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Original Article *Özgün Araştırma*

ANXIETY AND DEPRESSION IN TYPE 2 DIABETES MELLITUS: A STUDY INCLUDING NERVE CONDUCTION STUDY AND NEUROPATHIC PAIN

Tip 2 Diabetes Mellitusta Anksiyete ve Depresyon: Sinir İletim Çalışması ve Nöropatik Ağrıyı İçeren Bir Çalışma

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ABSTRACT

Objective: It is known that neuropathy, neuropathic pain and psychiatric disorders are associated with diabetes mellitus (DM). It was aimed to find out whether there is a relationship between nerve conduction study findings, neuropathic pain, depression and anxiety.

Material and Methods: Type 2 DM patients that applied to our clinical neurophysiology laboratory between September 2021 and January 2022 were included in this study. Median, ulnar, sural, peroneal and posterior tibial nerve conduction studies were performed on the patients. Douleur Neuropathique 4 Questions (DN4) was applied to the patients to evaluate neuropathic pain. Hospital Anxiety and Depression Scale (HADS) was applied to the patients. Anxiety (HADS-A) and depression (HADS-S) scores, which are the two subsections of HADS, were included in the analysis.

Results: Forty DM patients (27 males, 13 females) were included in the study. The mean age of the patients was 57.9±12.7 (min-max 23-83) years. The number of patients with neuropathic pain, polyneuropathy according to neurophysiological findings, abnormal HADS-A and HADS-D scores were 32 (80%), 23 (58%), 17 (43%), and 24 (60%), respectively. Neuropathic pain was present in 22 (96%) and 10 (59%) of the patients with and without polyneuropathy, respectively. Neuropathic pain was found in 22 (92%) patients with depression and 16 (63%) patients without depression (p=0.046). Among patients with neuropathic pain, compound nerve action potential amplitudes of median, ulnar and sural nerves were lower than those without neuropathic pain (p=0.011, p=0.027, p<0.001).

Conclusion: In this study, it was revealed that neuropathic pain, depression and anxiety can be seen in Type 2 DM patients. In addition, this study showed a relationship between sensory nerve conduction studies and neuropathic pain. It was also concluded that neuropathic pain was more common in DM patients with depression than in patients without depression.

Keywords: *Anxiety, depression, diabetes mellitus, nerve conduction study, neuropathic pain*

ÖZ

Amaç: Nöropati, nöropatik ağrı ve psikiyatrik bozuklukların diabetes mellitus (DM) ile ilişkili olduğu bilinmektedir. Sinir iletim çalışması bulguları ile nöropatik ağrı, depresyon ve anksiyete arasında bir ilişki olup olmadığının ortaya çıkarılması amaçlandı.

Gereç ve Yöntemler: Bu çalışmaya Eylül 2021 ile Ocak 2022 tarihleri arasında klinik nörofizyoloji laboratuvarımıza başvuran Tip 2 DM hastaları dahil edildi. Hastalara median, ulnar, sural, peroneal ve posterior tibial sinir iletim çalışmaları yapıldı. Hastalara nöropatik ağrıyı değerlendirmek için 4 Soru nöropatik ağrı anketi (DN4) uygulandı. Hastalara Hastane Anksiyete ve Depresyon Ölçeği (HADS) uygulandı. HADS'ın iki alt bölümü olan anksiyete (HADS-A) ve depresyon (HADS-D) puanları analizlere dahil edildi.

Bulgular: Çalışmaya 40 DM hastası (27 erkek, 13 kadın) dahil edildi. Hastaların yaş ortalaması 57.9±12.7 (min-maks 23-83) yıl idi. Nöropatik ağrısı olan, nörofizyolojik bulgulara göre polinöropatisi olan, HADS-A ve HADS-D skorları anormal olan hasta sayısı sırasıyla 32 (%80), 23 (%58), 17 (%43) ve 24 (%60) idi. Nöropatik ağrı, polinöropatisi olan ve olmayan sırasıyla 22 (%96) ve 10 (%59) hastada mevcuttu. Depresyonu olan 22 (%92) hastada ve depresyonu olmayan 16 (%63) hastada nöropatik ağrı saptandı (p=0.046). Nöropatik ağrısı olan hastalarda median, ulnar ve sural sinirlerin bileşik sinir aksiyon potansiyeli amplitüdleri nöropatik ağrısı olmayanlara göre daha düşüktü (p=0.011, p=0.027, p<0.001).

