

Prevalence and risk factors for diabetic peripheral neuropathy, neuropathic pain and foot ulceration in the Arabian Gulf region

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Keywords

Diabetic foot ulceration, Diabetic peripheral neuropathy, Painful diabetic peripheral neuropathy

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ABSTRACT

Aims/Introduction: This study determined the prevalence and risk factors for diabetic peripheral neuropathy (DPN), painful DPN and diabetic foot ulceration (DFU) in patients with type 2 diabetes in secondary healthcare in Qatar, Kuwait and the Kingdom of Saudi Arabia.

Materials and Methods: Adults aged 18–85 years with type 2 diabetes were randomly enrolled from secondary healthcare, and underwent clinical and metabolic assessment. DPN was evaluated using vibration perception threshold and neuropathic symptoms and painful Diabetic Peripheral Neuropathy was evaluated using the Douleur Neuropathique 4 questionnaire.

Results: A total of 3,021 individuals were recruited between June 2017 and May 2019. The prevalence of DPN was 33.3%, of whom 52.2% were at risk of DFU and 53.6% were undiagnosed. The prevalence of painful DPN was 43.3%, of whom 54.3% were undiagnosed. DFU was present in 2.9%. The adjusted odds ratios for DPN and painful DPN were higher with increasing diabetes duration, obesity, poor glycemic control and hyperlipidemia, and lower with greater physical activity. The adjusted odds ratio for DFU was higher with the presence of DPN, severe loss of vibration perception, hypertension and vitamin D deficiency.

Conclusions: This is the largest study to date from the Middle East showing a high prevalence of undiagnosed DPN, painful DPN and those at risk of DFU in patients with type 2 diabetes, and identifies their respective risk factors.

INTRODUCTION

Diabetic peripheral neuropathy (DPN) can lead to significant morbidity, including painful DPN and diabetic foot ulceration (DFU)¹. One in four patients with DFU are at risk of amputation², and their risk of death is increased 2.5-fold³. There is

high variability in the prevalence of DPN depending on the population and diagnostic criteria of DPN of the study. The prevalence of DPN has been reported to be 17–53% in the Middle East and North Africa^{4, 5}, 27–32% in Europe^{6,7}, 21–45% in the USA⁸, and 17–62% in China⁹. There is no approved treatment for DPN.¹⁰ Identifying and managing the risk factors for DPN are key to delay or prevent the development of DPN¹. DPN in type 2 diabetes is associated with age, duration of diabetes¹¹, hyperglycemia¹², obesity and hyperlipidemia^{13,14}.

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The American Diabetes Association advocates screening for DPN at diagnosis of type 2 diabetes and thereafter annually¹. According to the 2013 *IDF Diabetes Atlas*, Qatar, Kuwait and the Kingdom of Saudi Arabia (KSA) were in the world's top 10 countries for the prevalence of diabetes (22.9–23.9%). However, these Gulf Arab states have undergone rapid healthcare transformation with the implementation of disease prevention strategies and provision of universal health coverage, and according to the 2019 *IDF Diabetes Atlas*, the prevalence of diabetes has been reduced by 7–10%. There is a need for a multicenter study to determine the prevalence and risk factors for DPN, painful DPN and DFU using a standardized methodology in the Middle East.

Using the same methods and diagnostic criteria, the present study determined the overall and individual prevalence and associated risk factors for DPN, painful DPN and DFU in patients with type 2 diabetes attending four major secondary healthcare (SHC) diabetes centers in Qatar, Kuwait and KSA.

MATERIALS AND METHODS

This was a cross-sectional multicenter study. Individuals with type 2 diabetes aged between 18 and 85 years were randomly enrolled from the Diabetes Clinic in Hamad General Hospital and Al-Wakra Hospital in Qatar, Dasman Diabetes Institute in Kuwait, and Obesity Endocrine and Metabolism Center at King Fahad Medical City in KSA. Exclusion criteria included type 1 diabetes, chemotherapy, severe vitamin B₁₂ deficiency and hypothyroidism. Participants were enrolled on the day they attended the clinic for their diabetes review between June 2017 and May 2019. The present study received ethical approval from the Weill Cornell Medicine-Qatar (WCM-Q) IRB (IRB# 15-00078) and Hamad Medical Corporation (HMC) IRB (IRB# 16324/16) in Qatar, Dasman Center for Research and Treatment of Diabetes in Kuwait IRB (IRB# IRBH1 IORG0005964), and King Fahad Medical City in KSA IRB (IRB# IRB00010471). All participants consented to take part in the study. The study acted in accord to the tenets of the Declaration of Helsinki.

