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Presence of Subclinical Polyneuropathy in Patients with Elevation of Hba1c

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ABSTRACT

Introduction: It is aimed to investigate the relationship between the asymptomatic individiuals with elevated HbA1c and occurrence of polyneuropathy by way of comparison to normoglycemic condition.

Methods: The study includes 30 female patients diagnosed with subclinical elevation of HbA1c and 30 normoglycemic healthy female patients who applied to our hospital polyclinics with symptoms other than neuropathy between January-March 2017. Nerve conduction examination is done in these patients, parameters of both groups are compared.

Results: In regard to amplitude distribution; when compared to control group, tibial motor and ulnar sensory nerve amplitude is lower than the control group ($p<0.05$). In peroneal, median and ulnar motor nerves, distal latency values are extended compared to control group ($p<0.05$). Sural, median and ulnar sensory nerve latency is extended compared to control group. In terms of transmission rate distribution; in sural, median and ulnar sensory nerve, transmission speed is lower compared to the control group ($p<0.05$)

Conclusions: In asymptomatic cases with subclinical elevation of HbA1c, peripheral nervous system involvement is monitored, and early glycemic control should be provided in order to prevent development of neuropathy in patients.

Keywords: Electroneuromyography, HbA1c, polyneuropathy

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INTRODUCTION

Today, diabetes, due to its frequency and the problems it causes, has become a health problem which is increasingly becoming more important around the world. Along with the changes in lifestyle in all of the developed and developing countries, prevalence of especially type 2 diabetes increases at a fast pace. According to the data of 2013, while the number of diabetic patients was 382 million in the world, this number is predicted to reach 592 million by increasing at a rate of 55% by 2035 (1).

The diabetes or prediabetes is diagnosed with fasting plasma glucose, 2-hour oral glucose tolerance test and glycated hemoglobin A1 c (HbA1c) measurements. It is reported that the increase in HbA1c level increases the diabetes development risk. Therefore, determination of HbA1c as a strong indication for future diabetes development has caused HbA1c levels that are above normal but not within diabetic limits to be accepted as prediabetes (2).

The changes brought by diabetic neuropathy known to be associated with DM (diabetes mellitus) and correlated with glycemic control in nerve conduction examinations have been stated in numerous studies. However, whether the elevations of HbA1c that can be named as prediabetes lead to neuropathy is a field that needs more investigation. For this reason, in this study, it is aimed to investigate the relationship between the elevation of HbA1c in asymptomatic and still prediabetic patients and peripheral nerve activation with electroneuromyography (ENMG).

Highlights

- **Polyneuropathy is an important complication in diabetic patients.**
- **Polyneuropathy may ocur with asymptomatic high HbA1c levels.**
- **It is important to perform EMG in the early period with asymptomatic HbA1c elevation.**

METHODS

The study included 30 asymptomatic female patients who applied to the polyclinics of Istanbul Haydarpaşa Numune Training and Research Hospital, University of Health Sciences between January-March 2017 and had a HbA1c value between 5.7–6.4 and did not have any neuropathic symptom or examination findings, and 30 healthy volunteers. Prediabetic HbA1c value is the value that does not reach the limit of 6.4 stated in the DM diagnosis criteria, but progresses above the value of 5.7 which is accepted as the normal upper limit. There is no significant difference between the patient and control groups in terms of height, weight and body mass index. The patient and control groups complying with the inclusion criteria are prospectively examined for median motor and sensory, ulnar motor and sensory nerve conduction in right upper

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Table 1. The values detected in motor and sensory nerves in upper extremity

