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Predictors of Painful Diabetic Neuropathy in Saudi Patients with Type 2 Diabetes: A Case-Control Study

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Abstract

Objectives: Due to recent reports on the high rates of painful diabetic neuropathy (PDN) in Saudi Arabian patients, this study sought to investigate the predictors of PDN in Saudi patients with type 2 diabetes.

Methods: This case-control study selected 198 outpatients with type 2 diabetes, 99 patients with PDN, 99 who did not have PDN; from a diabetes treatment center in Almadinah Almunawwarah, Saudi Arabia, from September 2013 to April 2014. Demographic data, clinical assessment, laboratory investigation and history of diabetic complications were evaluated. Neuropathy symptom score and 10 gm. monofilament test were used to assess for neuropathy.

Results: The PDN group was significantly older (54.52 ± 11.01 vs. 50.53 ± 11.34 years), (p=0.031), had had diabetes longer (13.09+ ± 7.28 vs. 8.30 ± 4.78 years), (p=0.000), and consistent HbA1c measurements (9.19 ± 1.71 vs. 8.56 ± 1.65) than the non-PDN group. The prevalence of hypertension (73.7% vs. 50.5%), (p=0.001), cardiovascular disease (18.2% vs. 6.1%), (p=0.009), and stroke (7.1% vs. 1%), (p=0.031) was significantly higher in the PDN group than in the non-PDN group. The odds ratio (OR) (95% confidence intervals) of PDN increased significantly with patients who had diabetes for more than 10 years (3.38, 1.88-6.07), hypertension (2.85, 1.57-5.17), and cardiovascular disease (3.37, 1.28-8.89); it decreases significantly with glycemic control (0.422, 0.12-0.96).

Conclusions: Similar to other populations, predictors of PDN in Saudi patients with type 2 diabetes include age, duration, glycemic control, hypertension, cardiovascular disease and other microvascular diabetic complications. Further studies of a larger sample in a different region of Saudi Arabia are needed for better evidence and generalization.
Conclusion: WBV was effective at safely reducing pain and improving health related outcomes in our participant.

Keywords: Predictors; Painful diabetic neuropathy; Type 2 diabetes; Saudi Arabia

Introduction

Among chronic diabetic complications, diabetic peripheral neuropathy (DPN) is one of the most common, affecting 30-50% of patients with diabetes [1]. Painful diabetic neuropathy (PDN), a distal sensorimotor neuropathy, is generally considered the most distressing and clinically recognized variant of peripheral neuropathy (PN) in patient with diabetes. It is characterized by pain, paraesthesia, numbness and sensory loss [2]. Some evidence points to abnormal discharges from diseased peripheral neurons as the main cause of this pain [3,4]. Others point to the role of spontaneous activity in the peripheral nociceptor system in stimulating the central nervous system leading to hyperalgesia and allodynia [3,4]. However, the exact mechanisms involved in different pain sensations are still unknown. Hyperglycemia is believed to be the primary risk factor for DPN development [1]. Based on strong clinical evidence from the UKPDS (the United Kingdom Prospective Diabetes Study), prolonged hyperglycemia contributes to disease pathogenesis and progression [5,6]. The key pathological process of DPN, in both animal and human studies, is exposure to oxidative stress triggered by vascular abnormalities and associated with nerve micro-angiopathy [3,7]. The recognized independent risk factors for development of PDN include uncontrolled diabetic status, age, gender, duration of disease, cigarette smoking, hypertension, hypertriglyceridemia, obesity, and alcohol consumption [1]. Over the past two decades, the prevalence of diabetes mellitus (DM) in Saudi Arabia — up to 24% of the population — has dramatically increased and is now considered among one of the highest rates in the world [8]. Despite the high prevalence of type 2 diabetes in the Saudi population, limited Saudi studies have specifically addressed the prevalence of PDN [9]. One study examined 375 Saudi patients who had diabetes for 10 or more years and reported a 38% prevalence of DPN similar to other ethnic groups [10]. However, higher prevalence was detected in another study of 237 Saudi patients where 56% of patients had symptomatic DPN [11]. Another large national study of 1,039 patients from 100 outpatient clinics across the Kingdom detected higher than anticipated (65.3%) prevalence of DPN among Saudis [9]. The aim of this study is to address the predictors of development and progression of PDN among Saudi patients with type 2 diabetes attending a tertiary care diabetic treatment center at Almadinah Almunawwarah, Saudi Arabia, which is providing service for the patients from a region of 2 million people. Up to now no study has addressed PDN in Almadinah Almunawwarah region, these data will serve as foundation and database for interested researchers in the field to explore farther predictor in the future which may help to improve the quality of medical care for patient with Diabetic neuropathy.

