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ORIGINAL ARTICLE

Is there any association between low level of serum nesfatin-1 and fibromyalgia syndrome?

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ABSTRACT

Objectives: This study aims to investigate the relationship between serum level of nesfatin-1 and fibromyalgia syndrome (FMS) clinical parameters such as pain severity, disease activity, fatigue, emotional state, and sleep quality.

Patients and methods: Forty-six female patients with FMS (median age: 40 years; range, 18 to 53 years) and 46 healthy female controls (median age: 36 years; range, 19 to 52 years) were included in the study. Severity of pain, disease activity, fatigue, sleep quality, and emotional status were evaluated by Visual Analog Scale, Fibromyalgia Impact Questionnaire, Multidimensional Assessment of Fatigue (MAF), Pittsburgh Sleep Quality Index (PSQI), Beck Depression Inventory (BDI), and Beck Anxiety Inventory (BAI), respectively. Serum nesfatin-1 concentrations (pg/mL) were measured by enzyme-linked immunosorbent assay method.

Results: There was no significant difference with respect to demographic characteristics between the FMS patients and healthy controls. When clinical parameters were compared, MAF, BDI, BAI, and PSQI scores were significantly higher in FMS patients than controls ($p<0.05$). Serum nesfatin-1 concentration was significantly lower in patients with FMS ($p<0.05$). When compared to the FMS patients without anxiety, serum nesfatin-1 concentration was significantly increased in FMS patients with anxiety ($p<0.05$). Serum nesfatin-1 concentration was positively correlated with BAI scores in patients with FMS ($p<0.05$).

Conclusion: Low nesfatin-1 serum levels may contribute to pathological changes in FMS. In addition, nesfatin-1 may also be involved in the mediation of anxiety-related responses in FMS.

Keywords: Anxiety, fibromyalgia syndrome, nesfatin-1.

Fibromyalgia syndrome (FMS) is a complex syndrome characterized by chronic widespread pain and multiple symptoms including fatigue, sleep disturbances, cognitive dysfunction, anxiety, and depressive episodes. The prevalence of FMS in the general population is estimated to be between 0.5% and 5%[1] and the probability of FMS occurring in females is nine times higher than in males.[2] FMS etiopathogenesis is still unknown; however, genetic predisposition, environmental triggers, and neuromodulation are thought to be involved in the onset and course of the disease.[3] Previous studies have generally suggested alterations in the hypothalamic pituitary-adrenal (HPA) axis and sympathetic nervous system in FMS.[4] Hormones that have a direct effect on neurological and immunological functions have been found to vary in FMS patients. Adrenocorticotropic hormone and cortisol levels are associated with stress, pain, and depression, and have been found to be altered in FMS patients, suggesting an imbalance of the feedback mechanisms of stress and inflammation.[5] On the other hand, FMS has been classified as a pain regulation disorder and often a central

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susceptibility syndrome in the literature, as there is no evidence of tissue inflammation despite soft tissue pain symptoms.[6]

Nesfatin-1 was discovered in 2006 by Oh-I et al.[7] It is commonly expressed in regions of the central nervous system. Besides, nesfatin-1 is also expressed in peripheral tissues such as adipose tissue, stomach, endocrine pancreas, and testes. It can cross the blood brain barrier bilaterally without saturation.[8]

In many studies, physiological functions and certain pathologies related to nesfatin-1 have been described. The first function identified with the discovery of nesfatin-1 is the reduction of food intake.[7] In addition to the anorexigenic effect, the application of central nesfatin in experimental models has been found to be involved in the modulation of water uptake, body temperature, sleep, and slowing of gastrointestinal system functions.[9-11] Nesfatin-1 signaling is thought to play a role in insulin signaling and glucose homeostasis,[9,10] regulation of energy metabolism,[7] lipid metabolism,[12] and some cardiovascular functions.[9] Nesfatin-1 has been reported to be associated with anxiety and various psychological disorders.[9-11,13-15] Furthermore, findings suggest that nesfatin-1 plays a role in the regulation of sleep. Disruption of the nesfatin-1 signal has been found to suppress paradoxical rapid eye movement sleep (REMS).[16] In addition, REMS deprivation reduced nesfatin-1 protein expression in the dorsolateral hypothalamus, which is closely related to sleep-wake regulation and associated with depression.[17] Nesfatin-1 is associated with certain noninflammatory and inflammatory diseases such as osteoarthritis (OA) and rheumatoid arthritis (RA). In a recent study, high serum nesfatin-1 concentration and high nesfatin-1 gene expression have been reported in OA,[18] and another study has shown that high nesfatin-1 levels are associated with the severity of OA.[19] Kvlividze et al.[20] found that a higher serum level of nesfatin-1 was characteristic of patients with a more severe clinical course of the RA.

