Prevalence and management of diabetic neuropathy in secondary care in Qatar

A short title: **Diabetic Neuropathy in Qatar**

Georgios Ponirakis MPhil[1,2], Tarik Elhadd MD[3,4], Subitha Chinnaiyan ND[3], Zeinab Dabbous MD[3], Mashhood Siddiqui MD[3], Hamad Al-muhannadi[1], Ioannis Petropoulos PhD[1], Adnan Khan PhD[1], Khaled A. E. Ashawesh MD[4], Khaled M. O Dukhan MD[4], Ziyad R. Mahfoud PhD[1], Christopher Murgatroyd PhD[2], Mark Slevin PhD[2], Rayaz A. Malik MB ChB[1, 2, 3, 5]

[1]Weill Cornell Medicine-Qatar, Qatar Foundation, Education City, Doha, Qatar

[2]Manchester Metropolitan University, Faculty of Science and Engineering, Manchester, UK

[3]National Diabetes Center, Hamad General Hospital, Hamad Medical Corporation, Doha, Qatar

[4]National Diabetes Center, Al-Wakra Hospital, Hamad Medical Corporation, Doha, Qatar

[5]Institute of Cardiovascular Science, University of Manchester, Manchester, UK.

Corresponding author:

Professor Rayaz. A. Malik,

Weill Cornell Medicine-Qatar,

Qatar Foundation,

Education City.

Doha, PO Box: 24144, Qatar

Tel: +974-4492-8256

E Mail: ram2045@qatar-med.cornell.edu

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Abstract

Aims: Diabetic neuropathy (DN) is a 'Cinderella' complication, particularly in the Middle East. A high prevalence of undiagnosed DN and those at risk of diabetic foot ulceration (DFU) is a major concern. We have determined the prevalence of DN and its risk factors, DFU and those at risk of (DFU) in patients with T2DM in secondary care in Qatar.

Materials and methods: Adults with T2DM were randomly selected from the two National Diabetes Centers in Qatar. DN was defined by the presence of neuropathic symptoms and a vibration perception threshold (VPT)≥15V. Participants with a VPT≥25V were categorized as high risk for DFU. Painful DN was defined by a DN4 score ≥4. Logistic regression analysis was used to identify predictors of DN.

Results: In 1,082 adults with T2DM (age 54 ±11 years, duration of diabetes 10.0 ±7.7 years, 60.6% males) the prevalence of DN was 23.0% (95% CI: 20.5%-25.5%), of whom 33.7% (95% CI: 27.9%-39.6%) were at high risk of DFU and 6.3% had DFU. 82.0% of the patients with DN were previously undiagnosed. The prevalence of DN increased with age and duration of diabetes and was associated with poor glycemic control (HbA1c≥9%) AOR=2.1 (95%CI: 1.3-3.2), hyperlipidemia AOR=2.7 (95%CI: 1.5-5.0) and hypertension AOR=2.0 (95%CI: 1.2-3.4).

Conclusions: Despite, DN affecting 23% of adults with T2DM, 82% had not been previously diagnosed with 1/3 at high risk for DFU. This argues for annual screening and identification of patients with DN. Furthermore, we identify hyperglycemia, hyperlipidemia and hypertension as predictors of DN.

Keywords: Diabetic neuropathy; painful diabetic neuropathy, diabetic foot ulceration; type 2 diabetes mellitus

Introduction

Diabetic neuropathy (DN) imposes a significant health and economic burden to both the patient and health care providers [1]. DN leads to painful diabetic neuropathy (PDN) in 18-65% [2], erectile dysfunction in 53-73% [3] and diabetic foot ulcers in 2-17% [1] of patients with Type 2 diabetes (T2DM). One in four patients with diabetic foot ulcer are at risk of amputation [4]. The prevalence of diabetes in Qatar is 23%, almost 3-fold higher than the global average of 8% [5] and is associated with an increasing prevalence of the long term complications [6]. Estimates of the prevalence of DN in people with T2DM vary from 17-53% in the Middle East and North Africa (MENA) region [7-9], 27-32% in Europe [10-12], 21-45% in the US [13,14] and 17-62% in China [15,16]. This high variability may be attributed to the heterogeneity of the populations studied and differing criteria for the diagnosis of DN.

Screening annually for symptoms and signs of DN starting at diagnosis of T2DM is recommended by the 2017 American Diabetes Association position statement on DN [17]. However, the prevalence of undiagnosed DN and those at risk of diabetic foot ulceration (DFU) remains alarmingly high [18,19], despite the 5-year mortality of people with a diabetic foot ulcer being higher than many common cancers [20,21]. Indeed in Qatar, 25% of patients attending secondary care were being seen for foot problems [22].

