Peripheral neuropathy in type 2 diabetes mellitus in Isfahan, Iran: Prevalence and risk factors

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Abstract

Background: To estimate the prevalence and risk factors of peripheral neuropathy (PN) in people with type 2 diabetes mellitus. *Methods*: 810 patients with type 2 diabetes (289 male and 521 female) from Isfahan Endocrinology and Metabolism Research Centre outpatient clinics, Iran , were examined. Part of the examination included an assessment of neurological function including neuropathic symptoms and physical signs, and nerve conduction velocity. *Results*: The prevalence of PN was 75.1% (95% confidence interval (CI) 72.1, 78.0). Peripheral neuropathy was associated with age, proteinuria, and duration of diabetes, insulin-treatment, and presence of retinopathy and ischaemic heart disease (IHD). The age-adjusted prevalence rate of PN was 78% higher among patients with IHD, 64% higher among patients with any retinopathy, 66% higher among insulin-treated type 2 diabetes, and greater with duration of diabetes. Using a stepwise binary logistic regression model, age, duration of diabetes and proteinuria were significant independent predictors of PN. *Conclusion:* PN is a common complication in this population of Iranian type 2 diabetic patients. It increases with age, duration of diabetes and proteinuria. (Int J Diabetes Metab 14: 126-133, 2006)

Keywords*: Complications, diabetes mellitus, diabetic neuropathy, epidemiology, Iran, peripheral neuropathy, prevalence, risk factors.*

Introduction

Peripheral neuropathy is a major factor in the occurrence of foot ulcers in patients with diabetes.[1] The relationship between diabetes complications and PN is well established in clinic-, hospital,[2-5] and population based prevalence studies[6-12] in many different populations in developed nations.[2-17] The prevalence and pattern of PN vary from country to country, from as low as 1.5% to as high as 100% in patients with type 2 diabetes[7,11-15] depending on the differences in screening approaches, diagnostic criteria and the study population.[16] The neuropathy may be silent and go undetected. Up to 7.5% of patients with type 2 diabetes have clinical neuropathy at the time of diagnosis. This rate increases to 50% among patients with diabetes who have had diabetes for 25 years.[15] However, epidemiological studies of the impact of PN on type 2 diabetes in developing countries are scarce.

Type 2 diabetes and PN are common causes of foot ulceration, gangrene, and amputation and are serious problems in Iran but to our knowledge, there have been no studies describing the prevalence or risk factors of PN in patients with diabetes.

The objective of this study was to estimate the prevalence and risk factors of PN in patients with type 2 diabetes using routinely collected data from a clinical information system for diabetes at Isfahan Endocrinology and Metabolism Research Centre, Iran.

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Patients and Methods

Data source*:* We have conducted a cross-sectional study of 810 patients with type 2 diabetes at the Isfahan Endocrinology and Metabolism Research Centre outpatient clinics. Details of the recruitment and examination procedures of the Isfahan Endocrinology and Metabolism Research Centre outpatient clinics have been published previously.[18, 19] In brief, clinical data are collected for all consecutive patients at the first attendance and at review consultations (usually annually) using standard encounter forms. These include a retinal examination, lens, limbs, blood pressure and construction of a problem list by the clinician, measurement of fasting blood glucose, glycosylated haemoglobin (HbA_1), urinary protein, triglyceride, cholesterol and serum creatinine, and reporting of smoking as part of a completed questionnaire on demography, family history, and smoking by the patient. A registry clerk entered the data from these forms into the computer after the clinic.

Patients: Between 1992 and 2004, a total of 9,631 patients with type 2 diabetes were registered in the system. During 2000 to 2003, out of 2,692 patients with type 2 diabetes, we selected 810 (289 male and 521 female) patients. These patients were initially screened by an endocrinologist and then referred to neurologist to undergo clinical evaluation including the symptom profiles, neurologic examination and

nerve conduction velocity. All patients met the American Diabetes Association criteria for type 2 diabetes. Exclusion criteria were history of any laboratory findings suggestive of hereditary or acquired neuropathy, vasculitis, amyloidosis, leukodystrophy, Refsum's disease, hypothyroidism, alcohol abuse, or lack of compliance for diagnostic test.