		Control (n=30) Mean ± SD med (min-max)	Patient (n=30) Mean ± SD med (min-max)	p
Median motor	Distal latency	2.87+0.24 2.86 (2.5–3.54)	3.74+1.91 3.23 (2.29–13.13)	**<0.001**[1]
	Distal amplitude	9.57+2.92 9.25 (3.4–14.8)	9.73+2.04 9.7 (6.3–13.7)	0.810[2]
	Velocity	60.23+4.65 59.4 (51.9–69.2)	57.77+3.69 57.75 (50.5–65.2)	**0.027**[2]
Ulnar motor	Distal latency	2.11+0.22 2.14 (1.77–2.6)	2.51+0.26 2.52 (2.03–3.02)	**<0.001**[1]
	Distal amplitude	10.44+2.48 10.2 (5.5–16)	10.33+2.1 10.2 (7.1–14.8)	0.854[2]
	Velocity	61.23+4.85 60.32 (54–71.59)	59.29+4.84 59.2 (50.8–67.8)	0.169[1]
Median sensory	Latency	2.3+0.22 2.29 (1.93–2.86)	2.62+0.5 2.45 (2.03–4.11)	**0.006**[1]
	Amplitude	47.79+15 44.6 (19–82.3)	40.54+15.6 38 (7.2–66.1)	0.072[2]
	Velocity	57.78+5.05 57.5 (48–67.5)	51.36+8.05 53.1 (31.6–64)	**0.001**[1]
Ulnar sensory	Latency	1.94+0.2 1.93 (1.51–2.4)	2.19+0.19 2.21 (1.88–2.86)	**<0.001**[1]
	Amplitude	56.15+73.7 42.75 (18.5–440)	29.48+12.2 27.4 (11.9–60.8)	**<0.001**[1]
	Velocity	58.09+5.3 58.8 (45.9–72)	55.28+3.85 54.25 (49–64)	**0.022**[2]

[1]Mann-Whitney U, [2]Student t.

extremity and tibial motor, peroneal motor and sural sensory nerve conduction in right lower extremity with an ENMG device, Medelec-Synergy.

Study Inclusion Criteria for the Patient and Control Groups

- Being a female between the ages of 18–50
- HbA1c value being 5.7–6.4
- Not receiving antidiabetic treatment
- Not having systemic, metabolic, endocrine diseases likely to cause neuropathy
- Not using medicines or having no toxin exposure likely to cause neuropathy
- Not being pregnant
- Giving consent for ENMG examination

As statistical method, descriptive statistics are used to describe the continuous variables (average, standard deviation, minimum, median, maximum). Comparison of two continuous independently and normally distributed variables is done with Student t test while the comparison of two non-independent and non-normal variables is done with Mann-Whitney U. Statistical significance level is determined as 0.05. Analyses are conducted using MedCalc Statistical Software version 12.7.7 program. The study was approved by the ethics committee of the Haydarpaşa Numune Training and Resarch Hospital (register number: 7762-17.04.2017).

RESULTS

Mean age of the patient group is found as 41.9 standard deviation while it is 38 standard deviation in control group. The values detected in motor and sensory nerves in upper extremity are shown in Table 1 while the values detected in motor and sensory nerves in lower extremity in Table 2.

Median motor nerve distal latency and sensory nerve latency are extended and velocity slows down in the group with elevation of HbA1c compared to the control group ($p<0.05$). Ulnar motor nerve distal latency and sensory nerve latency are significantly extended compared to the control group ($p<0.05$). In the group with elevation of HbA1c, ulnar sensory nerve amplitude is lower and velocity is slow ($p<0.05$).

In the group with elevation of HbA1c, velocity is lower in sural nerve compared to the control group and average latency value is extended compared to the control group ($p<0.05$). Tibial nerve distal amplitude, when compared to the control group, is statistically significantly lower and peroneal nerve distal latency is extended ($p<0.05$).

DISCUSSION

Diabetes mellitus is a chronic disease increasing in prevalence and has a high risk of morbidity and mortality around the world. Neuropathy develops in almost half of the diabetic patients and there is presence of diabetic peripheral neuropathy in 20% of type-2 DM patients when diagnosed with diabetes. Early identification and control of the disease is important in order to prevent the complications (3).

Prediabetes is an indicator of high risk of developing diabetes in the future. Despite varying according to the population characteristics and the definition of prediabetes, some studies have demonstrated that about

