Clinical Study

Electrophysiological Investigations in Diabetıc Patients: Root Stimulation and Autonomic Investigations

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Abstract

Introduction: The aim of the study is to search proximal nerve involvement by using proximal root stimulation and possible autonomic neuropathy in type 2 diabetic patients with and without distal symmetric sensorimotor polyneuropathy (DSPN). **Patients and Methods:** Forty patients with type 2 diabetes and ten volunteers who had no history of diabetes and neuropathy were included. Diabetic patients were equally distributed into two groups according to nerve conduction studies (NCSs): First group comprised of with electrophysiologically confirmed DSPN and second group with normal NCSs. Electrophysiological tests included motor and sensory nerve conduction, needle electromyography, F-response, H-reflex, R-R interval, and sympathetic skin responses (SSRs) studies as well as lumbar root stimulation and cauda equina motor conduction time (CEMCT) calculation. **Results:** The patients with DSPN had significantly longer F-response latencies and had no H-reflex while H-reflex was observed in 35% of the patients in second group. In the first group, SSRs could not be obtained from both upper and lower limbs in 45% of the patients; however, in the second group, they were absent only in 10% of patients in lower limbs. R-R interval variability was significantly lower in both diabetic groups than volunteers. When compared to the volunteers, cauda equine motor conduction time was significantly prolonged in all diabetic patients, but there was no significant difference between the patient groups. **Conclusions:** CEMCT prolongation, absence of H-reflex, and decreased R-R interval abnormalities indicating dysautonomia were the most important findings of our study. These results show that early electrophysiological examinations using these methods are important in diabetic patients without polyneuropathy.

Keywords: *Autonomic investigations, cauda equina motor conduction time, diabetic polyneuropathy, root stimulation*

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Introduction

Diabetic peripheral neuropathy (DPN) is one of the most common complications of diabetes mellitus (DM) and can cause severe morbidity and mortality.[1-3] Once the disabling neuropathy is established, it cannot be improved with treatment. Therefore, early diagnosis and treatment are very essential.[4,5] Root stimulation at the laminar level is a technique that allows the evaluation of the entire motor axon from the nerve root to the target muscle and detects the proximal nerve damage at an early disease stage.[6]

The aim of this study is to assess the presence of proximal involvement in type 2 DM patients, with or without

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distal symmetric sensorimotor polyneuropathy (DSPN), using proximal root stimulation along with standard electrophysiological methods.

Patients and methods

Patients

This study was performed in our clinical neurophysiology laboratory. Twenty type 2 diabetic patients with DSPN (11 females and 9 males), 20 type 2 diabetic patients without DSPN (14 females and 6 males), and 10 (5 females, 5 males) age-matched controls were included in this study. The controls were selected among volunteers referred to the EMG laboratory for lower extremity radiculopathy or entrapment neuropathy examinations who were agreed to include in the study. They had no signs of peripheral nervous system involvement on neurological examination and no neuropathy or systemic disease history that could lead to nerve damage. Their electrophysiological investigations and lumbar spinal magnetic resonance imaging and/or computed tomography results were all normal. The exclusion criteria included patients under the age of 18 years, those who were pregnant, had clinical findings of autonomic involvement, or other diseases that might cause polyneuropathy (kidney failure, Vitamin deficiency, connective tissue diseases, hereditary neuropathy, porphyric neuropathy, etc.), had lumbar stenosis and/or lumbar disc herniation, or had abnormal neurological examination findings other than DPN. Height, weight, body mass index (BMI), and glycated hemoglobin values were recorded.

Ethics approval

This prospective study was approved by the ethics committee of İzmir Katip Çelebi University Atatürk Training and Research Hospital, and written informed consent was obtained from all subjects who participated.

Methods

Electrophysiological evaluations

A keypoint two-channel EMG-EP device (Medtronic, Skovlunde, Denmark) was used for nerve conduction studies (NCSs), needle EMG, and root stimulation, and for assessment of the F-response and H-reflex. A Medelec Synergy EMG-EP two-channel device (Oxford Instruments, Oxford, UK) was used for autonomic investigations (sympathetic skin response [SSR] and R-R interval). All examinations were performed at standard room and skin temperatures (32°C for the hands and feet).

