



Please cite the Published Version

Ponirakis, Georgios, Elhadd, Tarik, Chinnaiyan, Subitha, Hamza, Abdul H, Sheik, Sanaula, Kalathingal, Mohamed A, Anodiyil, Mohamed S, Dabbous, Zeinab, Siddique, MashhoodA, Al-muhannadi, Hamad, Petropoulos, Ioannis, Khan, Adnan, Ashawesh, Khaled AE, Dukhan, Khaled M, Mahfoud, Ziyad R, Zirie, Mahmoud A, Jayyousi, Amin, Murgatroyd, Christopher , Slevin, Mark  and Malik, Rayaz A (2021) Prevalence and risk factors for diabetic neuropathy and painful diabetic neuropathy in primary and secondary health care in Qatar. *Journal of Diabetes Investigation*, 12 (4). pp. 592-600. ISSN 2040-1116

DOI: <https://doi.org/10.1111/jdi.13388>

Publisher: Wiley Open Access

Version: Published Version

Downloaded from: <https://e-space.mmu.ac.uk/626515/>




Usage rights:  [Creative Commons: Attribution-Noncommercial 4.0](https://creativecommons.org/licenses/by-nc/4.0/)

Additional Information: This is an Open Access article published in *Journal of Diabetes Investigation*, published by Wiley, copyright The Author(s).

Enquiries:

If you have questions about this document, contact openresearch@mmu.ac.uk. Please include the URL of the record in e-space. If you believe that your, or a third party's rights have been compromised through this document please see our Take Down policy (available from <https://www.mmu.ac.uk/library/using-the-library/policies-and-guidelines>)

Prevalence and risk factors for diabetic neuropathy and painful diabetic neuropathy in primary and secondary healthcare in Qatar

Georgios Ponirakis^{1,2} , Tarik Elhadd^{3,4}, Subitha Chinnaiyan³, Abdul H Hamza⁵, Sanaulla Sheik⁶, Mohamed A Kalathingai⁷, Mohamed S Anodiyil⁸, Zeinab Dabbous³, Mashhood A Siddique³, Hamad Almuhanadi¹, Ioannis N Petropoulos¹, Adnan Khan¹ , Khaled AE Ashawesh⁴, Khaled M Dukhan⁴, Ziyad R Mahfoud¹, Mahmoud A Zirie³, Amin Jayyousi³, Christopher Murgatroyd², Mark Slevin², Rayaz A Malik^{1,2,3,9*} 

¹Weill Cornell Medicine-Qatar, Qatar Foundation, Education City, Doha, Qatar, ²Faculty of Science and Engineering, Manchester Metropolitan University, Manchester, UK, ³National Diabetes Center, Hamad General Hospital, Hamad Medical Corporation, Doha, Qatar, ⁴National Diabetes Center, Al-Wakra Hospital, Hamad Medical Corporation, Doha, Qatar, ⁵Umm Ghuwailina Primary Health Care, Umm Ghuwailina, Qatar, ⁶Al Khor Primary Health Care, Al Khor, Qatar, ⁷Al Daayen Primary Health Care, Al Daayen, Qatar, ⁸Al Rayyan Primary Health Care, Al Rayyan, Qatar, and ⁹Institute of Cardiovascular Science, University of Manchester, Manchester, UK

Keywords

Diabetes neuropathy, Diagnosis, Painful neuropathy

*Correspondence

Rayaz A Malik
Tel.: +974-4492-8256
Fax: +974-4492-8422
E-mail address:
ram2045@qatar-med.cornell.edu

J Diabetes Investig 2020

doi: 10.1111/jdi.13388

ABSTRACT

Aims/Introduction: This study determined the prevalence and risk factors for diabetic peripheral neuropathy (DPN) and painful DPN (pDPN) in patients with type 2 diabetes in primary healthcare (PHC) and secondary healthcare (SHC) in Qatar.

Materials and Methods: This was a cross-sectional multicenter study. Adults with type 2 diabetes were randomly enrolled from four PHC centers and two diabetes centers in SHC in Qatar. Participants underwent assessment of clinical and metabolic parameters, DPN and pDPN.

Results: A total of 1,386 individuals with type 2 diabetes (297 from PHC and 1,089 from SHC) were recruited. The prevalence of DPN (14.8% vs 23.9%, $P = 0.001$) and pDPN (18.1% vs 37.5%, $P < 0.0001$) was significantly lower in PHC compared with SHC, whereas those with DPN at high risk for diabetic foot ulceration (31.8% vs 40.0%, $P = 0.3$) was comparable. The prevalence of undiagnosed DPN (79.5% vs 82.3%, $P = 0.66$) was comparably high, but undiagnosed pDPN (24.1% vs 71.5%, $P < 0.0001$) was lower in PHC compared with SHC. The odds of DPN and pDPN increased with age and diabetes duration, and DPN increased with poor glycemic control, hyperlipidemia and hypertension, whereas pDPN increased with obesity and reduced physical activity.

Conclusions: The prevalence of DPN and pDPN in type 2 diabetes is lower in PHC compared with SHC, and is attributed to overall better control of risk factors and referral bias due to patients with poorly managed complications being referred to SHC. However, approximately 80% of patients had not been previously diagnosed with DPN in PHC and SHC. Furthermore, we identified a number of modifiable risk factors for DPN and pDPN.

INTRODUCTION

Diabetic peripheral neuropathy (DPN) is the most common complication of diabetes and yet often remains undiagnosed¹. Late diagnosis can lead to significant morbidity in the form of painful DPN (pDPN)², erectile dysfunction³, diabetic foot ulceration (DFU)⁴ and amputation⁵, as well as increased mortality⁶.

