RESEARCH ARTICLE

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Risk Factors for Diabetic Polyneuropathy

ABSTRACT

Objective: Diabetes Mellitus is one of the most common metabolic diseases. The most frequent complication of DM is diabetic polyneuropathy. Diabetic polyneuropathy is related to high mortality, morbidity, hospitalization rate and serious level of economic burden. We aimed in this study to determine the risk factors that affect DPN pathology.

Methods: Patients with abnormalities in the nerve conduction study constituted the polyneuropathy group, and patients without abnormalities formed the control group. When the laboratory values of the patients were analyzed, blood tests of 168 of 202 patients were reached. 117 of these patients had PNP and 51 did not have PNP.

Results: In patients with PNP, glycolyzed hba1c ratio and fasting blood sugar were significantly higher than patients without PNP (p<.001).

While HDL rate was lower in patients with PNP than those without PNP (p<0.01), TG/HDL ratio was higher (p<0.05). In patients with PNP, glycolyzed urea (p<0.001) and creatinine (p<0.01) were significantly higher than those without PNP. The serum level of 25(OH) vitamin D was significantly lower in patients with PNP than in patients without PNP (p<0.05). Ferritin was significantly higher in patients with PNP than patients without (p<0 .01).

Conclusions: Knowing and preventing risk factors for diabetic polyneuropathy, we can take a new direction to our treatment approaches and take early measures. Fasting blood sugar and hba1c control, regulation of lipid profile, monitoring of vitamin d and ferritin levels are particularly necessary for protection of polyneuropathy.

Keywords: Diabetic Polyneuropathy, HbA1c, Ferritin, Trigliceride/HDL (Atherogenix Index), 25(OH) Vitamin D

Diyabetik Polinöropati Risk Faktörleri

ÖZET

Amaç: Diyabet Mellitus(DM) en yaygın metabolik hastalıklardan biridir. DM' nin en sık görülen komplikasyonu diyabetik polinöropatidir. Diyabetik polinöropati yüksek mortalite, morbidite, hastaneye yatış oranı ve ciddi ekonomik yük ile ilişkilidir. Biz çalışmada DPN patolojisini etkileyen risk faktörlerini belirlemeyi amaçladık.

Gereç ve Yöntem: Sinir iletim çalışmasında anormalliği olan hastalar polinöropati grubunu, anormalliği olmayan hastalar kontrol grubunu oluşturdu. Hastaların laboratuvar değerleri incelendiğinde 202 hastanın 168'inin kan testlerine ulaşıldı. Bu hastaların 117'sinde PNP varken, 51'inde PNP yoktu.

Bulgular: PNP olan hastalarda glikolize hba1c oranı, açlık kan şekeri PNP olmayan hastalara göre anlamlı olarak yüksek bulundu (p<.001). PNP' si olan hastalarda HDL oranı PNP'si olamayan hastalara göre düşük saptanırken (p<0.01), TG/HDL oranı daha yüksek saptandı (p<0.05). PNP olan hastalarda glikolize üre (p<0.001) ve kreatinin (p<0.01), PNP olmayan hastalara göre anlamlı olarak yüksek saptandı. PNP olan hastalarda 25(OH) vitamin D düzeyi, PNP olmayan hastalara göre anlamlı olarak düşüktü (p<0.05). PNP olan hastalarda ferritin, olmayan hastalara göre anlamlı olarak daha yüksek saptandı (p<0.01).

Sonuç: Diyabetik polinöropati açısından risk faktörlerinin bilinmesi ve önlenmesi ile tedavi yaklaşımlarımıza yeni bir yön vererek, erken önlemler alabiriz. AKŞ; hba1c kontrolü, lipid profilinin düzenlenmesi, vitamin d ve ferritin düzeylerinin takibi özellikle korunma açısından önemlidir.

Anahtar Kelimeler: Diyabetik Polinöropati, HbA1c, Ferritin, Trigliserid/HDL İndeksi (Aterojenik İndeks), Vitamin D

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INTRODUCTION

Diabetes Mellitus is one of the most common metabolic diseases worldwide seen. The most frequent complication of DM is diabetic neuropathy, especially diabetic polyneuropathy (1). Diabetic polyneuropathy is related to high mortality, morbidity, hospitalization rate and serious level of economic burden (2,3). American Diabetes Association suggests to search for diabetic neuropathy at the time of diagnosis of type 2 DM and five years after the diagnosis of type 1 DM (3,4). EMG, nerve conduction studies can provide evidence before neuropathic symptoms evolve (5).