Given the lack of disease modifying treatments for DN [23,24], the identification of risk factors for DN is key in optimizing treatment and delaying the development and progression of DN [17]. Age and duration of diabetes are established risk factors for DN [8-10,12]. Whilst, poor glycemic control is associated with DN [9,25], there are conflicting data on the benefits of improved glycemic control on DN [26-31]. Studies also suggest that modifiable cardiovascular risk factors including hypertension [13,32-35] and hyperlipidemia [36,37] are associated with DN and treatment with angiotensin converting enzyme (ACE) inhibitor [38-40] may improve neuropathy and statins [41,42] and fibrates [43] may reduce amputation.

The objectives of this study were to establish the prevalence of DN and its risk factors, those at risk of DFU and with DFU in a large cohort of randomly selected people with T2DM attending the National Diabetes Centers in Qatar.

Materials and Methods

Subjects aged 18 - 85 years old with T2DM were enrolled from the National Diabetes Centers in Hamad General Hospital (HGH) and Al-Wakra Hospital. 1,161 subjects were randomly enrolled between June 2017 and February 2019. Exclusion criteria included type 1 diabetes, other causes of neuropathy including severe vitamin B12 deficiency, chronic hypothyroidism and chemotherapy.

This study was approved by the Institutional Review Board (IRB) of Weill Cornell Medicine-Qatar (WCM-Q) and Hamad Medical Corporation (HMC) and all subjects gave informed consent to take part in the study. The research adhered to the tenets of the declaration of Helsinki.

Demographic and metabolic measures

Age, gender, duration of diabetes and body mass index (BMI) were recorded. Ethnicity was categorized as Qatari Arabs, other Arabs, South Asians, and other ethnic groups. The average systolic (SBP) and diastolic blood pressure (DBP) of two readings were obtained from the subject's left arm while seated with the arm at heart level, using a standard zero mercury sphygmomanometer after 10-15 minutes of rest. A non-fasting blood sample of 10 ml was collected through venepuncture from each subject into EDTA tubes. The samples were kept at room temperature and transported within 2 hours to a central certified laboratory at HGH. Glycated haemoglobin (HbA1c), total cholesterol and triglyceride were measured by an autoanalyzer (Hitachi 747 autoanalyzer, Japan). Poor glycemic control was defined as HbA1c ≥9%. Hypertension was defined according to either an average SBP ≥140 mmHg and/or the use of anti-hypertensive medication, as described in the WHO/ISH Guidelines [44]. 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 WHO criteria with a BMI ≥30 Kg/m^2 [45]. 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 minutes/day for at least 3 times a week.

Assessment of diabetic neuropathy and neuropathic complications

DN was diagnosed clinically based on the presence of one or more neuropathic symptoms and impaired vibration perception in the feet. Neuropathic symptoms included burning pain, painful cold, electric shocks, tingling, pins and needles and numbness. Vibration perception was measured by a Neurothesiometer (Horwell, Scientific Laboratory Supplies, Wilford, Nottingham, UK) on the pulp of the large toe on both feet and the average value of three measurements was recorded as a vibration perception threshold (VPT) in Volts (V) ranging from 0 - 50V. A VPT ≥15V was defined as impaired vibration perception [46] and a VPT ≥25V as high risk for diabetic foot ulceration (DFU) [47]. Previously diagnosed DN was self-reported. Painful diabetic neuropathy (PDN) was diagnosed using the Douleur Neuropathique en 4 (DN4) questionnaire as previously described [2].

Statistical analysis

The overall prevalence of DN and those at high risk of DFU were computed along with their 95% confidence intervals. Prevalence of DN across different demographic and health factors as categorical variables was summarized using frequency distributions. Variables were compared between patients with and without DN using the Chi-squared test.

Binary logistic regression analysis was performed with age, duration of diabetes, gender, poor glycemic control, obesity, hyperlipidemia, hypertension, physical activity, smoking and ethnic

groups as independent variables, and DN as the dependent variable. The multiple logistic regression model included all variables with P value of ≤0.05 at the bivariate level. Adjusted odds ratios, their corresponding 95% confidence intervals (CI) and P value are presented.

All analyses were performed using IBM-SPSS (version 23; SPSS Inc, Armonk NY). A two-tailed P value of ≤0.05 was considered significant.