Early diagnosis and management of DPN might limit or reduce disease progression¹. However, screening for DPN and pDPN is inadequate^{7–9}. The prevalence of DPN and pDPN have been shown to range from 2.4 to 24.1%^{10,11} and 16 to 19%^{12,13} in primary care, and 32.1%¹⁴ and 21.0%¹⁵ in secondary care in patients with type 2 diabetes, respectively. This wide range has been attributed to differing populations and methods used to identify DPN and pDPN. We have recently reported that approximately 80% of patients with DPN⁹ and pDPN²

Received 4 June 2020; revised 6 August 2020; accepted 10 August 2020

have not previously been diagnosed in hospital clinics in secondary health care (SHC) in Qatar, which might lead to late presentation with DFU. Indeed, in Qatar it has been reported that 25% of patients with diabetes in SHC have foot problems¹⁶. This has serious consequences given that one in four patients with DFU is at risk of amputation⁵, and the 5-year mortality of people with a DFU is higher than many common cancers¹⁷. Currently, the American Diabetes Association recommends annual screening of DPN at diagnosis of type 2 diabetes and 5 years after the diagnosis of type 1 diabetes by neurological examination or monofilament testing, but there is no specific recommendation for pDPN¹.

There are currently no US Food and Drug Administration (FDA) approved therapies for DPN⁶. Lifestyle interventions, including physical activity¹⁸ and avoidance of smoking^{19,20} are advised, and optimization of glycemic control^{19,21}, treatment of hypertension^{22,23} and hyperlipidemia^{20,24} might improve DPN. FDA approved medications for treating painful symptoms include duloxetine, pregabalin and tapentadol²⁵.

According to the International Diabetes Federation, the prevalence of diabetes in adults aged 20–79 years in Qatar was 15.5% in 2020²⁶, which is almost twofold greater than the 2019 reported prevalence of 8.3% in the rest of the world²⁷. Given the high prevalence of diabetes, in 2015 Qatar launched the National Diabetes Strategy to improve the management of people with diabetes and its complications by establishing common clinical care pathways within and between primary healthcare (PHC) and SHC. We have, therefore, applied the same methods and diagnostic criteria in patients with type 2 diabetes to establish the prevalence and risk factors for DPN and pDPN in PHC and SHC. We believe the findings of the present study will be key to planning strategies to enable earlier diagnosis and optimal management of the often forgotten complication of diabetic neuropathy in Qatar and the region.

METHODS

This was a cross-sectional, multicenter study. Individuals aged 18–85 years with type 2 diabetes mellitus were enrolled from four PHC centers (Umm Ghuwailina, Al Khor, Al Daayen and Al Rayyan) and the only two National Diabetes centers in Qatar (Hamad General Hospital and Al-Wakra Hospital). Participants were randomly enrolled and screened for eligibility on the day they attended the clinic for their diabetes review between June 2017 and February 2019. Exclusion criteria included type 1 diabetes and other causes of neuropathy, including severe vitamin B₁₂ deficiency, chronic hypothyroidism and chemotherapy.

The present study was approved by the institutional review board of Weill Cornell Medicine-Qatar and Hamad Medical Corporation. All participants gave informed consent to take part in the study. The research adhered to the tenets of the declaration of Helsinki.

Demographic and metabolic measures

Sex, ethnicity, age, duration of diabetes and body mass index were recorded. The average systolic and diastolic blood pressure of two readings were obtained from the participant's left arm while seated with the arm at heart level, using a standard zero mercury sphygmomanometer after 10–15 min of rest. A non-fasting blood sample was collected through venepuncture from each participant into ethylenediaminetetraacetic acid tubes and transported within 2 h to a central certified laboratory at Hamad General Hospital. Glycated hemoglobin, total cholesterol and triglyceride were measured by an autoanalyzer (Hitachi 747 autoanalyzer; Tokyo, Japan). Poor glycemic control was defined as glycated hemoglobin $\geq 9\%$. Hypertension was defined according to either an average systolic blood pressure ≥ 140 mmHg and/or the use of antihypertensive medication, as described in the World Health Organization/International Society of Hypertension guidelines²⁸. Hyperlipidemia was defined according to a total cholesterol level ≥ 6.2 mmol/L and/or triglyceride level of ≥ 2.3 mmol/L or if the patient was treated with a statin. Obesity was classified according to World Health Organization criteria with a body mass index ≥ 30 kg/m²²⁹. Current cigarette smoking was defined as having smoked at least one cigarette every day for ≥ 1 year preceding the study visit. Physical activity was defined as doing some physical activity, including walking for ≥ 30 min/day, at least three times a week over the past year.

Assessment of diabetic neuropathy and painful neuropathy

The diagnosis of DPN was based on the presence of one or more neuropathic symptoms and impaired vibration perception threshold (VPT) in the feet. Subjective neurological symptoms, such as burning pain, painful cold, electric shocks, tingling, pins and needles, and numbness, were acquired through a face-to-face interview with the investigators. VPT was measured by a Horwell neurothesiometer (Scientific Laboratory Supplies, Nottingham, UK) on the pulp of the large toe on both feet, and the average value of three measurements was recorded in volts (V) ranging from 0 to 50 V. A VPT ≥ 15 V was defined as impaired vibration perception consistent with the presence of DPN³⁰ and a VPT ≥ 25 V as high risk for DFU³¹.

Painful DPN was assessed using the Douleur Neuropathique en 4 (DN4) questionnaire in Arabic and English, as previously described³². The DN4 questionnaire has been validated for its ability to distinguish neuropathic pain from non-neuropathic pain³³ and in the Arabic version³⁴, and for pDPN³². It consists of 10 questions: seven questions relating to the pain description (burning, painful cold, electric shocks) and associated abnormal sensations (tingling, pins and needles, numbness, itching), and the other three neurological examination outcomes in the painful area for hypoesthesia to touch and pin prick using disposable examination pins and allodynia to brushing. The scoring is based on a yes (1 point) or no (0 point) answer, and each question is equally weighted. A score ≥ 4 has a high sensitivity (80%) and specificity (92%) for pDPN³². The questionnaire was

administered by the investigator in either English or Arabic. Previously diagnosed pDPN was self-reported. Medications for pDPN were recorded.

