

Evaluation of clinical relationship of serum niacin and dopamine levels in patients with fibromyalgia syndrome

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ABSTRACT

Objectives: The aim of this study was to investigate the role of serum niacin and dopamine (DA) levels and their clinical importance in fibromyalgia syndrome (FMS) patients.

Patients and methods: Between April 2018 and October 2018, a total of 53 female patients (mean age: 38.3±5.5 years; range, 21 to 45 years) with a clinical diagnosis of FMS and 35 healthy female controls (mean age: 36.7±5.2 years; range, 25 to 44 years) were included in this cross-sectional study. The Visual Analog Scale (VAS), Beck Depression Inventory (BDI), and Fibromyalgia Impact Questionnaire (FIQ) were applied to the patients. Serum levels of niacin and DA were measured by high-performance liquid chromatography (HPLC) and enzyme-linked immunosorbent assay (ELISA) methods, respectively.

Results: Niacin and DA levels of the patient group were significantly lower than those of control group ($p=0.003$ and $p=0.02$, respectively). A very strong positive correlation was found between niacin and DA levels ($r=0.96$ $p<0.001$). Evaluation of the diagnostic performance of niacin and DA by the receiver operating characteristic analysis yielded an area under the curve (AUC) of 0.73 ($p<0.001$, 95% confidence interval [CI]: 0.62-0.85) and an AUC of 0.68 ($p=0.004$, 95% CI: 0.56-0.80), respectively.

Conclusion: Serum niacin and DA levels decrease in FMS patients in relation to the tender point numbers. It can be suggested that the levels of these two markers can be considered additional tools in the diagnosis of FMS.

Keywords: Dopamine, fibromyalgia syndrome, niacin, pain, point number, tender.

A set of disorders defined by chronic nonneuropathic and non-nociceptive pain are called as central sensitization syndromes (CSSs). The pain is not commensurate to the sort of injury and it must go with the existence of neurophysiological or neuropathological phenomena such as secondary hyperalgesia, allodynia.^[1] Central sensitization syndromes include a variety of diseases such as fibromyalgia syndrome (FMS), migraine, restless leg syndrome, and irritable bowel syndrome. Fibromyalgia syndrome is considered the most typical disease of CSSs since 2009.^[2] It is a chronic disease defined

by widespread musculoskeletal pain, stiffness, fatigue, cognitive impairment, sleep disturbance, and hyperalgesia.^[3] The necessity to provide a quantitative measure of widespread pain, the widespread pain index, severity scales that include key FMS symptoms and measure the extent and severity of symptoms of widespread pain, has been recognized by the FMS criteria since 2010.^[4] Dopaminergic neurons have been reported to be effective in controlling the perception of pain severity,^[5] predicting pain and giving emotional responses, as well as the regulation of pain sensation in the spinal cord.^[6] In FMS, there has been an

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altered dopamine (DA) levels causing aberrant pain perception. Although its etiopathogenesis cannot be determined precisely, many mechanisms such as central sensitization (CS), immunological, neurohormonal, genetic, environmental and nutritional factors, particularly vitamin deficiencies, are thought to play a role.^[7] Niacin, vitamin B3, has two vitamers, such as nicotinic acid (pyridine-3-carboxylic acid) and nicotinamide (nicotinic acid amide). These are transformed into biologically active coenzymes: nicotinamide adenine dinucleotide (NAD⁺ and NADH⁺) and nicotinamide adenine dinucleotide phosphate (NADP), respectively.^[8] The latter provides reductive equivalents and, consequently, the dihydrobiopterin, the oxidized form of tetrahydrobiopterin, can be recycled back to tetrahydrobiopterin by dihydropteridine reductase. Tetrahydrobiopterin is a coenzyme necessary for the conversion of tyrosine to levodopa by a reaction catalyzed by tyrosine hydroxylase (TH), the rate-limiting enzyme of DA synthesis.^[9]

An important risk factor of FMS causing altered DA levels in aberrant pain perception is nutritional factors, particularly niacin deficiency. Since niacin is a crucial vitamin of DA synthesis, changes of niacin levels can be considered in some rheumatological diseases, particularly in FMS leading to inadequate DA synthesis and, thereby, causing the major symptom of FMS, chronic widespread pain. In the present study, we, therefore, aimed to investigate the role of serum niacin and DA levels and their clinical importance in FMS patients.