The patients had a mean (standard deviation (SD) duration of diabetes of 8.2 (6.8) years and mean age of 52.7 (9.9) years. The characteristics of those selected and not selected are shown in Table 1. Compared to non-participants, those who participated were slightly younger at diagnosis of diabetes, had a longer duration of diabetes, higher HbA_1 and creatinine, lower body mass index (BMI) and triglyceride, and had a higher proportion of proteinuria and insulin-treated diabetes but were fewer males. The sample had similar distributions of age, systolic and diastolic blood pressure, fasting blood glucose, cholesterol, uric acid and smoking status as those not selected.

Risk factors for PN were assessed using the following data from the patient's registration consultation: gender, age at diagnosis, age, duration of diabetes, body mass index (BMI) (weight/height^2 (Kg/m^2), smoking status (never, current), haemoglobin A_1 (HbA_1) (measured by ion-exchange chromatography; as an indicator of diabetes control), fasting blood glucose (measured by the glucose oxidase method; Clinical Chemistry Analyser, Liasys, Italy), proteinuria (measured by precipitation with 3% sulfosalicylic acid and determination of turbidity by measuring absorbance at a wavelength of 550 nm), serum creatinine, triglyceride, cholesterol (measured using conventional laboratory techniques), blood pressure (systolic and diastolic) and diabetes treatment (insulin and no-insulin).

The diagnosis of retinopathy was confirmed (or not) by fundus photography. The term "any retinopathy" refers to both nonproliferative and proliferative retinopathy. Ischemic heart disease (IHD) was defined either as the presence of a past history of IHD (previous myocardial infarction, angina, coronary bypass grafting) or abnormal 12-lead electrocardiogram. Proteinuria was defined as urine protein excretion >500 mg/dl or albumin excretion >300 mg/dl.

A detailed neurological examination, including the assessment of neuropathic symptom, signs, measurement of vibration sensation and nerve conduction velocity, was performed. Neuropathy was suspected if the following symptoms were present over the previous six months: numbness or coldness in the feet; pricking sensation in the feet; deep or burning pains in the legs and unusual difficulty in climbing stairs.[20,21] Neurological examinations including ankle and knee reflexes were performed, with reinforcement if necessary. Vibration sensation was tested with a tuning fork (128 Hz) on each medial malleolus. The clinical neurological examination involved assessment of the following sections: A (sensory modalities), B (light touch sense at anatomic), C (muscle power) and D (ankle reflex). Section A including pain (pin prick) of dorsum of the foot, vibration sense of ankle, position sense of first toe, light touch sense of dorsum of foot. Each one was scored as: 0 normal; 2 impaired compared with proximal; 4 absent. Section B included: light touch sense at anatomic level and scored as 0 normal; 1 toe; 2 mid foot; 3 ankle; 4 mid calf; and 5 knee. Section C included muscular power of extensor hallucis longus (dorsal flexion of great toe) and gastrocnemius (plantar flexion of foot). Each item was scored as 0 normal, 2 impaired, 4 absent. Section D included ankle jerk was scored as 0 normal; 2 impaired compared to knee reflex; 4 absent. Summing up to a maximum score of 33 and graded as: 0 no neuropathy, 1-9 mild neuropathy, 10-18 moderate neuropathy ≥19 severe neuropathy. Nerve conduction velocity measurements and electromyography were made with a two-channel DISA 1500 electromyograph. Electrodiagnosis examination included motor and sensory nerve conduction velocities. Distal latencies and action potential amplitude were conducted for all moderate and severe cases. For this purpose, nerve conduction velocity, amplitude, duration and latency were assessed in 5 sensory/motor nerves (median, ulnar, tibial, peroneal and sural) on the non-dominant side of the body, according to standard techniques.[22] At least one abnormal test in more than one of these nerves was considered indicative of PN. Motor conduction studies were performed with surface electrodes on the muscles and supramaximal stimulation of the corresponding nerves. Median and ulnar nerves were stimulated at the wrist and elbow, with motor action potential being recorded over the abductor pollicis brevis and abductor digiti minimi, respectively. Peroneal and tibial nerves were stimulated at the ankle and knee, with motor action potential being recorded over the extensor digitorium brevis and adductor hallicus, respectively. Sensory nerve conduction studies were performed on the median, ulnar, and sural nerves, with antidromic stimulation at finger II, finger V, and lateral malleolus, respectively. The sensory action potentials of the median and ulnar nerves were recorded at the wrist and at the lower leg for the sural nerve. Abnormal conduction velocity was seen in 94% of patients in the moderate group and and 100% of patients in the severe group.