Demographic and clinical characteristics

Age, sex, diabetes duration, blood pressure, body weight, body mass index, glycated hemoglobin (HbA1c), lipid profile, vitamin B₁₂ and D, thyroid-stimulating hormone, free thyroxine, and medications were recorded.

Poor glycemic control was defined by a HbA1c $\geq 7\%$ ¹⁵. Hypertension was defined by a mean systolic blood pressure ≥ 140 mmHg or the use of blood pressure drugs¹⁶. Hyperlipidemia was defined by a total cholesterol ≥ 6.2 mmol/L, triglyceride ≥ 2.3 mmol/L or the use of statin, as described in the Mayo Clinic Guidelines. Obesity was classified as a body mass index ≥ 30 kg/m²¹⁷. Smoking cigarettes was defined by one or more cigarette/day over the past year. Physical activity was self-reported and defined as ≥ 30 min walking per day, three or more times in a week over the past year. Vitamin D was defined as normal (≥ 30 ng/mL), mild deficiency (20–29 ng/

mL), moderate deficiency (10–19 ng/mL) and severe deficiency (< 10 ng/mL)¹⁸.

DPN, painful DPN and DFU assessments

Vibration perception threshold (VPT) ranging from 0 to 50 V was assessed using a neurothesiometer (Horwell; Scientific Laboratory Supplies, Wilford, UK) on the pulp of the large toe of both feet. The assessment was repeated three times and the mean value was recorded. Instead of using a 128-Hz tuning fork, the cut-off of ≥ 15 V was used for detecting impaired VPT¹⁹.

The diagnosis of DPN is principally a clinical one and in line with the American Diabetes Association recommendation¹. DPN was defined based on one or more neuropathic symptom/s (numbness, burning pain, electric shocks, tingling, pins and needles and painful cold) and impaired VPT in the feet. Previously diagnosed DPN was self-reported. High risk of DFU was defined as a VPT ≥ 25 V¹⁹.

Painful DPN was defined by the presence of neuropathic pain using the Douleur Neuropathique 4 (DN4) questionnaire based on $\geq 4/10$ score²⁰ or the use of drugs for painful DPN. It has been validated for painful DPN (sensitivity 80%, specificity 92%)²⁰ and in the Arabic version²¹. It has three questions about pain description (burning, painful cold, electric shocks), four questions about abnormal sensations (tingling, pins and needles, numbness, itching) and three questions about neurological signs in the painful area (hypoesthesia to touch and pin prick, and allodynia to brushing). The questions are equally weighted, and 1 point is added for each positive answer. The DN4 was administered to the participant in English or Arabic. Previously diagnosed painful DPN was self-reported.

DFU was defined based on a break in the epidermis or dermis of the foot as per the International Working Group on the Diabetic Foot guidelines.²²

Training on the use and interpretation of the neurothesiometer and DN4 questionnaire was given to all investigators.

Statistical analysis

The prevalence of DPN, undiagnosed DPN, high risk of DFU, DFU, painful DPN, undiagnosed painful DPN, and demographic and clinical characteristics were summarized as categorical variables using frequency distributions, and compared between Qatar, Kuwait and KSA using the χ^2 -test.

In the binary logistic regression analysis, the independent variables were sex, age, diabetes duration, poor glycemic control, hyperlipidemia, hypertension, obesity, physical activity, smoking cigarettes and vitamin D deficiency, and the dependent variables were DPN, painful DPN and DFU. The variables with $P \leq 0.05$ at the bivariate level were included in the multiple logistic regression. Adjusted odds ratios (AOR), 95% confidence intervals (CI) and P -values are presented.

IBM SPSS (version 27; SPSS Inc, Armonk, NY, USA) was used for analyses. A two-tailed $P \leq 0.05$ was considered significant.

RESULTS

A total of 3,021 individuals with type 2 diabetes were recruited from four SHC centers in Qatar (*n* = 1,093), Kuwait (*n* = 1,168), and KSA (*n* = 760). Table 1 shows a comparison of demographic and clinical characteristics in patients with type 2 diabetes in SHC between Qatar, Kuwait and KSA.

Prevalence of DPN, painful DPN and foot ulceration

The overall prevalence of DPN was 33.3%, of whom 53.6% were undiagnosed (Figure 1; Table S1). The lowest prevalence of DPN was in Qatar compared with KSA and Kuwait (23.9 vs 35.9 vs 40.3%, *P* ≤ 0.0001). Kuwait had the lowest percentage of undiagnosed patients with DPN compared with KSA and Qatar (35.5 vs 57.5 vs 82.3%, *P* ≤ 0.0001). A total of 52.2% of those with DPN were at high risk of DFU, with the lowest prevalence being in Qatar compared with Kuwait and KSA (40.0 vs 54.9% and 59.3%, *P* ≤ 0.0001).