Methodology

This case-control study was conducted at the Prince Abdulaziz Bin Majed Diabetic Center in Almadinah Almunawwarah, Saudi Arabia, after obtaining Institutional Review Boards approval from local authorities. Eligible participants included Saudi patients with type 2 diabetes seeking outpatient care, age 25 years or older, of any gender or duration of diabetes, and on any type of anti-diabetic therapy. After assessing patients for PDN, 99 patients with and 99 patients

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without the condition were selected. Pregnant women, the severely ill, patients with malignancy, chronic inflammatory demyelinating polyneuropathy, paraproteinemia or any other cause of PDN were excluded from the study. Data were collected between September 2013 and April 2014 after obtaining informed consents from all patients according to the Declaration of Helsinki. Patients were interviewed to review their medical record file for HbA1c, drug therapy, smoking, alcoholism, hypertension, obesity, other microvascular complications (nephropathy, retinopathy) and macrovascular complications, such as cardiovascular disease (CVD), stroke, peripheral vascular disease (PVD), and history of diabetic foot. Glycemic control was determined based mainly on the latest HbA1c results using the American Diabetes Association (ADA) criterion of less than 7. Dyslipidemia was limited by the use of anti-hyperlipidemic drugs for all participants. The Visual Analogue Scale for pain was used to assess pain and for inclusion of patients with mild, moderate to severe pain. Diagnosis of DPN depends on a foot examination and the presence of at least 3 points on the Neuropathy Symptom Score [12,13] (i.e., burning, numbness and tingling is 2 points; fatigue, cramping and aching is 1 point; if these symptoms present in the feet, that is 2 points, in the calf 1 point; nocturnal exacerbation of the symptoms is 2 points; equal symptoms during day and night is 1 point; if symptoms wake the patient from sleep, 1 point). If symptoms are reduced by walking or standing that is 2 points and 1 point respectively. Participants' feet were examined for neuropathy relying mainly on insensitivity to the Semmes-Weinstein 5.07 (10 g) monofilament performed over the plantar aspects of the great toe, third, and fifth metatarsal heads. In addition, both feet were examined for superficial pain by pinprick, tactile sensation with the reverse end of a tuning fork, vibration sense by 128 Hz tuning fork, and thermal sensation using a cold sponge. A tendon hammer was used to determine ankle-deep tendon reflexes. Pedal pulses were also checked.

Statistical analysis

Study data were analyzed using the SPSS 17.0 software for Windows (PASW statistics 17). Student's t-tests were used to assess differences between continuous variables (expressed as mean ± SD); non-parametric tests (Mann-Whitney U tests) were used for categorical variables (expressed as number and percentage). Cross tabulation and chi-squared tests were used for determination of odds ratio (OR), 95% confidence intervals and significance of different risk factors. For all statistics, a two-sided p-value <0.05 was considered statistically significant.

Results

Table 1 demonstrates the demographic, clinical and metabolic data of the PDN and non-PDN groups of patients with type 2 diabetes. Both PDN and non-PDN groups were matched for gender (33.3% males and 66.7% females vs. 41.4% males and 58.6% females), (p=0.241), occupation (25.2% vs. 22.2% were working), (p=0.866) and anti-diabetic medications (insulin used in 59.6% vs. 44.5%), (p=0.695). The PDN group had significantly older patients (54.52 ± 11.01 vs. 50.53 ± 11.34 years), (p=0.031), with longer duration of diabetes (13.09 ± 7.28 vs. 8.30 ± 4.78 years), (p=0.000), and HbA1c (9.19 ± 1.71vs. 8.56 ± 1.65) with less glycemic control (10.1% vs. 20.2%), (p=0.036). The prevalence of hypertension (73.7% vs. 50.5%), (p=0.001), retinopathy (36.4% vs. 4.4%), (p=0.000), nephropathy (22.2% vs. 3%), (p=0.000), CVD (18.2% vs. 6.1%), (p=0.009), stroke (7.1% vs. 1%), (p=0.031), and PVD (7.1% vs. 1%), (p=0.031) were significantly higher in the PDN group than in the non-PDN group. Table 2 shows the OR (95% confidence intervals) of PDN. ORs increase significantly with patients older than 50 years (1.93, 1.09-3.41), illness duration of more than 10 years (3.38, 1.88-6.07), and the presence of hypertension (2.85, 1.57-5.17), retinopathy (13.22, 4.49-38.95), nephropathy (8.93, 2.58-30.94), and CVD (3.37, 1.28-8.89). It decreases significantly with glycemic control (0.422, 0.12-0.96).

	T2D with PDN N=99	T2D without PDN N=99	P
Gender: Males: n (%)	33 (33.3%)	41 (41.4%)	0.241
Females: n (%)	66 (66.7%)	58 (58.6%)	
Age: years	54.52 ± 11.01	50.53 ± 11.34	0.031
Working: n (%)	26 (25.2%)	22 (22.2%)	0.866
Duration of diabetes: years	13.09 ± 7.28	8.30 ± 4.78	0.000
Smoking: n (%)	5 (5.1%)	4 (4%)	0.734
Hypertension: n (%)	73 (73.7%)	50 (50.5%)	0.001
Retinopathy: n (%)	36 (36.4%)	4 (4%)	0.000
Nephropathy: n (%)	22 (22.2%)	3 (3%)	0.000
Cardiovascular diseases n (%)	18 (18.2%)	6 (6.1%)	0.009
Stroke: n (%)	7 (7.1%)	1 (1%)	0.031
Peripheral vascular diseases: n (%)	7 (7.1%)	1(1%)	0.031
Anti-diabetic drugs:			
Oral Anti-diabetics: n (%)	40 (40.4%)	55 (55.5%)	0.695
Insulin: n (%)	59 (59.6%)	44 (44.5%)	
HbA1c: n (%)	9.19 ± 1.71	8.56 ± 1.65	0.009
Glycemic control: n (%)	10 (10.1%)	20 (20.2%)	0.036

Table 1: The demographic, clinical and metabolic data of the PDN and non-PDN groups of type 2 diabetes patients.

