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ORIGINAL ARTICLE

Phrenic neuropathy in diabetic and prediabetic patients without neuromuscular complaint

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Abstract Neuropathy, one of the major reasons of morbidity in diabetes mellitus (DM), is associated with prediabetic conditions as well as DM. The present study aims to compare phrenic and peripheral nerves in prediabetic, diabetic patients and healthy controls. A total of 37 diabetic, 40 prediabetic patients and 18 healthy controls were enrolled in the study. All subjects underwent conventional sensory and motor nerve conduction studies. Bilateral phrenic and peripheric nerve conduction studies were performed. In both right and left phrenic nerves, the amplitudes were lower in prediabetic and diabetic patients than control subjects, respectively (p: 0.005 and p: 0.001). Both of the phrenic nerve conductions were altered similarly. The results of our study demonstrate that phrenic nerves are affected like peripheric nerves in prediabetic and diabetic patients. We suggest reminding phrenic neuropathy in newly onset respiratory failure in diabetic and prediabetic patients.

Keywords Diabetes Mellitus · Prediabetes · Phrenic nerve · Neuropathy

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Introduction

Diabetes mellitus (DM) is a major health problem for the population because of its high mortality and morbidity rates and high costs of therapy [1]. Because of the proceeding technology and sedative lifestyle, obesity is increasing widespread and DM is becoming more and more frequent throughout the world [2].

Neuropathy is one of the most common complications of DM [3]. The prevalence of neuropathy at onset and 25 years after the diagnosis is 7 and 50%, respectively [4]. It shows us that neuropathy is advancing with duration of DM. Demonstrating neuropathy at the diagnosing stage of the disease with a 7% prevalence shows that neuropathy occurs before DM in impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) phases [5, 6].

DM is the most common cause of peripheral neuropathy in the developed world. Bilateral symmetrical sensorimotor distal polyneuropathy is the most frequent type [7]. Due to increasing prevalence of DM, phrenic neuropathy is more recognized. Previous studies depicted that phrenic diabetic neuropathy identified in neuromuscular disorders could result in respiratory failure [8].

In this setting, the present study aimed to compare phrenic and peripheral nerve conduction studies in healthy, diabetic and prediabetic persons.

Materials and methods

In this cross-sectional study, 37 diabetic, 40 prediabetic (IFG + IGT) patients and 18 healthy controls were included. IFG and IGT were defined as prediabetes. None of the subjects had neurological or metabolic complaints such as pain, ataxia, loss of both sensory and motor functions or deep tendon reflexes, numbness and tingling.

DM was diagnosed by a fasting glucose $\geq$126 mg/dl (7.0 mmol/L), a two-hour post glucose challenge value $\geq$200 mg/dl (11.1 mmol/L) with classic symptoms of hyperglycemia (thirst, polyuria, weight loss, blurry vision) and known diabetes treated with diet or drugs or both. After an overnight fast of at least 8 h, participants underwent a standard 75-g oral glucose tolerance test (OGTT). IFG, IGT and normal glucose tolerance were defined according to the American Diabetes Association criteria [2].

IGT was defined as having a 2-h post-glucose load of between 140 and 200 mg/dl and IFG as having a fasting level of between 100 and 125 mg/dl.

All subjects underwent conventional sensory and motor nerve conduction studies. Bilateral phrenic nerve conduction studies were also performed. In all subjects, right median, ulnar, deep peroneal and tibial motor nerves and right median, ulnar and sural sensory nerves were studied with Meledec Synergy EMG machine (Meledec Synergy, Oxford Instruments Surrey, UK). Filter settings were 20–2,000 Hz bandpass for sensory nerve studies and 2–10,000 Hz bandpass for motor nerve studies. Limb temperature was maintained above 31–32°C in all subjects and was usually between 31 and 34°C [7].

Phrenic nerve conduction studies were performed bilaterally with Medelec Synergy EMG machine. Subjects were studied lying supine, then the phrenic nerve was transcutaneously stimulated at the posterior border of the sternocleidomastoid muscle in the supraclavicular fossa, just above the clavicle, using bipolar surface bar electrodes with the cathode placed caudally. A constant-current stimulator delivering rectangular pulses of 0.2-ms duration was used. Supramaximal stimulation was given with an average of 80–90 mA. The diaphragmatic compound muscle action potential was recorded with surface electrodes applied to the seventh intercostal space in the anterior axillary line as the G1 electrode and to the eighth intercostal space along the lines as the G2 electrode. The ground electrode was placed on the chest wall between stimulation electrodes and recording electrodes. Filters were set at 20 Hz to 2 kHz. Two supramaximal responses were obtained, and averaged values were calculated. Latency was determined from onset of the negative peak and amplitude from baseline to the negative peak [9].