The relationship between nesfatin and the pathological conditions such as sleep disorders, anxiety, pain, and depression has been investigated in the literature. These pathological conditions are also symptoms of FMS, while there are no studies in the literature on the relationship between nesfatin and these symptoms in patients with FMS. Therefore, in this study, we aimed to investigate the relationship between serum level of nesfatin-1 and FMS clinical parameters such as pain severity, disease activity, fatigue, emotional state, and sleep quality.

PATIENTS AND METHODS

This cross-sectional study was conducted at the Department of Physical Medicine and Rehabilitation, and Department of Biochemistry of Medical Faculty of Ondokuz Mayıs University, School of Medicine between January 2017 and November 2017. Forty-six female patients (median age 40 years; range, 18 to 53 years) diagnosed as FMS according to the 1990 American College of Rheumatology (ACR) criteria[21] and 46 age-, sex-, and body mass index (BMI)-matched healthy female controls (median age 36 years; range, 19 to 52 years) with no history of FMS were included in the study. The study protocol was approved by the Ondokuz Mayıs University, School of Medicine Ethics Committee (B.30.2.ODM.0.20.08/582-2016/373). A written informed consent was obtained from each participant. The study was conducted in accordance with the principles of the Declaration of Helsinki.

A priori power analysis using data from a previous study[18] assessing serum nesfatin-1 level in patients with OA indicated that 46 subjects in each group would have 0.80 power and $p<0.05$ based on serum nesfatin-1 levels.

Patients who applied for the first time and did not receive specific treatment for FMS were included. Patients with other rheumatic diseases, severe somatic or psychiatric disorders, metabolic syndrome, diabetes mellitus, endocrinological or cardiac disorders, those receiving medications for insomnia or psychiatric treatment, those aged under 18 years and male patients were excluded.

All participants were initially examined by the same physician with regard to the selection criteria. Socio-demographic data including age, weight, height, BMI (kg/m^2), and duration of disease (month) were obtained.

Venous blood samples were taken from the patients after fasting overnight. Samples were centrifuged at 3000 × g (NÜVE NF800,

SNo: 04.4136, Ankara, Turkey) for 10 min to obtain serum and stored at -40°C until the day of analysis. Serum nesfatin-1 levels were measured by using commercial enzyme-linked immunosorbent assay kit (Human NES1 ELISA Kit, Elabscience, Catolog No: E-EL-H2373, 96T, Houston, TX, USA), absorbance of each well was measured at 450 nm with a microtiter plate reader (BioTek Synergy™ 4, Serial No: 233513, BioTek Instruments Inc., Winooski, VT, USA), and the results were expressed as pg/mL.

Widespread pain severity was assessed by Visual Analog Scale (VAS) pain score (0-100 mm, with higher scores indicating more pain).[22]

Fibromyalgia Impact Questionnaire (FIQ) scale was used for FMS severity.[23] The FIQ is the most frequently used instrument for obtaining a standardized measure for patient-reported disease severity. The FIQ consists of 20 questions pertaining to morning stiffness, mood, pain, and the ability to perform daily life activity. Scores range from 0 to 100 with a higher value indicating a greater impact of the disorder. According to this scale, a moderate FMS patient scores 50, whereas a more severely affected FMS patient scores 70 or more.[24]

Multidimensional Assessment of Fatigue (MAF) scale was used for fatigue assessment. MAF scale contains five dimensions of fatigue: degree, severity, distress, impact on activities of daily living, and timing. Each 100-mm VAS was changed to a 10-point numerical rating scale. Scores ranged from 0 (no fatigue) to 50 (severe fatigue).[25]

Beck Depression Inventory (BDI) was used for depression assessment.[26] The BDI is a 21-item scale that gathers information on different symptoms of depression. Each item on the scale is scored from 0 to 3. It provides information about both the presence and severity of depression in terms of somatic, emotional, cognitive, and motivational dimensions. Higher scores indicate the presence of more depression. The scores of the patients were evaluated as follows: <10 points=normal, ≥10 points=depression (points of 10-16=mild depression, 17-29=moderate depression, and 30-63=severe depression).[27]

