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Physical activity and albuminuria were associated with painful diabetic polyneuropathy in type 2 diabetes in an ethnic Chinese population

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ABSTRACT

Background: Diabetic neuropathy is a common complication in patients with type 2 diabetes. However, the prevalence of painful diabetic polyneuropathy (PDPN) have been less studied. We examined the prevalence and risk factors of PDPN in outpatients with type 2 diabetes in an ethnic Chinese population.
Methods: This retrospective study enrolled 2358 outpatients with type 2 diabetes who had completed the Douleur Neuropathique en 4 Questions (DN4) questionnaire from January 2013 to October 2013. Patients with a total score ≥4 were defined as having PDPN.
Results: In all, 179 patients were diagnosed as having PDPN with a score of 4.49 on the DN4 questionnaire, compared with 0.66 for patients without PDPN. After adjusting the possible confounding factors, the risk of painful neuropathy was increased in the group without physical activity (Odds ratio 3.38, 95% CI 1.54–9.79), and in the group with macroalbuminuria (Odds ratio 2.31, 95% CI 1.44–3.73). Besides, there was a joint effect of macroalbuminuria and no physical activity habit on PDPN risk.
Conclusions: The prevalence of PDPN was 7.6% among our outpatients with type 2 diabetes. Less physical activity and albuminuria, respectively, increased the risk of PDPN and had a joint effect.

1. Introduction

Diabetic neuropathy is one of the most common chronic complications of patients with type 2 diabetes (T2DM) [1], and is associated with an increased risk of foot ulcerations and even foot amputation [2,3]. It is estimated that about 13.3–34% of diabetic patients with diabetic neuropathy, including sensorimotor polyneuropathy [4–6], may have painful diabetic polyneuropathy (PDPN) [7–10], which can lead to a worsening of quality of life [8,9,11,12]. At present, several pharmacological treatments have been developed to manage PDPN [13–16], although most current therapies, except glycemic control [17], are often ineffective.

The diagnosis of PDPN is very complex, and PDPN is easily underdiagnosed in clinical practice [7,8]. Due to the great impact of PDPN on diabetic patients, utilization of some clinical characteristics, such as risk factors, may be helpful in achieving an early recognition of PDPN. It has been shown that diabetic neuropathy is associated with several traditional cardiovascular risk factors, including elevated triglyceride, body mass index (BMI), smoking, and hypertension [18]. In addition, some studies revealed that less physical activity, smoking, and alcohol drinking may also increase the risk of diabetic sensorimotor polyneuropathy [19–21]. Increased physical activity and smoking cessation have been shown to decrease the occurrence of neuropathy, its symptoms and progression [22–24]. However, whether these findings observed in diabetic sensorimotor polyneuropathy can also be applied to PDPN has been less studied, especially among Asians. Thus, the aims of the present study were to examine the prevalence of PDPN in

Abbreviations: PDPN, painful diabetic polyneuropathy.

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a diabetic population in Taiwan, and to identify the risk factors of PDPN, such as albuminuria and physical activity. In addition, the present study also aimed to determine whether there was a joint effect of the related risk factors on the development of PDPN. In the present study, the diagnosis of PDPN was by questionnaire, the DN4, which was designed for painful neuropathy in 2005 [22]. There are only four questions on the questionnaire, two of which are objective parameters. The sensitivity and specificity have been published, and the validation for diabetic patients was also reported [23].

2. Subjects, materials, and methods

2.1. Subjects

This retrospective, observational study, conducted from January 2013 to October 2013, involved 2358 patients with T2DM who visited the outpatient department of a medical center in central Taiwan. These patients were routinely referred to the diabetic educators, general physical and laboratory examinations were performed, and educational topics were offered. Patients were excluded if they were <20 years or had human immunodeficiency virus (HIV) infection. The study was approved by the Institutional Review Board of Taichung Veterans General Hospital, Taichung, Taiwan.

2.2. Data collection and diagnosis of painful diabetic polyneuropathy

Patient characteristics, including age, sex, DM duration, anti-diabetic medication, anti-hypertensive and lipid-lowering medication, systolic blood pressure, waist circumference, body weight and height, and duration of daily exercise, were collected by the diabetic educators during the routine DM education program. A Chinese-language edition Douleur Neuropathique en 4 Questions (DN4) questionnaire composed of two parts, including oral questions and physical examinations, was used to diagnose PDPN, and finished by a well-trained diabetic educator [25]. The PDPN was defined as DN4 score ≥4 [23]. Finally, 2358 patients all completed the measurements of the urinary albumin excretion ratio, HbA1c, LDL, serum creatinine, and DN4 questionnaire. The certification for this study was approval by the institutional review board of Taichung Veterans General Hospital.