Results

Prevalence of DN and those at risk of DFU

1,082 subjects with T2DM (60.6% male) were recruited. We excluded 75 subjects with T1DM and 4 subjects with T2DM <20 years old. The mean age and duration of diabetes were 54.3 ±11.4 years and 10.0 ±7.7 years, respectively.

The prevalence of DN was 23.0% (n=249/1,082) (95% CI: 20.5%-25.5%) of whom 33.7% (n=84/249) (95% CI: 27.9%-39.6%) were at high risk of DFU (VPT≥25V) and 6.3% (n=15/237) had diabetic foot ulcers (Table 1). Impaired vibration perception in the feet (VPT≥15V) was detected in all subjects with clinical DN, but was also present in 7.2% (n=60/833) of subjects without DN. A high risk of DFU was detected in 2.2% (n=18/833) of subjects without DN. Foot ulcers were observed in more subjects with DN compared to subjects without DN (6.3% vs 2.1%, P=0.001) and in more subjects at high risk of DFU compared to subjects at low risk of DFU (11.1% vs 2.2%, P<0.0001). Painful diabetic neuropathy (DN4 score≥4) was present in 24.4% (n=203/833) of subjects without DN and in 78.7% (n=196/249) of subjects with DN. 82.0% (n=201/249) of patients with DN were previously undiagnosed, even though 62.7% of them were aware that they had foot numbness and 7.6% were at high risk of DFU. In those with DN, 20.5% (n=51/249) were unaware they had impaired vibration perception and 4.8% (n=12/249) were unaware they were at high risk of DFU. The mean total cholesterol (4.3±1.1 vs 4.5±1.2, P<0.01) and low-density lipoprotein (LDL) (2.4±0.9 vs 2.6±0.9, P=0.01) in patients with DN were significantly lower compared to patients without DN. Triglycerides (1.7±0.9 vs 1.8±1.3, P=0.14) and high-density lipoprotein (HDL) (1.1±0.4 vs 1.1±0.3, P=0.89) were comparable between patients with and without DN.

Prevalence of diabetic neuropathy in relation to clinical and demographic factors (Table 2)

The prevalence of DN was lower in those with increasing physical activity (P=0.004) and higher with increasing age (P<0.0001), duration of diabetes (P<0.0001), poor glycemic control (P<0.0001), hyperlipidemia (P<0.0001) and hypertension (P<0.0001) and was comparable between genders. The prevalence of DN was significantly higher in Qatari Arabs (29.5%) compared to South Asians (17.1%) (P=0.001).

Diabetic neuropathy risk factors

The results of binary logistic regression used to explore the odds of developing DN in relation to age, duration of diabetes, poor glycemic control, hyperlipidemia, hypertension, physical activity and ethnic groups are shown in Table 3. Obesity and smoking were not associated with DN

(P=0.2). The odds of developing DN were 2.5 times greater among subjects aged 51-60 years (P=0.001) and 3.1 times greater among subjects aged >60 years compared to subjects aged 20-50 years (P<0.0001). The odds increased from 2.2 times greater with 11-20 years of diabetes (P=0.001) to 7.2 times greater with >20 years of diabetes (P<0.0001) compared to those with ≤10 years of diabetes. The odds of developing DN were 2.1 times greater with poor glycemic control (P=0.001), 2.7 times greater with hyperlipidemia (P=0.002) and 2.0 times greater with hypertension (P=0.01) compared to subjects with HbA1c <9%, without hyperlipidemia and without hypertension. Physical activity was associated with a reduced prevalence of DN (odds ratio 0.6; 95% CI: 0.4 to 0.8; P=0.002), but after controlling for other significant predictors of DN, physical activity had no impact on DN (adjusted odds ratio 0.9; 95% CI: 0.6 to 1.4; P>0.05).

The odds of developing DN in Qatari Arabs was 1.4 times greater compared to other Arabs (P=0.04) and 2.0 times greater compared to South Asians (P<0.0001). However, these associations with DN were lost after controlling for other significant predictors of DN. When comparing the prevalence of risk factors across the ethnic groups, there were more Qataris aged ≥60 years (37.5% vs 24.4% and 11.0%, P<0.0001) and less Qataris aged 20-50 years (30.0% vs 43.5% and 48.7%, P<0.0001) compared to other Arabs and South Asians, respectively. There were also more Qataris with 11-20 years of diabetes compared to other Arabs and South Asians (40.1% vs 23.4% and 22.0%, P<0.0001) whilst there were less Qataris with ≤10 years of diabetes (47.5% vs 69.9% and 72.5%, P<0.0001). The prevalence of hypertension in Qataris was higher compared to other Arabs (72.5% vs 56.4%, P=0.001) but comparable with South Asians (64.0%).