All investigators underwent a formal training session on the use and interpretation of the neurothesiometer and DN4 questionnaire.

Statistical analysis

The prevalence of DPN and pDPN across different demographics and risk factors as categorical variables were summarized using frequency distributions. Variables in patients with DPN or pDPN were compared between PHC and SHC using the χ^2 -test.

Binary logistic regression analysis was carried out with age, duration of diabetes, sex, poor glycemic control, obesity, hyperlipidemia, hypertension, physical activity, smoking, ethnicity and healthcare as independent variables, and DPN or pDPN as the dependent variable. The multiple logistic regression model included all variables with a P -value of ≤ 0.05 at the bivariate level. Adjusted odds ratios, their corresponding 95% confidence intervals and P -value are presented.

All analyses were carried out using IBM SPSS (version 26; SPSS Inc., Armonk, NY, USA). A two-tailed P -value of ≤ 0.05 was considered significant.

RESULTS

Prevalence of DPN and pDPN in PHC compared with SHC

A total of 1,386 individuals with type 2 diabetes were recruited from PHC ($n = 297$) and SHC ($n = 1,089$; Figure 1; Table 1). The prevalence of DPN (14.8% vs 23.9%, $P = 0.001$) was significantly lower in PHC compared with SHC. The percentage of patients undiagnosed with DPN was comparable (79.5% vs 82.3%, $P = 0.66$) between PHC and SHC. The prevalence of pDPN (18.1% vs 37.5%, $P < 0.0001$) and percentage of patients undiagnosed with pDPN (24.1% vs 71.5%, $P < 0.0001$) was significantly lower in PHC compared with SHC. The mean VPT (10.4 ± 7.2 V vs 12.5 ± 9.4 V, $P < 0.0001$), DN4 score (1.0 ± 1.6 vs 2.5 ± 2.6 , $P < 0.0001$) and percentage of patients with all neuropathic symptoms including burning, painful cold, electric shocks, tingling, pins and needles, numbness, and itching were significantly lower in PHC compared with SHC (Table 2). Although no patients in PHC had DFU, 6.2% had DFU in SHC. However, the prevalence of those at high risk for DFU was comparable (31.8% vs 40.0%, $P = 0.3$) between PHC and SHC.

Risk factor management in PHC compared with SHC

More patients with type 2 diabetes aged >60 years (30.5% vs 23.2%, $P = 0.001$) and fewer patients aged 20–50 years (29.8% vs 41.5%, $P = 0.001$) were under the care of PHC compared with SHC. The body mass index (29.8 kg/m^2 vs 31.5 kg/m^2 , $P = 0.0003$) and percentage of patients with obesity (40.8% vs 53.3%, $P = 0.001$) was significantly lower in PHC compared with SHC. Glycated hemoglobin was comparable, but the

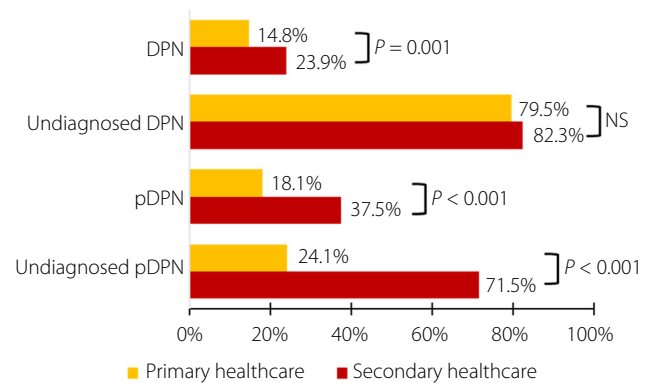


Figure 1 | Prevalence of diabetic peripheral neuropathy (DPN), painful diabetic neuropathy (pDPN), undiagnosed DPN and pDPN in type 2 diabetes in primary and secondary healthcare. NS, not significant.

percentage of patients with poor glycemic control (36.8% vs 44.0%, $P = 0.04$) was lower in PHC compared with SHC. In PHC, the total cholesterol (3.9 mmol/L vs 4.4 mmol/L, $P < 0.0001$) was lower and triglycerides were comparable compared with SHC. However, hyperlipidemia was present in a significantly lower percentage of patients in SHC compared with PHC (73.2% vs 80.3%, $P = 0.02$). The systolic and diastolic blood pressure, and percentage of patients with hypertension was comparable between PHC and SHC. More patients undertook physical activity (57.5% vs 38.2%, $P < 0.0001$), and fewer patients smoked cigarettes (9.9% vs 17.3%, $P = 0.003$) in PHC compared with SHC.

Association of risk factors for DPN in PHC and SHC

The odds of developing DPN increased by 2.4-fold in patients aged 51–60 years ($P < 0.0001$), and 2.9-fold in those aged >60 years compared with patients aged 20–50 years ($P < 0.0001$; Table 3). The odds increased 2.2-fold with 11–20 years of diabetes ($P < 0.0001$), to 3.9-fold with >20 years of diabetes ($P < 0.0001$) compared with ≤ 10 years of diabetes. The odds for DPN was 1.4-fold greater in men ($P = 0.02$). The odds increased 1.5-fold in those with poor glycemic control ($P = 0.02$), and 1.6-fold in patients treated with insulin and other antidiabetic therapy compared with patients treated with metformin and other antidiabetic therapy ($P = 0.006$). The odds increased 1.8-fold in those with hyperlipidemia ($P = 0.006$), and 1.5-fold in those with hypertension ($P = 0.05$). The association with obesity and ethnicity for DPN was lost after controlling for risk factors. However, even after adjusting for all risk factors, the odds of developing DPN in SHC remained 2.1-fold higher than in PHC ($P = 0.001$).