Sonuç: Bu çalışmada Tip 2 DM hastalarında nöropatik ağrı, depresyon ve anksiyetenin görülebileceği ortaya konmuştur. Ek olarak bu çalışma, duyusal sinir iletim çalışmaları ve nöropatik ağrı arasında bir ilişki olduğunu göstermiştir. Ayrıca nöropatik ağrının depresyonu olan DM hastalarda, depresyonu olmayan DM hastalarına göre daha yaygın olduğu sonucuna varıldı.

Anahtar Kelimeler: *Anksiyete, depresyon, diabetes mellitus, sinir iletim çalışması, nöropatik ağrı*

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INTRODUCTION

Neuropathy is one of the complications of diabetes mellitus (DM) (1,2). Nerve conduction studies have a key role in the diagnosis of neuropathy in DM, in revealing the type of neuropathy (3). It can be in the form of mononeuropathy such as carpal tunnel syndrome, or it can progress with length-dependent polyneuropathy. Therefore, patients may experience hypoesthesia and muscle weakness. Moreover, patients may develop neuropathic pain. For all these reasons, the daily activities of the patients may be restricted (1,4).

Diabetic polyneuropathy can be seen in up to 50% and neuropathic pain in up to 30% of type 2 DM (1-4). Neuropathic pain can be very severe in some patients and may lead to disorders such as depression or poor sleep in DM patients (2,5). Psychiatric disorders are also reported to be comorbid with DM (2,5-9). Some studies have revealed that there may be a relationship between neuropsychiatric disorders such as depression or anxiety and DM (2,5-9). In this study, it was aimed to find out whether there is a relationship between anxiety, depression, neuropathic pain, and nerve conduction study findings.

MATERIALS AND METHODS

Study Design and Subjects

Ethical approval of the study was given by the Ethics Committee of the University of Health Sciences Adana City Training and Research Hospital (number 104/1903, 2022).

Type 2 DM patients over the age of 18 who applied to the Clinical Neurophysiology Laboratory of of Health Sciences University Adana City Training and Research Hospital between September 2021 and January 2022 were included in this retrospective study. The diagnosis of DM was made as previously suggested (10). Before the treatment was given for DM, the fasting blood glucose value should be >126 mg/dl. Patients with DM were excluded from the study if they had the following characteristics: 1) Presence of a condition that may cause neuropathy or neuropathic pain, such as radiculopathy or plexopathy 2) neurodegenerative disease 3) Receiving treatment for psychiatric disorders or neuropathic pain. If the clinical and electrodiagnostic features were compatible with polyneuropathy, the patient was considered to have DM-related polyneuropathy. For polyneuropathy due to DM, the patient should have the following clinical features (11,12): 1) Absence or decrease in deep tendon reflexes 2) Presence of sensory abnormality in neurological examination. Douleur Neuropathique 4 Questions (DN4) consisting of 10 items, which has two subgroups, Patient Interview and Patient Examination, were applied to all patients for neuropathic pain, the cut-off value was accepted as four (13). In addition, anxiety and depression in patients were evaluated with the Hospital Anxiety and Depression Scale (HADS). Scores of HADS-Anxiety (HADS-A) and HADS-Depression (HADS-D) subgroups were considered abnormal if they were >10 and >7, respectively (14). Ethical approval of the study was given by the Ethics Committee of the University of Health Sciences Adana City Training and Research Hospital (number 104/1903, 2022).

Nerve Conduction Study

Cadwell Sierra Summit EMG unit (Cadwell Laboratories, Kennewick, Washington, USA) was used for nerve conduction study. Nerve conduction study was performed using previously suggested methods (15-17). Nerve conduction study was performed if the temperature of the extremities was above 32 degrees, otherwise cold extremities were warmed. Superficial electrodes were used for stimulation and recording. Low-high band filters for motor and sensory nerve conduction studies were set to 20 Hz - 10 kHz and 20 Hz – 2 kHz, respectively. Nerve conduction studies were performed on both lower extremities and one upper extremity of the patients. Median, ulnar, posterior tibial, peroneal and sural nerve conduction studies were performed. Findings from an upper and lower extremity nerve conduction studies were used for group comparisons and correlation analysis. Both compound

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nerve action potential (CNAP) and compound muscle action potential (CMAP) amplitudes were calculated by measuring peak to peak. Sensory nerve conduction studies were performed antidromically. Peak latency was used for sensory nerve conduction velocity. Previously recommended reference values were used for the reference values for the nerve conduction study. In case of abnormality of both sural nerve CNAP and posterior tibial nerve CMAP, it was considered as polyneuropathy according to the electrodiagnostic features (11).