Diabetic peripheric neuropathy (DPN) is a late phase microvascular complication that evolve in 50% of the patients (6). DPN is related to irreversible structural and functional changes due to demyelinisation, axonal atrophy and decline in regeneration of neurons (7). Although the cause is not fully understood, this event can be explained by endothelial dysfunction, disturbed endoneuronal blood flow, hypoxia and ischemia development in the neurons due to chronic hyperglycemia (6).

Atherosclerosis has also important effect on microvascular and macrovascular complications seen in diabetic patients. Also oxidative stress and inflammation caused by advanced glyco-oxidation end products are also known to contribute to these complications (8,9).

In studies conducted, age, male gender, duration of diabetes, diabetic control are shown to be risk factors for DPN (10). Elevation of fasting blood sugar and HbA1c levels and low vitamin D values have been reported in many studies to be risk factors for development of DPN (9-14).

Risk factors for atherosclerosis; hypertension, smoking, changes in the lipid profile are also shown in studies to be risk factors for DPN. However, there are difference results between the studies (10). We aimed in this study to determine the risk factors that affect DPN pathology. By this way we can take early measures and give a new direction to our treatment approaches.

MATERIAL AND METHODS

Demographic data; including duration of illness and medications of patients with DM diagnosis who applied to Electrophysiology laboratory of Zonguldak Bülent Ecevit University Health Practice and Research Hospital, in between 2016-2019 were recorded retrospectively.

From patients' files glycolyzed HgA1c, fasting blood sugar, TSH, free T4, free T3, lipid profile including serum cholesterol, triglycerides (TG), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C), liver and kidney function tests, 25 (OH) vitamin D serum levels, vitamin b12, folate, ferritin levels were recorded. Electrolyte values, (calcium, magnesium, phosphorus, chlorine, sodium, potassium), hemoglobin, hematocrit, platelet levels were recorded.

Patients underwent standard electrophysiological study. All of the physiological studies were performed with 2 channeled Medelec EMG device. In all of the recordings, superficial electrodes were used. In motor conduction studies, the median, ulnar, peroneal and tibial nerves were stimulated, and compound muscle action potentials (CMAPs), distal latency (DL) and nerve conduction velocities (NCVs) were recorded. Sensory responses were obtained with orthodromic methods. In sensory conduction studies, the median, ulnar and sural nerves were stimulated, and sensory conduction velocities (SCVs), sensory response peak latencies and sensory action potentials (SAPs) were recorded.

Nerve conduction velocities were accepted as abnormal values below 50 m/s in the upper limb and below 40 m/s in the lower limb. Median nerve SAP amplitude below 12 μV, CMAP amplitude below 5 mV and motor DL values above 4.0 ms were accepted as abnormal values. Ulnar nerve SAP amplitude values below 8 μV, CMAP amplitude below 5 mV and motor distal latency above 4.0 ms were accepted as abnormal values.

Posterior tibial nerve CMAP amplitude values below 4 mV, peroneal nerve CMAP amplitude below 2 mV, and sural nerve SAP amplitude below 10 μV were considered as abnormal values.

In cases suggesting polyneuropathy, the presence of polyneuropathy was evaluated according to presence of electrophysiological multiple nerve involvement and presence of pathological findings (decrease in SNAP amplitude, slowing in SNCV, lengthening in DL, decrease in CMAP amplitude).

Patients with abnormalities in the nerve conduction study constituted the polyneuropathy group, and patients without abnormalities formed the control group.

Ethics committee approval was received for this study from the ethics committee of Bulent Ecevit University School of Medicine (Decision No: 2019/09).