PATIENTS AND METHODS

This cross-sectional study was conducted at Tokat Gaziosmanpaşa University Faculty of Medicine, Departments of Physical Medicine and Rehabilitation and Clinical Biochemistry between April 2018 and October 2018. A total of 53 female patients (mean age: 38.3±5.5 years; range, 21 to 45 years) with a clinical diagnosis of FMS according to the 2010 American College of Rheumatology (ACR) diagnostic criteria were included in the study. Similarly, a total of 35 healthy age- and body mass index (BMI)-matched female volunteers from our hospital staff (mean age: 36.7±5.2 years; range, 25 to 44 years) were included as the control group. Exclusion criteria were as follows: pregnancy, breastfeeding, having chronic inflammatory, systemic or metabolic diseases such as diabetes mellitus, hypertension, cancer, ischemic heart disease, susceptibility to thrombotic or bleeding

disorders, and having a BMI of ≥ 35 kg/m², as well as taking medications such as anticoagulants, corticosteroid and vitamin supplements. Alcohol users and smokers were also excluded. All participants were not known for their niacin and DA levels before the study. Severity of disease was self-reported by the patients using valid and reliable tools: the Visual Analog Scale (VAS), Beck Depression Inventory (BDI),^[10] and Fibromyalgia Impact Questionnaire (FIQ).^[11] Tender point numbers (TPNs) of all patients were determined manually by the same physician with finger pressure method. A written informed consent was obtained from each participant. The study protocol was approved by the Tokat Gaziosmanpaşa University Faculty of Medicine Clinical Research Ethics Committee (date, no: February 20, 2018/18-KAEK-055). The study was conducted in accordance with the principles of the Declaration of Helsinki.

The BDI was originally developed by Beck et al.^[12] in 1961 to assess definitive attitudes and symptoms of depression. It is a 21-item, self-report rating inventory. In the Turkish population, the validity and reliability of BDI were carried out by Hisli.^[13] Higher scores indicate a more severe depression (0-9 points: minimum depression; 10-18 points: slight depression; 19-29 points: moderate depression; 30-63 points: severe depression).

The FIQ was developed in the late 1980s to evaluate the status, prognosis and outcomes of FMS patients.^[14] It is a 10-item measuring tool. In the Turkish population, its validity and reliability were conducted by Sarmer et al.^[15] The total score of FIQ ranges from 0 to 100. A higher score indicates a greater effect of FMS on functionality.

Biochemical assays

After at least 8 h of fasting, early morning blood samples were taken from the participants for routine examination and centrifuged for 10 min at 3,500 rpm after 30-min resting. All samples were collected and studied by the same researchers at one session. Serum niacin levels were measured by using high-performance liquid chromatography (HPLC)^[16] method via the Agilent 1100 HPLC-UV device (Agilent, Santa Clara, CA, USA). Serum DA levels were determined with commercial kits (Sunred Biological Technology Co. Ltd., Shanghai, China) using the enzyme-linked immunosorbent assay (ELISA)^[17] method by the Chromate® Microplate Reader 4300 (Awareness Technology Inc., Palm City, FL, USA) device.

TABLE 1
Baseline characteristics of patients

Variables	FMS patient group (n=53)			Control group (n=35)			p
	Mean±SD	Median	25 th -75 th percentiles	Mean±SD	Median	25 th -75 th percentiles	
Age (year)	38.3±5.5			36.7±5.2			0.17*
Body mass index (kg/m ²)	29.4±5.0			27.8±4.3			0.14*
Niacin (ng/mL)		36.61	6.87-503.57		94.12	5.0-503.57	0.003**
Dopamine (nmol/L)		206.86	50.30-6,083.95		478.01	48.53-6,513.65	0.02**

SD: Standard deviation; * Independent samples t-test; ** Mann Whitney U test.

TABLE 2
Quantitative variables of FMS patients (n=53)

Variables	Mean±SD	Min-Max
Visual Analog Scale	7.88±1.84	0-10
Tender point number	13.46±2.7	0-18
Body mass index	23.34±10.3	0-63
Fibromyalgia impact questionnaire	65.12±12.7	0-100

FMS: Fibromyalgia syndrome; SD: Standard deviation.

Statistical analysis

The study power and sample size calculation were performed using the G*Power version 3.1.9 Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany.^[18] Based on the study of Muss et al.,^[19] the effect size was determined as $d=0.55$. With 80% power and 0.05 alpha level, the minimum sample size to be included in the study was calculated as 88 (control group $n=35$ and patient group $n=53$).

