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ORIGINAL RESEARCH

Prevalence and Risk Factors for Diabetic Peripheral Neuropathy Among Saudi Hospitalized Diabetic Patients: A Nested Case-Control Study

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Objective: To determine the prevalence and the risk factors of diabetic peripheral neuropathy (DPN) in hospitalized adult Saudi diabetics.

Methods: This is a retrospective, nested case-control study conducted at King Abdulaziz Medical City (KAMC) in Riyadh, Saudi Arabia. All diabetic patients admitted to the hospital between the January 1, and December 31, 2018 were considered for inclusion in the study. Patients with DPN were identified and three controls per case were randomly selected from the remaining diabetic patients without peripheral neuropathy (PN).

Results: A total of 2,096 adult diabetic patients were identified during the study period. Of these, 73 patients (3.5%) were confirmed to be suffering from DPN and 219 were included as controls. When comparing diabetic with the control cases, DPN cases were significantly older (p=0.002), had a significantly higher proportion of type 2 diabetes (p=0.023), chronic kidney disease (p<0.0001), cerebral vascular stroke (p=0.027), hypertension (p=0.005), dyslipidemia (p=0.002), peripheral vascular disease (p<0.0001), osteoarthritis (p=0.034), diabetic ketoacidosis (p=0.003), foot ulcers (p=0.006), gangrene (p=0.001), lower limb ischemia (p=0.001), increased duration with diabetic disease (p=0.031), increased BMI (p=0.003), higher serum creatinine (p<0.001) and lower serum albumin levels (p=0.035). In the multivariate logistic regression, only older age {odds ratio (OR) 1.02, 95% CI 1.01–1.04, p=0.031}, chronic kidney disease (OR 2.39, 95% CI 1.23–4.64, p=0.010) and peripheral vascular disease (OR 3.14, 95% CI 1.39–7.13, p=0.006) were independently associated with DPN.

Conclusion: This study identified several risk factors that contributed to the development of DPN in Saudis. These must be considered in strategies and campaigns aimed at risk reduction of cardiovascular and chronic diseases, and consequently progression of DPN.

Keywords: diabetes mellitus, diabetic peripheral neuropathy, risk factors

Introduction

Diabetic peripheral neuropathy DPN is defined as, "the presence of symptoms and/or signs of peripheral nerve dysfunction in patients with diabetes after the exclusion of other causes," and may be present despite a lack of symptoms.[1] The diagnosis relies on clinical signs as well as quantitative electrophysiological testing:[1] DPN is a common complication in patients with diabetes and its consequences can be distressing, as patients may develop neuropathic feet pain and decreased sensation that can lead to frequent falls and injuries. Patients may also develop foot ulcers. All these consequences of DPN will unavoidably end in the reduction in the quality

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of life and significant economic burden both to the patients and society.[2–5] Although up to 50% of patients with DPN are asymptomatic, some patients may manifest burning feet pain, due to progressive sensory impairment, which responds poorly to analgesics. Rarely, this sensory impairment could lead to foot ulceration and eventually to lower limb amputation;[6,7] diabetes is a leading cause of "non-traumatic" lower limb amputation.[8]

There is wide agreement that DPN is a consequence of diabetes longstanding hyperglycemia which is critical for peripheral nerve damage and distal-predominant nerve fiber degeneration.[9–11] The chronic diabetes hyperglycemia is compounded by numerous metabolic aberrations and diabetic microvascular complications resulting from disturbed nutritional support especially of the most distal parts of very long nerve axons originating in the spinal cord and travel long distances to supply the lower limbs and the feet, in particular. Additionally, the sparse vascular supply in this area, resulting from diabetes, is likely to cause further hypoxic nerve damage. Other confounding metabolic aberrations resulting from chronic hypoglycemia include the excessive release of cytokines, and exaggerated oxidative stress. This topic has been reviewed in detail elsewhere.[9] Although diabetes is considered the main underlying cause of DPN, the pre-diabetic stage with other comorbidities such as: obesity, hypertension and hyperlipidemia may increase the risk of neuropathy.-[12–15] Moreover, treatment modalities received by diabetic patients (insulin and/or oral hypoglycemic agents) play an additional important role in delaying the development of this complication among diabetic patients. A meta-analysis conducted on 1,228 patients with type 1 diabetes and 6,669 patients with type 2 diabetes revealed significant reduction of neuropathy when blood sugar is controlled within the limits of normal.[13]

Type 2 diabetes mellitus is becoming a rapidly growing health problem in the affluent oil rich Gulf Council states (Saudi Arabia, Oman, Kuwait, Bahrain, and the United Arab Emirates). Its prevalence is highest in Saudi Arabia (31.6%, 29.0%.25.4%. 25.0%, 25.0%, and 16.7%, respectively).[16] This high prevalence of type 2 diabetes was found to be significantly associated with the high Gross Domestic Product (GDP) and energy consumption. In contrast the lowest prevalence was found in the poorest Arab countries (Mauritania, 4.7% and Somalia, 3.9%).