Conventional electrophysiological evaluation

Conventional NCSs of the median, ulnar, peroneal, posterior tibial, and sural nerves, the F-response of median and posterior tibial nerves, and the soleus H-reflex were recorded using standard methods. Distal latency, conduction velocity, compound muscle action potential, compound sensory nerve action potential amplitudes, F-response, and H-reflexes were evaluated. Sterile disposable concentric needle electrodes (Neuroline, 50 mm; Ambu, Copenhagen, Denmark) were used for needle EMG. Insertional activity, spontaneous activity (fibrillation, positive sharp waves, fasciculations, and complex repetitive discharges), and motor unit action potential firing pattern were investigated in the biceps brachii, abductor pollicis brevis, extensor digitorum brevis, tibialis anterior, gastrocnemius, and rectus femoris muscles.[7]

Autonomic investigations

Autonomic investigations were conducted in a semidark, quiet room with subjects lying in a supine position.

Four consecutive SSRs were recorded from the right hand and foot using a previously defined standard recording technique in all cases.[7-9] Ag/AgCl disc electrodes were used for recordings. Active electrodes were placed on the palm and sole of the foot, and reference electrodes were placed on the dorsum of the hand and foot. A ground electrode was placed on the wrist. The sweep velocity was set up 10–20 s and the filters were set up 0.1–2 Hz to 3 kHz. A single stimulus of 0.1–0.5 millisecond (ms) duration and 10–100 milliamper (mA) intensity was applied at irregular time intervals to the opposite median nerve at the wrist, to the opposite posterior tibial nerve at the ankle. Response latency and amplitude were evaluated. The absence of SSR was considered abnormal.[8]

Twenty R-R interval responses were recorded during rest and deep breathing (6/min) using previously defined standard recording technique.[7-9] The ring electrodes were used for recordings. Active ring electrode was placed on the right thumb and reference electrode was placed on the left thumb. A ground electrode was placed on the one wrist. The sweep velocity was set up 200–300 ms and the filters were set up 16–80 Hz. Using the triggering mode and delay line, the oscilloscope display was adjusted by the trigger sensitivity and sweep speed. Two QRS complexes were displayed on the screen. Twenty traces were recorded and superimposed during rest and deep breathing at six breaths per min. The difference between minimum and maximum R-R interval (a) and the mean R-R interval (b) were measured. The R-R interval was expressed as percentage of the average R-R interval using the following formula: RRIV = a/b × 100. The average of the recordings at rest was termed R%, that of the recordings during deep breathing was D%.

The difference between these two measures (D%-R%) and the ratio of the two measurements (D/R) were also calculated. When the R-R interval percentage was below the 95% confidence limit for a normal result, it was considered abnormal.[7-9]

Root stimulation

The lumbar electrical root stimulation technique described by Ertekin *et al*. was used for proximal root stimulation.[6,10-15]

Distal stimulation

With the patient lying in a prone position, M-responses were recorded from the gastrocnemius muscle, using the tendon–belly method and superficial Ag/AgCl electrodes. The active electrode was placed on the midpoint of the muscle, and the reference electrode was placed on the Achilles tendon and fixed with tape. Then, the posterior tibial nerve was superficially stimulated at the poplitea. Two consecutive M-responses were recorded from the muscle. Latencies and peak-to-peak amplitudes of the M-responses were calculated.

Proximal root stimulation

Lumbar laminar stimulation was performed with subjects lying in a prone position using previously fixed recording disc electrodes, as described previously.[13,16] Teflon-coated 26-G monopolar needle electrodes (50 mm and 38 mm) were used for laminar stimulation. The tip of the active needle electrode (50 mm) was placed at the dorsal part of laminae of the L1 spine between the spinal processes of L1 and L2. The reference electrode (38 mm) was inserted in the midline subcutaneously, 2 or 3 levels above the active electrode. Rectangular electrical pulses of 1.0-ms duration and increasing intensity were delivered at the laminar level until the first motor threshold level was reached. The stimulus intensity was then set to 2.5 times the threshold level. Four consecutive responses to L1 laminar stimulation were recorded from the gastrocnemius muscle via the previously fixed electrodes. The same procedure was followed for L5 laminar stimulation between the spinal processes of L5 and S1. Therefore, same nerve roots were stimulated at L1 and L5 laminar levels and recorded from mainly S1 innervated gastrocnemius muscle. The L1 and L5 latencies were measured, and the difference in latency (L1-L5) was calculated to obtain the cauda equina motor conduction time (CEMCT). The latency and amplitude of the M-responses and the CEMCT values were compared among the groups. A schematic view of the lumbar root stimulation technique and needle locations at the spinal level is shown in Figure 1.