Association of risk factors for pDPN in PHC and SHC

The odds of developing pDPN was 1.5-fold greater in patients aged >50 years ($P = 0.02$) compared with those aged 20–

Table 1 | Prevalence of diabetic peripheral neuropathy, painful diabetic neuropathy, undiagnosed diabetic peripheral neuropathy and painful diabetic neuropathy, and those at high risk of diabetic foot ulceration and their risk factors in type 2 diabetes in primary and secondary healthcare

	Primary health care		Secondary health care		P-value PHC vs SHC
Diabetic peripheral neuropathy	44/297	14.8%	260/1,089	23.9%	0.001
High risk for diabetic foot ulceration	14/44	31.8%	104/260	40.0%	0.30
Diabetic foot ulcer	0/44	0.0%	16/260	6.2%	0.13
Painful diabetic neuropathy	54/298	18.1%	410/1,092	37.5%	<0.0001
Undiagnosed cases					
Undiagnosed diabetic peripheral neuropathy	35/44	79.5%	214/260	82.3%	0.66
Undiagnosed painful diabetic neuropathy	13/54	24.1%	293/410	71.5%	<0.0001
Risk factors					
Age					
20–50 years	88/295	29.8% [†]	445/1,073	41.5% [‡]	0.001
51–60 years	117/295	39.7% [†]	379/1,073	35.3% [†]	
>60 years	90/295	30.5% [†]	249/1,073	23.2% [‡]	
Duration of diabetes					
≤10 years	204/296	68.9% [†]	690/1,080	63.9% [†]	0.26
11–20 years	73/296	24.7% [†]	303/1,080	28.1% [†]	
>20 years	19/296	6.4% [†]	87/1,080	8.1% [†]	
Lifestyle modifiable risk factors					
Physical activity	158/275	57.5% [†]	326/854	38.2% [‡]	<0.0001
Smoking	27/274	9.9%	157/909	17.3%	0.003
Cardiovascular modifiable risk factors					
Poor glycemic control	98/266	36.8% [†]	436/991	44.0% [‡]	0.04
Hyperlipidemia	208/259	80.3% [†]	738/1,008	73.2% [‡]	0.02
Hypertension	176/274	64.2% [†]	669/1,040	64.3% [†]	0.98
Obesity	87/213	40.8% [†]	510/957	53.3% [‡]	0.001
Systolic blood pressure (mmHg)	131.7 ± 15.5		132.5 ± 18.0		0.42
Diastolic blood pressure (mmHg)	78.8 ± 8.0		78.2 ± 10.2		0.32
BMI (kg/m ²)	29.8 ± 5.4		31.5 ± 7.4		0.0003
HbA1c (mmol/mol)	63.1 ± 19.7		65.5 ± 21.9		0.08
HbA1c (%)	7.9 ± 1.8		8.1 ± 2.0		0.08
Cholesterol (mmol/L)	3.9 ± 1.0		4.4 ± 1.2		<0.0001
Triglyceride (mmol/L)	1.8 ± 1.0		1.8 ± 1.2		0.96

Variables were summarized using means and standard deviations for numeric variables, and frequency distribution for categorical variables. Continuous and categorical variables were compared using unpaired *t*-test and χ^2 -test, respectively. [†]†Rows with the same symbols are not statistically significant, and different symbols are significantly different. BMI, body mass index; HbA1c, glycated hemoglobin; PHC, primary healthcare; SHC, secondary healthcare.

50 years ($P < 0.0001$; Table 4). The odds increased from 2.2-fold with 11–20 years of diabetes ($P < 0.0001$) to 4.4-fold with >20 years of diabetes ($P < 0.0001$) compared with ≤10 years of diabetes. The odds also increased by 1.7-fold in participants treated with insulin/plus other antidiabetic therapy compared with those treated with metformin/plus other antidiabetic therapy ($P < 0.0001$). The odds increased 1.6-fold with obesity ($P = 0.002$), and 1.4-fold in Arab participants compared with South Asian participants ($P = 0.03$). However, the odds decreased by 1.7-fold with physical activity ($P = 0.01$). The association of poor glycemic control, hyperlipidemia, hypertension and sex with pDPN was lost after controlling for these risk factors. However, even after adjusting for all risk factors, the odds of developing pDPN in SHC was 2.4-fold higher than in PHC ($P < 0.0001$).

DISCUSSION

The present study shows that the prevalence of DPN is 1.6-fold lower and pDPN is twofold lower in PHC compared with SHC. Furthermore, the percentage of patients with undiagnosed DPN (~80%) and those at risk of DFU (32–40%) was extremely high, and comparable between PHC and SHC, despite the introduction of national diabetes care pathways. DPN was associated with poor glycemic control, hyperlipidemia and hypertension, whereas pDPN was associated with obesity, and was lower in patients undertaking physical activity at least 3 days per week. The higher prevalence of DPN and pDPN in SHC remained significant, even after controlling for risk factors. This might partly be attributed to referral bias, with more patients with poorer control of risk factors and diabetic complication being referred to SHC.