The Beck Anxiety Inventory (BAI) is a self-reported questionnaire that assesses anxiety symptoms during the week prior to the interview.[28] Higher score shows increased anxiety of the subjects. The scores of the patients were evaluated as follows: <10 points=normal, ≥10 points=anxiety (points of 10-18=mild anxiety, 19-29=moderate anxiety, and 30-63=severe anxiety).[29]

The Pittsburgh Sleep Quality Index (PSQI) was used for the subjective evaluation of sleep quality. The PSQI is a questionnaire consisting of 19 items coded on a four-point scale (0-3) in seven subcategories, including sleep duration, sleep disturbances, sleep latency, daytime dysfunction, sleep efficiency, sleep quality, and medication use. The sum of all sub-scores represents the total sleep quality score, ranging between 0-21. Higher scores represent lower sleep quality. Participants are asked to vote on their sleep in the last month.[30]

Statistical analysis

Statistical analyses were performed with the PASW version 18.0 for Windows (SPSS Inc., Chicago, IL, USA). Kolmogorov-Smirnov test was used to analyze the normal distribution assumption of quantitative results. According to the test, all data were not normally distributed. Descriptive data were presented as (median) minimum-maximum. Data were compared by Mann-Whitney U test for non-normal data distribution. The relationship between variables was evaluated by Spearman rank correlation. The chi-square test was used to evaluate group characteristics such as anxiety and depression and data were presented as frequency (n, %). A p value less than 0.05 was considered as statistically significant.

RESULTS

Demographic characteristics of patients with FMS and healthy controls are shown in Table 1. No significant differences were found regarding age (year), height (cm), weight (kg), or BMI (kg/m^2) between the patients and controls ($p>0.05$). A statistically significant difference was found between the groups in terms of the presence of anxiety and depression ($p<0.05$). While 74% of FMS patients were anxious and depressed, only 26% were anxious and 13% were depressed in the control group (Table 1).

Table 1. Demographic characteristics of patients with FMS and healthy controls

	Patients with FMS (n=46)				Healthy controls (n=46)				
Characteristics	n	%	Median	Min-Max	n	%	Median	Min-Max	*p*
Age (year)			40	18-53			36	19-52	>0.05
Height (cm)			161	150-172			160	150-169	>0.05
Weight (kg)			66	40-100			62	50-100	>0.05
Body mass index (kg/m^2)			25	15-37			23	19-37	>0.05
Presence of anxiety									<0.001
Yes (BAI score ≥10)	34	74			12	26			
No (BAI score ≤9)	12	26			34	74			
Presence of depression									<0.001
Yes (BDI score ≥10)	34	74			6	13			
No (BDI score ≤9)	12	26			40	87			

FMS: Fibromyalgia syndrome; Min: Minimum; Max: Maximum; BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory; P value is significant when <0.05.

Comparison of serum nesfatin-1 levels and clinical parameters of patients with FMS and healthy controls is shown in Table 2. Serum nesfatin-1 concentration was lower in FMS patients than healthy controls ($p<0.05$). MAF scale, PSQI total, BAI, and BDI scores were significantly higher in FMS patients than healthy controls ($p<0.001$) (Table 2).

Correlations between serum nesfatin-1 levels and clinical parameter scores in patients with FMS and healthy controls are shown in Table 3. There was a weak positive correlation between serum nesfatin-1 levels and BAI score in FMS patients ($p<0.05$, r: 0.326) (Table 3).

Comparison of nesfatin-1 levels of participants with and without anxiety is shown in Table 4. In FMS patients with anxiety, nesfatin-1 level was significantly higher than those without anxiety ($p<0.05$) (Table 4).

DISCUSSION

To the best of our knowledge, no studies have investigated the relationship between nesfatin-1 and FMS to date. However, the relationship between nesfatin-1 and common or comorbid symptoms of FMS such as pain, sleep disturbance, anxiety, and depression has been published in the

Table 2. Comparison of serum nesfatin-1 levels and clinical parameters of patients with FMS and healthy controls

	Patients with FMS (n=46)		Healthy controls (n=46)		
Parameters	Median	Min-Max	Median	Min-Max	*p*
Serum nesfatin-1 level (pg/mL)	17	11-762	14	9-614	0.04
MAF scale (0-50)	36	18-50	16	1-36	<0.001
PSQI total (0-21)	11	1-23	4	0-13	<0.001
BAI score (0-63)	17	0-39	5	0-26	<0.001
BDI score (0-63)	18	0-59	2	0-21	<0.001
Pain VAS (0-100) (mm)	70	30-90	-	-	-
FIQ score (0-100)	62	31-87	-	-	-

FMS: Fibromyalgia syndrome; MAF: Multidimensional Assessment of Fatigue; PSQI: Pittsburg Sleep Quality Index; BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory; VAS: Visual Analog Scale; FIQ: Fibromyalgia Impact Questionnaire; P value is significant when <0.05.