Statistical analysis was performed using the IBM SPSS version 19.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean \pm

standard deviation (SD) or median (25th-75th percentile) or number and frequency. Normally distributed continuous data were compared using the independent samples t-test. The Mann-Whitney U test was used to compare non-normally distributed continuous data. The Pearson or Spearman correlation coefficient were used to analyze the correlation between the variables. The receiver operating characteristic (ROC) analysis was used to evaluate the diagnostic performance of niacin and DA in FMS. A p value of <0.05 was considered statistically significant.

RESULTS

The mean BMI values of the patients and controls were 29.4 ± 5.0 kg/m² and 27.8 ± 4.3 kg/m², respectively. There was no significant difference between the patient and control groups in terms of age and BMI values ($p=0.017$ and $p=0.14$, respectively). The median niacin level was 36.61 (range, 6.87 to 503.57) ng/mL in the FMS group and 94.12 (range, 5.0 to 503.57) ng/mL in the control group, indicating a statistically significant difference ($p=0.003$). Similarly, the median DA level

TABLE 3
Bivariate correlation of quantitative variables

Variables	Niacin (ng/mL)	Dopamine (nmol/L)	TPN (0-18)
TPN (0-18)			
r	-0.42	-0.41	
p	0.001	0.003	
FIQ (0-100)			
r	-0.21	-0.23	
p	0.09	0.11	
Dopamine (nmol/L)			
r	0.80		
p	<0.001		

TPN: Tender point number; FIQ: Fibromyalgia impact questionnaire; * Pearson correlation coefficient; for the others, Spearman correlation coefficient was used.

TABLE 4
The results of ROC analysis

Variables	Cut off	AUC	95% CI of AUC	Sensitivity	Specificity	PPV	NPV	<i>p</i>
Niacin (ng/mL)	≤44.53	0.733	0.622-0.845	0.774	0.714	0.804	0.676	<0.001
DA (nmol/L)	≤281.99	0.678	0.556-0.800	0.774	0.686	0.788	0.667	0.004

ROC: Receiver operating characteristic; AUC: Area under curve; CI: Confidence interval; PPV: Positive predictive value; NPV: Negative predictive value; DA: Dopamine.

was 206.86 (range, 50.30 to 6,083.95) nmol/L in the patient group and 478.01 (range, 48.53 to 6,513.65) nmol/L in the control group, indicating a statistically significant difference ($p=0.02$) (Table 1). The mean self-reported VAS, FIQ, and TPN scores were also significantly higher in the FMS group: 7.9 ± 1.8 (range, 0 to 10), 65.1 ± 12.7 (range, 0 to 100), and 13.5 ± 2.7 (range, 0 to 18), respectively. The mean BDI scores were moderately higher in the FMS group (23.3 ± 10.3 ; range, 0 to 63) (Table 2).

In the patient group, there was a strong positive correlation between niacin and DA levels ($r=0.96$; $p<0.001$). A moderate negative correlation was found between the TPN and niacin values ($r=-0.45$; $p=0.001$). Similarly, a moderate negative correlation was found between the number of TPN and DA levels ($r=-0.40$; $p=0.004$). The FIQ showed a weak negative relation with niacin and DA levels without a statistical significance ($r=-0.25$; $p=0.81$, $r=-0.23$; $p=0.12$, respectively). However, no significant correlation was found among the DA and niacin levels

and kinetic parameters such as VAS and BDI ($p>0.05$) (Table 3).

According to the diagnostic performance of niacin and DA by ROC analysis, the area under the curve (AUC) values were found to be 0.73 ($p<0.001$, 95% confidence interval [CI]: 0.62-0.85) and 0.68 ($p=0.004$, 95% CI: 0.56-0.80), respectively. Niacin showed the ability to distinguish FMS patients and controls with 77.4% sensitivity and 71.4% specificity with a cut-off value of 44.53 ng/mL. In addition, DA showed the ability to distinguish FMS patients and controls with 77.4% sensitivity and 68.6% specificity with a cut-off value of 281.99 nmol/L (Table 4). The ROC curves for niacin and DA are shown in Figure 1.

DISCUSSION

In the present study, we investigated the role of serum niacin and DA levels and their clinical importance in FMS patients. To the best of our knowledge, this is the first study to investigate niacin deficiency and its relations with disease symptoms in FMS. All patients and healthy controls were age- and BMI-matched females in this study. The median DA and serum niacin levels were significantly lower than the healthy controls ($p=0.02$ and $p=0.003$, respectively). In addition, DA and niacin showed correlations not only with each other, but also with the FIQ and TPN. Also, DA and niacin showed a high sensitivity and specificity with cut-off values of 281.99 nmol/L and of 44.53 ng/mL, respectively.