The highest percentage of patients with undiagnosed DPN was among those aged 20–50 years compared with those aged 51–60 years and >60 years (71.6 vs 56.8 and 48.2%, *P* ≤ 0.0001), and with type 2 diabetes for ≤10 years compared

with those with 11–20 years and >20 years (70.4 vs 55.6 and 39.8%, *P* ≤ 0.0001).

The overall prevalence of painful DPN was 43.3%, of whom 54.3% were undiagnosed. Kuwait had the highest prevalence of painful DPN compared with Qatar and KSA (51.2 vs 37.5 and 39.5%, *P* ≤ 0.0001), but it also had the lowest percentage of patients not previously diagnosed with painful DPN (31.8 vs 71.5 and 75.7%, *P* ≤ 0.0001).

DFU was present in 2.9% of participants, and was comparable between countries (2.9 vs 2.6 vs 3.3%, *P* = 0.65).

Risk factors for DPN

The AOR for DPN increased 2.0–3.1-fold with age (*P* ≤ 0.0001), 2.2–5.0-fold with diabetes duration (*P* ≤ 0.0001), 2.0-fold with obesity (*P* ≤ 0.0001), 1.6-fold with poor glycemic control (HbA1c >7%; *P* ≤ 0.0001), 1.5-fold with smoking cigarettes (*P* < 0.01) and 1.4-fold with hyperlipidemia (*P* = 0.01), and decreased 1.7-fold with physical activity (*P* ≤ 0.0001) and 1.4-fold with being female (*P* ≤ 0.0001; Figure 2; Table 2). The prevalence of DPN differed significantly between countries, but after adjusting for confounders, this difference was lost

Table 1 | Comparison of demographic and clinical characteristics in patients with type 2 diabetes in secondary healthcare between Qatar, Kuwait and the Kingdom of Saudi Arabia

	Gulf Arab states		Qatar (<i>n</i> = 1,093)		Kuwait (<i>n</i> = 1,168)		KSA (<i>n</i> = 760)		<i>P</i> -value
Age (years)	57.9 ± 11.7		52.4 ± 11.3 [†]		63.3 ± 9.9 [‡]		57.1 ± 11.2 [§]		≤0.0001
Duration of diabetes (years)	14.4 ± 9.2		10.0 ± 7.7 [†]		18.0 ± 9.2 [‡]		15.2 ± 8.3 [§]		≤0.0001
Female, % (<i>n</i>)	46.8	1,408/3,011	39.4 [†]	428/1,086	47.3 b	552/1,167	56.5 [§]	428/758	≤0.0001
Poor glycemic control, % (<i>n</i>)	72.9	2,025/2,776	67.2 [†]	666/991	71.0 [†]	746/1,051	83.5 [‡]	613/734	≤0.0001
Hyperlipidemia, % (<i>n</i>)	75.3	2,135/2,835	73.2 [†]	738/1,008	69.3 [†]	751/1,083	86.8 [‡]	646/744	≤0.0001
Hypertension, % (<i>n</i>)	65.4	1,926/2,945	64.3 [†]	669/1,040	60.0 [†]	691/1,151	75.1 [‡]	566/754	≤0.0001
Obesity, % (<i>n</i>)	56.9	1,584/2,785	53.3 [†]	510/957	56.6 ^{†‡}	624/1,102	62.0 [‡]	450/726	≤0.01
Physical activity, % (<i>n</i>)	33.7	932/2,763	38.2 [†]	326/854	28.5 [‡]	332/1,163	36.7 [†]	274/746	≤0.0001
Smoking, % (<i>n</i>)	22.5	635/2,821	17.3 [†]	157/909	27.4 [‡]	319/1,163	21.2 [†]	159/749	≤0.0001
Vitamin D									
≥30 ng/mL	33.6	755/2,248	21.1 [†]	142/674	44.8 [‡]	383/854	31.9 [§]	230/720	≤0.0001
20–29 ng/mL	33.2	747/2,248	37.5 [†]	253/674	32.3 ^{†‡}	276/854	30.3 [‡]	218/720	
10–19 ng/mL	29.2	656/2,248	37.1 [†]	250/674	19.3 [‡]	165/854	33.5 [†]	241/720	
<10 ng/mL	4.0	90/2,248	4.3 [†]	29/674	3.5 [†]	30/854	4.3 [†]	31/720	
Systolic blood pressure (mmHg)	131.6 ± 25.2		132.5 ± 18.0 [†]		129.9 ± 33.4 ^{†‡}		132.7 ± 18.2 [†]		<0.05
Diastolic blood pressure (mmHg)	73.1 ± 11.8		78.2 ± 10.2 [†]		71.4 ± 11.1 [‡]		69.0 ± 12.6 [§]		≤0.0001
BMI (kg/m ²)	32.0 ± 7.3		31.5 ± 7.4 [†]		32.4 ± 7.5 [‡]		32.3 ± 6.8 ^{†‡}		≤0.01
HbA1c (%)	8.2 ± 1.9		8.1 ± 2.0 [†]		7.9 ± 1.5 [‡]		8.9 ± 2.0 [§]		≤0.0001
HbA1c (mmol/mol)	66.5 ± 20.7		65.5 ± 21.9 [†]		62.4 ± 16.7 [‡]		73.8 ± 22.1 [§]		≤0.0001
Cholesterol (mmol/L)	4.2 ± 1.3		4.4 ± 1.2 [†]		3.9 ± 1.4 [‡]		4.1 ± 1.1 [§]		≤0.0001
Triglyceride (mmol/L)	1.7 ± 1.2		1.8 ± 1.2 [†]		1.5 ± 1.2 [‡]		1.8 ± 1.3 [†]		≤0.0001
HDL (mmol/L)	1.12 ± 0.41		1.05 ± 0.31 [†]		1.21 ± 0.48 [‡]		1.05 ± 0.37 [†]		≤0.0001
LDL (mmol/L)	2.36 ± 2.32		2.56 ± 0.94 [†]		2.15 ± 3.51 [‡]		2.40 ± 0.92 ^{†‡}		≤0.0001
Vitamin D (ng/mL)	26.4 ± 12.3		23.3 ± 11.2 [†]		29.5 ± 12.8 [‡]		25.6 ± 12.0 [§]		≤0.0001