Laboratory and clinical tests were evaluated, which consisted of fasting blood glucose, insulin, glomerular filtration rate (GFR), plasma levels of total cholesterol (TC), low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol, and triglyceride.

Those patients, on dialysis, with malign disease, severe liver failure, thyroid disease, connective tissue disease, history of local trauma, chest and neck surgery, myocardial infarction, asthma, chronic obstructive pulmonary disease, hemiplegia, epilepsy, obesity, usage of alcohol, smoking, insulin therapy, deficiency of vitamin B12 and use of drugs that cause neuropathy were excluded from the study.

Oral informed consent was obtained from all participants, and the study design was in accordance with the guidelines issued by the ethics committee at our institution. The investigation conforms with the principles outlined in the Declaration of Helsinki.

Statistical analysis

SPSS (Statistical Package for Social Sciences) for Windows 15.0 program was used for statistical analysis. All data were entered into a database and were verified by a second independent person. The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov–Simirnov test) to determine whether or not they are normally distributed. Descriptive statistics were generated for all study variables, including mean $\pm$ SD for continuous variables and relative frequencies for categorical variables. Chi-square method for categorical, student t-test and ANOVA for continuous data were performed for univariate analysis. Levene test was used to assess the homogeneity of variances, and then tukey test was used for post hoc analysis. Parameters of nerves were normally distributed, and the correlation coefficients and their significance were calculated using the Pearson test. Two-sided values of $p < 0.05$ were considered as statistically significant.

Results

A total of 95 subjects were included in the study. Seventy-seven patients (diabetic and prediabetic) and 18 healthy controls were enrolled. Patients were divided into two groups as prediabetics (40 patients) and diabetics (37

Table 1 Demographic properties and laboratory parameters of the study population

Parameters	Patients		Controls	p*
	Prediabetic	Diabetic		
Age (years)	47.58 ± 6.44	49.9 ± 5.73	47.3 ± 6.86	0.194
BMI (kg/m^2)	28.50 ± 2.91	28.36 ± 2.63	26.91 ± 4.11	0.170
Gender (male)	15 (38.5%)	14 (35.9%)	10 (25.6%)	0.381
FBG (mg/dl)	108.6 ± 9.16	170.05 ± 64.77	90.33 ± 9.17	0.001
Insulin (IU/ml)	12.75 ± 5.74	12.70 ± 7.80	15.82 ± 21.69	0.572
HOMA-IR	3.39 ± 1.47	4.86 ± 2.59	3.53 ± 4.73	0.054
TC (mg/dl)	200.70 ± 50.21	180.94 ± 37.01	189.16 ± 30.22	0.122
LDL-C (mg/dl)	125.01 ± 45.68	104.77 ± 32.44	105.16 ± 31.95	0.047
HDL-C (mg/dl)	51.60 ± 5.50	49.83 ± 11.34	53.16 ± 14.08	0.488
TG (mg/dl)	120.50 ± 72.29	130.51 ± 55.96	152.33 ± 139.81	0.413
GFR (mg/dl)	114.87 ± 26.18	124.86 ± 29.44	121.19 ± 23.86	0.270

BMI body mass index, *FBG* fasting blood glucose, *HOMA-IR* homeostatic model assessment- insulin resistance, *TC* total cholesterol, *LDL* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *TG* triglyceride, *GFR* glomerular filtration rate

* Overall difference between the study groups

patients). The mean age of diabetic and prediabetic patients and healthy controls were 49.9 ± 5.73, 47.5 ± 6.44 and 47.3 ± 6.86, respectively. Baseline characteristics and laboratory parameters of the patients and control cases are shown in Table 1.

