Prevalence and Characteristics of Diabetic Polyneuropathy in Passo Fundo, South of Brazil

ABSTRACT

Purposes: The aim of the study was to investigate the prevalence of peripheral diabetic neuropathy (PDN) and associated characteristics among type 2 diabetic mellitus (DM2) patients in Passo Fundo, a city on Southern Brazil. **Basic procedures:** A cross-sectional study was conducted with 340 patients with type 2 diabetes mellitus. Tests were performed to evaluate vibration (tuning fork), light touch (10-g monofilament), temperature, and pain (pinprick) sensations, as well as ankle reflexes and heel walking. The condition was classified as peripheral diabetic neuropathy when results in at least three of these tests were negative. The electrically induced Hoffmann reflex test was performed in a group of patients to define the criterion standard used in the assessment of clinical examination sensibility in the diagnosis of neuropathy. Sensitivity was 83%, specificity, 91%, positive predictive value, 63%, and negative predictive value, 90%. The monofilament, pinprick and deep tendon reflex were the most accurate tests in the diagnosis of neuropathy. **Main findings:** Seventy-five patients (22.1%) had peripheral diabetic neuropathy, nephropathy in 29.5% and retinopathy in 28.8%. **Conclusions:** Logistic regression revealed that only duration of diabetes, creatinine and glycated hemoglobin concentrations were significantly associated with neuropathy. **(Arq Bras Endocrinol Metab 2007;51/6:987-992)**

Keywords: Type 2 diabetes mellitus; Diabetic neuropathy; Diabetic complications

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RESUMO

Prevalência e Características da Polineuropatia Diabética em Passo Fundo, Sul do Brasil.
Propósito: O objetivo deste estudo foi investigar a prevalência da neuropatia diabética periférica (NDP) e características associadas entre pacientes com diabetes melito tipo 2 (DM2) na cidade de Passo Fundo, sul do Brasil. **Procedimentos básicos:** Um estudo de corte foi realizado com 340 pacientes portadores de DM2. Testes foram conduzidos a fim de avaliar sensações de vibração (diapasão), de toque leve (monofilamento 10 g), de temperatura e de dor (agulha), bem como reflexos do tornozelo e caminhar com os calcanhares. A condição foi classificada como NDP quando os resultados em pelo menos três desses testes foram negativos. O teste reflexo de Hoffman induzido eletricamente foi conduzido em um grupo de pacientes a fim de determinar o critério padrão usado na avaliação da sensibilidade do exame clínico no diagnóstico de neuropatia. A sensibilidade foi de 83%, especificidade, 91%, valor preditivo positivo, 63% e valor preditivo negativo, 90%. O teste do monofilamento, a dor e o reflexo do tendão foram os mais precisos no diagnóstico de neuropatia. **Principais achado:** Setenta e cinco pacientes (22,1%) foram diagnosticados com NDP, nefropatia em 29,5% e retinopatia em 28,8%. **Conclusões:** Regressão logística revelou que somente a duração do diabetes e as concentrações de creatinina e hemoglobina glicada foram significativamente associadas à neuropatia. **(Arq Bras Endocrinol Metab 2007;51/6:987-982)**

Descritores: Diabetes mellitus tipo 2; Neuropatia diabética; Complicações diabéticas

DIABETES MELLITUS (DM) IS A chronic disorder of the metabolism of glucose, lipids and proteins caused by a defect in insulin action or secretion. This metabolic disorder is responsible for chronic complications that affect macro and microcirculation (1). The manifestations of microvascular complications are more frequently found in the eyes, kidneys, and nerves, and those of macrovascular disease, in heart, brain, and leg arteries (2-4).

As DM prevalence has risen from 25% to 50% in Latin America, affecting 4–16% of the population, an increase in the number of such complications is expected (4). The prevalence of DM among adults in Brazil is 7.6% (5).

The damage to nerves in DM has been assumed to be a result of the interaction of metabolic defects complicated by vasa nervorum abnormalities. Neuropathic disorders may affect both somatic and autonomic nervous functions (6). In peripheral nerves such injuries cause loss of protective sensation impairing patient's ability to perceive incipient or even apparent ulcerations in the feet that is considered a main risk factor for amputation (7).