The Institutional Review Board and Medical Ethics Committee of the Isfahan University of Medical Sciences approved the protocol. The study complied with the current version of the Declaration of Helsinki.

Analysis: Student's *t* test, chi square test, and stepwise binary logistic regression were used. Two types of statistical analyses were used in this report: Crude relative prevalence (RP) based on prevalence rates and adjusted odds ratio (OR) determined by a logistic regression analysis using the SPSS for Windows computer package (SPSS Inc., Chicago, IL, USA) which simultaneously adjusts for other covariates. Independent variables entered into the model were those having a significant association with PN ($P<0.05$) in previous analyses. Adjustment for age was examined in separate models. To save space and confusion, confidence intervals around the RP and OR were given, although significant P values ($P<0.05$) have been reported.

Table 1: Group mean and proportion comparison of selected characteristics between participants and non-participants type 2 diabetic patients.

Characteristics	Mean (SD) Participants	Mean (SD) Non-participants	Différences (95% CI)
Age (yr)	52.7 (9.9)	52.4 (10.5)	0.3 (-0.4, 1.0)
Duration of diabetes (yr.)	8.2 (6.8)	6.3 (6.4)	1.9 (1.4, 2.3)***
Age at diagnosis (yr.)	44.5 (10.3)	46.1 (10.5)	-1.6 (-2.4, -0.9)***
BMI (Kg/m^2)	26.3 (3.9)	27.6 (4.6)	-1.3 (-1.6, -0.9)***
Systolic BP (mmHg)	128.2 (22.9)	126.8 (22.0)	1.4. (-0.2, 3.0)
Diastolic BP (mmHg)	78.0 (12.6)	77.4 (12.0)	0.6 (-0.3, 1.5)
Fasting blood glucose (mg/dl)	207.7 (70.9)	204.6 (74.9)	3.1 (-2.4, 8.5)
HbA1 (%)	11.0 (2.4)	10.1 (2.3)	0.9 (0.7, 1.1)***
Triglyceride (mg/dl)	222.1 (153.2)	233.8 (153.7)	-11.7 (-23.1, -0.4)*
Cholesterol (mg/dl)	224.7 (54.0)	226.1 (54.0)	-1.4 (-5.4, 2.5)
Uric acid (mg/dl)	5.1 (1.9)	5.0 (2.1)	0.1 (-0.1, 0.4)
Creatinine (μM/l)	1.2 (1.5)	1.0 (0.9)	0.2 (0.1, 0.3)***
	No. (%)		
Gender			
Male	289 (35.7)	3799 (43.1)	-7.4 (-10.8, -3.9)***
Female	521 (64.3)	5022 (56.9)	-
Smoking			
Never-smoker	632 (82.7)	6755 (85.4)	-2.7 (-5.5, 0.1)
Current-smoker	132 (17.3)	1153 (14.6)	-
Proteinuria			
Present	246 (39.0)	1053 (29.3)	9.7 (5.7, 13.8)***
Absent	384 (61.0)	2540 (70.7)	-
Therapeutic regimen			
Insulin	215 (29.9)	1242 (14.5)	15.3 (11.9, 18.8)***
Non-insulin	505 (70.1)	7313 (85.5)	-

CI =Confidence interval. *P<0.05, **P<0.01, ***P<0.001 for the difference in the mean and proportion of the variables between Participants and non-participants.

Results

Prevalence

Of the 810 patients, 608 (392 men and 216 women) had PN. Overall prevalence of PN was 75.1% (95% CI: 72.1, 78.0). Of the 810 patients, 202 (24.9%) were normal; 376 (46.4 %%) had mild; 199 (24.6%) had moderate and 33 (4.1 %%) severe polyneuropathy. There was a significantly increased prevalence of PN with increasing age, from 57.7% in the <50 year age group to 82.8% in the ≥70 year age group ((P<0.001). The prevalence of PN increased with duration of diabetes, and was present in 63.9% of patients with diabetes duration of less than 5 years and in 86.9% of those with diabetes duration ≥12 years. Prevalence rates were similar in women (75.2% (95% CI: 71.5, 78.9) and men (74.7% (95% CI: 69.7, 79.8). Of the 215 patients who had insulin-treated diabetes, 172 had PN, giving a prevalence of 80.0% (95% CI: 74.7, 85.3). This was greater than the prevalence rates seen for non-insulin-treated patients, 70.5% (95% CI: 66.5, 74.5).