Statistical Analysis

Categorical variables were expressed as frequency and percentage, and numerical variables were expressed as mean standard deviation, median, and min-max. Pearson's Chi-square and Fisher's exact tests were used to compare categorical data. Numerical variables were compared between groups using the Mann-Whitney U test. Correlation analysis was performed with Spearman correlation test. If $P<0.05$, it was considered statistically significant. SPSS 22.0 was used for statistical analysis.

RESULTS

Forty DM patients (27 males, 13 females) were included in the study. The mean age of the patients was 57.9±12.7 (min-max 23-83) years. The mean duration of DM of the patients was 13.8±8.2 (min-max 1-30) years. The mean height, weight and body mass index (BMI) of the patients were 168.7±7.3 (min-max 155-185) cm, 81.7±16.5 (min-max 55-125) kg and 28.7±5.6 (min-max 19.9-45.2) kg/m^2, respectively. Eighteen of the patients were using oral antidiabetic drugs, two were using insulin, and twenty were using both oral antidiabetic drugs and insulin.

According to nerve conduction study findings, 23 (58%) of the patients had polyneuropathy. Nerve conduction study findings of the patients are shown in Table 1.

The mean DN4 score of the patients was 6.7±2.4 (min-max 1-10). According to DN4 scores, 32 (80%) of the patients had neuropathic pain. The mean HADS-A and HADS-D scores of the patients were 9.8±5.0 (min-max 0-20) and 9.0±4.3 (min-max 0-19), respectively. The number of patients with abnormalities in HADS-A and HADS-D were 17 (43%) and 24 (60%), respectively. Figure 1 shows the comparison of polyneuropathy, HADS-A and HADS-D scores between groups with and without neuropathic pain. According to HADS-A, 10 (59%) of 17 patients with anxiety and 13 (57%) of 23 patients without anxiety had polyneuropathy (p=0.894). According to HADS-D, polyneuropathy was found in 15 (63%) of 24 patients with depression and in eight (50%) of 16 patients without depression (p=0.433). Comparison of nerve conduction study findings between patients with and without neuropathic pain, and patients with and without anxiety and depression according to HADS is shown in Table 2. Table 3 shows the correlation between DN4, HADS, nerve conduction study findings and clinical features.

Figure 2 shows the correlation between DN4 score and sural nerve CNAP amplitude. The number of patients with neuropathic pain, anxiety and depression was not statistically different between the group using oral antidiabetic drug or insulin for DM and the group using both insulin and oral antidiabetic drugs (p=0.235, p=0.749, p=0.197). While 8 (40%) of 20 patients using oral antidiabetic drug or insulin for DM had polyneuropathy, 15 (75%) of 20 patients using both oral antidiabetic drugs and insulin for DM had polyneuropathy (p=0.025).

DISCUSSION

In this study, the relationship between depression, anxiety, nerve conduction study and neuropathic pain in type 2 DM was investigated. Depression was present in 60% of type 2 DM patients, and neuropathic pain was more common in patients with depression. Also, unlike motor nerve conduction studies, a relationship was found between sensory nerve conduction studies and neuropathic pain.

Neuropathy is one of the important complications of DM. Patients may develop symptoms ranging from painless paresthesias to very severe pain. These pains can limit the patients' activities of daily living (1,4). In

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this current study, abnormalities in nerve conduction study and HADS-D scores were found more in DM patients with neuropathic pain than in DM patients without neuropathic pain. This may be explained by the fact that routine nerve conduction study can evaluate myelinated large nerve fibers (11,18).