2.3. Statistical analysis

Descriptive statistics for continuous variables are expressed as means and standard deviation (SD). Differences in clinical variables between groups were compared by Student's *t*-test for continuous variables, and Fisher's exact test for categorical variables. Generalized linear model (GLM) analysis was used to investigate the association between exercise duration and DN4 score value, as well as the association between urine albumin-to-creatinine ratio (UACR) and DN4 score. The impacts of exercise and UACR on painful neuropathy were tested using the GLM with logit analysis. The joint effects of exercise and UACR were also tested using the GLM. All reported p-values were two-sided and considered significant when <0.05. In addition, 95% confidence intervals are reported. Statistical analysis was performed by using SPSS program ver 22.

3. Results

Of the 2358 diabetic patients, 7.6% had painful diabetic polyneuropathy (PDPN). There were more female patients among the 7.6%, and they were older, had longer diabetes duration, higher systolic blood pressure, lower LDL-c, higher HbA1c, lower eGFR, more albuminuria, less habitual exercise, and more insulin use. About 37.4% of the patients had albuminuria and 60% had no exercise habits (Table 1).

Among all subjects and in the group without painful neuropathy, shorter duration of physical activity was associated with greater DN4 score severity, P for trend <0.001. However, there were no such trends in the painful neuropathy group (DN4 ≧ 4) (Table 2).

In addition, we found that patients with macroalbuminuria had the highest mean DN4 score among all subjects and patients without PDPN (P for trend <0.001). However, there was no such trend in the group with painful neuropathy (DN4 score ≥4).

Patients without the habit of exercise were associated with a higher risk of painful neuropathy after adjusting for sex, age, diabetes duration, neuropathy medication usage, insulin user, oral anti-diabetics drugs, systolic blood pressure, BMI, glycated hemoglobin, low-density lipoprotein, and eGFR (P for trend = 0.006) (Table 3). In addition, it was found that macroalbuminuria was associated with a higher risk of painful

Table 1
Baseline characteristics of the subjects with and without painful diabetic polyneuropathy.

Variable	All subjects (N = 2358)	No PDPN (N = 2179)	PDPN (N = 179)	p
Men (%)	1347 (57.1)	1264 (58.0%)	83 (46.4%)	0.003
Age (y)	63.5 ± 13.2	63.0 ± 13.2	69.6 ± 12.5	<0.001
BMI (kg/m^2)	25.5 ± 3.9	25.6 ± 4.0	25.5 ± 4.1	0.881
Diabetic duration (y)	10.0 ± 8.3	9.76 ± 8.19	13.3 ± 9.3	<0.001
SBP (mm Hg)	130 ± 13.9	130.5 ± 13.7	131.4 ± 16.4	<0.001
DBP (mm Hg)	77 ± 8.9	77.1 ± 8.9	77.3 ± 10.6	0.812
DN4 score	0.95 ± 1.40	0.66 ± 0.98	4.49 ± 0.75	None
DN4 score >4	179 (7.6)	0	179 (100%)	None
LDL-c (mg/dl)	101 ± 31.5	101.9 ± 31.7	96.7 ± 29.5	0.036
HbA1C (%)	7.4 ± 1.5	7.46 ± 1.46	7.78 ± 1.70	0.014
eGFR (ml/min per 1.73 m^2)	79.5 ± 31.1	80.6 ± 31.0	66.7 ± 30.0	<0.001
UACR				
Normal	1475 (62.6)	1393 (63.9%)	82 (45.8%)	<0.001
Albuminuria (UACR ≥30 mg/g)	883 (37.4)	786 (36.1%)	97 (54.2%)	
Daily exercise duration				
>30 min	311 (13.2)	302 (13.9%)	9 (5.0%)	0.001
≤30 min	632 (26.8)	590 (27.1%)	42 (23.5%)	
No exercise	1415 (60.0)	1287 (59.1%)	128 (71.5%)	
Neuropathy medication usage	400 (17.0)	347 (15.9%)	53 (29.6%)	<0.001
OAD usage	2033 (86.2)	1880 (86.3%)	153 (85.5%)	0.856
Insulin usage	420 (17.8)	379 (17.4%)	41 (22.9%)	<0.001
Current smoking	221 (9.4)	208 (9.5%)	13 (7.3%)	0.265

Data are N (%) or mean (SD).
Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; DN4, Douleur Neuropathique en 4 questions; ALT, alanine transaminase; OAD, oral anti-diabetic drug; UACR, urine albumin to creatinine ratio; PDPN, painful diabetic polyneuropathy.