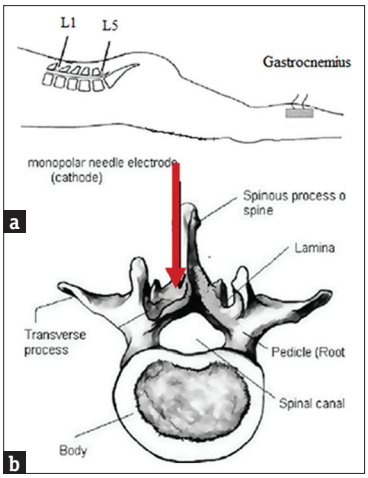

Figure 1: (a) Schematic representation of the L1 and L5 laminar stimulation technique, (b) red arrow shows insertion of needle position during laminar stimulation[17]

Statistical analyses

All statistical analyses were performed using the IBM SPSS Statistics Standard Concurrent User V 26 package program (IBM Corp., Armonk, New York, USA). Descriptive analyses were obtained for all parameters. A two-sided Pearson's Chi-square test probability values with the exact method were used to compare the differences between the groups for the categorical variables. Spearman correlation coefficient analysis was applied to determine the relationships among the variables. Shapiro–Wilk's test was used and a histogram and qq plot were examined to assess the data normality. Levene's test was used to assess the variance homogeneity. Normal and homogeneously distributed variables were analysed by one-way analysis of variance. Welch's test was applied when the homogeneity of the variance assumption was violated. Nonnormal distributed variables were analysed by Kruskal–Wallis analysis. Tukey hypertonic saline dextran and Dunn–Bonferroni tests were used for correction method in multiple group comparisons. A statistically significant difference was accepted at $P < 0.05$.

Results

The cases were divided into three groups: group 1: type 2 DM patients with DSPN; group 2: type 2 DM patients without DSPN; and group 3 (control group): healthy individuals. The demographic data of the groups are shown in Table 1.

The age and gender distributions did not differ significantly between the patient groups and control group. The DM duration of group 1 was significantly longer than that of group 2 (*P*0.029). Although BMI did not differ significantly between the patient groups with and without polyneuropathy (*P* 0.07), it was

significantly higher in the diabetic patient group than the control group (*P* 0.015 and 0.007 respectively). The insulin use and glycated hemoglobin values in group 1 were significantly higher than in group 2 (*P* 0.001 and 0.012, respectively) [Table 1].

Electrophysiological findings

Conventional electrophysiological investigations

DSM-PN with axonal involvement described as significant slowing in the conduction velocity of sensory and motor nerves with decrease of amplitude or loss of response and existence of spontaneous potentials in needle EMG[8] was found in all patients in Group 1. Conventional nerve conduction examinations and needle EMG findings of Group 2 and the control group were in normal limits. Some F-response abnormalities were found in group I: absent F-response, prolonged median, and tibial nerve F-response latencies in four, five, and six patients, respectively. Patients in group 2 and three had normal F-responses. When latencies were compared group 1 had significantly longer latencies than the other two groups (*P* 0.001), but there was no significant difference between groups 2 and 3. The H-reflex was absent in all group I patients while it was obtained in seven patients (35%) in group 2. There was no abnormality in group 3 concerning H-reflex.

Autonomic investigations

SSRs could not be obtained in nine patients (45%) in group one and two patients (10%) in group 2, whereas SSRs were normal in group 3. Group I patients had significantly longer latencies in hand recordings and lower amplitudes in foot recordings in comparison to the other groups [Table 2].