Risk factors

Table 2 shows the group mean (SD) and proportions for those participants with and without PN. Those with PN had slightly higher systolic blood pressure (129.2 vs. 125.0 mmHg; P<0.05), lower HDL-cholesterol (43.1 vs. 50.1 mg/dl; P<0.05), and were older (53.8 vs. 49.4; P<0.001). They had a longer duration of diabetes (9.1 vs. 5.5 year; P<0.001) and higher proportion used insulin (32.6% vs. 22.4%; P<0.05), had proteinuria (42.5 vs. 29.0; P<0.01), any retinopathy (62.7% vs. 46.7%; P<0.01) and IHD (36.3 vs. 21.6; P<0.01).

To determine the influence of potential factors on the prevalence of PN, univariate analysis was first performed (Table 3). Crude RP showed that those who had PN were more likely to be older, have longer duration of diabetes, higher blood pressure, proteinuria, IHD, any retinopathy and insulin-treatment. Also, age-adjusted OR showed that significant risk factors for developing PN were longer duration of diabetes, proteinuria, and IHD, any retinopathy and insulin treatment.

To determine the independent predictors of the prevalence of PN a forward stepwise binary logistic regression was performed to test 6 predictor variables; age, duration of diabetes (included as continuous variables), IHD, any retinopathy, proteinuria (present and absent) and mode of treatment (insulin and non-insulin). The dependent variable was the PN (present, absent). Older age (OR 1.03 (95% CI: 1.004, 1.05), longer duration of diabetes (OR 1.09 (95% CI: 1.05, 1.14) and proteinuria (OR 1.57 (95% CI: 1.04, 2.36) significantly increased the risk of PN. IHD, retinopathy, and insulin treatment were not significant when other covariates were considered.

Table 2: Group means and proportions for selected variables between 608 participants with and 202 without peripheral neuropathy.

Variables	*Mean (SD)* *With neuropathy*	*Without neuropathy*	*Difference (95% CI)@*
Age (year)	53.8 (9.8)	49.4 (9.6)	4.4 (2.8, 5.9)***
Duration of diabetes (year)	9.1 (6.9)	5.5 (5.5)	3.6 (2.5, 4.6)***
Age at diagnosis of diabetes (year)	44.7 (10.5)	43.9 (9.6)	0.8 (-0.8, 2.4)
BMI (Kg/m^2)	26.3 (4.1)	26.5 (3.7)	-0.2 (-0.9, 0.4)
Height (Cm)	159.6 (9.4)	160.4 (9.6)	-0.8 (-2.3, 0.8)
Weight (Kg)	67.0 (11.4)	67.9 (10.5)	-0.9 (-2.7, 0.9)
Systolic BP (mmHg)	129.2 (23.4)	125.0 (21.3)	4.2 (0.6, 7.9)*
Diastolic BP (mmHg)	78.4 (12.8)	76.7 (12.0)	1.7 (-0.4, 3.7)
Fasting blood glucose (mg/dl)	210.0 (72.1)	200.6 (66.8)	9.4 (-2.1, 20.7)
HbA1 (%)	11.2 (2.5)	10.5 (2.2)	0.7 (-0.1, 1.1)
Triglyceride (mg/dl)	224.6 (163.3)	214.4 (117.4)	10.2 (-14.8, 35.1)
Total cholesterol (mg/dl)	225.8 (54.9)	221.2 (51.3)	4.6 (-4.2, 13.4)
HDL- cholesterol (mg/dl)	43.1 (11.0)	50.1 (30.8)	-7.0 (-13.4, -0.7)*
LDL- cholesterol (mg/dl)	130.2 (36.6)	131.1 (39.9)	-0.9 (-14.2, 12.5)
Creatinine (µM/l)	1.2 (1.7)	1.0 (0.8)	0.2 (-0.1, 0.6)
Uric acid (mg/dl)	5.1 (2.0)	5.1 (1.7)	0.0 (-0.5, 0.5)
	No. (%)		
Gender			
Male	216 (35.5)	73 (36.1)	-0.6 (-8.3, 7.0)
Female	392 (64.5)	129 (63.9)	-
Smoking			
Never-smoker	471 (82.3)	161 (83.9)	-1.5 (-7.5, 4.6)
Current-smoker	101 (17.7)	31 (16.1)	-
Proteinuria			
Absent	269 (57.5)	115 (71.0)	-13.5 (-21.8, -5.2)**
Present	199 (42.5)	47 (29.0)	-
Family history of diabetes			
No	147 (26.7)	55 (32.7)	-6.0 (-14.0, 2.0)
Yes	403 (73.3)	113 (67.3)	
Therapeutic regimen			
Non-insulin	356 (67.4)	149 (77.6)	-10.2 (-17.3, -3.1)*
Insulin	172 (32.6)	43 (22.4)	-
Residential area			
Urban	585 (96.2)	189 (94.0)	2.2 (-1.4, 5.8)
Rural	23 (3.8)	12 (6.0)	
Any retinopathy			
No	152 (37.3)	72 (53.3)	-16.1 (-25.7, -6.4)**
Yes	256 (62.7)	63 (46.7)	
Ischemic heart disease			
No	202 (63.7)	80 (78.4)	-14.7 (-24.3, -5.1)**
Yes	115 (36.3)	22 (21.6)	