In Pirart's classic study, a 7.5% neuropathy prevalence rate at the time of diagnosis and a linear prevalence increase of about 1.7% per year were found. This rate was 20% to 30% after 10 to 15 years from diagnosis, and reached 50% after 25 years (8). A population-based study conducted in France with DM2 patients reported that 37% of the patients had at least one chronic complication. In another population-based study conducted in England, neuropathy was found in 42% of the patients (9).

The frequency of neuropathy may vary according to the criteria used for diagnosis. The most prevalent form of diabetic neuropathy is sensory polyneuropathy (PNP) (10).

According to the Neurodiab Executive Committee, PNP affects at least 30% of patients with DM (11). Although neuropathy is a common complication of DM, it has not been studied as often as macrovascular complications or retinopathy and nephropathy (12).

The purposes of this study were to evaluate the prevalence of PND using a sensitive clinical method of diagnosis, and to identify factors associated with the development of this complication in Passo Fundo, South of Brazil.

MATERIAL AND METHODS

A cross-sectional study was conducted with 340 patients with DM2 defined according to WHO criteria. Patients enrolled in the study were consecutively seen at the Outpatient Diabetes Clinic of Hospital São Vicente de Paulo, Passo Fundo, Brazil, from 2001 to 2002. This city has 170,000 inhabitants and lies in a semi tropical region in the southern state of Brazil. The ethnic background is European, predominantly Portuguese, German, and Italian immigrants.

The Michigan Neuropathy Screening Instrument (MNSI), a 15-item questionnaire, was applied to access the presence of symptoms of neuropathy (13), and at physical examination six neurological tests were performed to evaluate sensation, deep reflexes, and force. Sensation was tested on the dorsum and tip of the first toe. A 10-gram Semmes-Weinsten monofilament was used to test light touch, pinprick to test pain sense, 128-cycle tuning fork for vibration sense, and a cylinder with different temperatures for temperature sense. Deep tendon reflex was tested by striking the Achilles tendon with a reflex hammer. Muscle strength was tested by asking the patient to walk on heels. Neuropathy was diagnosed when three or more tests were negative.

Exclusion criteria were history of nerve root compression, hypothyroidism, or use of drugs that may cause peripheral neuropathy.

Hoffmann reflex recordings were obtained from a group of 40 patients, half with and half without neuropathy on physical examination. A Nihon-Kohden Neuropack® electromyograph was used. This test provides latency and amplitude of response of a peripheral nerve to an electrical stimulus of increasing intensity applied to the tibial nerve in the leg, and it identifies axonal, demyelinating, or combined forms of neuropathy. An individual with normal H-reflex will rarely have neuropathy (14). Diabetic neuropathy was diagnosed if any abnormal nerve conduction values were found. The Hoffmann reflex was used as the gold standard criterion to test the neurological examination and to check the sensitivity and specificity of clinical examination.

Patients answered a standard questionnaire about age, sex, and ethnicity, known duration of DM, DM treatment, and smoking habits. Smokers were defined as those who smoked at the time of the study or who had smoked for one year or more and who had not quit for at least 6 months before the evaluation. Patients were weighed in light clothing and without shoes; height was measured, and body mass index (BMI) was calculated as weight/height^2 (kg/m^2). Waist circumference was measured at the narrowest point, and hip circumference, at the widest point; waist-to-hip ratio (WHR) was calculated. Sitting blood pressure was measured twice after a 10-minute rest, using a standard aneroid sphygmomanometer (phases I and V of Korotkoff sounds). Hypertension was diagnosed when blood pressure was $\geq 140/90$ mmHg, or when the patient was taking antihypertensive drugs. Coronary artery disease was defined as the presence of angina or possible infarct according to WHO Cardiovascular Questionnaire (15) and/or abnormalities compatible with ischemia or necrosis on resting ECG (Minnesota code): Q and QS codes (1.1–2, 1.3); junctional ST segment and ST segment depression (4.1–4); T-wave abnormalities (5.1–3) and left bundle branch block (7.1) (15).

A trained ophthalmologist conducted the eye examinations using indirect ophthalmoscopy with dilation of pupils. Diabetic retinopathy (DR) was graded as: 1) no signs

of DR, 2) non-proliferative DR (microaneurysms, hemorrhage, and hard exudates), or 3) proliferative DR (new blood vessels and/or scar tissue growing into the vitreous).