Statistical Analysis: Statistical analysis of the research is performed with SPSS 19.0 package program. Descriptive statistics of continuous variables in the study are shown with mean, standard deviation, median, minimum and maximum values; descriptive statistics of categoric variables are shown with frequency and percentage. Independent sampling t-test analysis is used in two groups comparisons of the normally distributed variables. Mann Whitney U test was used in two groups comparisons of the variables those which aren't normally distributed and Chi-square tests were used for categorical variables. For all of the statistical analysis of the research p value under 0,05 was accepted as significant

RESULTS

While polyneuropathy was observed in 131 of 202 patients included in our study, polyneuropathy was not observed in 71 patients. Out of the patients with polyneuropathy, 68 were female and 63 were male, 41 of the patients without polyneuropathy were female and 30 were male. The average age of patients without PNP was determined as 57.48; the mean age of patients with PNP was determined as 64.34. The average age of those with PNP was significantly higher than those without PNP ($p < 0.001$) (Table 1). The mean diabetes duration was found to be 14.30±10.78 in patients with PNP and the diabetes duration was found to be 12.42±5.69 in patients without PNP. Electrophysiological examination revealed 103 sensory-predominant sensorimotor (78.6%), 21 sensory (16%), 4 motor (3.1%), 3 motor-predominat sensorimotor (2.3%) polyneuropathy in 131 patients. 80 patients had axonal (61.1%), 2 had demyelinating (1.5%), and 49 had mixed type (37.4%) polyneuropathy.

Table 1. Demographical parameters of patients with and without diabetic polyneuropathy

	N=202	Male	Female	Age
With DPNP	131	63	68	64.34
Without DPNP	71	41	30	57.48

DPNP: Diabetic polyneuropathy

When the laboratuary values of the patients were analyzed, blood tests of 168 of 202 patients were reached. 117 of these patients had PNP and 51 did not have PNP. In patients with PNP, glycolyzed hba1c ratio and fasting blood sugar were significantly higher than patients without PNP. ($p<.001$) While HDL rate was lower in patients with PNP than those without PNP ($p < 0.01$), TG / HDL ratio was higher ($p < 0.05$). In patients with PNP, glycolyzed urea ($p < 0.001$) and creatinine ($p < 0.01$) were significantly higher than those without PNP. The serum level of 25 (OH) vitamin D was significantly lower in patients with PNP than in patients without PNP ($p < 0.05$). Ferritin was significantly higher in patients with PNP than patients without ($P < 0.01$).

Table 2. Laboratory characteristics of patients with and without diabetic polyneuropathy

	With DPNP	Without DPNP	P value
HbA1c(%)	8.81 ± 12.02	8.39 ± 2.07	**<0.001**
Fasting blood glucose(mg/dl)	149.02 ± 74.001	188.48 ± 85.676	**<0.001**
Total cholesterol (mg/dl)	199.14 ± 52.339	194.21 ± 61.583	0.198
LDL-cholesterol (mg/dl)	119.21 ± 37.869	115.52 ± 49.113	0.361
Triglycerides(mg/dl)	157.98 ± 49.11	189.50 ± 81.69	0.307
HDL-cholesterol (mg/dl)	55.9 ± 24.23	47.08 ± 31.05	**0.001**
Trigliserit/HDL (AIP)	3.35 ± 2.41	4.69 ± 4.82	**0.035**
Cholesterol/HDL	4.00 ± 1.41	4.47 ± 1.47	0.099
25(OH) Vitamin D	24.7 ± 13.37	18.44 ± 9.26	**0.009**
Ferritin	44.27±32.87	78.90 ±67.81	**<0.01**
Ure	34.6 ± 14.94	48.22 ± 33.12	**<0.001**
Creatinin	1.45 ± 4.70	1.61 ± 5.07	**0.001**
Calsiyum	9.62 ± 0.5	9.44 ± 0.9	0.326
Magnesium	1.94 ± 0.295	1.93 ± 0.292	0.923
Potassium	4.49 ± 0.38	4.56 ± 0.56	0.148
Sodium	131.82 ± 31.94	131.82 ± 31.94	0.405

DNPN: Diabetic Polyneuropathy; LDL: low-density lipoprotein; HDL: high-density lipoprotein, AIP: atherogenic index of plasma

DISCUSSION

Diabetic Neuropathy is considered as one of the most common microvascular complications of both type 1 and 2 DM (13). The relationship between diabetes mellitus and neuropathy is clear.

As the duration of diabetes extends, the incidence of neuropathy increases and affects more than 50% of patients (15).