Discussion

In adults with T2DM attending secondary care in Qatar the prevalence of DN was 23%, of whom one-third were at high risk of DFU, and 6% had diabetic foot ulcers. However, 82% of patients with DN had not been previously diagnosed, even though 63% were aware they had foot numbness. Age, duration of diabetes, poor glycemic control, hyperlipidemia and hypertension are risk factors for DN in this population.

The prevalence of DN varies in different countries and clinical settings. In a large clinic based study of 6487 patients in the UK, the prevalence of DN was 32.1% in patients with T2DM and increased with increasing age and duration of diabetes [10]. It has been reported to be as high as 45% in the US [13] and 62%, in China [15], but their mean age of 73 and 66 years, respectively was much higher than our cohort aged 54 years. The higher prevalence of DN in Bahrain (37%)[9] and Turkey (60%)[25] compared to Qatar (23%) may be attributed to poorer glycemic control as the proportion with a HbA1c ≥9% in Bahrain (65%) and Turkey (79%) was much higher compared to our cohort in Qatar (29%).

We show an alarmingly high prevalence of undiagnosed DN in 82% of patients attending secondary care in Qatar. Indeed, Wang et. al. [18] have also previously reported that 79% of patients have undiagnosed DN and Herman et al. [19] reported that 51% of patients with DN in the US had not been previously diagnosed. The high prevalence of undiagnosed DN in secondary care in Qatar

can be attributed to the lack of annual screening for DN and use of the 10-g monofilament which will identify only those with advanced neuropathy[17]. The prevalence of DFU in Qatar was comparable to the global prevalence of 6.3% [48].

The early diagnosis and treatment of DN is key in preventing DFU and amputation [17]. Indeed, in line with previous studies [9,25] we show that poor glycemic control is an independent risk factor for DN. The Kumamoto trial [26] reported that tight glucose control prevents progression of DN and the ACCORD [27] and the BARI 2D [28] trials reported a reduced incidence of DN with better glycemic control. However, the UKPDS [29], VA-CSDM [30] and Steno-2 trial [31] have shown a limited effect of intensive glucose control on DN. This study shows an association of DN with hyperlipidemia and hypertension, which is consistent with previous studies showing that DN is associated with hypertension [13,32-35], hyperlipidemia [36,37], BMI [9,11,13], cigarette smoking [9,36] and physical activity [8]. Indeed, treatment with angiotensin converting enzyme (ACE) inhibitors [38-40] and statins [49,50] may slow the progression of DN. We also show a relationship between reduced physical activity and the prevalence of DN, which is consistent with a study showing that diet and exercise can improve neuropathy in subjects with impaired glucose tolerance [51]. Previously, we reported that South Asians, have a lower prevalence of DN compared to Caucasians [52], particularly small fibre neuropathy [53]. This study shows that South Asians have a lower prevalence of DN compared to Qatari Arabs but the association between ethnic groups and DN was lost after controlling for significant predictors of DN including, age, duration of diabetes, poor glycemic control, hyperlipidemia, hypertension and physical activity as these factors differed in the different ethnicities.

There are several limitations of this study including the diagnosis of DN which was based on symptoms and assessment of VPT as reflected by the finding that 7.2% of participants without clinical DN had an abnormal VPT. This may reflect issues with the reliability and validity of establishing a vibration perception threshold value which like all psychophysical tests relies on standardisation and the participants concentration and ability to detect a sensation. Whilst we show associations between risk factors and DN, the cross-sectional design of this study limits the predictive validity of these risk factors.

In conclusion, although the prevalence of DN was relatively low compared to previous studies from the Middle East region, alarmingly 82% were undiagnosed and one-third of patients with DN were at high risk of DFU, highlighting the need for screening for DN. The identification of hyperglycemia, hyperlipidemia and hypertension as modifiable risk factors provides potential treatment targets for DN.

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Conflict of interest statement

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship and are not listed. We confirm that the order of authors listed in the manuscript has been approved by all authors. None of the authors have received or anticipate receiving income, goods or benefit from a company that will influence the design, conduct or reporting of the study.