Peripheral vascular disease (PVD) was diagnosed in the presence of intermittent claudication assessed according to the WHO questionnaire for cardiovascular disease (15), and/or of medial or posterior tibial pulse.

Glucose was measured by a glucose oxidase method, glycated hemoglobin (HbA_{1c}) by high-pressure liquid chromatography (HPLC, Merck-Hitachi L-9100 glycated hemoglobin analyzer; reference range: 4.7–6.0%; Merck, Darmstadt, Germany), creatinine by Jaffé's reaction, cholesterol and triglycerides by enzymatic colorimetric method, and HDL cholesterol by the direct method; LDL cholesterol was estimated by the Friedewald equation (LDL = total cholesterol – [tryglicerides/5 + HDL]).

Albuminuria was measured by immunoturbidimetry, Cobas Mina Roche®, in a random urine sample. Protein loss was classified into three groups according to the presence of albumin in the urine sample: normal albuminuria = up to 16 mg/L; microalbuminuria = from 17 to 176 mg/dL; and macroalbuminuria = more than 176 mg/dL (16).

Renal failure was defined as creatinine concentrations higher than 1.99 mg/dL. End-stage renal disease (on dialysis) was diagnosed with nephropathy when they presented with proteinuria, hypertension, DR and no signs of other renal diseases.

Statistical analysis

Unpaired Student's t test, Mann-Whitney U test, chi-square (χ^2) test and one-way analysis of variance (ANOVA) were used for comparison of parametric and non-parametric variables. Multiple logistic regression models were used to evaluate possible risk factors for neuropathy (dependent variable) and to identify potential confounding variables. Independent variables in these models were selected according to statistical significance by univariate analyses and to biological relevance. Results are presented as mean ± standard deviation, as median (range) for variables without a normal distribution, or as percentage of patients that had the characteristic under analysis. $p < 0.05$ (two-tailed) were considered statistically significant. Calculations were performed using the software SPSS 10.0 and EPI INFO 6.04d.

RESULTS

The 340 patients, included in this study had the following general characteristics: age = 57.8 ± 11 years; duration of diabetes = 8 ± 6.7 years; BMI 29.3 ± 5.3 kg/m²; WHR 0.96 ± 0.07; sex = 60% female. The frequency of use of insulin alone or together with oral agents was 47%; 17% of the patients were smokers and 65.8% had hypertension. Diabetic nephropathy was diagnosed in 92 (29.5%) patients, renal failure, in nine (2.7%), and retinopathy, in 97 (28.8%).

More than half of the patients had an unfavorable lipid profile demonstrated by total cholesterol levels higher than 200 mg/dL in 59%, LDL higher than 100 mg/dL in 78.5%, HDL lower than 45 mg/dL in 60%, and triglycerides higher than 150 mg/dL in 55%.

The Michigan questionnaire identified twice as many (46%) patients with diabetic neuropathy as the physical examination (22%), but the physical examination was more sensitive in diagnosing PDN (Michigan questionnaire: sensitivity 67%, specificity 77%, and physical examination: sensitivity 83%, specificity 91%). Therefore, only the neurological examination was used to establish a diagnosis of PDN.

Seventy-five patients (22%) were diagnosed with diabetic neuropathy. These patients were older, had DM and used insulin for longer time. The values of HbA_{1c}, urea, creatinine, and microalbuminuria were higher for patients with neuropathy. No differences were found when BMI, WHR, HDL, LDL, total cholesterol, triglycerides, systolic and diastolic blood pressure values were compared between the two groups of patients (table 1).

Neuropathy was significantly associated with male sex (chi-square 5.4; p = 0.019), positive answer to Michigan questionnaire (chi-square 23.4; p < 0.001), history of intermittent claudication (chi-square 15.4; p < 0.001), no posterior tibial pulses (chi-square = 6.2; p = 0.013), $HbA_{1c} > 7\%$ (chi-square 5.5; p = 0.019), any degree of DR (chi-square 21; p < 0.001). There were no significant associations between neuropathy and hypertension, use of alcohol, body weight or shape, or ethnicity.