Variables are summarized using means and standard deviations for numeric variables and frequency distribution for categorical variables. Continuous and categorical variables were compared using ANOVA and χ^2 , respectively. Symbols (†, ‡, §): rows with similar symbols are not statistically significant and different symbols are significantly different.

BMI, body mass index; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein

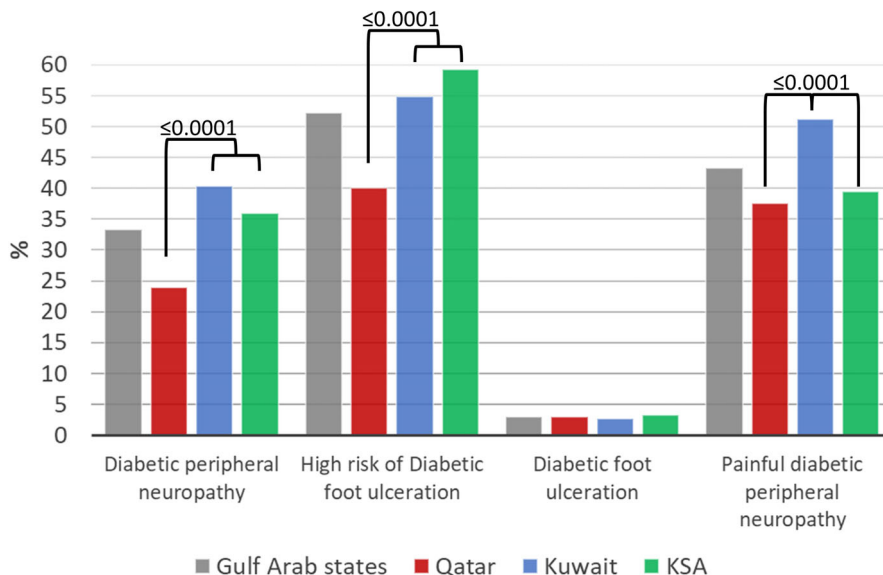


Figure 1 | Prevalence of diabetic peripheral neuropathy, those at risk of foot ulceration, diabetic foot ulceration and painful diabetic peripheral neuropathy in patients with type 2 diabetes in secondary healthcare in Qatar, Kuwait and the Kingdom of Saudi Arabia (KSA). Variables were compared between countries using the χ^2 -test.