Table 2 | Mean vibration perception threshold, Douleur Neuropathique en 4 questionnaire score, and percentage of neuropathic symptoms in type 2 diabetes in primary and secondary healthcare

	PHC	SHC	P-value PHC vs SHC
Vibration perception threshold (V)	10.4 ± 7.2	12.5 ± 9.4	<0.0001
DN4 score	1.0 ± 1.6	2.5 ± 2.6	<0.0001
Burning pain (%)	22.6	46.7	<0.0001
Painful cold (%)	7.7	26.5	<0.0001
Electric shocks (%)	5.1	22.3	<0.0001
Tingling (%)	20.2	32.0	<0.0001
Pins and needles (%)	16.2	35.1	<0.0001
Numbness (%)	12.5	42.0	<0.0001
Itching (%)	7.8	16.7	<0.0001

Variables were summarized using means and standard deviations for numeric variables and frequency distribution for categorical variables. Continues and categorical variables were compared using unpaired *t*-test and χ^2 , respectively. DN4, Douleur Neuropathique en 4 questionnaire; PHC, primary healthcare; SHC, secondary healthcare.

Table 3 | Predictors for diabetic peripheral neuropathy in primary and secondary healthcare

Diabetic peripheral neuropathy	AOR	95% CI	P-value
Sex			
Male	1		
Female	0.7	0.5–0.9	0.02
Ethnic groups			
Arabs	1		
South Asians	0.8	0.5–1.1	0.19
Age			
20–50 years	1		
51–60 years	2.4	1.6–3.5	<0.0001
>60 years	2.9	1.9–4.5	<0.0001
Duration of diabetes			
≤10 years	1		
11–20 years	2.2	1.6–3.0	<0.0001
>20 years	3.9	2.4–6.4	<0.0001
Poor glycemic control	1.5	1.1–2.0	0.02
Hyperlipidemia	1.8	1.2–2.8	0.006
Hypertension	1.5	1.0–2.2	0.05
Obesity	1.3	0.9–1.8	0.20
Antidiabetic therapy			
Metformin/plus	1		
Insulin/plus	1.6	1.2–2.3	0.006
Primary healthcare	1		
Secondary healthcare	2.1	1.4–3.2	0.001

The multiple logistic regression model included all variables with *P*-values of ≤0.05 at the bivariate level. Adjusted odds ratios (AOR), their corresponding 95% confidence intervals (CI) and *P*-value are presented.

The DN4 questionnaire was chosen to define pDPN for three reasons: (i) its diagnostic ability to distinguish neuropathic pain from non-neuropathic pain, including osteoarthritis, inflammation and mechanical low back pain (common differentials, especially in PHC) for which it has been validated with

Table 4 | Predictors for diabetic painful neuropathy in primary and secondary healthcare

Painful neuropathy	AOR	95% CI	P-value
Sex			
Male	1		
Female	1.2	0.9–1.6	0.32
Ethnic groups			
Arabs	1		
South Asians	0.7	0.5–1.0	0.03
Age			
20–50 years	1		
51–60 years	1.5	1.1–2.0	0.02
>60 years	1.5	1.1–2.2	0.02
Duration of diabetes			
≤10 years	1		
11–20 years	2.2	1.6–3.0	<0.0001
>20 years	4.4	2.7–7.1	<0.0001
Poor glycemic control	1.2	0.9–1.6	0.2
Hyperlipidemia	1.1	0.8–1.5	0.58
Hypertension	1.3	0.9–1.8	0.13
Obesity	1.6	1.2–2.2	0.002
Physical activity	0.6	0.4–0.9	0.01
Antidiabetic therapy			
Metformin/plus other therapy	1		
Insulin/plus	1.7	1.3–2.4	<0.0001
Primary healthcare	1		
Secondary healthcare	2.4	1.6–3.5	<0.0001

The multiple logistic regression model included all variables with *P*-value of ≤0.05 at the bivariate level. Adjusted odds ratios (AOR), their corresponding 95% confidence intervals (CI) and *P*-value are presented.

86% sensitivity and 83% specificity³³; (ii) its diagnostic ability specifically for pDPN with 80% sensitivity and 92% specificity³², and (iii) validation using the Arabic version showing 88% sensitivity and 75% specificity³⁴. The higher prevalence of

pDPN compared with DPN might be attributed to the criteria used to define these conditions. pDPN was defined according to DN4, whereas DPN was based on symptoms and an elevated VPT (>15 V).

There are currently no FDA approved therapies for DPN⁶. However, screening annually for symptoms and signs of DPN starting at diagnosis of type 2 diabetes is advocated on the basis that early management of risk factors for DPN might reduce the rate of disease progression, and treatment to relieve neuro-pathic symptoms might improve the patient's quality of life¹. We have recently assessed the prevalence of DPN and pDPN in SHC in Qatar^{2,9}. This is the first study to compare the prevalence of DPN and pDPN in PHC and SHC using the same criteria and in the same population. The prevalence of DPN in both PHC and SHC in Qatar is lower compared with the prevalence in SHC in other countries; for example, 37% in Bahrain¹⁹, 60% in Turkey²¹, 49% in Iran³⁵, 45% in the USA³⁶, 32% in the UK¹⁴, 31% in Italy³⁷ and 62% in China³⁸. The prevalence of pDPN is also lower in both SHC and PHC in Qatar compared with studies from SHC, with a reported prevalence of 65% in Saudi Arabia³⁹, 61% in Egypt⁴⁰, 58% in Jordan and 54% in Lebanon.