The mean amplitude of right phrenic nerve of diabetic patients (0.29 ± 0.16 mV) was lower than prediabetics (0.31 ± 0.27 mV) and controls (0.51 ± 0.21 mV) (p: 0.005). After post hoc analyses, statistically significant difference was found between right phrenic nerve amplitudes of prediabetic patients and control subjects (p: 0.01). The mean amplitude of left phrenic nerve of diabetic patients (0.34 ± 0.18 mV) was lower than prediabetics (0.36 ± 0.27 mV) and controls (0.60 ± 0.24 mV) (p: 0.001). And also after post hoc analyses, statistically significant difference was found between left phrenic nerve amplitudes of prediabetic patients and control subjects (0.002). Phrenic nerve conduction studies are shown in Table 2.

In diabetic patients, the latencies of median and sural sensory nerves were more prolonged, the amplitudes of median, ulnar and sural sensory nerves were lower, and the conduction velocities of median, ulnar and sural sensory nerves were slower than the other two groups. Conduction studies of median, ulnar and sural sensory nerves are shown in Table 2.

In diabetic patients, the latencies of peroneal and tibial motor nerves were more prolonged, conduction velocity of median, ulnar, peroneal and tibial motor nerves were slower when compared with the other two groups. Conduction studies of median, ulnar, peroneal and tibial motor nerves are shown in Table 2.

Discussion

Neuropathy, one of the major complications of DM, is an important cause of morbidity and mortality. The prevalence of diabetic neuropathy is changing from 5 to 60% in various studies [3, 10]. The difference between the ratio of prevalence is due to using different diagnostic criteria and searching methods [7]. In the last two decades, electrodiagnostic studies revealed subclinical forms of diabetic neuropathies. Neuropathy is also associated with IGT, and the prevalence of neuropathy in IGT is 11% [5]. The ratio of IGT in people with neuropathic pain and idiopatic neuropathy is 35 and 10%, respectively [11, 12]. It is reported that the symptoms of polyneuropathy in IGT is similar to sensorimotor polyneuropathy in early DM [13]. Skin biopsies showed axonal loss in intradermal unmyelinated fibers in persons with IGT whose nerve conduction studies were normal [14]. The results of the studies support IGT-related peripheric neuropathy in three ways [5, 11, 13, 15]. Firstly, the prevalence of IGT in patients with idiopathic neuropathy is three times higher than healthy population. Secondly, it is hard to differentiate the painful sensory neuropathy in patients with IGT from the typical symptoms of diabetic neuropathy. Thirdly, there is no alternative etiological reason confirmed.

Diabetic patients sometimes have breathing difficulties without any cardiac and respiratory illness [16–18]. According to the some previous studies, although there is pulmonary dysfunction in diabetic patients, this alternation does not seem to be at enough level to cause respiratory failure [17, 19–22]. This dysfunction caused by nonenzymatic glycolization of matrix proteins like collagen,

Table 2 Conduction studies of phrenic and peripheric nerves of the study population

	Parameters	Patients		Controls	*p**
		Prediabetics	Diabetics		
Phrenic nerve conduction study	RPlat (ms)	8.61 ± 2.01	8.85 ± 1.10	8.13 ± 0.74	0.266
	RPamp (mV)	0.31 ± 0.27	0.29 ± 0.16	0.51 ± 0.21	0.005
	LPlat (ms)	8.95 ± 2.54	8.65 ± 0.20	8.11 ± 0.17	0.290
	LPamp (mV)	0.36 ± 0.27	0.34 ± 0.18	0.60 ± 0.24	0.001
Sensory nerve conduction study (NCS)	Median latency	3.16 ± 0.61	3.14 ± 0.46	2.82 ± 0.54	0.048
	Median amplitude	28.99 ± 9.54	26.19 ± 9.47	35.65 ± 11.23	0.005
	Median velocity	56.74 ± 8.52	54.82 ± 77.05	62.29 ± 5.42	0.003
	Ulnar latency	2.53 ± 0.21	2.66 ± 0.35	2.61 ± 0.35	0.185
	Ulnar amplitude	28.93 ± 10.55	24.22 ± 8.65	34.23 ± 11.70	0.003
	Ulnar velocity	59.30 ± 5.42	56.23 ± 5.54	56.91 ± 4.54	0.037
	Sural latency	3.03 ± 0.73	3.47 ± 0.53	3.25 ± 0.48	0.012
	Sural amplitude	18.14 ± 9.12	12.65 ± 4.14	16.27 ± 6.03	0.004
	Sural velocity	52.23 ± 7.94	47.70 ± 5.07	49.86 ± 7.55	0.022
Motor nerve conduction study (NCS)	Median latency	3.56 ± 0.94	3.77 ± 1.51	3.16 ± 0.41	0.177
	Median amplitude	9.48 ± 2.55	9.64 ± 2.81	10.81 ± 2.96	0.215
	Median velocity	58.01 ± 4.65	54.43 ± 4.88	57.11 ± 3.31	0.003
	Ulnar latency	2.53 ± 0.34	2.69 ± 0.51	2.46 ± 0.23	0.091
	Ulnar amplitude	10.81 ± 0.31	10.54 ± 0.39	11.12 ± 1.96	0.635
	Ulnar velocity	66.39 ± 6.64	57.58 ± 5.13	62.19 ± 4.78	0.001
	Peroneal latency	4.14 ± 0.67	4.47 ± 0.78	3.78 ± 0.88	0.007
	Peroneal amplitude	5.64 ± 2.68	5.35 ± 2.57	7.05 ± 3.39	0.100
	Peroneal velocity	53.50 ± 4.18	45.94 ± 4.08	52.08 ± 5.71	0.001
	Tibial latency	3.75 ± 0.56	4.02 ± 0.61	3.63 ± 0.52	0.038
	Tibial amplitude	12.05 ± 3.48	10.31 ± 3.32	11.05 ± 3.37	0.089
	Tibial velocity	47.80 ± 3.86	45.10 ± 5.25	48.50 ± 4.11	0.011