In our research, diabetic PNP was detected in 131 of 200 patients. The most common form of diabetic polyneuropathy is distal, symmetrical, sensory-predominant sensorimotor and axonal involvement (13,16). In our study, the frequency of sensory-predominant sensorimotor axonal type polyneuropathy was high. In our study, similar to the studies performed, the frequency of diabetic polyneuropathy was increasing with age (15,17,18). We think that DPN should be investigated and screened especially in elderly diabetic patients. Patients with polyneuropathy were mostly female patients, but difference was not statistically

significant. Booya et al and Tamer et al showed neuropathy more commonly in diabetic male patients (19,20). However Kaplan et al, Barbaros et al and Perkins et al did not show a significant difference between sex, similar to our study (10,21,22). In our study, there was a significant relationship between increased fasting blood sugar and hb a1c levels and diabetic PNP. Studies have shown that diabetic PNP progression and severity are closely related to glycemic control.

The level of glycosylated hemoglobin (HbA1c) is a good indicator of blood glucose control over the past three months and is considered the "gold standard" in the evaluation of long-term glycemic control in diabetic patients (9,12,13). [Diabetic peripheral neuropathy is thought to develop due to oxidative stress and inflammation due to nerve dysfunction and cell death. Hyperglycemia causes dysregulation of the metabolic pathway, causing imbalance in the mitochondrial redox state and releasing mitochondrial and cytosolic reactive oxygen particles. This causes axonal injury and neuropathy in the peripheral nerves (23,24). We suggest that keeping glucose levels, especially HbA1c under control is an important factor in preventing diabetic polynoropathy.

Atherosclerosis also has an important effect on microvascular and macrovascular complications in diabetic patients, for which dyslipidemia is a risk factor (25). In studies, especially increase in TG and decrease in HDL levels were held responsible. Atherogenic index of plasma (AIP) is calculated as the the ratio between the triglyceride value and high density lipoprotein value (mg/dL). (TG/ HDL-C) AIP is a major risk factor for cardiovascular diseases and metabolic syndrome (26). The high TG / HDL ratio causes endothelial dysfunction, impaired endoneuronal blood flow, nerve hypoxia and ischemia, and consequently neuropathy. Miric et al. showed that AIP was higher in patients with 2 DM patients who developed neuropathy (6). In their study, Li et al. stated that the incidence of diabetic neuropathy and metabolic syndrome is higher in patients with elevated AIP (27). In our study, the risk of developing diabetic PNP was higher in patients with low HDL and high AIP index. This study is the first study to show the relationship between serum atherogenicity index and diabetic polyneuropathy.

In studies conducted, Vitamin D levels are observed to be low in DM patients (14,28). Studies showed that Vitamin D deficiency has an effect and an important role in the development and severity of DPN (1,14). In our study, 25 (OH) vitamin D serum levels were significantly lower in patients with PNP than in patients without PNP. 25 (OH) vitamin D is the major circulating form of Vitamin D. There are several studies on how low vitamin D levels cause DPN. Vitamin D, especially the D3 form, has been shown to reduce demyelination in animal studies (1, 29). Demyelination increases in nerves with low vitamin D. In animal studies, it has been shown that low vitamin D causes a decrease in nerve growth factor (neurotropin) level, disrupts neuronal calcium homeostasis and accordingly increases nerve damage (30). As a result, vitamin D deficiency impairs nociceptor functions, increases nerve damage, and lowers the pain threshold. In order to prevent PNP development in patients with diabetes, vitamin D values should be followed and supplemented in their deficiency.

In our study, hemoglobine, platelet, white blood cells (WBC) values were determined as normal. Serum ferritin level was found to be significantly higher in patients with diabetic polyneuropathy. In studies performed, high ferritin levels were found to be related to increased triglyceride and glucose levels (31). Elevated ferritin level is associated with type 2 diabetes; however, the mechanism underlying this relationship is uncertain (32). In a study by El-Tagui et al; with patients with beta thalassemia, peripheral neuropathy especially with motor impairment was observed in patients with high ferritin levels (33). They thought that this might be due to the increase in iron oxidative stress to the height of the iron. In the study conducted by Bayhan et al, neuropathy was not observed in patients with high ferritin levels (34). Although sensory nerves were not affected, motor nerve studies revealed only prolongation of peroneal nerve latency. Studies are needed regarding the relationship between elevated ferritin levels and polyneuropathy.

CONCLUSISON

Diabetic polyneuropathy is associated with high mortality, morbidity, hospitalization rate and serious economic burden. Knowing and preventing risk factors for diabetic polyneuropathy, we can take a new direction to our treatment approaches and take early measures. Fasting blood sugar and hba1c control, regulation of lipid profile, monitoring of vitamin d and ferritin levels are particularly necessary for protection of polyneuropathy.

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