Table 1: Nerve conduction study findings of the patients

Nerve conduction studies	Mean±SD (median)	Min-Max
Sensory nerve conduction studies		
Median nerve CNAP amp. (μV) (n=40)	15.3±14 (12.8)	0-56.5
Median NCV across 2nd finger-wrist segment (m/s) (n=33)	34±5.6 (34)	24-48
Ulnar nerve CNAP amp. (μV) (n=40)	15.6±13.1 (14.7)	0-62.2
Ulnar NCV across 5th finger-wrist segment (n=36)	36.3±6.3 (36.5)	25-50
Sural nerve CNAP amp. (μV) (n=40)	6.4±8.8 (0)	0-35.4
Sural NCV (m/s) (n=22)	43.4±7.3 (43)	30±57
Motor nerve conduction studies		
Median CMAP amp. (mV) (n=40)	10±4.2 (9.6)	1.1-19.2
Median NCV across wrist-elbow segment (m/s) (n=40)	51±7.6 (51.5)	36-66
Ulnar CMAP amp. (mV) (n=40)	11.8±3.6 (12.1)	2.3-20.5
Ulnar NCV across wrist-elbow segment (m/s) (n=40)	54.4±9.1 (53)	33-78
Peroneal CMAP amp. (mV) (n=40)	3.8±4.3 (3.1)	0-18.8
Peroneal NCV across ankle-below fibular head (m/s) (n=26)	42.8±9.6 (41.5)	29-62
Posterior tibial CMAP amp. (mV) (n=40)	4.4±4.8 (2.3)	0-19.4
Posterior tibial NCV across ankle-popliteal fossa (m/s) (n=34)	37.3±5.9 (37.3)	28.0-53

amp: Amplitude; CMAP: Compound muscle action potential; CNAP: Compound nerve action potential, NCV: Nerve conduction velocity, SD: Standard deviation.

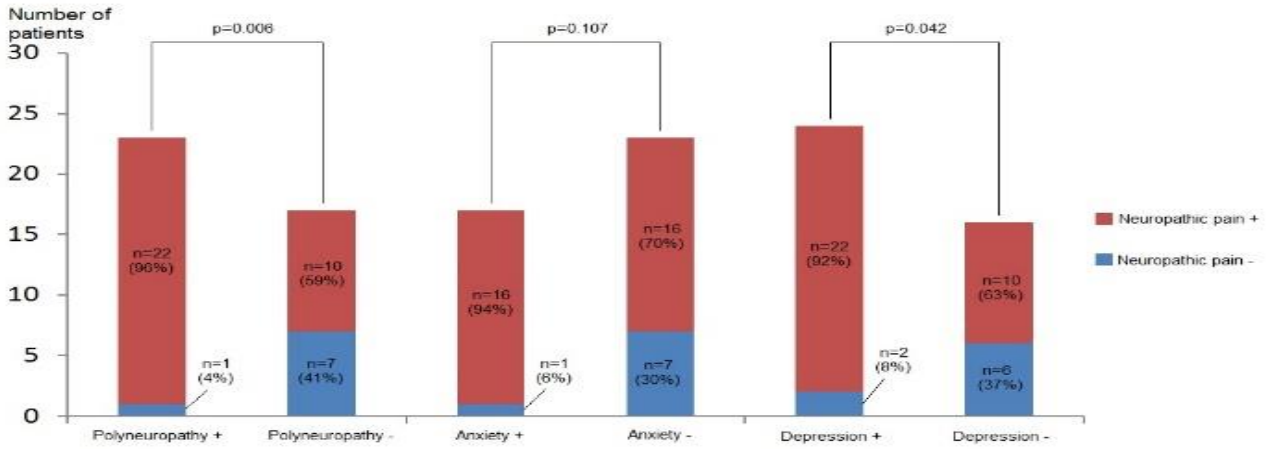

Figure 1: Comparison of the number of patients with polyneuropathy/anxiety/depression between DM patients with and without neuropath

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Table 2: Comparison of nerve conduction study findings between patients with and without neuropathic pain, and patients with and without anxiety and depression