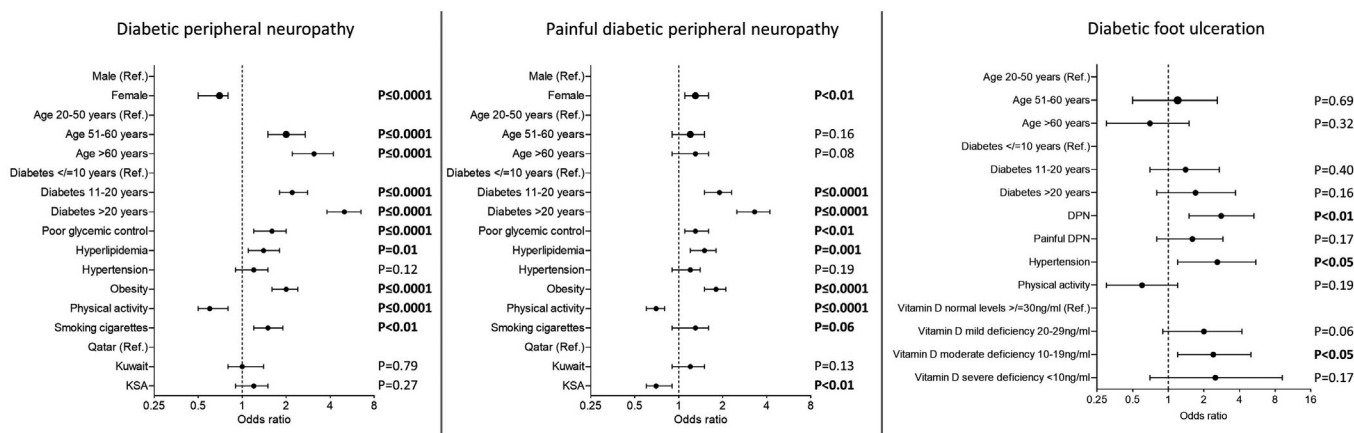


Figure 2 | Predictors for diabetic peripheral neuropathy, painful diabetic peripheral neuropathy and diabetic foot ulceration in patients with type 2 diabetes in secondary healthcare in Qatar, Kuwait and Kingdom of Saudi Arabia (KSA). The variables with $P \leq 0.05$ at the bivariate level were included in the multiple logistic regression. Adjusted odds ratios, 95% confidence intervals are presented.

($P = 0.27-0.79$). Hypertension also lost its association with DPN after adjusting for confounders ($P = 0.12$).

Apart from age and diabetes duration, risk factors for DPN differed between countries. The risk factors with the highest odds ratio for DPN were diabetes duration >20 years (AOR 2.7, $P = 0.001$) and hyperlipidemia (AOR 2.4, $P < 0.01$) in Qatar, diabetes duration >20 years (AOR 5.1, $P \leq 0.0001$) and obesity (AOR 2.7, $P < 0.0001$) in Kuwait, and >20 years of diabetes (AOR 4.8, $P \leq 0.0001$) and physical activity (AOR 0.3, $P < 0.0001$) in KSA.

Risk factors for painful DPN

The AOR for painful DPN increased 1.9–3.3-fold with diabetes duration ($P \leq 0.0001$), 1.8-fold with obesity ($P \leq 0.0001$), 1.5-fold with hyperlipidemia ($P = 0.001$), 1.3-fold with poor glycaemic control ($P < 0.01$) and 1.3-fold with being female ($P < 0.05$), and decreased 1.4-fold with physical activity ($P \leq 0.0001$; Figure 2; Table 3). After adjusting for confounders, age ($P = 0.08-0.16$) and hypertension ($P = 0.14$) lost their association with painful DPN, but the association between countries and painful DPN remained significant ($P < 0.01$).

Table 2 | Predictors for diabetic peripheral neuropathy in type 2 diabetes in secondary healthcare in Qatar, Kuwait and the Kingdom of Saudi Arabia

Diabetic peripheral neuropathy	Gulf Arab states			Qatar			Kuwait			KSA		
	AOR	95% CI	P-value	AOR	95% CI	P-value	AOR	95% CI	P-value	AOR	95% CI	P-value
Sex												
Male	1			1			1			1		
Female	0.7	0.5–0.8	≤0.0001	0.6	0.4–0.9	<0.05	0.6	0.4–0.8	<0.01	0.9	0.6–1.4	0.69
Age												
20–50 years	1			1			1			1		
51–60 years	2.0	1.5–2.7	≤0.0001	2.1	1.2–3.5	<0.01	1.6	0.9–3.0	0.13	1.9	1.2–3.2	0.01
>60 years	3.1	2.2–4.2	≤0.0001	2.7	1.5–4.8	0.001	3.1	1.7–5.6	≤0.0001	2.6	1.6–4.4	≤0.0001
Diabetes duration												
≤10 years	1			1			1			1		
11–20 years	2.2	1.8–2.8	≤0.0001	2.0	1.3–3.1	<0.01	2.7	1.9–3.9	≤0.0001	1.8	1.2–2.8	<0.01
>20 years	5.0	3.8–6.5	≤0.0001	7.1	3.6–13.7	≤0.0001	5.1	3.4–7.6	≤0.0001	4.8	2.9–8.1	≤0.0001
Poor glycemic control	1.6	1.2–2.0	≤0.0001	1.8	1.1–2.8	<0.05	1.6	1.2–2.2	<0.01	1.3	0.8–2.1	0.39
Hyperlipidemia	1.4	1.1–1.8	0.01	2.4	1.3–4.4	<0.01	1.0	0.7–1.4	0.98	2.2	1.2–4.2	0.01
Hypertension	1.2	0.9–1.5	0.12	1.5	0.9–2.4	0.15	1.3	0.9–1.8	0.16	1.0	0.6–1.6	0.98
Obesity	2.0	1.6–2.4	≤0.0001	1.7	1.1–2.6	<0.05	2.7	2.0–3.7	<0.0001	1.4	0.9–2.0	0.12
Physical activity	0.6	0.5–0.8	≤0.0001	0.9	0.6–1.4	0.71	0.7	0.5–0.9	<0.05	0.3	0.2–0.5	<0.0001
Smoking cigarettes	1.5	1.2–1.9	<0.01	0.9	0.5–1.6	0.64	2.0	1.4–2.9	<0.0001	1.1	0.7–1.8	0.68
Countries												
Qatar	1											
Kuwait	1.0	0.8–1.4	0.79									
KSA	1.2	0.9–1.5	0.27									