During deep breathing, the percentage of the R-R interval and D%–R% difference were significantly lower in groups 1 and 2 than in the control group (*P* 0.006 and 0.001, respectively). There was not any significant difference of resting state R-R interval percentage between the groups. However, the ratio of the two measurements (D/R) was significantly lower in group 2 than controls [Table 2].

Root stimulation

Distal stimulation findings

The latency of motor responses obtained from the gastrocnemius muscle with distal stimulation was significantly longer in group 1 compared with the other groups (*P* 0.023), and the amplitude of gastrocnemius M-response was significantly lower in group 1 than in groups 2 and 3 (*P* 0.012) [Table 3 and Figure 2].

Root stimulation findings

In group 1, the mean latencies of the M-responses recorded from the gastrocnemius muscle under L1 and L5 laminar stimulation were significantly longer (*P* 0.0001 and 0.0001 respectively), and their amplitudes were significantly lower, than the other groups (*P* 0.003 and 0.012 respectively) [Table 3 and Figure 3].

The CEMCT values of the gastrocnemius muscle were significantly longer in patient groups 1 and 2 than in

Table 1: Demographical data of all groups

	Group 1 (*n*=20)	Group 2 (*n*=20)	Controls (*n*=10)
Age (years), mean±SD (range)	59.7±9.3 (47-78)	54.5±9.8 (39-70)	57.1±19.7 (24-84)
Sex female/male, *n* (%)	11 (55)/9 (45)	14 (70)/6 (30)	5 (50)/5 (50)
DM duration (years), mean±SD (range)	13.9±7.8 (1-30)	8.7±7.3 (1-24)	-
Insuline use (%)	90	15	-
Glycated haemoglobin, mean±SD (range)	9.7±2.9 (4.6-17)	7.7±1.6 (5.2-12.5)	-
BMI, mean±SD (range)	28.8±4.4 (18.8-40.1)	31.1±5.7 (20-44.4)	24.7±5.08 (19.1-36.3)

DM: Diabetes mellitus, SD: Standard deviation, BMI: Body mass index

Table 2: Sympathetic skin response and R-R interval study results of the groups

SSR hand	Group 1 (*n*=13)	Group 2 (*n*=20)	Controls (C) (*n*=10)	*P* (1 vs. 2)	*P* (1 vs. C)	*P* (2 vs. C)
Latency (msec), mean±SD (range)	1.7±0.3 (1.15-2.37)	1.5±0.4 (1.1-2.8)	1.5±0.2 (1.3-2)	0.026	0.017	NS
Amplitude (mV), mean±SD (range)	1.1±0.8 (0.2-3.1)	1.5±0.8 (0.2-2.7)	1.4±0.9 (0.5-3.1)	NS	NS	NS
SSR foot	**Group 1 (*n*=12)**	**Group 2 (*n*=18)**	**Controls (C) (*n*=10)**	***P* (1 vs. 2)**	***P* (1 vs. C)**	***P* (2 vs. C)**
Latency (msec), mean±SD (range)	2.3±0.6 (1.68-4.12)	2.1±0.5 (1.5-3.4)	2.1±0.4 (1.8-3)	NS	NS	NS
Amplitude (mV), mean±SD (range)	0.6±0.5 (0.09-1.8)	1.2±0.6 (0.3-2.8)	1.4±0.8 (0.2-2.6)	0.006	0.021	NS
R-R intervalstudy	**Group 1 (*n*=20)**	**Group 2 (*n*=20)**	**Controls (C) (*n*=10)**	***P* (1 vs. 2)**	***P* (1 vs. C)**	***P* (2 vs. C)**
R-R resting, mean±SD (range)	8.6±12.2 (1.3-55)	7.3±2.9 (2.6-16.6)	12.9±7.9 (2-30)	NS	NS	NS
R-R deepbreathing, mean±SD (range)	12.3±13.1 (2.5-58)	9.7±3.5 (3.1-14.9)	29.6±24.1 (5.1-86)	NS	0.006	0.001
%D-%R, mean±SD (range)	4.5±4.3 (0.2-15)	3.4±3.07 (0.01-8.9)	16.7±21.1 (0.5-71)	NS	0.012	0.006
%D/%R, mean±SD (range)	1.9±1.07 (0.7-4.4)	1.4±0.6 (0.5-3)	2.6±1.8 (1.1-6)	NS	NS	0.028