Table 2. The values detected in motor and sensory nerves in lower extremity

		Control (n=30) Mean ± SD med (min-max)	Patient (n=30) Mean ± SD med (min-max)	p
Tibial nerve	Distal latency	3.36+0.4 3.28 (2.4–3.96)	3.42+0.4 3.33 (2.61–4.22)	0.592[2]
	Distal amplitude	10.48+3.38 10.75 (4.4–17)	8.62+3.13 8.55 (4–18.2)	**0.031[2]**
	Velocity	46.8+3.9 45.55 (41.3–59.32)	47.14+3.43 46.7 (41.1–55.1)	0.469[1]
Peroneal nerve	Distal latency	3.63+0.5 3.59 (2.29–4.43)	4.04+0.47 4.06 (3.28–5)	**0.002[2]**
	Distal amplitude	4.83+1.41 4.85 (2.5–8.4)	4.43+1.76 4.05 (0.8–9)	0.335[2]
	Velocity	51.13+4.54 50.6 (42.2–58.6)	51.19+3.39 50.6 (44–62)	0.952[2]
Sural nerve	Latency	2.37+0.3 2.29 (1.88–2.92)	2.52+0.2 2.5 (2.03–2.86)	**0.024[1]**
	Amplitude	19.62+7.7 19.1 (7.2–40.8)	16.78+7.34 15.55 (7.5–43.3)	0.086[1]
	Velocity	56.44+6.02 56.7 (45.2–65.7)	51.68+3.71 52 (45.4–59.4)	**<0.001[2]**

[1]Mann-Whitney U, [2]Student t.

5–10% of prediabetic individuals progress to diabetic stage annually (4). In recent years, it has been reported that a HbA1c value between 5.5 and 6.0% increased the risk of diabetes development at a rate of 9–25% while the value between 6.0 and 6.5% at a rate of 25–50% (5). The importance of HbA1c test is that it helps in a thorough understanding of insulin and insulin resistance and is used in the diagnosis and prognosis of diabetic patients. In healthy individuals with normal glucose tolerance, it is indicated that HbA1c is more strongly associated with insulin sensitivity (6).

Today, DM is the most common cause of neuropathy around the world (7). Diabetic neuropathy is one of the chronic microvascular complications of DM. It is a heterogeneous clinical picture that develops when different nerve fibers are affected at varying degrees in different individuals in peripheral and autonomous nerves. Depending on the methods used to detect neuropathy and the population, diabetic neuropathy prevalence varies between 10–90% in studies (8). Its incidence is reported to be about 2% annually (9). One of the most observed long-term complications of diabetes, neuropathy is an important cause of morbidity and mortality.

Although diabetic sensorimotor polyneuropathy (DSP) is the most observed symptom, there are different neuropathy syndromes that can appear in diabetes mellitus. These include asymmetric and focal processes such as mononeuropathy, cranial neuropathy and radiculoplexus neuropathy as well as small fiber and autonomous neuropathy (10).

Several studies in literature indicate that there is a direct relationship between chronic hyperglycemia in DM and nerve conduction examination results. In most of the studies, neurologically symptomatic and asymptomatic patients are evaluated together, the patients with HbA1c levels above 7.5% are the patients with poor glycemic control (11). The number of studies that give detailed information about neuropathy development in prediabetic and asymptomatic patients is insufficient when compared to the studies conducted with diabetic patients.

The study conducted on 195 DM and 198 control patients by Ziegler et al. revealed that 81 control patients had normal glucose tolerance and the polyneuropathy prevalence was 7.4%. This rate is 28% in diabetic patients, 13% in impaired glucose tolerance and 11.3% in impaired fasting glucose tolerance (12). In this study, in prediabetic patients, similar to the patients with diabetes and neuropathy, subclinical polyneuropathy where axonal and demyelinating involvement are together is detected. Therefore, it is contemplated that HbA1c measurements will likely reflect peripheral nervous system condition in prediabetic patients.

In the study by El-Salem et al., HbA1c average is found as 8.7 in one half of 50 asymptomatic diabetic patients with normal neurological examination and 6.5 in the other half. Subclinical neuropathy is detected in 52% of the patients, a demyelinating involvement including usually sural and peroneal nerves is also present in patients and presence of neuropathy is highly correlated with HbA1c levels (13).

Also in this study, when the presence of neuropathy is investigated in asymptomatic prediabetic patients (with HbA1c value being between 5.7–6.4), extension in upper and lower extremity motor and sensory nerve distal latency ($p<0.05$) and a decrease in velocity are detected compared to the control group. Although an apparent polyneuropathy or entrapment focal involvement finding is not detected, low tibial motor and ulnar sensory nerve amplitude is marked.

In this study, a relationship between the asymptomatic prediabetic HbA1c values and peripheral nerve activation is detected. The studies to be conducted on this area will likely reform the diabetic polyneuropathy treatment in a way to comprise subclinical periods when neuropathic involvement starts.

Ethics Committee Approval: The study was approved by the ethics committee of the Haydarpaşa Numune Training and Resarch Hospital (register number: 7762-17.04.2017).

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