Author contributions

RAM and GP had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: RAM and GP.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: GP and RAM.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: GP and ZRM.
Obtained funding: RAM.
Administrative, technical, or material support: All authors.
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Table 1. Prevalence of diabetic neuropathy, impaired vibration perception, high risk of diabetic foot ulcers, painful diabetic neuropathy, and prevalence of patients who are undiagnosed or unaware of diabetic neuropathy.

	Diabetic neuropathy			
	No		Yes	
n %	833	77.0%	249	23.0%
Impaired vibration perception (VPT ≥15V)	60/833	7.2%	249/249	100.0%
High risk of diabetic foot ulceration (VPT ≥25V)	18/833	2.2%	84/249	33.7%
Diabetic foot ulcers	17/809	2.1%	15/237	6.3%
Painful diabetic neuropathy (DN4 ≥4)	203/833	24.4%	196/249	78.7%
Undiagnosed with diabetic neuropathy			201/249	82.0%
Undiagnosed with diabetic neuropathy but aware of foot numbness			156/249	62.7%
Undiagnosed with diabetic neuropathy but at high risk of foot ulceration			19/249	7.6%
Unaware of impaired vibration perception (VPT ≥15V)			51/249	20.5%
Unaware of impaired vibration perception but at high risk of foot ulceration			12/249	4.8%

Table 2. Prevalence of diabetic neuropathy in relation to clinical and demographic factors.

		Total		Diabetic neuropathy				
				No		Yes		P value
n (%)		1082	100.0%	833	77.0%	249	23.0%	N/A
Gender	Male	651	60.6%	496	76.2%	155	23.8%	NS
	Female	424	39.4%	333	78.5%	91	21.5%	
Age	20-50 years	440	41.4%	392	89.1%	48	10.9%	<0.0001
	51-60 years	375	35.3%	269	71.7%	106	28.3%	
	>60 years	247	23.3%	156	63.2%	91	36.8%	
Duration of diabetes	≤10 years	682	63.7%	588	86.2%	94	13.8%	<0.0001
	11-20 years	302	28.2%	201	66.6%	101	33.4%	
	>20 years	86	8.0%	37	43.0%	49	57.0%	
Poor glycemic control	No	695	70.8%	562	80.9%	133	19.1%	<0.0001
	Yes	287	29.2%	197	68.6%	90	31.4%	
Obesity	No	442	46.6%	350	79.2%	92	20.8%	NS
	Yes	507	53.4%	383	75.5%	124	24.5%	
Hyperlipidemia	No	236	24.7%	209	88.6%	27	11.4%	<0.0001
	Yes	721	75.3%	526	73.0%	195	27.0%	
Hypertension	No	366	35.5%	318	86.9%	48	13.1%	<0.0001
	Yes	664	64.4%	472	71.0%	193	29.0%	
Physical activity	Yes	321	38.1%	268	83.5%	53	16.5%	0.004
	No	522	61.9%	389	74.5%	133	25.5%	
Smoking	No	742	82.6%	572	77.1%	170	22.9%	NS
	Yes	156	17.4%	128	82.1%	28	17.9%	
Ethnic groups	Qatari Arabs	322	30.0%	227	70.5%	95	29.5%	0.001
	Other Arabs	300	28.0%	233	77.7%	67	22.3%	
	South Asians	397	37.0%	329	82.9%	68	17.1%	
	Others	54	5.0%	38	70.4%	16	29.6%	

Variables were summarized in frequency distribution and compared using x^2.

Table 3. Predictors for diabetic neuropathy using multiple logistic regression analysis.

Independent variables		AOR	95% CI	P value
Age	20-50 years	1		
	51-60 years	2.5	1.4 – 4.3	0.001
	>60 years	3.1	1.7 – 5.7	<0.0001
Duration of diabetes	≤10 years	1		
	11-20 years	2.2	1.4 – 3.4	0.001
	>20 years	7.2	3.8 – 13.9	<0.0001
Poor glycemic control		2.1	1.3 - 3.2	0.001
Hyperlipidemia		2.7	1.5 - 5.0	0.002
Hypertension		2.0	1.2 - 3.4	0.01
Physical activity		0.9	0.6 - 1.4	NS
Ethnic groups	Qatari Arabs	1		
	Other Arabs	1.0	0.6 - 1.6	NS
	South Asians	0.7	0.4 - 1.1	NS
	Others	1.4	0.5 – 3.9	NS

Outcome variable: diabetic neuropathy. Independent variables: Age, duration of diabetes, poor glycemic control, hyperlipidemia, hypertension, physical activity and ethnic groups were considered in the fitted model with a P value ≤0.05. AOR=Adjusted odd ratio; CI= confidence interval.