SSR: Sympathetic skin responses, SD: Standard deviation, D: Deep breathing, R: Resting, NS: Not significant

Table 3: Electrophysiological data of root stimulation in all groups

Recording: Gastrocnemius	Group 1 (*n*=20)		Group 2 (*n*=20)		Controls (*n*=10)	
	Latency (msec)	Amplitude (mV)	Latency (msec)	Amplitude (mV)	Latency (msec)	Amplitude (mV)
DS, mean±SD	5.2±1.1	10.9±5.3	4.3±0.7	15.3±7.1	4.5±0.7	19.0±6.1
L1 RS, mean±SD	19.6±2.5	3.5±2.5	16.3±2.5	5.7±2.8	15.3±1.3	5.8±2.4
L5 RS, mean±SD	16.9±1.9	6.6±4.1	13.4±1.6	8.9±5.8	13.9±1.0	13.6±5.0
CEMCT (msec), mean±SD	2.7±1.7		2.9±1.7		1.5±0.8	

L: Lumbar, DS: Distal stimulation, RS: Root stimulation, CEMCT: Central motor conduction time, SD: Standard deviation

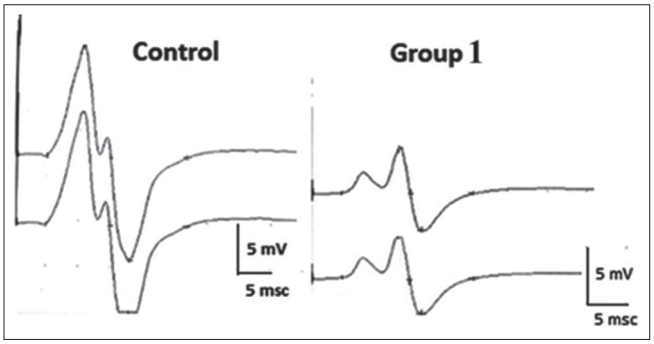

Figure 2: First figure shows the M responses obtained from a control subjects' gastrocnemius muscle by distal stimulation. Second figure shows the same response from a patient in Group 1

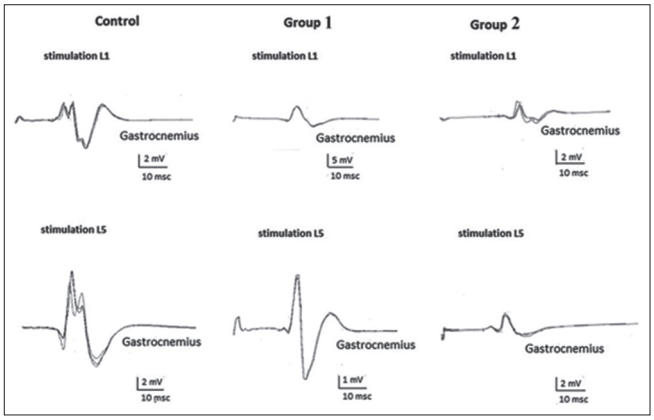

Figure 3: Figure shows the M responses obtained from gastrocnemius muscles with L1 and L5 laminar stimulations in control and patients groups. As seen in figure, amplitudes are lower and latencies are longer in patients' groups

the control group (*P* 0.023). There was no difference between groups 1 and 2 [Table 3 and Figure 4]. However, CEMCT values were not correlated with glycated hemoglobin, BMI, or DM duration (*P* 0.18, 0.2, and 0.25, respectively).

Discussion

DPN is one of the most common complications of DM. Polyneuropathy is considered caused by metabolic factors as well as vascular and immunological changes.[16] Previous studies have shown that poor glycemic control and long-duration DM are risk factors for DPN.[17-19] In our study, the DM duration was longer, and glycated hemoglobin levels were higher in DM patients with DPN than in those without.