NCSs	NP + (mean±SD)	NP - (mean±SD)	P value	HADS-A + (mean±SD)	HADS-A - (mean±SD)	P value	HADS-D + (mean±SD)	HADS-D - (mean±SD)	P value
Sensory NCSs									
Median CNAP amp. (μV) (n=40)	12.6±12.4	15.3±14.0	0.011*	15.3±16.0	15.3±14.0	0.794	15.6±16.2	15.3±14.0	0.729
Median NCV (m/s) (n=33)	33.7±4.8	34.0±5.6	0.800	34.8±5.5	34.0±5.6	0.293	34.0±5.4	34.0±5.6	0.799
Ulnar CNAP amp. (μV) (n=40)	13.4±11.6	15.6±13.1	0.027*	13.9±12.1	15.6±13.1	0.622	14.9±13.3	15.6±13.1	0.456
Ulnar NCV (m/s) (n=36)	35.2±6.5	36.3±6.3	0.030	36.7±6.4	36.3±6.3	0.673	35.7±6.9	36.3±6.3	0.416
Sural CNAP amp. (μV) (n=40)	3.8±6.5	6.4±8.9	<0.001*	4.9±7.6	6.4±8.8	0.369	5.6±9.1	6.4±8.8	0.311
Sural NCV (m/s) (n=22)	43.2±43.4	43.4±7.3	0.929	44.8±6.7	43.4±7.3	0.637	42.0±6.9	43.4±7.3	0.328
Motor nerve conduction studies									
Median nerve CMAP amp. (mV) (n=40)	10.5±4.3	10.0±4.2	0.257	9.8±4.4	10.0±4.2	0.632	10.0±4.3	10.0±4.2	0.912
Median NCV (m/s) (n=40)	50.3±7.9	51.0±7.6	0.264	51.8±8.4	51.0±7.6	0.443	50.1±7.3	51.0±7.6	0.525
Ulnar nerve CMAP amp. (mV) (n=40)	11.4±3.7	11.8±3.6	0.361	11.8±2.9	11.8±3.6	0.989	11.8±3.6	11.8±3.6	0.978
Ulnar NCV (m/s) (n=40)	53.9±9.6	54.4±9.1	0.360	55.2±10.9	54.4±9.1	0.622	54.3±9.9	54.4±9.1	0.846
Peroneal CMAP amp. (mV) (n=40)	3.4±4.3	3.8±4.3	0.102	3.3±3.3	3.8±4.3	0.867	4.5±5.1	3.8±4.3	0.634
Peroneal NCV (m/s) (n=26)	42.1±10.0	42.8±9.6	0.411	44.9±9.6	42.8±9.6	0.342	43.5±9.4	42.8±9.6	0.662
PT nerve CMAP amp. (mV) (n=40)	3.6±4.1	4.4±4.8	0.040*	3.3±4.2	4.4±4.8	0.319	4.4±5.4	4.4±4.8	0.648
PT NCV (m/s) (n=34)	36.5±6.2	37.3±5.9	0.143	35.8±7.5	37.3±5.9	0.342	36.6±6.7	37.3±5.9	0.334

amp: Amplitude, CMAP: Compound muscle action potential, CNAP: Compound nerve action potential, HADS: Hospital anxiety and depression scale, HADS-A: HADS-Anxiety, HADS-D: HADS-Depression, PT: Posterior tibial, NCV: Nerve conduction velocity, NP: Neuropathic pain, SD: Standard deviation. *: p<0.05.

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Table 3: Correlation between clinical features, electrodiagnostic findings, DN4 and HADS scores

Clinical and electrodiagnostic features	**HADS-A score**	**HADS-D score**	**DN4 score**
Age (years)	p=0.487 r=-0.113	p=0.545 r=-0.099	p=0.522r=0.104
Duration of DM	p=0.571 r=-0.092	p=0.776 r=0.047	p=0.468 r=0.118
BMI	p=0.919 r=0.017	p=0.172 r=0.220	p=0.172 r=0.220
Median nerve CNAP amp./ SNCV	p=0.887 r=-0.023 / p=0.196 r=0.231	p=0.638 r=0-.077/ p=0.925 r=-0.017	p=0.001* r=-0.488 / p= 0.571 r=-0.102
Ulnar nerve CNAP amp./SNCV	p=0.964 r=0.007 / p=0.705 r=0.065	p=0.377r=-0.143 / p=0.924 r=-0.017	p=0.032* r=-0.340 / p=0.311r=-0.174
Sural nerve CNAP amp./SNCV	p=0.757r=-0.050 / p=0.728 r=-0,088	p=0.262 r=-0.182=/ p=0.335 r=-0.241	p=0.002* r=-0.474/p=0.619 r=0.126
Median nerve CMAP amp./MNCV	p=0.983 r=0.004 / p=0.395 r=0.138	p=0.762 r=0.049/p= 0.248r=-0.187	p=0.110 r=0.257 / p=0.110 r=-0.257
Ulnar nerve CMAP amp./MNCV	p=0.416 r=0.132 / p=0.501 r=0.110	p=0.394 r=-0.138 / p= 0.397r=-0.138	p= 0.733 r=-0.056 / p=0.453 r=-0.122
Peroneal nerve CMAP amp./MNCV	p=0.712 r=0.065 / p=0.242 r=0.238	p=0.412 r=-0.143 / p=0.995 r=-0.001	p=0.075 r=-0.305 / p=0.479 r=-0.145
PT CMAP amp./MNCV	p=0.533r=-0,116 / p=0.127r=-0.314	p=0.356 r=-0.172 / p=0.342 r=-0.198	p=0.303 r=-0.191 / p=0.208 r=-0.261

amp: Amplitude, BMI: Body mass index, CMAP: Compound muscle action potential, CNAP: Compound nerve action potential, DM: Diabetes mellitus, DN4: Douleur neuropathique 4 questions, HADS: Hospital anxiety and depression scale, HADS-A: HADS-Anxiety, HADS-D: HADS-Depression, PT: Posterior tibial, MNCV: Motor nerve conduction velocity, SNCV: Sensory nerve conduction velocity. *: $p<0.05$.