CI =Confidence interval. *P<0.05, **P<0.01, ***P<0.001. @ The difference in the mean or percentage of the variables between with and without peripheral neuropathy.

Discussion

In this study of 810 diabetes clinic attenders, we found an overall prevalence of PN of 75.1% (608 patients). To the best of our knowledge, no other prevalence rates for PN among Iranian diabetic patients have been reported. This prevalence seems surprisingly high for patients with type 2 diabetes from a developing country like Iran. Prevalence rates in various studies from around the world show considerable variation as a result of variations in study design, detection methods, the examination of patients at different stages in the natural history of diabetes, or in the definition of PN, and the study of selected populations, from as low as 1.5% to as high as 100%.[7, 11-16] making comparisons between studies of limited value. Discrepancies among these studies were due especially to difficulties of defining diabetic neuropathy and wide age range of the population studied. Some authors considered findings of physical examination as indicative of neuropathy while others regarded minor paresthesia as neuropathic manifestations in yet asymptomatic patients. The EURODIAB IDDM Complications study found a prevalence of PN of 28% among the subjects with type 1 diabetes..[23] In another study from the UK, the prevalence in type 1 diabetic patients was 22.7% and in type 2 diabetic patients it was 32.1%.[4] In San Luis Valley Diabetes Study, USA, the prevalence of distal symmetric (sensory)

Table 3: Prevalence rates and relative prevalence of peripheral neuropathy by selected characteristics.

