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Prevalence of Peripheral Neuropathy in Type 2 Diabetic Patients Attending a Diabetes Center in Turkey

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Abstract. The aim of this study was to determine the prevalence and risk factors for neuropathy in type 2 diabetic patients attending a major Turkish diabetes center. Eight hundred and sixty-six consecutive type 2 diabetic patients were included in the study. A single observer performed biothesiometry studies on these patients. The presence of diabetic neuropathy was investigated using neurological symptom scale (NSS) and neurological disability score (NDS) performed. Neuropathy was determined with standardized neurological examinations and defined as the presence of abnormal NSS and NDS together with abnormal sensory or motor signs and symptoms as well as decreased great toe vibration perception. Overall, 60% (n = 520) of the patients were diagnosed as having neuropathy. The prevalence of neuropathy increased with age ($p<0.001$) and duration of diabetes ($p<0.001$). Multiple logistic regression analysis revealed the duration of diabetes ($p<0.001$) and HbA1c levels ($p<0.001$) as the risk factors for neuropathy. The overall prevalence of neuropathy in Turkish type 2 diabetic population was 60%. Age, duration of diabetes, and poor glycemic control were considered to be the risk factors for neuropathy.

Key words: Diabetes, Neuropathy, Toe vibration threshold

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NEUROPATHY is one of the degenerative complications of diabetes. Clinically diabetic neuropathy is a destructive disease of the peripheral nerve leading to symptoms of pain or paresthesia or problems arising from neurological deficit [1]. Diabetic neuropathy (DN) is an important health problem affecting the quality of life of the patient. Detection of neuropathy and direction of treatment is also an important issue. Disability in 44% of the patients with type 1 diabetes and partial restriction of daily activity in 74% of type 2 diabetic patients with sensory neuropathy have been reported [2].

The frequency of diabetic neuropathy varies according to the different studies, from 7 to 80% [3, 4]. The differences in frequencies among series are based on the variations in the age of patients and difficulties in defining neuropathy. Many risk factors may also affect the prevalence and the development of diabetic neuropathy. The duration of diabetes, HbA1c levels, cigarette smoking and male gender were reported to be associated with diabetic neuropathy [2–4]. In this study, we investigated the prevalence of neuropathy and related conditions in patients with type 2 diabetes in a major diabetes center in Turkey.

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Methods

A cross-sectional study was carried out in type 2 diabetic patients who attended the Diabetic Clinic of Kartal Training and Research Hospital. This study was done on 866 subjects (M/F = 1.6 and mean age 57.23 R: 30–81 years). The study sample was homogenous with respect to anthropometrical characteristics, age

and socioeconomic factors in this country. In accordance with the new criteria for diabetes mellitus proposed by the ADA in 1997, patients were collected at our clinic at 2002 from 25 January to 25 June and examined for condition of diabetes mellitus and its complications. Patients with vitamin deficiency, alcoholism, malnutrition, intoxication, hypothyroidism, uremia, hereditary neuropathies, hypoglycemia, paraneoplastic disorders or inflammatory demyelinating neuropathies were not included in this study. Detailed information of the age, sex, body mass index, type and duration of diabetes mellitus, mode of treatment, degree of glycemic control, presence of hypertension, hyperlipidemia, smoking, family history of diabetes mellitus and hypertension were recorded in each patient. Hypertension was considered to be present if systolic blood pressure was over 160 mm Hg or a diastolic pressure over 95 mm Hg and if there was a history of the treatment for high blood pressure. Hypercholesterolemia was considered to be present if serum cholesterol levels exceeded 200 mg/dL. Hyperglycemia was considered to be present if serum glucose level of 126 mg/dL or if treatment for diabetes was already started. Laboratory investigations, physical examination of vascular disorders, and fundoscopic examinations were also performed. In this study, the presence of diabetic polyneuropathy was assessed for diabetic neuropathy using neurological symptoms and disability scores, and quantitative sensory examination. Using standardized neurological examinations, neuropathy was defined as the presence of abnormal neurological symptom scale (NSS) and neurological disability score (NDS) tests together with abnormal sensory or motor signs and symptoms consistent with neuropathy, and decreased great toe vibration perception as well. NSS and NDS rating scales were developed by Dyck *et al.* [5]. NSS is a questionnaire employed for the evaluation of all the symptoms and complaints of patients [5, 6]. Total scores between 0-18 indicating an NSS of ≥1 were considered abnormal. An NDS of = 2 was also deemed as abnormal with total scores ranging between 0–240 points [7].

The results of previous electrophysiological examinations conducted within the last 6 months were also referred to. Besides, the patients underwent an ophthalmologic examination in Department of Retinal Disorders of Clinics of Eye Diseases in our hospital as for the presence of diabetic retinopathy. Eight hundred and sixty-six cases with fully completed records were analyzed.