Careful search in the literature uncovered only two small studies on painful DPN undertaken in different primary health facilities.[17,18] The first study[17] which was undertaken in a Primary Health Centre (PHC) in Riyadh found 35% of patients with type-2 diabetes (n =242) suffering from DPN. On the other hand, the second study[18] which was also a PHC study found the prevalence of DPN to be 30.1% (n = 235). With this alarming prevalence of DPN in Saudi diabetics we felt the need to have better documentation of DPN. Thus, the aim of the current study was to determine the prevalence and risk factors associated with the development of DPN in a large population of hospitalized adult Saudi diabetics.

Methods

This is a retrospective, nested case-control study conducted at King Abdulaziz Medical City (KAMC); a tertiary health care facility in Riyadh, Saudi Arabia. All adult patients, who were admitted with diabetes mellitus at KAMC, during the study period (from January 1 to December 31, 2018) were considered for inclusion in the study. Additionally, they met the ADA diagnosis criteria (fasting blood glucose ≥7.0 mmol/L, glycosylated hemoglobin [HbA1C] ≥6.5%, classic symptoms of hyperglycemia, hyperglycemic crisis with a random plasma glucose ≥11.1 mmol/L or 2-hour plasma glucose ≥11.11 mmol/L). Of these, patients with confirmed DPN diagnosis were identified and served as case patients. Whereas, three controls per case were randomly selected from the remaining diabetic patients without peripheral neuropathy (PN). Patients who were under the age of 18 or did not fulfill the eligibility criteria were not considered for participation in the study.[19] DPN confirmation was based on the following criteria: 1) abnormal clinical examination for pain, touch, vibration, pressure, power, and ankle reflex; and 2) abnormal nerve conduction studies (NCS) and/or electromyography.

Medical records of all enrolled patients (cases and controls) were accessed and the collected data were recorded in computerized format. These data included: demographic characteristics: age, gender, body mass index (BMI), type of diabetes, presence and duration of diabetic neuropathy, hypertension, kidney disease, dyslipidemia, and other comorbidities, life style (smoking and alcohol use), blood biochemistry indices (fasting blood glucose, HbA1C, lipid profile), medications, particularly insulin, oral hypoglycemic agents and diet, blood pressure and other clinical complications.

All methods and procedures were performed in accordance with the relevant institutional guidelines and regulations. The study was approved by the Institutional Review

Board at King Abdullah International Medical Research Center (KAIMRC). The ethical committee waived the need for written informed consent due to the retrospective nature of the study.

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences Program (IBM SPSS Statistics version 24). Continuous data were presented as medians (interquartile range), and categorical data as frequencies (%). Data were compared using Mann–Whitney *U*-test or χ^2-test; as appropriate. Conditional logistic regression analysis was conducted to identify the factors associated with the DPN. Factors found statistically significant in logistic univariate analyses were included in the final multivariate model. Strength of the association was expressed as odds ratios (OR) with 95% confidence interval. All tests were two-sided and a *p*-value less than 0.05 was considered statistically significant.

Results

A total of 2,906 patients with diabetes were identified during the study period. Of these, 73 patients (3.5%) were found and labeled in the electronic chart by the treating clinician with DPN and 219 patients (three to one DPN case) were randomly selected as a control group. Table 1 shows the basic characteristics of the two groups. Females represented 51.8% and 63.0% of the DPN and the controls, respectively. The median (IQR) age of patients in the DPN group was significantly higher than in the controls [65 (58–75) vs 61 (45–71), p=0.002)] and the duration of diabetes of patients with DPN was significantly higher than in the controls [8.5 (5.5–16) vs 6.5 (4–15), p=0.031]. Type 2 DM was diagnosed in 66 (90.4%) patients with DPN, compared with 173 (78.6%) patients in the control group, and 7 (9.6%) patients with DPN were diagnosed with type 1 DM compared with 47 (21.4%) patients in the control group. The median BMI of patients with DPN was significantly higher than controls [31 (26–35) vs 27 (22–33), p=0.003]. However, the two groups were similar in gender distribution (p=0.096), treatment modalities (p=0.072), smoking status (p=0.131) and alcohol consumption (p=0.413). Biochemical indices and assessment parameters were also similar in both groups (Table 1).