Variables	Prevalence (%)	Crude Relative prevalence (95% CI)	Age-adjusted odds ratio (95%CI)†
Gender			
Male	74.7	1.00	1.00
Female	75.2	1.01 (0.93, 1.09)	1.24 (0.88, 1.74)
Age (yr.)			
<50	57.8	1.00	-
50-59	69.8	1.21 (0.99, 1.48)	-
60-69	75.3	1.30 (1.07, 1.59)***	-
≥70	82.8	1.43 (1.18, 1.74)***	-
Age at diagnosis (year)			
<30	84.2	1.00	-
30-59	74.1	0.88 (0.76, 1.02)	-
≥60	81.8	0.97 (0.81, 1.17)	-
Duration of diabetes (year)			
<5	63.9	1.00	1.00
5-7	89.1	1.12 (0.98, 1.20)	1.37 (0.88, 2.14)
8-11	83.6	1.31 (1.17, 1.46)***	2.62 (1.58, 4.32)***
≥12	86.9	1.36 (1.23, 1.50)***	3.01 (1.88, 4.82)***
Systolic blood pressure (mmHg)			
<140	72.2	1.00	1.00
140-159	80.7	1.12 (1.01, 1.23)*	1.32 (0.82, 2.14)
≥160	87.3	1.13 (1.02, 1.25)*	1.33 (0.78, 2.27)
Diastolic blood pressure (mmHg)			
<70	73.7	1.00	1.00
70-89	74.5	1.01 (0.90, 1.14)	0.90 (0.56, 1.45)
≥90	77.7	1.05 (0.92, 1.21)	0.91 (0.51, 1.63)
Fasting blood glucose (mg/dl)			
<126	76.9	1.00	1.00
126-179	69.9	0.91 (0.78, 1.05)	0.72 (0.40, 1.32)
≥180	77.7	1.01 (0.89, 1.15)	1.20 (0.67, 2.15)
HbA1 (%)			
<7.5	71.4	1.00	1.00
7.5-9.4	69.2	0.97 (0.68, 1.37)	0.93 (0.27, 3.17)
≥ 9.5	76.9	1.08 (0.77, 1.51)	1.41 (0.43, 4.68)
Cholesterol (mg/dl)			
<200	72.9	1.00	1.00
200-219	78.2	1.07 (0.96, 1.20)	1.32 (0.82, 2.11)
>220	75.5	1.04 (0.94, 1.14)	1.11 (0.76, 1.62)
HDL-cholesterol (mg/dl)			
<40	75.4	1.00	1.00
≥40	75.7	1.00 (0.84, 1.20)	0.98 (0.48, 2.04)
LDL-cholesterol (mg/dl)			
<100	75.8	1.00	1.00
≥100	75.0	0.99 (0.80, 1.23)	0.96 (0.34, 2.34)
Triglyceride (mg/dl)			
<150	75.9	1.00	1.00
150-449	74.7	0.98 (0.90, 1.07)	0.90 (0.64, 1.29)
≥450	75.6	0.99 (0.83, 1.19)	1.11 (0.52, 2.34)
BMI (Kg/m^2)			
<25	77.8	1.00	1.00
25-29.99	74.6	0.96 (0.88, 1.04)	0.88 (0.61, 1.26)
≥30	71.5	0.92 (0.82, 1.04)	0.78 (0.49, 1.24)
Smoking			
Never-smoker	74.5	1.00	1.00
Current-smoker	76.5	1.03 (0.92, 1.14)	0.98 (0.63, 1.54)
Proteinuria			
Absent	70.1	1.00	1.00
Present	80.9	1.15 (1.06, 1.26)**	1.75 (1.18, 2.58)**

Creatinine (μM/l)			
<1.5	76.9	1.00	1.00
≥1.5	86.1	1.12 (0.97, 1.29)	1.79 (0.68, 4.75)
Uric acid (mg/dl)			
<7	75.9	1.00	
≥7	74.3	0.98 (0.80, 1.20)	
Ischemic heart disease			
No	71.6	1.00	1.00
Yes	83.9	1.17 (1.06, 1.30)**	1.78 (1.04, 3.05)*
Any retinopathy			
No	67.9	1.00	1.00
Yes	80.3	1.18 (1.06, 1.31)**	1.64 (1.09, 2.46)*
Residential area			
Rural	65.7	1.00	1.00
Urban	75.6	1.15 (0.90, 1.47)	1.56 (0.74, 3.26)
Therapeutic regimen			
Non-insulin	70.5	1.00	1.00
Insulin	80.0	1.13 (1.04, 1.24)**	1.66 (1.13, 2.46)*

*P<0.5, **P<0.01, ***P<0.001. †Odds ratio (with 95% CI) calculated by binary logistic regression analysis.

neuropathy was 27.8% in type 2 diabetes mellitus.[8] In the Rochester Diabetic Neuropathy Study neuropathy was present in 66% of diabetic patients.[12] Pirart reported a prevalence of 50% among patients with diabetes who have had diabetes for 25 years.[15] One study in Hopi and Navajo Indians who live in North-Eastern Arizona, found 21% of type 2 diabetic patients with more than 10 years duration had PN, and 28% had either amputations or peripheral vascular disease.[17] In another study, Partanen et al. reported a prevalence of 41.9% among diabetic patients of 10 years duration.[24] In a Turkish study the overall prevalence of neuropathy in patients with type 2 diabetes was 60% [25] Other study based on electrophysiological signs of PN reported a prevalence of 82% among newly diagnosed patients with diabetes.[26] Our clinic-based prevalence is higher than the values reported in studies undertaken in developed nations. [4, 8, 12, 15, 17, 23-27] Higher rates in our study could have been due to a different definition of PN, which includes ankle and knee reflexes, vibration sensation, nerve conduction velocity and electromyography. Inclusion and exclusion criteria, and differences in medical care access and therapy might be other reasons. On the other hand, the great toe vibration protocol we used may have yielded a higher sensitivity for the detection of PN compared to other studies. The studies that report prevalence rates must be compared with caution, since they include rather different definitions, relatively small numbers of subjects and a selected population of patients with diabetes. However, it seems that the prevalence of PN among these Iranian patients with type 2 diabetes was high.