For statistical analysis, chi-square test was performed using a SSPS 11.5 software program. Two-tailed p values<0.05 were accepted as statistically significant. The odds ratio (OR) and 95% confidence interval (CI) were calculated for each independent variable.

Results

Eight hundred and sixty-six type 2 diabetic Turkish patients were included in this study. Mean age of patients was 57.2 ± 10.3 years (R: 30–81 years) at the time of referrals to our clinic. Subjects' characteristics are summarized in Table 1. A family history of diabetes in first-degree relatives was present in 65% of the cases. Complications of diabetes presented in this study included neuropathy (60%, n = 520) and retinopathy (27.8%, n = 241). In our study a positive correlation was present between the presence of neuropathy and age of the patient (r: 0.18, p<0.001). Mean values of NSS and NDS were 2.47 ± 1.63 (R: 0–9) and 6.35 ± 6.27 (R:0–26), respectively. Regression analysis showed that complications of diabetes were significantly related to the duration of diabetes and HbA1c (p<0.05: chi-square test). Especially the disease duration exceeding 5 years held increased risk of polyneuropathy (see Table 2). The frequency of complications in patients with good glycemic control (HbA1c<7) was lower when compared with poorly controlled patients. When evaluating the cases with established neuropathy, a statistically significant correlation between the presence of neuropathy and retinopathy and levels of HbA1c with p values <0.001 (chi-square test) was detected. As it was shown in Table 2, multivariate analysis showed that gender, smoking, alcohol consumption,

Table 1. Characteristics of Type 2 diabetic subjects in the study

Subject Characteristics	Result
Demographic characteristics	
Mean Age (yr)	57.2 ± 10.3 (R: 30–81)
Female/Male	1.66
Clinical	
Mean diabetes duration (yr)	8.52 ± 7.13 (R: 0–39)
Treated with insulin (%)	33.5% (n = 280)
HbA1c (%, mean ± SD)	7.42 ± 1.83 (R: 4.7–18.2)
Percentages (n) of complications	
Neuropathy (%)	60% (n = 520)
Retinopathy (%)	27.8% (n = 241)

Table 2. Multivariate analysis of risk factors of affecting the prevalence of diabetic neuropathy

		n	n of DN (%)	Ors	95% CI
Duration of diabetes					
(years)	1–5	353	183 (51.8)	1	
	6–10	205	128 (62.4)	1.54	1.09–2.19
	11–20	228	165 (72.4)	2.43	1.70–3.48
	>20	62	47 (75.8)	2.91	1.57–5.40
Metabolic control					
(HbA1c)	Good (<7%)	380	205 (53.9)	1	
	Fair (7–8%)	138	99 (71.7)	2.17	1.42–3.30
	Poor (8–9%)	85	70 (82.4)	3.98	2.20–7.21
	Very poor (>9%)	112	88 (78.6)	3.13	1.91–5.13
Retinopathy		241	173 (32.5)	1.89	1.37–2.60
Hypertension		563	354 (86.6)	1.05	0.66–1.66
Hyperlipidemia		99	58 (47.5)	0.55	0.30–1.02
Smoking		127	72 (13.9)	1.30	0.89–1.91
Alcohol		37	22 (4.3)	1.13	0.57–2.20

hypertension and dyslipidemia were not risk factors ($p>0.05$). EMG obtained previously from 28 of these patients due to their symptomatic complaints showed abnormal patterns indicating neuropathic signs in 26 (92%) of them. The frequency of DN was increased with duration of diabetes and HbA1c (Table 2).

Discussion

In various studies different rates of prevalence were reported for diabetic neuropathy. Some of them have indicated a prevalence of <5%, while the others reported rates above 70% [3, 4]. In nerve conduction studies its prevalence has risen to 100% without considering neuropathic signs and symptoms [4]. Discrepancies among these studies performed were especially due 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.

For the diagnosis of diabetic polyneuropathies, more easily applied clinical diagnostic methods, which could be used in routine evaluations, might provide additional benefits compared with electrophysiological methods. Ideal diagnostic tests for neuropathy should be simple, as well as reproducible and sensitive. Unfortunately not a single test encompassing all of these qualities is available at the moment. NSS, which lists major symptoms encountered in polyneuropathies, allows an integrated assessment of clinical and electrophysiological data. In reports of the Rochester Diabetic Neuropathy Study Group, which conducted one of the most comprehensive studies to date, has indicated that NSS and NDS tests are very sensitive for early detection of the disease yielding similar results to those of electrophysiological examinations performed during follow-up of the patients [5]. In our study 28 patients have taken diagnosis of polyneuropathy previously as a result of electrophysiological examination. We detected neuropathy in 92.9% of these cases. In our study a significant correlation was revealed between NSS, NDS, and also EMG, which is considered a reference test for the evaluation of neuropathy ($p<0.05$). Using nerve-conduction studies as the "gold standard" diagnostic criteria, the best alternative test for the presence of polyneuropathy was toe vibration perception threshold (sensitivity 74%, specificity 56%) [6]. In the present study, DN was defined as the presence of abnormal NSS and NDS results together with abnormal sensory or motor signs and symptoms consistent with neuropathy, and decreased great toe vibration perception as well.