About 3% of adults, with a female-to-male ratio of about 5:1, are affected by FMS worldwide.^[3,12] In search for interaction of nutritional factors with chronic widespread pain in FMS, the levels of vitamins were found to be lower in many patients compared to the healthy controls, and replacement of these factors have shown to contribute to the relief of symptoms, particularly chronic widespread pain. To determine whether vitamin D contributes to the pathology of FMS and to examine the effect of vitamin D replacement in treatment, Ellis et al.^[11] conducted a literature review

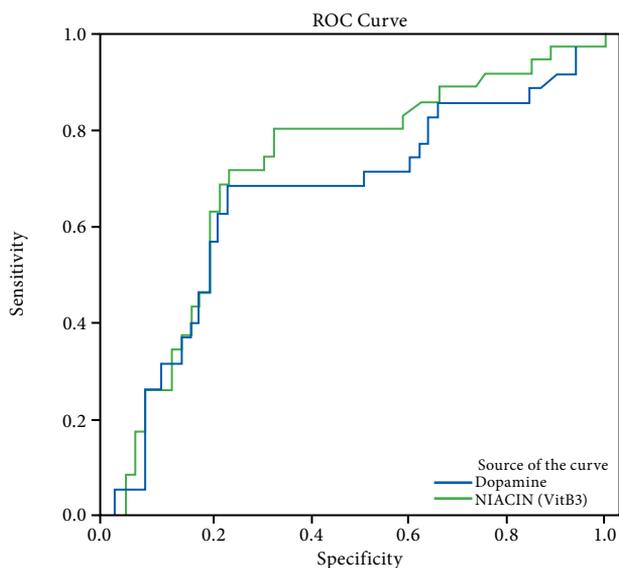


Figure 1. Receiver operating characteristic curves of dopamine and niacin.

and showed a relation between FMS and vitamin D deficiency. Elma et al.^[16] also performed a systematic review about interaction of nutritional factors with chronic musculoskeletal pain and they found that dietary changes indicated pain-relieving effect in seven of nine experimental studies. A lower intake of proteins, lipids, carbohydrates, vitamin A-E-K, folate, zinc, and selenium was reported in FMS patients. Pain threshold showed a positive association with protein intake in FMS. Consistent with the studies investigating the relation of some nutritional factors with pain in FMS, our study showed significantly low serum levels of niacin in FMS patients compared to the controls ($p=0.003$).

The production or enhancement of spontaneous firing activity, decreased activation threshold for normal stimuli, after application of a nociceptive stimulus the more intense and long-standing activation, and larger receptive fields development are some neurophysiological properties of CSS neurons.^[17] Since neurons have plastic properties, CS is defined as a modification in the physiological status of the central nervous system (CNS) determined by an enhanced release of excitatory transmitters and constant activation of particular nervous pathways.^[20] The relationship between DA and migraine, one of the CSSs, is clear. Therefore, it may help us to anticipate the relationship of DA and FMS. In a patient with DA receptor (DR) hypersensitivity due to a chronic dopaminergic deficit, an ictal DA release could be the characteristic feature of migraine attacks. Dopaminergic dysfunction in migraine has been confirmed by the pharmacological studies. It has been demonstrated by challenges with DA agonists that dopaminergic hypersensitivity is a particular feature in migraineurs.^[21] Since migraine decline in Parkinsonian patients could be due to the substantia nigra (SN) degeneration, an efficient DA system is needed for migraine.^[22] Brake activity of DA on trigeminocervical neurons through DRD2 has been shown in experimental studies.^[23] A chronic dopaminergic hypofunction due to genotype defects related to DA, defects of DA levels or all together is the main point of migraine. Making the patient more susceptible to DA stimulation and a declined inhibitory control on trigeminocervical neurons may be caused by dopaminergic dysfunction guiding to a DR upregulation. Blockage of peripheral DRD2- and central DRD2-mediated sensitization in an acute manner, can be achieved by antidopaminergic agents, whereas migraine can be prevented by the help of chronic dopaminergic