Despite the introduction of national diabetes pathways in Qatar, the present study confirms an alarmingly high prevalence of undiagnosed DPN in PHC and SHC^{2,9}. It highlights the considerable need to educate both patients and physicians on DPN and pDPN⁴¹. This might explain why up to 25% of patients with diabetes in SHC in Qatar have foot problems¹⁶. Currently, DPN is not assessed systematically, even using the 10-g monofilament, which in itself identifies only those with advanced neuropathy¹. Given that one in four patients with DFU are at risk of amputation⁵, the present study highlights the need for the National Diabetes Strategy to implement annual DPN screening in PHC and SHC. This should be carried out using evidence-based screening tests to detect incipient small fiber damage to detect sudomotor dysfunction using Sudoscan⁴² or Neuropad⁴³, or vibration perception using a neurothesiometer⁴⁴, or cold or warm perception thresholds using NerveCheck⁴⁵; as opposed to monofilament testing, which is convenient, but only detects advanced large fiber neuropathy. A common reason for the underdiagnosis of pDPN is that patients with symptoms are often unaware that the pain is related to DPN and do not report them to their physician^{13,46}. Questionnaire, such as the DN4³², and Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) pain scale⁴⁷, can be used to screen for neuropathic pain, and the Neuropathic Pain Scale (NPS)⁴⁸, Neuropathic Pain Symptom Inventory (NPSI)⁴⁹ and Diabetic Peripheral Neuropathic Pain Impact measure (DPNPI)⁵⁰ can characterize subgroups of neuropathic pain patients who might benefit from specific therapies, as well as monitor the impact of treatment⁵¹. Reassuringly, we show a much lower prevalence of patients with undiagnosed pDPN in PHC, which might reflect a more systematic approach to identify neuropathic symptoms as part of a general screen for

complications, as opposed to SHC, where there is no formal screening unless the physician refers for further assessment.

The lack of an FDA approved therapy for DPN often creates a negative attitude toward the need to diagnose early DPN⁵². However, the present study has identified a range of modifiable risk factors for DPN, including poor glycemic control^{19,21}, hypertension^{22,23} and hyperlipidemia^{20,24}, and for pDPN, including obesity^{40,53–55} and reduced physical activity^{56,57}. Although, intensive glycemic control is advocated, the data for an impact on DPN in type 2 diabetes patients are limited^{58–60}, and other cardiovascular risk factors, such as hypertension, hyperlipidemia and obesity, might play a more important role. Indeed, treatment with angiotensin converting enzyme inhibitors^{22,23}, statins^{61,62} or glucagon-like peptide-1 receptor agonists^{63–65} might have a beneficial effect on DPN.

A limitation of the present study was the relatively small number of participants from PHC, thus limiting the generalizability of the findings. A further limitation was the cross-sectional design of this study, which limited the predictive validity of the observed associations between the various risk factors with DPN and pDPN.

In conclusion, the present study identified a lower prevalence of DPN and pDPN in PHC compared with SHC, which might be attributed to better overall risk factor control in PHC and referral bias due to patients who are poorly managed with complications being referred to SHC. Alarmingly, an equally high proportion (~80%) of patients with DPN were undiagnosed in both PHC and SHC, highlighting the need for the National Diabetes Strategy to implement annual DPN screening. The identification of hyperglycemia, hyperlipidemia and hypertension as modifiable risk factors for DPN, and obesity and physical activity as modifiable risk factors of pDPN provide a robust argument to establish protocols for the early diagnosis and management of DPN and pDPN.

ACKNOWLEDGMENTS

We thank all the participants for their efforts, will and commitment to be involved in the study. Qatar National Research Fund, Grant BMRP-5726113101; Pfizer Gulf FZ LLC, W1230787

DISCLOSURE

The authors declare no conflict of interest.

REFERENCES

1. Pop-Busui R, Boulton AJ, Feldman EL, et al. Diabetic neuropathy: a position statement by the American Diabetes Association. *Diabetes Care* 2017; 40: 136–154.
2. Ponirakis G, Elhadd T, Chinnaiyan S, et al. Prevalence and risk factors for painful diabetic neuropathy in secondary healthcare in Qatar. *J Diabetes Investig* 2019; 10: 1558–1564.
3. Kouidrat Y, Pizzol D, Cosco T, et al. High prevalence of erectile dysfunction in diabetes: a systematic review and meta-analysis of 145 studies. *Diabet Med* 2017; 34: 1185–1192.