Previous studies have demonstrated that clinical and electrophysiological findings are not always well correlated.[5] Therefore, it is recommended that both clinical and electrophysiological findings should be used to detect DPN. Some cases may exhibit abnormal electrophysiological data in the absence of clinical symptoms and signs, or electrophysiolgical investigations reveals normal findings in a clinically symptomatic patient. The former condition is called "subclinical neuropathy," and the latter is called "early neuropathy" or "clinically defined neuropathy."[5] When irreversible changes develop in the nerves, neuropathy becomes symptomatic. Therefore, it is essential to identify cases at the subclinical stage to prevent disease progression. Adding F-response and autonomic tests, fiber density amplitude measurements, and macro-MUP analysis to standard nerve examinations, as well as skin biopsies, has proven useful for early detection of DPN.[3-5]

The F-response allows the assessment of proximal motor conduction and is one of the most sensitive and reliable nerve conduction evaluation methods in patients with neuropathy, especially in cases with acquired focal demyelinating neuropathies.[20] Pan *et al*. showed that the addition of F-response analysis to routine NCSs increased the sensitivity of detection of subclinical neuropathy.[21] In our study, additional F-response investigation did not give extra information about subclinical neuropathy although CEMCT technique revealed subclinical proximal involvement of DM patients without neuropathy.

H-reflex is used for the evaluation of the proximal parts of peripheral nerves. In compressive radicular lesions or acute radiculoneuropathies such as Guillain-Barré syndrome (GBS) it is known that long latency or absence of H-reflex is possible while peripheral NCSs are normal. (The loss of the H-reflex or prolongation of its latency are known to occur at the early stage of radiculopathy or acute neuropathies such as GBS, even routine NCSs are normal).[8] This suggests that it is selectively retained central extensions of spinal sensory

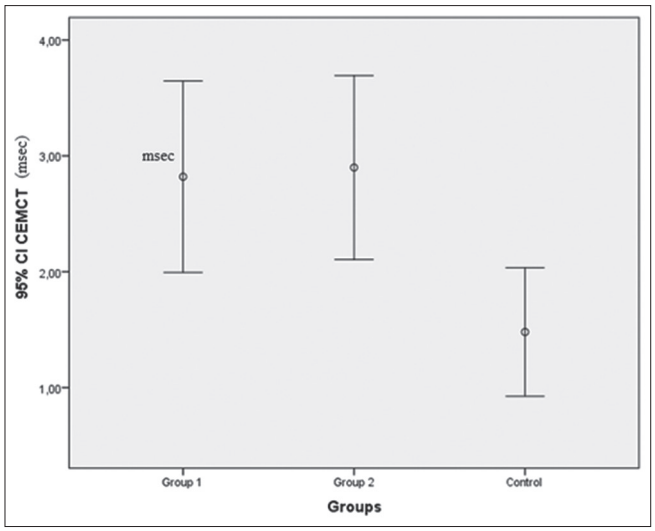

Figure 4: The graphic of CEMCT value in control and patients' groups. CEMCT values are longer in patients' groups as shown in figure. CEMCT: Cauda equina motor conduction time

ganglion cells to the dorsal funiculus and segmental spinal cord against peripheral extensions of spinal sensory ganglion cells and especially peripheral IA afferents are normal.[8] Although this is controversial in chronic neuropathies, it is reported that H-reflex abnormalities can occur in diabetic, alcoholic and uremic neuropathies.[8] In our study, H-reflex could not be obtained in 65% of diabetic patients without neuropathy. This result may suggest that in DPN pathological changes begin at early stage in the cell body and proximally.

Autonomic neuropathy is a poorly recognized subtype of DPN that can either be clinically obvious or subclinical. With electrophysiological autonomic tests, the diagnostic rate of autonomic neuropathy is 7%–30%.[22] In our study, we excluded patients with autonomic complaints and/or clinical signs of autonomic involvement. The high variability of SSRs limits their clinical and physiological use, and only a complete absence of SSRs can be considered a definite sign of abnormality.[23] Therefore, an absence of SSRs was accepted as an abnormality in our study. In the group with polyneuropathy, SSRs could not be obtained in the lower and/or upper extremities in nine (45%) patients, whereas in the group without polyneuropathy, SSRs could not be obtained in the lower extremities in only two (10%) patients. In addition, although previous studies have suggested that a decrease in SSR amplitude may indicate the presence of subclinical autonomic neuropathy,[24,25] only the mean amplitude of lower extremity SSRs was significantly lower in the group with polyneuropathy in our study. We did not find any correlation between SSRs and subclinical polyneuropathy as mentioned before in other literature.