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. KSA, Kingdom of Saudi Arabia.

Risk factors for diabetic foot ulceration

The AOR for DFU increased 2.8-fold with DPN (*P* < 0.01), 2.6-fold with hypertension (*P* < 0.05) and 2.4-fold with moderate vitamin D deficiency (*P* < 0.05; model 1), or 2.6-fold with high risk of DFU (*P* = 0.01; model 2; Figure 2; Table S2). After adjusting for confounders, age (*P* = 0.32–0.69), diabetes duration (*P* = 0.16–0.40), painful DPN (*P* = 0.60) and physical activity (*P* = 0.19) lost their association with DFU.

Risk factors

The Kuwait cohort had the highest prevalence of those aged >60 years (62.2 vs 23.3% and 37.1%, *P* ≤ 0.0001), with type 2 diabetes duration >20 years (32.0 vs 8.1 and 20.9%, *P* ≤ 0.0001) and cigarette smokers (27.4 vs 17.3 and 21.2%, *P* ≤ 0.0001), and the lowest prevalence of those undertaking physical activity (28.5 vs 38.2 and 36.7%, *P* ≤ 0.0001; Table 1). The KSA cohort had the highest prevalence of those with poor glycemic control (83.5 vs 67.2 and 71.0%, *P* ≤ 0.0001), obesity (62.0 vs 53.3 and 56.6%, *P* ≤ 0.01) and hyperlipidemia (86.8 vs 73.2 and 69.9%, *P* ≤ 0.0001).

DISCUSSION

In the present cross-sectional study of 3,021 patients with type 2 diabetes from SHC in Qatar, Kuwait and KSA, one in three patients had DPN, of whom one in two were at high risk

of DFU, and yet over half of these patients had not been previously diagnosed. Similarly, painful DPN was present in one in three patients, and had not been previously diagnosed in half of them. Both DPN and painful DPN were associated with greater diabetes duration, obesity, poor glycemic control, hyperlipidemia and lower physical activity. DPN was associated with increasing age and smoking cigarettes, and although women had a lower risk of DPN, their risk of painful DPN was higher. The risk of DFU was higher in those with DPN, as was more severe neuropathy as evidenced by a higher VPT as well as hypertension and vitamin D deficiency.

We recently showed a higher-than-expected prevalence of DPN and painful DPN in Qatar^{23, 24}. We now extend these findings to show that the prevalence of DPN, painful DPN and risk for DFU differed significantly in SHC in Qatar, Kuwait and KSA using the same diagnostic methods, which might be attributed to differing management of risk factors. The overall prevalence of DPN was comparable to the UK (32%)⁶ and Italy (31%)⁷, but relatively lower compared with Turkey (60%)²⁵, Iran (49%)²⁶, USA (45%)⁸ and China (62%)⁹. This variability in the prevalence of DPN might be attributed to different study populations and diagnostic criteria of DPN used. These encouraging results might also reflect an increase in the number of healthcare centers providing universal health coverage and population-based measures to reduce the prevalence of diabetes

Table 3 | Predictors for painful diabetic peripheral neuropathy in type 2 diabetes in secondary healthcare in Qatar, Kuwait and the Kingdom of Saudi Arabia