A logistic regression model was used to investigate which characteristics were determinant to the development of neuropathy. The dependent variable was neuropathy and the independent variables were sex, age, duration of DM, HbA1c, renal failure, and retinopathy. The duration of DM (p = 0.001), renal failure (p = 0.039), and HbA_{1c} (p = 0.05) were significantly associated with neuropathy (table 2).

Diabetic nephropathy was diagnosed in 92 (29.5%) patients (microalbuminuria 19.2%, macroalbuminuria 3.2%, proteinuria 7.1%). Nine patients had renal failure; almost half of these patients (44%) had neuropathy, whereas only 16.4% of those without microalbuminuria had neuropathy (chi-square = 18.7; p < 0.001). Age, BMI, WHR, HDL, and LDL were similar in the three groups. The frequency of neuropathy was significantly greater for 19 patients with moderate renal impairment (creatinine > 1.4 to 1.9 mg/dL) and seven with renal failure (creatinine ≥ 2 mg/dl) (chi-square 17 and 66) than for those with normal creatinine concentrations (p < 0.001).

Table 1. Clinical characteristics and laboratory findings of 340 studied patients, and for patients with and without neuropathy (results are mean ± standard deviation).

Variable	All patients (n = 340)	With neuropathy (n = 75)	Without neuropathy (n = 265)	p
Age (years)	57.8 ± 11	68.3 ± 10.8	57 ± 11	p = 0.025
Sex (m/f)	137/203	39/36	98/167	p = 0.02
Duration of diabetes (years)	8 ± 7	11.7 ± 7	7 ± 6.4	p < 0.001
BMI (kg/m^2)	29.3 ± 5.3	28.5 ± 5	29.6 ± 5	NS
Systolic BP (mmHg)	138.9 ± 25	141 ± 27	138 ± 24	NS
Diastolic BP (mmHg)	85 ± 13	84 ± 14	86 ± 13	NS
WHR	0.96 ± 0.07	0.97 ± 0.06	0.96 ± 0.07	NS
Glucose (mg/dl)	192 ± 75.3	199 ± 73	190 ± 76	NS
Hemoglobin A1C (%)	8.1 ± 2.09	8.5 ± 2	7.9 ± 2	p = 0.049
Total cholesterol (mg/dl)	218 ± 53	216 ± 51	218 ± 54	NS
HDL cholesterol (mg/dl)	43 ± 11	42 ± 10	44 ± 11	NS
LDL cholesterol (mg/dl)	136 ± 57	144 ± 86	140 ± 46	NS
Triglycerides (mg/dl)	210 ± 175	224 ± 220	206 ± 160	NS
Urea (mg/dl)	37.2 ± 18.1	46 ± 31	35 ± 11	p < 0.001
Creatinine (mg/dl)	1.11 ± 0.51	1.3 ± 0.9	1.1 ± 0.3	p < 0.001
Microalbuminuria (mg/l)*	104.3 ± 346	189.5 ± 475.4	80.2 ± 296.2	p = 0.02

BMI = Body Mass Index, WHR = Waist to hip ratio. * Data for 312 patients.

Table 2. Logistic regression using neuropathy as a dependent variable, and sex, age, HbA1c, diabetes duration, renal insufficiency (creatinine > 2 mg/dL), and retinopathy as independent variables.

Variables	B	SE	Significance	Exp(B)
Sex	0.436	0.306	0.153	1.547
Age	0.015	0.015	0.311	1.015
Hgb A1c	0.142	0.072	0.050	1.152
Renal insufficiency	1.829	0.854	0.039	6.229
Retinopathy	0.517	0.331	0.119	1.677
DM duration	0.071	0.023	0.001	1.074

The eye examination showed that 71% of diabetic patients had a normal fundus and 28.8% had RD. Of those patients with RD, 72% had pre-proliferative lesions and 28%, proliferative lesions. The prevalence of neuropathy was 50% for patients without retinopathy, 36% in patients with pre-proliferative, and 14% in proliferative retinopathy (chi-square 16; p < 0.001). The difference in the prevalence of neuropathy was also evident in the group of patients with retinopathy and abnormally high HgA_{1c} (> 7%) (Chi-square = 11.5; p = 0.003).