4. Raghav A, Khan ZA, Labala RK, *et al.* Financial burden of diabetic foot ulcers to world: a progressive topic to discuss always. *Ther Adv Endocrinol Metab* 2018; 9: 29–31.
5. Apelqvist J, Agardh CD. The association between clinical risk factors and outcome of diabetic foot ulcers. *Diabetes Res Clin Pract* 1992; 18: 43–53.
6. Azmi S, Ferdousi M, Kalteniece A, *et al.* Diagnosing and managing diabetic somatic and autonomic neuropathy. *Ther Adv Endocrinol Metab* 2019; 10: 2042018819826890.
7. Herman WH, Kennedy L. Underdiagnosis of peripheral neuropathy in type 2 diabetes. *Diabetes Care* 2005; 28: 1480–1481.
8. Wang W, Balamurugan A, Biddle J, *et al.* Diabetic neuropathy status and the concerns in underserved rural communities: challenges and opportunities for diabetes educators. *Diabetes Educ* 2011; 37: 536–548.
9. Ponirakis G, Elhadd T, Chinnaiyan S, *et al.* Prevalence and management of diabetic neuropathy in secondary care in Qatar. *Diabetes Metab Res Rev* 2020; 36: e3286.
10. Cabezas-Cerrato J. The prevalence of clinical diabetic polyneuropathy in Spain: a study in primary care and hospital clinic groups. Neuropathy Spanish Study Group of the Spanish Diabetes Society (SDS). *Diabetologia* 1998; 41: 1263–1269.
11. Kostev K, Jockwig A, Hallwachs A, *et al.* Prevalence and risk factors of neuropathy in newly diagnosed type 2 diabetes in primary care practices: a retrospective database analysis in Germany and U.K. *Prim Care Diabetes* 2014; 8: 250–255.
12. Davies M, Brophy S, Williams R, *et al.* The prevalence, severity, and impact of painful diabetic peripheral neuropathy in type 2 diabetes. *Diabetes Care* 2006; 29: 1518–1522.
13. Daousi C, MacFarlane IA, Woodward A, *et al.* Chronic painful peripheral neuropathy in an urban community: a controlled comparison of people with and without diabetes. *Diabet Med* 2004; 21: 976–982.
14. Young MJ, Boulton AJ, MacLeod AF, *et al.* A multicentre study of the prevalence of diabetic peripheral neuropathy in the United Kingdom hospital clinic population. *Diabetologia* 1993; 36: 150–154.
15. Abbott CA, Malik RA, van Ross ER, *et al.* Prevalence and characteristics of painful diabetic neuropathy in a large community-based diabetic population in the U.K. *Diabetes Care* 2011; 34: 2220–2224.
16. Al-Thani AA, Farghaly A, Akram H, *et al.* Knowledge and perception of diabetes and available services among diabetic patients in the state of Qatar. *Cent Asian J Glob Health* 2019; 8: 333.
17. Armstrong DG, Wrobel J, Robbins JM. Guest Editorial: are diabetes-related wounds and amputations worse than cancer? *Int Wound J* 2007; 4: 286–287.
18. Al-Kaabi JM, Al-Maskari F, Zoubeid T, *et al.* Prevalence and determinants of peripheral neuropathy in patients with type 2 diabetes attending a tertiary care center in the United Arab Emirates. *J Diabetes Metab* 2014; 5: 1–7.
19. Al-Mahroos F, Al-Roomi K. 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. *Ann Saudi Med* 2007; 27: 25–31.
20. Tesfaye S, Chaturvedi N, Eaton SE, *et al.* Vascular risk factors and diabetic neuropathy. *N Engl J Med* 2005; 352: 341–350.
21. Boru UT, Alp R, Sargin H, *et al.* Prevalence of peripheral neuropathy in type 2 diabetic patients attending a diabetes center in Turkey. *Endocr J* 2004; 51: 563–567.
22. Malik RA, Williamson S, Abbott C, *et al.* Effect of angiotensin-converting-enzyme (ACE) inhibitor trandolapril on human diabetic neuropathy: randomised double-blind controlled trial. *Lancet* 1998; 352: 1978–1981.
23. Reja A, Tesfaye S, Harris ND, *et al.* Is ACE inhibition with lisinopril helpful in diabetic neuropathy? *Diabet Med* 1995; 12: 307–309.
24. Smith AG, Singleton JR. Obesity and hyperlipidemia are risk factors for early diabetic neuropathy. *J Diabetes Complications* 2013; 27: 436–442.
25. Javed S, Petropoulos IN, Alam U, *et al.* Treatment of painful diabetic neuropathy. *Ther Adv Chronic Dis* 2015; 6: 15–28.
26. IDF Middle East and North Africa Region. Prevalence of diabetes in adults in Qatar 2020. Available from: <https://idf.org/our-network/regions-members/middle-east-and-north-africa/members/45-qatar.html> Accessed March 2020.
27. International Diabetes Federation. IDF DIABETES ATLAS 9th edition 2019. Available from: <https://www.diabetesatlas.org/en/sections/demographic-and-geographic-outline.html> Accessed March 2020.
28. Moser M. World Health Organization-International Society of Hypertension Guidelines for the Management of Hypertension-Do These Differ From the U.S. Recommendations? Which guidelines should the practicing physician follow? *J Clin Hypertens (Greenwich)* 1999; 1: 48–54.
29. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organ Tech Rep Ser* 2000; 894: i–xii, 1–253.
30. Wiles PG, Pearce SM, Rice PJ, *et al.* Vibration perception threshold: influence of age, height, sex, and smoking, and calculation of accurate centile values. *Diabet Med* 1991; 8: 157–161.
31. Young MJ, Breddy JL, Veves A, *et al.* The prediction of diabetic neuropathic foot ulceration using vibration perception thresholds – a prospective-study. *Diabetes Care* 1994; 17: 557–560.
32. Spallone V, Morganti R, D'Amato C, *et al.* Validation of DN4 as a screening tool for neuropathic pain in painful diabetic polyneuropathy. *Diabet Med* 2012; 29: 578–585.
33. Bouhassira D, Attal N, Alchaar H, *et al.* Comparison of pain syndromes associated with nervous or somatic lesions and

