholds at various sites on the body surface.[9] Perception of vibration sense was elicited by the participants after the probe was applied to the distal pulp of their hallux. The intensity of the stimulus was gradually increased from null to a voltage at which vibration was first detected.[10] Three separate tests were recorded with subjects' eyes closed. The average of three VPTs tests were recorded. Patients acknowledging the presence of vibration sense while the device was inactive were considered malingers and were excluded from the study. Reduced vibration perception was defined by a vibration perception threshold >25 Volts in either foot.[11]

RESULTS

Characteristics of the study participants are shown in **Table 1**, and participation was based on the diagnosis of DPN. Among the 549 participants, 117 were diagnosed as having DPN, giving a prevalence of 21.3% [95% confidence interval (CI), 17.7% – 24.5%]. The mean age of this population was 49.5 years. The likelihood of DPN was higher among Qatari subjects and those who had longer duration of diabetes, higher fasting blood glucose level, hypertension,

Table 1. Characteristics of participants according to diabetic peripheral neuropathy status.

	Non-DPN Case	DPN Case	P †
	(N=432)	(N=117)	
Sex, Male ‡	248 (57.4)	59 (50.4)	0.567
Nationality **Qatari** **Non Qatari**	269 (62.2)	61 (52.1)	0.042
Education			0.201
Illiterate	159 (36.8)	49 (41.8)	
High School	119 (25.4)	26 (22.2)	
University	129 (29.8)	24 (20.5)	
Income Level (QR/Month)			**0.232**
<5000	166 (38.4)	49 (41.8)	
5000–10000	152 (35.1)	33 (28.2)	
>10000	114 (26.3)	17 (14.5)	
Obesity	210(48.6)	59 (50.4)	0.052
Smoking	88 (20.3)	19 (16.2)	0.659
Duration of Diabetes			**<0.001**
2–5	122 (28.2)	8 (6.8)	
5–10	132 (30.5)	13 (11.1)	
10–20	145 (33.5)	35 (29.9)	
>20	33 (7.6)	61 (52.1)	
Hypertension	265 (61.3)	83 (70.9)	0.015
Age (years) §	49.5 (46.0–58.0)	59.5 (50.0–66.0)	<0.001
Body Mass Index (kg/cm^2)	28.7 (25.9–34.1)	29.8 (26.4–36.5)	0.256
Fasting Blood Glucose (mmol/L)	9.3 (7.5–11)	9.6 (7.8–12.9)	0.003
HbA1c (%)	9.0 (8.0–10.5)	9.0 (8.0–11.1)	0.149
LDL (mmol/L)	3.1 (2.5–3.7)	3.0 (2.4–3.6)	0.755
Creatinine (umol/L)	76.0 (64.0–88.0)	81.0 (75.0–103.0)	0.040

Abbreviations: DPN, diabetic peripheral neuropathy; QR, Qatari riyal (currency unit of Qatar); HbA1c, glycated hemoglobin; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; CRP, C-reactive protein.
†P-values were calculated from logistic regression models for categorical variables or quantile regression for continuous variables adjusted for age, sex, and nationality when applicable.
‡n (%) for all such values,§median (25% percentile–75% percentile) for all such values

Table 2: Association between risk factors and prevalence of diabetic peripheral neuropathy among patients with Type 2 diabetes (n=117).

	Cases (%)	Odds Ratio (95% CI)
Education		
Illiterate	53 (24.9)	**Reference**
High School	34 (29.0)	**0.89 (0.54–1.76)**
University	30 (25.6)	**0.89 (0.51–1.59)**
Income Level (QR/Month)		
5000	54 (22.3)	**Reference**
5000–10000	36 (19.2)	**0.89 (0.56–1.58)**
≥10000	27 (22.5)	**0.90 (0.43–1.71)**
Obesity	59 (21.8)	**1.46 (1.00–2.46)**
Smoking vs Never-smoker	21 (17.8)	**1.16 (0.66–2.05)**
Duration of Diabetes (years)		
2–5	8 (5.6)	**Reference**
5–10	11 (8.1)	**1.39 (0.46–3.73)**
10–20	37 (21.5)	**3.69 (1.37–8.59)**
≥20	54 (46.5)	**12.16 (5.13–26.36)**
Hypertensive vs. Normotensive	86 (23.2)	**1.75 (1.07–2.69)**
Fasting Blood Glucose (mmol/L)		
7.5	26 (18.1)	**Reference**
7.5–9.5	27 (18.8)	**0.90 (0.48–1.69)**
9.5–11.0	24 (20.5)	**1.16 (0.57–2.13)**
≥11.06	33 (21.9)	**1.61 (0.78–3.00)**
HbA1c (%)		
7.0	27 (21.1)	**Reference**
7.0–8.0	16 (16.5)	**0.61 (0.30–1.12)**
8.0–9.5	37 (20.1)	**0.95 (0.48–1.68)**
≥9.5	30 (20.9)	**1.16 (0.61–2.20)**
LDL (mmol/L)		
1.8	28 (19.4)	**Reference**
1.8–2.5	27 (22.2)	**1.53 (0.79–2.84)**
2.5 – 3.0	28(16.5)	**1.07(0.48-2.01)**
≥3.0 -	27 (18.9)	**1.19(0.58- 2.19)**
Creatinine (umol/L)		
65.0	15 (10.3)	**Reference**
65.0–78.0	29 (18.4)	**2.28 (1.14–4.65)**
78.0–90.0	23 (19.9)	**2.49 (1.17–5.41)**
≥90.0	43 (29.5)	**3.59 (1.76–7.75)**

Abbreviations: QR, Qatari riyal; HbA1c, glycated hemoglobin; cholesterol; LDL, low-density lipoprotein cholesterol
{Logistic regression model adjusted for sex, age (continuous) and nationality (Qatari, non-Qatari).
For ordinal variables, P-value was estimated from the linear trend test.

and high creatinine levels compared with their counterparts without DPN.