Painful diabetic peripheral neuropathy	Gulf Arab states			Qatar			Kuwait			KSA		
	AOR	95% CI	P-value	AOR	95% CI	P-value	AOR	95% CI	P-value	AOR	95% CI	P-value
Sex												
Male	1			1			1			1		
Female	1.3	1.1–1.6	<0.01	1.5	1.0–2.3	<0.05	1.2	0.9–1.5	0.35	1.4	0.9–2.2	0.08
Age												
20–50 years	1			1			1			1		
51–60 years	1.2	0.9–1.5	0.16	1.5	0.9–2.3	0.07	0.8	0.5–1.4	0.56	1.2	0.8–1.8	0.44
>60 years	1.3	0.9–1.6	0.08	2.1	1.3–3.3	<0.01	1.0	0.6–1.6	0.94	0.9	0.5–1.4	0.54
Diabetes duration												
≤10 years	1			1			1			1		
11–20 years	1.9	1.5–2.3	≤0.0001	2.1	1.4–3.0	<0.0001	1.9	1.4–2.6	<0.0001	1.6	1.1–2.9	<0.05
>20 years	3.3	2.5–4.2	≤0.0001	5.9	3.0–11.5	<0.0001	3.0	2.1–4.3	<0.0001	3.2	2.0–5.2	<0.0001
Poor glycemic control	1.3	1.1–1.6	<0.01	1.7	1.1–2.4	<0.01	1.3	0.9–1.8	0.07	1.0	0.6–1.6	0.93
Hyperlipidemia	1.5	1.2–1.8	0.001	1.2	0.8–1.9	0.37	1.5	1.1–2.1	<0.01	1.4	0.8–2.4	0.21
Hypertension	1.2	0.9–1.4	0.19	1.4	0.9–2.1	0.10	1.1	0.8–1.5	0.52	0.9	0.6–1.4	0.72
Obesity	1.8	1.5–2.1	≤0.0001	2.0	1.4–2.9	<0.0001	2.0	1.6–2.7	<0.0001	1.4	0.9–1.9	0.10
Physical activity	0.7	0.6–0.8	≤0.0001	0.8	0.6–1.2	0.36	0.7	0.5–0.9	0.01	0.5	0.4–0.8	0.001
Smoking cigarettes	1.3	0.9–1.6	0.06	1.8	1.1–3.0	0.01	1.2	0.9–1.6	0.33	1.1	0.7–1.8	0.68
Countries												
Qatar	1											
Kuwait	1.2	0.9–1.5	0.13									
KSA	0.7	0.6–0.9	<0.01									

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. KSA, Kingdom of Saudi Arabia.

from 22.9% to 15.6% in Qatar, 23.1% to 12.2% in Kuwait and 23.9% to 15.8% in KSA between 2013 and 2019 according to the *IDF Diabetes Atlas*. These improvements might have impacted on the prevalence of painful DPN, as the current study shows a lower prevalence in KSA⁴ and Kuwait⁵ (39.5 vs 65.3 and 51.3%). The prevalence of DPN in the current study was higher than a previous study from KSA (35.9 vs 19.9%)²⁷; however, they defined DPN based on a higher vibration perception of ≥ 25 V compared with ≥ 15 V in the current study. The higher prevalence of painful DPN compared with DPN in the present study might be attributed to the criteria used to define these conditions. Painful DPN was defined according to DN4, whereas DPN was based on symptoms from DN4 and an elevated VPT (>15 V).

Our current study identified modifiable risk factors for DPN and painful DPN consistent with our previous findings. It identified that DPN was associated with physical activity, obesity and smoking cigarettes, painful DPN with physical activity, poor glycemic control and hyperlipidemia, and DFU with DPN, hypertension and moderate vitamin D deficiency. Indeed, poor glycemic control is associated with nerve damage¹², and improving HbA1c has been associated with nerve repair in patients with DPN²⁸. Obesity and hyperlipidemia are independently associated with DPN in type 2 diabetes patients^{13,14}, and longitudinal studies have shown that weight, body mass index,

high-density lipoprotein and low-density lipoprotein levels are associated with incident DPN¹⁴. In a cohort of obese patients with type 2 diabetes undergoing bariatric surgery, weight loss and an improvement in triglycerides was associated with an improvement in neuropathic symptoms and corneal nerve fiber regeneration²⁹. Al Rashah *et al.*³⁰ also showed that the corneal nerve migration rate correlates with physical activity, and we have shown that the presence of insulin resistance limits nerve fiber regeneration after intensive glycemic control³¹. Balducci *et al.*³² reported that aerobic exercise training was associated with a reduced incidence of impaired vibration perception and abnormal NCS. In this study, after adjusting for the modifiable risk factors, the prevalence of DPN did not differ between countries, suggesting that these factors are associated with DPN. Although active management of risk factors is advocated for all patients with type 2 diabetes, the present study shows a high heterogeneity in the management of risk factors between three Persian Gulf countries with mature health systems. Hence, more attention is required to implement DPN screening and better management of risk factors, particularly to encourage physical activity and reduce obesity.