Univariate analysis shows an expected pattern of association for many variables with the PN. In multivariate analysis fewer remain independently associated. Consistent with prior studies, the present study confirms the well-established association between the prevalence of PN and age [4, 6, 8, 23, 25, 27] and duration of diabetes, [4, 6, 8, 15, 23, 25, 27] in a diabetic population. The association observed in age-adjusted analyses between PN and the presence of IHD and any retinopathy have also been previously described.[15, 23, 27]

In univariate analysis, we found that the prevalence of PN was higher in patients treated with insulin than in non-insulin treated patients. A higher prevalence of PN among insulin-treated patients could be attributable to their longer duration of diabetes, delay in insulin treatment and possible insulin neuritis at the time of neurologic examination than in non-insulin-treated type 2 diabetes. After adjustment for other covariates in the multivariate analysis, the type of treatment was non-significant, indicating that insulin treatment is at least partially confounded by duration of diabetes.

The level of hyperglycaemia, as measured by one glycosylated haemoglobin determination, was not associated with PN. Lack of correlation between metabolic control of diabetes and neuropathy has been stressed by some authors, [28-30] but other studies have yielded evidence of the association between poor metabolic control and increased prevalence and severity of diabetic neuropathy.[14, 15, 31-34] Klein *et al*. in Wisconsin, USA, after 10 years of follow-up, were unable to show a significant relationship to glycaemia among older non-insulin-using subjects, though they did report a significant association in insulin-using patients with older age at onset.[35] Our study did not show poor metabolic control to be an important risk factor for PN because HbA_1 as an indicator of metabolic control was measured only in 542 patients due to unavailability of the test in our centre in the past few years. However, this warrants further study. Although these data have failed to confirm a relationship between metabolic control and the prevalence of PN, they in no way diminish the need for optimal glycaemic control for the prevention of type 2 diabetes complications, which has been well demonstrated both epidemiologically and interventionally.[36]

In this study, smoking (classified in two simple categories of never, and current) was not related to prevalence of PN. Although data from some studies suggest a positive relationship between cigarette smoking and PN,[23, 27] other studies have failed to confirm this relationship.[7, 37, 38] This

lack of association may reflect some pattern of survivorship. Those who smoked may have died of a smoking-related illness, including cardiovascular disease, neoplasia and other causes of death, before having opportunity to develop PN.

Consistent with prior studies in type 2 diabetes,[39] the present study was not able to find associations with PN for blood pressure or lipid status.

Our diagnosis of PN was based on a single examination. Nevertheless, three different qualified neurologists made observations over the years, and problems of observer error need to be considered. It seems reasonable to assume that observer error is independent of such variables as age, gender, duration of diabetes and type of treatment of the patient. If this is so, misclassification resulting from observer error will tend to reduce rather than increase the significance of differences between groups of patients. If therefore a significant difference is found between two otherwise comparable groups of patients, it is reasonable to infer that it is not due to observer error but must reflect a true difference. In this study slight difference in age, HbA_1, creatinine, BMI, triglyceride, proteinuria and therapeutic regimen between study participants and the entire population of registered patients with type 2 diabetes could slightly limit the generality of our findings. The electrophysiological study was not carried out in all of the patients, but only in those with clinical score of moderate/severe neuropathy. There were differences in duration of diabetes between study participants and the entire registered population of patients with type 2 diabetes. The duration of diabetes also significantly affected the prevalence rates of PN. . Therefore, the prevalence of neuropathy in Isfahan including the non-participants may be slightly overestimated. Another limitation was the fact that causes of PN, like renal insufficiency, HIV, syphilis, plasmocytoma, vitamin B deficiency, PCP, rheumatoid arthritis, CIDP, MGUS, porphyria, paraneoplasia, were not exclusion criteria. Nevertheless, this study provides new data from Iran, a developing country, which has been under-represented in past studies. We cannot infer causality between PN and the associated variables because of the limitation of the cross-sectional design.

In conclusion, the prevalence of PN in type 2 diabetes is 75.1% in the Isfahan area. The high prevalence may be attributed to the definition of PN, and inclusion and exclusion criteria. Since PN poses a formidable threat to diabetic patients, early and comprehensive neurological investigations for PN in patients with diabetes are warranted.

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