- development of a new neuropathic pain diagnostic questionnaire (DN4). *Pain* 2005; 114: 29–36.
34. Terkawi AS, Abolkhair A, Didier B, *et al.* Development and validation of Arabic version of the douleur neuropathique 4 questionnaire. *Saudi J Anaesth* 2017; 11(Suppl 1): S31–S39.
 35. Kiani J, Moghimbeigi A, Azizkhani H, *et al.* The prevalence and associated risk factors of peripheral diabetic neuropathy in Hamedan, Iran. *Arch Iran Med* 2013; 16: 17–19.
 36. Mold JW, Vesely SK, Keyl BA, *et al.* The prevalence, predictors, and consequences of peripheral sensory neuropathy in older patients. *J Am Board Fam Pract* 2004; 17: 309–318.
 37. Salvotelli L, Stoico V, Perrone F, *et al.* Prevalence of neuropathy in type 2 diabetic patients and its association with other diabetes complications: The Verona Diabetic Foot Screening Program. *J Diabetes Complications* 2015; 29: 1066–1070.
 38. Lu B, Yang Z, Wang M, *et al.* High prevalence of diabetic neuropathy in population-based patients diagnosed with type 2 diabetes in the Shanghai downtown. *Diabetes Res Clin Pract* 2010; 88: 289–294.
 39. Halawa MR, Karawagh A, Zeidan A, *et al.* Prevalence of painful diabetic peripheral neuropathy among patients suffering from diabetes mellitus in Saudi Arabia. *Curr Med Res Opin* 2010; 26: 337–343.
 40. Jambart S, Ammache Z, Haddad F, *et al.* Prevalence of painful diabetic peripheral neuropathy among patients with diabetes mellitus in the Middle East region. *J Int Med Res* 2011; 39: 366–377.
 41. Malik RA, Andag-Silva A, Dejthevaporn C, *et al.* Diagnosing peripheral neuropathy in South-East Asia: a focus on diabetic neuropathy. *J Diabetes Investig* 2020; 11: 1097–1103.
 42. Selvarajah D, Cash T, Davies J, *et al.* SUDOSCAN: a simple, rapid, and objective method with potential for screening for diabetic peripheral neuropathy. *PLoS One* 2015; 10: e0138224.
 43. Ponirakis G, Petropoulos IN, Fadavi H, *et al.* The diagnostic accuracy of Neuropad for assessing large and small fibre diabetic neuropathy. *Diabet Med* 2014; 31: 1673–1680.
 44. Bril V, Perkins BA. Comparison of vibration perception thresholds obtained with the Neurothesiometer and the CASE IV and relationship to nerve conduction studies. *Diabet Med* 2002; 19: 661–666.
 45. Ponirakis G, Odriozola MN, Odriozola S, *et al.* NerveCheck: an inexpensive quantitative sensory testing device for patients with diabetic neuropathy. *Diabetes Res Clin Pract* 2016; 113: 101–107.
 46. Eichholz M, Alexander AH, Cappelleri JC, *et al.* Perspectives on the impact of painful diabetic peripheral neuropathy in a multicultural population. *Clin Diabetes Endocrinol* 2017; 3: 12.
 47. Bennett M. The LANSS Pain Scale: the Leeds assessment of neuropathic symptoms and signs. *Pain* 2001; 92: 147–157.
 48. Jensen MP, Friedman M, Bonzo D, *et al.* The validity of the neuropathic pain scale for assessing diabetic neuropathic pain in a clinical trial. *Clin J Pain* 2006; 22: 97–103.
 49. Bouhassira D, Attal N, Fermanian J, *et al.* Development and validation of the Neuropathic Pain Symptom Inventory. *Pain* 2004; 108: 248–257.
 50. Brod M, Blum SI, Bushnell DM, *et al.* Development and validation of the Diabetic Peripheral Neuropathic Pain Impact (DPNPI) measure, a patient-reported outcome measure. *Qual Life Res* 2015; 24: 3001–3014.
 51. Attal N, Bouhassira D, Baron R. Diagnosis and assessment of neuropathic pain through questionnaires. *Lancet Neurol* 2018; 17: 456–466.
 52. Malik RA, Aldinc E, Chan SP, *et al.* Perceptions of painful diabetic peripheral neuropathy in South-East Asia: results from patient and physician surveys. *Adv Ther* 2017; 34: 1426–1437.
 53. Van Acker K, Bouhassira D, De Bacquer D, *et al.* Prevalence and impact on quality of life of peripheral neuropathy with or without neuropathic pain in type 1 and type 2 diabetic patients attending hospital outpatients clinics. *Diabetes Metab* 2009; 35: 206–213.
 54. Ziegler D, Landgraf R, Lobmann R, *et al.* Painful and painless neuropathies are distinct and largely undiagnosed entities in subjects participating in an educational initiative (PROTECT study). *Diabetes Res Clin Pract* 2018; 139: 147–154.
 55. Aslam A, Singh J, Rajbhandari S. Prevalence of painful diabetic neuropathy using the self-completed leeds assessment of neuropathic symptoms and signs questionnaire in a population with diabetes. *Can J Diabetes* 2015; 39: 285–295.
 56. Ziegler D, Rathmann W, Meisinger C, *et al.* Prevalence and risk factors of neuropathic pain in survivors of myocardial infarction with pre-diabetes and diabetes. The KORA Myocardial Infarction Registry. *Eur J Pain* 2009; 13: 582–587.
 57. Smith AG, Russell J, Feldman EL, *et al.* Lifestyle intervention for pre-diabetic neuropathy. *Diabetes Care* 2006; 29: 1294–1299.
 58. Ohkubo Y, Kishikawa H, Araki E, *et al.* Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. *Diabetes Res Clin Pract* 1995; 28: 103–117.
 59. Ismail-Beigi F, Craven T, Banerji MA, *et al.* Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. *Lancet* 2010; 376: 419–430.
 60. Pop-Busui R, Lu J, Brooks MM, *et al.* Impact of glycemic control strategies on the progression of diabetic peripheral neuropathy in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) Cohort. *Diabetes Care* 2013; 36: 3208–3215.
 61. Davis TM, Yeap BB, Davis WA, *et al.* Lipid-lowering therapy and peripheral sensory neuropathy in type 2 diabetes: the Fremantle Diabetes Study. *Diabetologia* 2008; 51: 562–566.

62. Villegas-Rivera G, Roman-Pintos LM, Cardona-Munoz EG, *et al.* Effects of Ezetimibe/Simvastatin and Rosuvastatin on oxidative stress in diabetic neuropathy: a randomized, double-blind, placebo-controlled clinical trial. *Oxid Med Cell Longev* 2015; 2015: 756294.
63. Kan M, Guo G, Singh B, *et al.* Glucagon-like peptide 1, insulin, sensory neurons, and diabetic neuropathy. *J Neuropathol Exp Neurol* 2012; 71: 494–510.
64. Himeno T, Kamiya H, Naruse K, *et al.* Beneficial effects of exendin-4 on experimental polyneuropathy in diabetic mice. *Diabetes* 2011; 60: 2397–2406.
65. Ponirakis G, Abdul-Ghani MA, Jayyousi A, *et al.* Effect of treatment with exenatide and pioglitazone or basal-bolus insulin on diabetic neuropathy: a substudy of the Qatar Study. *BMJ Open Diabetes Res Care* 2020; 8: e001420.