Discussion

This study found significant associations between PDN and age, duration of underlying diabetes, glycemic control, waist circumference, hypertension, and micro and macrovascular diabetic complications in Saudi patients with type 2 diabetes. However, significant predictors included age, duration, glycemic control, hypertension, CVD, retinopathy and nephropathy. The most important significant predictors were, in order: retinopathy (OR 13.22), nephropathy (OR 8.93), duration (OR 3.38) and CVD (OR 3.37). There was no significant association with patients' gender, occupation, smoking or the use of insulin. These results are somewhat similar to other Saudi studies, which apart from gender, found similar associations between PDN, age, and duration with no significant association with smoking [9]. One study found age, duration, and glycemic control were risk factors associated with DPN [11]. Another study of 136 diabetes patients, found that duration, insulin use and glycemic control were the most important risk factors associated with diabetic neuropathy [14]. However, researchers did not find any significant association with age, gender, type of DM, hypertension, hyperlipidemia or smoking. The differences in these results may be due to variations in study methodology and the association between predictors and nerve conduction abnormalities in symptomatic patients with type 1 and type 2 diabetes. For other populations, the role of age, diabetes duration and chronic hyperglycemia in the prediction of DPN has been well documented in many studies including the UKPDS [5,6]. In this study, HbA1c was positively associated with PDN; better glycemic control produced a decreased OR for PDN (0.422). Also, hypertension as a co-existing disease was prevalent in this study population, but

	Odds Ratio	95% Confidence Interval		P
		Lower	Upper	
Gender (Male/ Female)	1.34	0.75	2.39	0.322
Age (>50 years)	1.93	1.09	3.41	0.023
Occupation	1.03	0.53	2.01	0.926
Duration (>10)	3.38	1.88	6.07	0.000
Smoking	1.24	0.32	4.75	0.756
Hypertension	2.85	1.57	5.17	0.000
Retinopathy	13.22	4.49	38.95	0.000
Nephropathy	8.93	2.58	30.95	0.000
Cardiovascular Disease	3.37	1.28	8.89	0.010
Stroke: n (%)	7.38	0.89	61.16	0.650
Peripheral vascular diseases: n (%)	7.30	0.88	60.49	0.650
Glycemic Control	0.42	0.12	0.96	0.035
The Use of Insulin	1.67	0.95	2.94	0.076

Table 2: The odds ratios and 95% confidence intervals of PDN in type 2 diabetes patients (predictors of PDN).

more significantly prevalent in PDN (73.7%) than in non-PDN patients (50.55). Supported by other studies that demonstrate strong associations between hypertension and DPN, there is an association between hypertension and PDN with significantly increased OR (2.85) [15]. This study's results emphasized the concurrent development of PDN and, not only other microvascular diabetic complications, but also macrovascular complications, mainly CVD. This study showed no significant association between PDN and gender, occupation, or smoking. Results of many other studies do not agree on the association between PDN and gender, smoking and the use of insulin. Other studies [11,16,17] found significant association between PDN and smoking, which may be attributed in part to smoking's direct vascular effects [16]. In this study, no significant association was found between the use of insulin and the development of PDN, an association found by others [14,17].

Apart from age and diabetes duration, this study demonstrates the association between PDN and some modifiable risk factors, such as hypertension, hyperglycemia, and diabetic complications in Saudi patients with type 2 diabetes. Strong predictors are retinopathy, nephropathy, diabetes duration, and CVD. Several risk factors, such as gender, smoking and the use of insulin, identified as predictors of DPN in other studies, did not emerge as independent predictors for PDN in this study. These results are in partial accordance with the few studies performed in other populations, which did not address these risk factors as primary outcome variables. There were some limitations in this study; e.g., the case-control design allows detection of ORs but not cause-and-effect relationships. Also, diagnosis of different micro- and macrovascular complications is based on past history which has its own constraints; and limitations of the diagnostic tests may affect the results, and consequently, their generalization. Further studies are required to define the role of different risk factors in development and progression of PDN in the Saudi population in different regions. As well to investigate farther risk factor like hypothyroidism, body mass index and different type of treatment for DM. For better evidence, further interventional trials are needed to establish cause-effect relationship in large population-based investigations. The ultimate goal may be early detection and treatment of the risk factors associated with the progression and development of PDN in Saudi patients to further reduce morbidity and mortality.

Competing Interests

The study was self-funded. The author declares he has no competing interests.

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