The median number of comorbidities in DPN patients was significantly higher than in controls [5(4–7.5) vs 4 (2–5.75), p<0.001]. Hypertension was more prevalent in the DPN patients (p=0.005); so were peripheral vascular disease (p<0.001), cerebral vascular accident (p=0.027), chronic kidney disease (p<0.001) and dyslipidemia (p=0.002), than in control patients. Other comorbid diseases were similar in both groups. The DPN patients developed diabetic complications more than the control patients (Table 2).

Table 3 shows the results of the final multivariate logistic regression for factors associated with DPN. The independent factors associated with the likelihood of DPN were age (OR 1.02, 95% CI 1.01–1.05, p=0.031), peripheral vascular disease (OR 3.14, 95% CI 1.39–7.127, p=0.006) and chronic kidney disease (OR 2.39, 95% CI 1.23–4.64, p=0.010). However, the presence of hypertension, cerebral vascular disease and dyslipidemia were not significantly associated with DPN.

Discussion

DPN is a very distressing chronic complication of diabetes with an array of poor outcomes. For example, DPN leads to neuropathic pain and diminished sensation which in turn can lead to frequent falls and injuries, restriction of movement, poor quality of life and difficulties with earning a living. Other serious complications include: leg ulcers that can eventually end in leg amputation.[1–5,20,21]

DPN is classified into numerous types and subtypes based on a mixture of phenomenological, aetiological, pathological and neurophysiological parameters.[1,22–24] In a retrospective study, like the present one, it is difficult to assure the reliability of information on the details of these types or subtypes and be confident that such information has been documented in every patient. Accordingly, we restricted the definition of DPN, as mentioned earlier, to the presence of symptoms and/or signs of peripheral nerve dysfunction in patients with diabetes after the exclusion of other causes.[1]

Interest in DPN stems from the fact that it has recently been recognized as the most common of all the neuropathy complications worldwide.[25] However, the reported prevalence of DPN varies widely from study to study and is heavily dependent on the type of diabetes, the population selected, and criteria used for defining cases, including the degree of control of the hyperglycemia.[26] The most classical citation of DPN is a study conducted in France[27] in which 4,400 adults with diabetes were followed for 36 years (1937–1973). Approximately 50% of these patients developed DPN at the end of the follow-up period. Pirart[27] found that two thirds of patients with diabetes had

Table 1 Clinical and Demographic Characteristics of the DPN and Control Patients

Variables	Control (n=220)	DPN (n=73)	*p*-value
Age, years (median, IQR)	61 (45–71)	65 (58–75)	0.002
Gender, n (%)			0.096
Male	106 (48.2)	27 (37.0)	
Female	114 (51.8)	46 (63.0)	
Duration of diabetes years, median (IQR)	6.5 (4–15)	8.5 (5.5–16)	0.031
Type of DM, n (%)			0.025
Type I	47 (21.4)	7 (9.6)	
Type II	173 (78.6)	66 (90.4)	
Type of treatment, n (%)			0.072
Insulin	158 (72.8)	62 (86.1)	
Oral hypoglycemic	53 (24.4)	9 (12.5)	
Diet	6 (2.8)	1 (1.4)	
BMI kg/cm^2, median (IQR)	27 (22–33)	31 (26–35)	0.003
Smoking status	29 (13.2)	15 (20.5)	0.131
Alcohol status	2 (0.9)	0 (0.0)	0.413
Laboratory indices			
Fasting blood glucose mmol/L (median, IQR)	9 (7–12)	10 (6–14)	0.507
HbA1C (median, IQR)	9 (7–10)	9 (7–10)	0.851
Systolic blood pressure mmHg (median, IQR)	124 (107–139)	125 (110–143)	0.254
Diastolic blood pressure mmHg (median, IQR)	69 (58–76)	66 (55–73)	0.158
Micro-albuminuria (median, IQR)	26 (2–100)	50 (50–200)	0.092
Proteinuria (median, IQR)	2 (1.25–2)	2 (1–2)	0.218
Serum Creatinine umol/L (median, IQR)	71 (61–117)	103 (80–192.5)	<0.001
Cholesterol mmol/L (median, IQR)	4 (3–5)	4 (3–4.75)	0.649
Triglycerides mmol/L (median, IQR)	1(1–2)	1 (1–2)	0.356
Albumin g/L (median, IQR)	37 (32–40)	35 (30–39)	0.035

Abbreviations: BMI, body mass index; DPN, diabetes peripheral neuropathy; IQR, interquartile range.