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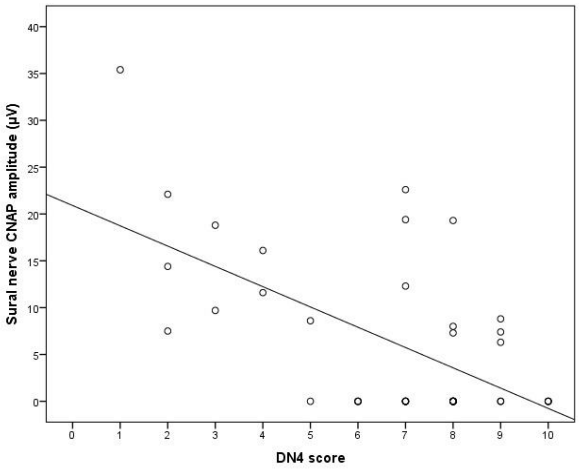

Figure 2: Correlation between DN4 score and sural nerve CNAP amplitude.

CNAP: compound nerve action potential; DN4: Douleur Neuropathique 4 Questions.

When myelinated large nerve fibers are affected, small nerve fibers known to be associated with pain are expected to be affected as well. Moreover, a negative correlation was found between CNAP amplitudes and DN4 scores of sensory nerves, and also, CNAP amplitudes of sensory nerves were lower in DM patients with neuropathic pain than in DM patients without neuropathic pain. It is known that injuries to the sensory nerves are more associated with neuropathic pain (19).

The relationship between depression and DM has been reported in many studies (2,5,7). Many mechanisms including immune mechanisms, lifestyle, diet for DM, dysregulation of hypothalamo-pituitary-adrenal axis are blamed for depression developing in DM (5,20,21). One of the reasons explaining the relationship between depression and neuropathic pain found in the current study may be the changes in lifestyle. Neuropathic pain affects activities of daily life, and the lifestyle of DM patients may change (1,2,4). Therefore, the treatment of neuropathic pain and depression is important. One of the treatments for neuropathy in DM is blood glucose regulation (3). The fact that neuropathic pain is more common in DM patients receiving both insulin and oral antidiabetic drugs compared to those receiving oral antidiabetic drug or insulin in this current study supports this situation. Therefore, adequate treatment of DM and its complications will allow improvement of neuropathic pain and depression (2,3,22). This study also pointed out that DM patients may have anxiety (8). In contrast to depression, this study found no association between anxiety and neuropathic pain/nerve conduction study findings. This may explain that anxiety in DM develops with a mechanism independent of neuropathy. However, further studies with larger number of patients are needed.

This study had some limitations as well as strengths. Determining the polyneuropathy with stricter criteria and using both neurophysiological tests and two separate questionnaires were the strengths of this study. The extent of DM varied between patients. As the duration of DM increases, neuropathic pain and other complications may increase (2,4). Therefore, we think that the rate of DM patients with neuropathic pain and depression is high in this study. In addition, the visual analog scale associated with pain was not used, which can be considered a limitation. The small number of patients and the absence of other biochemical blood tests such as blood glucose were other limitations. Finally, complications of DM, such as retinopathy, were not included in the analyses. However, it should be kept in mind that DM patients with disorders that may cause neuropathy such as radiculopathy are excluded.

In conclusion, this study showed that patients with Type 2 DM can have neuropathic pain, depression and anxiety, and there is a strong correlation between neuropathic pain and sensory nerve conduction study findings. In addition, it was concluded that neuropathic pain was more common in patients with depression.

Conflict of interest: The authors have no conflicts of interest to declare.

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Ethics Committee Approval: Ethics Committee of University of Health Sciences Adana City Training and Research Hospital (number 104/1903, 2022).

Researchers' Contribution Rate Statement:

Concept/Design: ŞB, HF; Analysis/Interpretation: ŞB, HF; Data Collection: ŞB, HF, MY, ZA; Writer: ŞB, HF,

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MY, ZA; Critical Review: ŞB, HF, MY, ZA; Supervision: ŞB, HF, MY, ZA.

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