Screening annually for DPN starting at diagnosis of type 2 diabetes is advocated by the American Diabetes Association¹. The present study shows an alarmingly high prevalence of undiagnosed DPN (57.5–82.3%) and painful DPN (71.5–75.7%)

in Qatar and KSA, and highlights the need for annual national screening for DPN³³. Readily available and sensitive tests for diagnosing early DPN include VPT testing using a neurothesiometer, NerveCheck,³⁴ or sudomotor testing using Sudoscan or Neuropad³⁵, and for painful DPN, questionnaires, such as the DN4²⁰, Leeds Assessment of Neuropathic Symptoms and Signs pain scale, and Neuropathic Pain Symptom Inventory.

The worldwide prevalence of DFU is 6.3%, and varies from 1.5 to 16.6%³⁶. The low prevalence of DFU in Qatar, Kuwait and KSA ranging from 2.6 to 3.3% is consistent with previous studies from the Middle East and North Africa region, showing a prevalence of 2.3% in KSA, 5.9% in Bahrain, 6.2% in Egypt and 4.2% in Jordan, compared to the USA (13.3%), Canada (14.8%), India (11.6%) and Belgium (16.6%). We confirm that the presence of DPN and loss of vibration perception are risk factors for DFU, in addition to prior history of DFU, foot deformities and peripheral vascular disease^{37,38}.

The present study also shows that the odds ratio for DFU was 2.6-fold higher in patients with hypertension, and 2.4-fold higher in those with moderate vitamin D deficiency. A meta-analysis of 801,985 patients with diabetes from 33 countries showed that the prevalence of hypertension was higher in patients with DFU compared to those without (63.4% vs 53.1%)³⁶. Zubair *et al.*³⁹ reported that patients with DFU had significantly lower vitamin D levels compared to those without DFU. Vitamin D deficiency is associated with an increased susceptibility to wound infection⁴⁰. Although the present study found no association between vitamin D deficiency and DPN, a meta-analysis of 1,484 patients with type 2 diabetes showed that the odds of DPN was 2.7-fold higher in those with vitamin D deficiency.⁴¹ Our previous study¹⁸ also showed that the odds ratio for painful DPN was 4.4-fold higher with vitamin D insufficiency (<30 ng/mL), and 9.8-fold higher with vitamin D deficiency (<20 ng/mL).

We acknowledge the outcomes of the present study are from patients attending SHC, which limits the generalizability of the results to all people with type 2 diabetes. We also acknowledge that VPT is a subjective psychophysical test, dependent on patient motivation, alertness and concentration¹⁰, and neurological evaluation of ankle reflexes might have improved the diagnosis of DPN. The cross-sectional design of this study limits causal association between risk factors and DPN. However, this is the largest prevalence study to date that has deployed standardized methodology in the Gulf region to show that DPN, painful DPN and DFU occurs in 33.3, 43.3 and 2.9% of patients with type 2 diabetes attending SHC. Alarming, >50% of patients had not previously been diagnosed with DPN. We also identified obesity, poor glycemic control, hyperlipidemia, smoking cigarettes and reduced physical activity as modifiable risk factors for DPN and loss of vibration perception, and DPN, hypertension and vitamin D deficiency as risk factors for DFU. These findings argue for a systematic approach to the diagnosis and management of risk factors for DPN.

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DISCLOSURE

The authors declare no conflict of interest.

Approval of the research protocol: The research protocol was approved by Weill Cornell Medicine-Qatar (WCM-Q) IRB (IRB# 15-00078) and Hamad Medical Corporation (HMC) IRB (IRB# 16324/16) in Qatar, Dasman Center for Research and Treatment of Diabetes in Kuwait IRB (IRB# IRBH1 IORG0005964), and King Fahad Medical City in KSA IRB (IRB# IRB00010471).

Informed consent: All participants consented to take part in the study. The study acted in accordance with the tenets of the declaration of Helsinki.

Registry and the registration no. of the study/trial: N/A.

Animal studies: N/A.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 | Prevalence of diabetic peripheral neuropathy, painful diabetic peripheral neuropathy, undiagnosed diabetic peripheral neuropathy and painful Diabetic Peripheral Neuropathy foot ulceration, and those at risk of foot ulceration with type 2 diabetes in secondary healthcare in Qatar, Kuwait and the Kingdom of Saudi Arabia.

Table S2 | Predictors for diabetic foot ulceration in type 2 diabetes patients in secondary healthcare in Gulf Arab states.