In Turkish studies aiming at estimation of prevalence of DN, higher rates of occurrence have been reported for type 1 diabetics, and rates of DN in type 2 diabetics varied between 21% and 63.5% [7]. In our study the prevalence of DN was found to be 60% (520 patients) similar to those of previous studies performed in our country [7].

In the Diabetes Control and Complications Study, after exclusion of individuals with severe complications, DN was discovered to be related to duration of diabetes, age, male gender and height of the patient [2, 3, 8]. In the literature, multiple logistic regression analyses showed that age had a significant association with retinopathy and DN. Especially the studies conducted by Wandell, Cheng *et al.*, and Cabezas-Cerrato showed that there were significant correlations between age and DN [9–11]. In our study a positive correlation was present between neuropathy and age of the patients as well ($r: 0.18$, $p<0.001$). In only one report was male sex was found to be a risk factor for DN [10]. Although female population was greater, gender had little impact on the frequency of DN in the present study (OR: 0.841) [6, 8, 9].

In several studies risk factors associated with DN have been investigated. Prolonged and poorly controll-

Table 3. Frequencies of DN, retinopathy and factors affecting them in other studies conducted previously

Study	Neuropathy	Retinopathy	HbA1c	Age	Duration
Maser RE *et al.*	34%		+	+	++
Franklin GM *et al.*	25.8%		+	+	++
Young MJ *et al.*	32.1%			+	++
Shaw JE *et al.*	8.5%				++
Oohashi H *et al.*	47%	++	+	+	++
Ramachandran A	27.5%	++	+	+	++
Harris M *et al.*	37.9%			–	++
Dyck PJ *et al.*	45%	+			
Franklin GM *et al.*	22.8%	+	++	+	++
Elmahdi EM *et al.*	31.5%		++		++
Cheng WY *et al.*	11.1%		++	++	
Cabezas *et al.*	24.1%	++		++	++
Mohan V *et al.*	69.8%				++

ed diabetes mellitus, its duration, age and smoking are risk factors for symptomatic DN. Researches are still needed in order to establish a satisfactory treatment [12, 13]. Glycemic control and reduction of risk factors as management of type 2 diabetics indeed directly connect with the importance of risk factors for successful prevention of complications of type 2 diabetics. A study done by Maser *et al.* found correlations between the duration of diabetes, HbA1c, cigarette smoking and HDL cholesterol with a higher frequency of DN in patients over 30 years of age [14]. Hypertension and hypercholesterolemia were also reported to be important risk factors for development of DN in different study reports. Though Maser *et al.* found a relationship between DN development and smoking, many other studies have reported contrary results [14–19]. In our study, hypertension and hypercholesterolemia had little impact on the frequency of DN ($p>0.05$).

The prevalence of DN was closely associated with the duration of the disease [2, 3, 8]. Our study also confirmed significant correlation between the duration of diabetes and the presence of neuropathy ($p<0.001$). Mohan *et al.* examined patients with a 25 year or more duration of diabetes and found a high frequency of DN, similar to us [20].

The studies in the literature showed that high HbA1c, which was an indicator of blood glucose control, increased the risk of neuropathy (see Table 3). The incidence of nephropathy, retinopathy, and DN was higher in type 2 diabetic patients treated with insulin when compared with those taking oral hypoglycemic agents (OHA), independent of duration of diabetes, fasting blood glucose, glycosylated hemoglobin, age, and blood pressure level [19]. Another study showed there was no difference between the severe and moderate type 2 diabetes with regard to the progression of DN over a 5-year follow-up period [18]. In our study a greater prevalence of DN was detected in patients with HbA1c more than 7% ($p<0.001$). Type of therapy had little impact on the development of DN in the present study.

In summary, we found that the majority of type 2 diabetic Turkish patients suffered from neurological symptoms, although half of such symptoms were not considered to be related to DN by physicians. The prevalence of diabetic neuropathy (60% [$n = 520$]) found in the present study was similar to those of previous studies performed in our country. This rate was higher than those in other countries (see Table 3) [5, 14, 21, 22, 24–26]. This may be related to our study method, which consisted of neurological scales, and hospital based population. On the other hand, the great toe vibration we used may have yielded a higher sensitivity for the detection of DN compared to the others.

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