objective evidence of some form of neuropathy. The most common was DPN; affecting 50% of type 2 diabetics. Outside Europe, particularly in Asia and Africa, a very wide range of prevalences were reported. For examples Saudi Arabia (19.9; n = 552);[28] Turkey (60%; n = 550),[29] China: (61.8%, n = 435);[30] and Tanzania (72.2%, n = 327).[31] On the other hand, recent studies from Europe and the US have reported prevalences ranging from 6% to 51% depending on the population studied.[1] We noted that the frequency of DPN in our patients was considerably lower than expected. This maybe owing to the fact that, typically, DPN is often diagnosed clinically with little further laboratory investigations to confirm the diagnosis or poorly captured in patients' records. In a study by Day et al,[32] more than 40% of diabetic patients in general practice had no biochemical evaluation, eye or foot examination.[32]

The wide geographical variations in prevalence of DPN highlight the need for a global multicenter study in which the selection criteria for diabetic patients are unified to the finest detail. Hopefully, then, the true reflection of the geographical and ethnic differences in the prevalence of DPN can be meaningful and may shed some light in the mechanism underlying the differences in the prevalences in the DPN in different ethnic groups.

This possibility proved to be true in a comparative study between South Asians and Caucasians living in Britain where the prevalence of DPN was found to be significantly lower in South Asians (38.1%) than White Caucasians (54.3%). Further observations uncovered

Table 2 Associated Comorbidities and Diabetes Complications

Variables	Control (n=220)	DPN (n=73)	*p*-value
Number of comorbid disease (median, IQR)	4 (2–5.75)	5 (4–7.5)	<0.001
Ischemic heart disease, n (%)	92 (42)	37 (50.7)	0.196
Congestive heart failure, n (%)	53 (24.4)	23 (31.5)	0.226
Chronic kidney disease, n (%)	32 (14.6)	27 (37)	<0.001
Cerebral vascular stroke, n (%)	32 (14.7)	19 (26)	0.027
Hypertension, n (%)	160 (73)	65 (89)	0.005
Dyslipidemia, n (%)	119 (54.6)	55 3(75.)	0.002
Peripheral vascular disease, n (%)	15 (7)	17 (24)	<0.001
Osteoarthritis, n (%)	15 (6.9)	11 (15)	0.034
Hypoglycemia, n (%)	10 (4.6)	2 (2.7)	0.492
Diabetes ketoacidosis, n (%)	30 (13.8)	1 (1.4)	0.003
Diabetes complications, n (%)			
Retinopathy	28 (12.8)	16 (21.9)	0.061
Foot ulcer	15 (6.9)	13 (17.8)	0.006
Gangrene	3 (1.4)	7 (9.6)	0.001
Lower limb ischemia	7 (3.2)	10 (13.7)	0.001

Abbreviations: DPN, diabetes peripheral neuropathy; IQR, interquartile range.

foot insensitivity as assessed by 10 g monofilament perception, was more common in Caucasians (43.9% vs 23.8%). South Asians have better preserved small nerve fiber integrity than equivalent Europeans. Corneal nerve fiber length (22.0 ± 7.9 vs 19.3 ± 6.3 mm/mm^2), corneal nerve branch density [(geometric mean (range): 60.0 (4.7–246.2) vs 46.0 (3.1–129.2) no./mm^2], and heart rate variability [(geometric mean

Table 3 Univariate and Multivariate Conditional Logistic Regression for Risk Factors Associated with DPN

Factor	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age	1.03 (1.01–1.05)	<0.001	1.02 (1.01–1.04)	0.031
Chronic kidney disease				
Yes	3.43 (1.87–6.28)	<0.001	2.39 (1.23–4.64)	0.010
No	1		1	
Cerebral vascular stroke				
Yes	2.05 (1.08–3.89)	0.029	1.64 (0.80–3.33)	0.176
No	1		1	
Peripheral vascular disease				
Yes	4.11 (1.93–8.74)	<0.001	3.14 (1.39–7.13)	0.006
No	1		1	
Hypertension				
Yes	3.00 (1.36–6.62)	0.007	083 (0.27–2.54)	0.740
No	1		1	
Dyslipidemia				
Yes	2.54 (1.40–4.61)	0.002	1.56 (0.78–313)	0.181
No	1		1	

Abbreviations: CI, confidence interval; OR, odds ratio.