stimulation causing high negative effect of DA on trigeminocervical neurons. Currently, drugs showing effect on the DA system constitute the mainstay of the migraine treatment.^[24] Based on the common points derived from CCSs, we can make some suggestions for further studies. As an efficient DA system is needed for CCSs, neuroimaging studies can be carried out to clarify anatomical structure and intactness of dopaminergic system. In addition, whether there is any brake complex such as the trigeminocervical complex to reverse trigeminal sensitization in FMS needs to be clarified. Dopaminergic hypersensitivity and induced central or peripheral DRs for FMS can be examined, as well. In addition to conventional medication, acute and chronic DA replacement therapies can be evaluated. Since there is an ictal DA release in migraine, it can be also investigated that whether any release pattern exist in FMS or not. Dopaminergic hypofunction needs to be clarified whether it is due to DA-related genetic defects or defective DA-levels which we attempted to investigate in our study. In this study, serum DA levels in FMS patients were significantly lower than the healthy controls ($p=0.02$), implying a chronic dopaminergic hypofunction due to defective DA levels. There have been some studies indicating low-levels of DA in FMS. Mease et al.^[25] compared biogenic amines levels in the cerebrospinal fluid (CSF) of primary FMS patients with controls. They found that CSF levels of metabolites from all three neurotransmitters (i.e., serotonin, norepinephrine, and DA) were lower in primary FMS patients than the controls. Proposed hypothesis of a metabolic defect in primary FMS is supported by a low turnover rate of various neurotransmitters and it proposes a neuroregulatory level defect.^[26]

All these studies mentioned above and the findings of our study suggest that an alteration of inhibitory neurotransmitter DA levels due to nutritional factors, particularly niacin deficiency, may play a role in FMS etiopathogenesis. In the current literature, there is no study available investigating the relationship of DA and niacin in FMS. However, in some conditions, the relationship between DA and niacin-transformed coenzyme, NADH, has been investigated. Birkmayer et al.^[27] considered using NADH to increase endogen DA synthesis and relieve Parkinson's disease (PD) symptoms. Some conditions that support the use of NADH in PD treatment include claims that NADH stimulates TH and DA biosynthesis in tissue cultures and humans, as well as series of cases combining intravenous and oral NADH administration with

PD Rating Scale improvements. In our study, we found a strong positive correlation between serum niacin and DA levels and a negative correlation between niacin levels and TPNs in FMS patients.

In the present study, the cut-off values of niacin and DA were 44.53 ng/mL and 281.99 nmol/L, respectively. These results indicate that niacin and DA may help to differentiate and follow FMS patients in relation to TPNs. This is the first study to examine the diagnostic performance of niacin and DA in FMS. Contrary to our hypothesis, Joustra et al.,^[28] in their review, searched the use of nutritional supplements in chronic fatigue syndromes and FMS. Their evidences were little to support the hypothesis that deficiencies of vitamin and minerals take part in the pathophysiology of chronic fatigue syndromes including FMS, and their replacement is effective.

In general, FMS patients encounter many symptoms that considerably affect their daily life, and they are measured by some self-reported tools.^[26] In this study, the FMS patients' self-reported scores were significantly higher for VAS, FIQ, and TPN and moderately higher for BDI. In line with our results, there are various studies of chronic musculoskeletal pain syndromes showing the vitamin, mineral and biogenic amines deficiencies with replacement therapies and their relations with high scores of VAS, BDI, FIQ, and TPNs. Riva et al.,^[29] in their study, found a mean score of 15.7 ± 2.2 for TPNs, similar to our result. Holman et al.^[30] assessed the efficacy and safety of pramipexole in patients with FMS. There were primary outcomes of improvement in VAS and secondary outcomes of the FIQ, pain improvement scale, and TPN scores. A total of 42% of patients receiving pramipexole and 14% of patients receiving placebo gained >50% decrease in pain. Total FIQ scores were favoring pramipexole over placebo. In the subgroup analysis, pramipexole treatment increased the scores on evaluation of pain, function, fatigue, and global status. In the present study, while DA and niacin showed a strong, positive and significant correlation with each other, both of them showed a moderate negative correlation with TPNs. There were also weak, negative and non-significant correlations of FIQ scores with both of niacin and DA. The non-significant relationships of both niacin and DA levels with FIQ, VAS, and BDI may be due to the subjective nature of these tools.

Our study has some limitations. Although we determined the sample size at an optimum level before the study, our results need to be confirmed

with larger-scale, prospective cohort studies to generalize these results and to demonstrate the effects of replacement of deficient vitamin of niacin. The lack of comparison of clinical findings and DA levels in groups formed with low and normal niacin levels according to the cut-off levels determined was another limitation. The conditions causing widespread chronic pain such as hypothyroidism and vitamin D deficiency and Diarrhea causing niacin deficiency could not be ruled out, as well. The TPN measurements were could be performed with an algometer, instead of manual finger pressure method. The DA levels could only be measured in serum and were unable to be measured in CSF^[31] or urine^[32] samples.

In conclusion, our study results suggest that serum niacin and DA levels decrease in FMS patients in relation to the TPNs. Based on these findings, the levels of these two markers can be considered additional tools in the diagnosis of FMS.

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Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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