Cardiac autonomic neuropathy, which can lead to death in diabetic patients, may occur subclinically. Indeed, it can be present subclinically for years before resting tachycardia, exercise intolerance, postural hypotension, silent ischemia, left ventricular dysfunction, or diabetic cardiomyopathy occurs.[26] A decrease in heart rate variability with deep breathing has been accepted as a diagnostic test for cardiac autonomic neuropathy in many studies.[27] The risk of mortality and sudden death is increased in patients with cardiac autonomic neuropathy.[27] In our study, one of the most interesting findings was that the R-R interval during deep breathing was abnormal in all diabetic patients without peripheral neuropathy, which implies that autonomic cardiac involvement precedes peripheral involvement. Early diagnosis of cardiac autonomic neuropathy in DM patients is important in prognosis.

Electrophysiological root stimulation has been used in many studies. Detection of conduction blocks and conduction time latency prolongation were studied in demyelinating neuropathies (GBS, multifocal motor neuropathy, chronic inflammatory demyelinating neuropathy), lumbar spinal stenosis, and lumbar disc herniation through the use of root stimulation.[6,12-14,28-30] Damage to proximal nerves can also be detected with the root stimulation technique at an early disease stage. Although it is an invasive procedure, proximal root stimulation with a monopolar needle electrode at the laminar level, as done in our study, is less painful and superior for detecting the presence of lesions.[11,13,14] In a few studies, root stimulation was performed with single-level electrical stimulation or stimulation with magnetic coils in diabetic patients.[10,31] Tataroglu *et al*. found that the lumbar plexus conduction time to L3 root stimulation was significantly prolonged in diabetic patients with DSPN compared to normal controls.[10]

In one study examining CEMCT in diabetic patients with distal symmetric sensorimotor neuropathy using magnetic coil stimulation showed prolongation of CEMCT in only 1 of 12 diabetic patients.[31] The authors concluded that axonal damage affected myelinated and nonmyelinated fibers. Furthermore, although this process was most prominent in distal areas, myelin loss was also found in the proximal nerve roots.[31] In our study, the CEMCT was longer in diabetic patients with and without neuropathy compared to normal controls. In addition, in the group with polyneuropathy, the latency of the response in the gastrocnemius muscle under distal stimulation was longer than in the other groups. Experimental studies show that all neurons from perikarya (cell bodies) to the nerve terminal are targeted by diabetes. However, it is unknown whether

the damage primarily targets peripheral axons, Schwann cells, or neuron perikarya.[32] Some studies have emphasized proximal involvement in distal symmetrical polyneuropathy. SEP examinations performed with the multimodal recording technique showed that the somatosensory central conduction time was longer in diabetic patients. Furthermore, the authors of that study emphasized that this showed that central sensory axons were affected in diabetic patients.[3] In our study, all patients with diabetes, including those without DPN, had longer CEMCTs than normal controls. Prolonged CEMCTs and H-reflex abnormalities in the diabetes group without neuropathy may provide evidence of proximal motor involvement in the early period of the disease.

Conclusions

The transition time of diabetic neuropathy from the subclinical to the clinical stage is still unknown. Early diagnosis and treatment are important for slowing its progression and thus reducing morbidity and mortality. CEMT prolongation and H-reflex abnormalities in diabetic patients without polyneuropathy is an indication of proximal involvement of nerves in the subclinical stage which is normally unexpected in distal sensorimotor polyneuropathy. These findings may suggest that there is an involvement of proximal parts of peripheral nerves in diabetic patients who had neuropathic complaints but normal peripheral electrophysiological findings in EMG. The method used in our study is easy and can be applied in any electrophysiology laboratory. Therefore, the current root stimulation technique may be effective for detecting early stage nerve damage in diabetic patients with neuropathic complaints. In addition, cardiac autonomic abnormalities are early findings in diabetic patients without polyneuropathy, as we showed in our study. Diabetic neuropathy treatment studies are still ongoing and patients will have a chance to be treated in the future. Subclinical stage neuropathy is probably the most accurate group in treatment strategies.

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Conflicts of interest

There are no conflicts of interest.

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