The prevalence of neuropathy was not different between patients with or without hypertension, angina pectoris. The percentage of patients with neuropathy was found in patients with probable ischemia or infarctions (27%) than patients with normal ECG findings (17%), (chi-square 2.9; p = 0.08). There was a sig-nificant association between peripheral arterial disease (PAD) and neuropathy (chi square 6.3; p = 0.012): 60% of the patients with PAD had neuropathy.

Clinical examination in the diagnosis of neuropathy had a sensitivity of 83%, specificity of 91%, positive predictive value of 63%, and negative predictive value of 90%.

Sensitivity and specificity for the different tests were: monofilament test, 100% and 87%; pinprick, 100% and 80%; deep tendon reflex, 75% and 89%; vibration sense test, 83% and 68%; temperature sense test, 83% and 68%; walking on heels, 100% and 67%.

The association of two neurological tests was also assessed. Altogether, the association of the pinprick and monofilament tests showed a sensitivity of 100%, a specificity of 61%, a positive predictive value (PPV) of 60%, and a negative predictive value (NPV)

of 100%. The combination of the pinprick test and the ankle reflex revealed a sensitivity of 85%, a specificity of 61%, PPV of 63% and NPV of 84%, whereas the combination of the monofilament test and the ankle reflex had a sensitivity of 92%, specificity of 63%, PPV of 63%, and NPV of 92%.

Therefore, the association did not improve the sensitivity of the clinical examination in the diagnosis of neuropathy; however, using the monofilament test and the ankle reflex may be more appropriate, as these tests can be more easily applied.

DISCUSSION

Our study found a 22% prevalence rate of diabetic neuropathy, which is similar to the rate reported in the classic study by Pirart, who found 20% to 30% prevalence after 10 to 15 years of disease (8). This prevalence rate was also found in other studies (17).

Our patients were comparable to other populations with DM2, which are characteristically obese and have hypertension, dyslipidemias, and coronary artery disease.

Sixty-six percent of our patients were hypertensive. Studies have shown that 40–50% of patients with DM2 are hypertensive. The higher prevalence of hypertension might be assigned to the large number of overweight or obese patients (84%), or to a selection bias that might have resulted from the fact that our diabetes outpatient clinic centralizes the most severely affected patients.

One third of our patients had some degree of protein loss, which is maybe a sign of diabetic nephropathy. In the literature, the prevalence rate of nephropathy among patients with type 2 diabetes is about the same. Almost half of patients with microalbuminuria had neuropathy (18,19). Hypertension has also been shown to be an independent risk factor for the development and progression of nephropathy (20), retinopathy (21), and, more recently, neuropathy. This association suggests that vascular dysfunctions may be a common mechanism underlying all the long-term complications of diabetes.

Cigarette smoking increases the risk for diabetic nephropathy, retinopathy, and neuropathy, probably because of its metabolic effects in combination with increased inflammation and endothelial dysfunction (22). The fact that no difference in the prevalence of neuropathy among smokers, ex-smokers, and non-smokers was found in this study may be explained by the low percentage of current smokers.

The positive association between HbA_{1c}, blood urea nitrogen (BUN), and creatinine levels and neuropathy has been reported in several other studies (23). These associations were also found in this study after controlling for sex, age, and retinopathy. Duration of diabetes (p = 0.001), renal failure (p = 0.039) and HbA_{1c} (p = 0.05) were found to be significantly associated with neuropathy.

Sixty-two patients (18.2%) had peripheral artery disease, and this macrovascular complication was associated with an increased number of individuals with neuropathy. Our group described this association recently (24). It has already been described that impairment in motor nerve conduction velocity and pressure perception threshold are associated with the development of ulceration and lower limb amputation (25).

In conclusion, this study showed one fifth percent of DM2 patient of the city of Passo Fundo, South of Brazil. The physical examination is a more accurate method of diagnosis of peripheral neuropathy. Physical examination consists of monofilament, pinprick and deep tendon reflex tests. The association of the monofilament test and the ankle reflex was practical and accurate enough to be used in clinical grounds. PDN is associated with duration of diabetes, renal function, and diabetes control. PDN is also associated with other diabetic microvascular complications, such as retinopathy, nephropathy, and peripheral artery disease, but not with ischemic heart disease.

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