(range): 7.9 (1.4–27.7) vs 6.5 (1.5–22.0)], were significantly higher in South Asians than Europeans.[33,34]

As mentioned earlier DPN is believed to be a consequence of the diabetes longstanding hyperglycemia which is critical for peripheral nerve damage and distal-predominant nerve fiber degeneration.[9–11] The hyperglycemia of the chronic diabetes process is compounded by numerous metabolic aberrations and diabetic microvascular complications resulting from the disturbed nutritional support especially of the most distal parts of very long nerve axons originating in the spinal cord and travel long distances to supply the lower limbs and the feet in particular. Additionally, the sparse vascular supply in this area resulting from diabetes is likely to cause further hypoxic nerve damage. Other confounding metabolic aberrations resulting from the chronic hypoglycemia include excessive release of cytokines, and exaggerated oxidative stress. This topic has been reviewed in detail elsewhere.[9]

It is also becoming clear that the duration of diabetes and glycemic control are the most significant risk factors for DPN.[35] In regard to the benefit of blood glucose control, there are reports indicating that aggressive blood glucose control was associated with lower prevalence of DPN.[36–39] In support of this notion, in the current study, we found an association between DPN and blood glucose control as reflected by the fasting blood glucose level, HbA1c and the type of treatment. Therefore, like others[40] the most effective approach to reduce the progression to neuropathy is aggressive treatment of diabetes hyperglycemia towards normoglycemia.

Our finding that multiple risk factors are associated with the development of DPN in diabetic patients should direct the attention towards the link between these risk factors and the increase in diabetes-related complications, morbidity as well as mortality.[40,41] It was also clear that age is a significant risk factor that predisposes to DPN and this finding was observed by others.[1,20–22] In the present study the vast majority of patients with DPN were type 2 diabetes (90.4%). Similarly, Kästenbauer et al,[23] showed a higher percentage (16% vs 37.5%) of type 2 diabetic patients with symptoms of neuropathy compared with type 1 diabetic patients.[23] Other risk factors including BMI, number of comorbid diseases such as chronic kidney disease, hypertension, dyslipidemia, cerebral vascular stroke, peripheral vascular disease and diabetic ketoacidosis were also found to be significantly associated with DPN. The close association between DPN and modifiable cardiovascular risk factors (cardiometabolic disease) including elevated triglyceride levels (hyperlipidemia), body mass index (BMI), smoking, hypertension and cardiovascular disease was documented repeatedly in previous studies.[1,20,21,24,42] However, no specific mechanisms linking DPN with cardiovascular disease have been suggested in any of these studies.

It also worth adding that the findings of the present study are consistent with those reported from the neighboring Gulf state of Bahrain. The Bahraini study[22] found that older age, poor glycemic control, longer duration of diabetes, elevated cholesterol levels, current smoking, obesity, large waist circumference, elevated triglycerides levels and hypertension but not gender were significant risk factors for DPN. However, the vast majority of the DPN patients in the study were females and were on insulin therapy. In contrast, there were no significant differences in gender distribution or treatment modalities when compared to controls. On the other hand, many other studies have reported a significant association between female gender and the prevalence of DPN.[1,20,21,24]

In the multivariate model, we identified three risk factors that independently correlate with the presence of DPN. These were age, chronic kidney disease and peripheral vascular disease. These risk factors were closely associated with DPN and this association has been reported before.[1,24,26,37–43]

However, we did not find any correlation between smoking and DPN.[24,26,44] Nonetheless, the following diseases were found to be associated with DPN: PVD, kidney disease, hypertension, dyslipidemia, foot ulcer and amputation, which is in line with many earlier studies.[15,37,39,44,45]

Our findings concur with those reported in recent published studies on the factors associated with DPN. These studies were noticeable multi-center studies of long-term follow-up of 20–25 years.[46,47] Most of these studies confirmed that old age, longer diabetes duration, and elevated HbA1c were the commonest risk factors for the development of DPN.[45–48]

We acknowledge several limitations in our study. The nature of study design as a retrospective study limits the accurate assessment of the association between DPN and risk factors. Therefore, prospective studies are needed to fully characterize the sequel of DPN in diabetes patients. Poor documentation of DPN diagnosis and supportive laboratories investigations (nerve conduction studies and electromyography) reduced our ability to access important data needed for the study and to confirm how DPN

diagnosis was made. Therefore, it is likely that some DPN patients were missed.

Conclusion

This study identified several risk factors that contributed to the development of DPN in Saudis. These must be considered in strategies and campaigns aimed at risk reduction of cardiovascular and chronic diseases, and consequently progression of DPN.

Ethics

The study was approved by the Institutional Review Board, King Abdullah International Medical Research Centre, King Saud bin Abdulaziz University for Health Sciences, National Guard Health Affairs. All patient data accessed complied with relevant data protection and privacy regulations. All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest for this work.

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