Table 2 shows the associations between the correlates and DPN after adjusting for age, sex, and nationality. A significant and positive association between duration of diabetes and odds of DPN was observed (P =0.001). Similar significant associations were seen with older age (<.001), being a Qatari (p=0.042), having a longer duration of diabetes (p<0.001), being hypertensive (p=0.015), having a high fasting blood glucose (p=0.003), and having a higher serum creatinine level (p=0.001).

DISCUSSION

Peripheral DPN is a common comorbidity among diabetes patients; the reported prevalence of DPN in Europe ranged from 0.7% to 34% overall in Type 1 or Type 2 diabetes mellitus patients. Excluding outliers, the prevalence range was found to be 5.8–34%.[12-21] However, in the Middle East the prevalence of painful DPN is much higher, ranging from 37.1% to 65.3%.[22,23] Nonetheless, a similar study done in a neighboring country, Saudi Arabia,[24] has reported a prevalence of 19.9% that is similar to our study.

The huge variation of prevalence in the Middle East countries is due to the variation in tools and definitions used to assess peripheral neuropathy. These include questionnaires, monofilaments, the Michigan Diabetic Neuropathy Score, and neurothesiometer.

We observed that a higher level of fasting blood glucose was associated with a higher odds of DPN but not higher values of HbA1c. This may be attributed in part to glycemic excursions or variability regardless of HbA1c level as demonstrated by Xu et al.[25] They found that glycemic variability was the most important independent risk factor for the development of DPN. Current management guidelines seek to maintain fasting and postprandial glucose levels close to the target to prevent or delay diabetic complications, with glycosylated hemoglobin A1c (HbA1c) being the gold-standard assessment of long-term overall glycemic control. However, very little attention is paid to the glycemic variability

with its resultant oxidative stress. Glucose variability can be described as within-day variability, with differences between fasting and postprandial blood glucose values throughout 24 hours, and between-day variability, reflecting differences in blood glucose control from day-to-day. This glucose variability is not reflected in A1c and may represent an additional risk factor for the development of diabetes complications. Nalysnyk et al. conducted a systematic review of English language literature from January 1990 through November 2008 on glycemic variability and its influence on the development or progression of micro vascular diabetic complications. The authors concluded that glucose variability, characterized by extreme glucose excursions, could be a predictor of diabetic complications.[26, 27]

Being a Qatari conferred a higher risk of DPN, which is not surprising since 37% of the Qatari population suffers from metabolic syndrome according to the International Diabetes Federation.[28] Furthermore, our population generally has a high BMI, a well-recognized factor for the development of DPN.[29] With the discovery of oil and natural gas, Qatar has gone through a very rapid socioeconomic transition in the last 40 years. This has resulted in a sedentary life style and embracing a high calorific diet that adversely interacts with a genetic susceptibility for obesity and diabetes. Before the discovery of oil and natural gas Qataris were manual workers and sailors and had very little cultivation due to the arid nature of the desert. This resulted in people having very little to eat. Mothers had little food, leading to unfavorable conditions in the intrauterine environment. Undernourishment in early development produces future changes that include both reduced insulin secretion and insulin resistance—hallmarks of diabetes according to the thrifty phenotype theory.[30] This survival advantage will translate later on into obesity and diabetes. Hence, we have experienced an epidemic of obesity and being overweight, estimated as being 70% and 37% respectively.[31] Prevalence estimates for 2030 (based on anticipated changes in population size and demography) suggest that this will remain the case.[32] According to the International Diabetes Federation 2003 estimates, diabetes prevalence in Qatar is one of the highest in the world at 20.2%.[33]

Our data indicated that systolic hypertension was a significant and independent correlate for DPN. Current literature suggests that optimal treatment of hypertension can have an important role in DPN prevention and treatment.[34,35,36] We also observed a strong positive association between elevated level of creatinine and DPN in our sample. Peripheral neuropathy is a known complication among people suffering with end stage renal disease (ESRD) and also is common in people with diabetes. Peripheral neuropathy is present among 65% of people with ESRD when beginning dialysis treatment. Although neural axons become damaged and demyelinated, the exact pathology of peripheral neuropathy remains unclear. Evidence suggests that elevated levels of parathyroid hormone may raise intracellular calcium levels of peripheral nerves, leading ultimately to the development of peripheral neuropathy.[37]

Strengths and Limitations

To our knowledge this is the first study on prevalence and correlates of DPN in a Qatari population. The strengths of this study include a representative sample size, and a comprehensive and objective assessment of DPN utilizing the neurothesiometer. However, several limitations still remain including a high attrition rate and the cross-sectional nature of this study design. These weaknesses limit the inference of causal relationship between measured correlates and DPN. Therefore, our findings need to be confirmed in prospective studies.

In conclusion, a higher prevalence of DPN was observed in this Qatari population with diabetes. This has important consequences for health care policy makers and stakeholders since diabetes in this country, and the region as a whole, is plagued by the diabetes epidemic.

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