RPlat right phrenic latency, *RPamp* right phrenic amplitude, *LPlat* left phrenic latency, *LPamp* left phrenic amplitude

* Overall difference between the study groups

elastin; microangiopathic changes and anomalities of pneumocyte [19–21]. Postmortem studies demonstrated that alveolar epithelial and capillary basal lamina are thickened in diabetic patients. Besides pulmonary dysfunction, the volume of lung is also reduced depending on the weakness of diaphragm [16].

Compared with other inspiratory muscles, diaphragmatic muscles are more affected, and this is related to the phrenic neuropathy. In a previous study, it is noticed that the diaphragm strength is weakened by measuring transdiaphragmatic pressure in type I diabetic patients [16, 18, 23]. Phrenic neuropathy in DM is rarely mentioned in the literature. White et al. [24] presented a 51-year-old diabetic man with bilateral diaphragmatic paralysis due to phrenic neuropathy. The results of respiratory function tests were in restrictive pattern, and the median, ulnar and radial nerve conduction studies were in normal ranges. No response could be obtained from phrenic nerve by stimulating transcutaneously. White et al. [24] suggested that diabetic patients with orthopnea and unexplained breathlessness should be considered for diaphragmatic dysfunction due to phrenic neuropathy.

In a series of 30 diabetic patients, Wolf et al. [18] compared the nerve conduction studies of phrenic and peripheral nerves. Slowing of phrenic nerve conduction has been reported in 23.3% of the patients. In these patients, there was a strong correlation between clinical complaints of breathlessness and phrenic neuropathy [18].

In another study, phrenic nerve latency and amplitude were compared between 14 healthy control subjects and 14 patients with type I DM who have impaired diaphragm function and diabetic neuropathy [16]. The results revealed no significant differences between the groups.

In our study, the amplitudes of phrenic nerve are lowest in diabetic patients and highest in control group. The latencies of phrenic nerve are longer in prediabetic and diabetic patients. The difference between the amplitudes is statistically significant. Conduction velocity and

amplitudes of all sensory nerves except ulnar nerve latency were found statistically significant between groups except latencies of ulnar nerve.

Histopathologically axonal degeneration, segmental demyelination and muscle denervation were demonstrated in diabetic patients with phrenic nerve involvement [25]. It was considered that these changes were related to ischemic nerve degeneration. Phrenic neuropathy in diabetic rats was examined, and besides lateral and longitudinal asymmetry, there was also difference between proximal and distal segments in phrenic nerve. In diabetic rats, firstly, axon diameter was decreasing without myelin changes [26]. Axon diameter is an important parameter for nerve conduction, and decreasing of it causes impaired nerve function in DM. Another experimental study in diabetic rats showed that axonal injury in phrenic nerve could be prevented by insulin treatment [27].

The phrenic nerves innervate the diaphragm and respiratory muscles. Deficiency of these nerves may cause weakness of diaphragm and respiratory failure. We suggest that all clinicians should be aware of phrenic neuropathy in prediabetic and diabetic patients who complain dyspnea and orthopnea.

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