Table 3. Correlations between serum nesfatin-1 levels and demographics and clinical variables in patients with FMS and healthy controls

Clinical parameters	Patients with FMS	Healthy controls
Age		
r	0.168	0.136
p	0.26	0.37
Body mass index		
r	0.075	0.056
p	0.62	0.71
Pain Visual Analog Scale score		
r	0.095	-
p	0.53	-
Fibromyalgia Impact Questionnaire score		
r	0.184	-
p	0.22	-
PSQI total score		
r	0.271	-0.068
p	0.07	0.65
Multidimensional Assessment of Fatigue scale score	0.121	0.067
r	0.42	0.66
p		
Beck Anxiety Inventory score		
r	0.326	0.030
p	0.02*	0.84
Beck Depression Inventory score	0.225	0.087
r	0.13	0.57
p		

FMS: Fibromyalgia syndrome; PSQI: Pittsburg Sleep Quality Index; r: Spearman correlation coefficient. * Significant p<0.05.

literature, each separately.[13,31-34] In this study, serum nesfatin-1 levels of females with FMS and healthy control subjects compatible in terms of age, sex, and BMI were compared. The relationships between serum nesfatin-1 levels and demographic features and clinical parameters such as pain severity, disease activity, fatigue, emotional status, and sleep quality were evaluated in patients with FMS.

In the present study, we have found the serum nesfatin-1 level to be lower in patients with FMS than healthy controls. Additionally, FMS patients with anxiety had a higher nesfatin-1 level than FMS patients without anxiety. On the other hand, there was no relationship between serum nesfatin-1 level and demographics, and other clinical parameters in the FMS and control groups.

Chronic widespread pain is the main symptom of FMS and results in decreased quality of life as well as physical and psychosocial disorders.[35] The current literature provides strong evidence that changes in central nervous system mechanisms (alterations in the HPA axis and stress response) associated with pathogenesis of pain and other non-pain symptoms such as fatigue, sleep, and mood problems are extremely common in FMS.[36] It has been determined that nesfatin-1 is distributed in stress-related brain regions, such as the hypothalamic paraventricular nucleus (PVN), supraoptic nucleus, nucleus of the solitary tract, raphe pallidus nucleus, and locus coeruleus. Also, nesfatin-1 is colocalized with corticotropin-releasing factor (CRF) that is the initiator of stress response in PVN. CRF shows its biological actions by interacting with CRF receptors (CRFR).[7,37] It has been well established that the brain CRF/CRFR signaling system modulates pain responses.[35] Nesfatin-1 has also been reported to participate in the activation of the HPA axis.[38] These data indicate that in addition to its anorexigenic properties and the other metabolic and emotional effects,[33] nesfatin-1 may be effective in the pathogenesis of FMS pain. There are no studies investigating the relationship between pain and nesfatin-1 in FMS. However, in a study conducted with ghrelin, an orexigenic peptide which stimulates energy metabolism, low levels of ghrelin was found to

Table 4. Comparison of nesfatin-1 level of participants with and without anxiety

	Patients with FMS (n=46)					Healthy controls (n=46)				
	With anxiety (n=34)		Without anxiety (n=12)			With anxiety (n=12)		Without anxiety (n=34)		
	Median	Min-Max	Median	Min-Max	*p*	Median	Min-Max	Median	Min-Max	*p*
Serum nesfatin-1 level (pg/mL)	18	10-464	15	12-109	0.03	15	9-271	14	9-465	0.95

FMS: Fibromyalgia syndrome; Min: Minimum; Max: Maximum; P value is significant when <0.05.

be associated with FMS and negatively correlated with pain of FMS. On the other hand, in the same study, leptin, which is an anorexigenic peptide, was found to be increased, while no correlation was found with pain in FMS patients.[39] Similar to nesfatin-1 synthesized in the hypothalamus, these peptides also regulate appetite; however, they are synthesized by peripheral tissues and show their effects on the hypothalamus. In our study, there was no correlation between severity of pain and nesfatin-1 level, although nesfatin-1 levels were low in FMS patients.

Fatigue is a well-known feature of FMS and appears commonly.[21] Previous studies have reported that 78 to 100% of FMS patients are fatigued, and this is greater in severity than the other arthritic conditions. Fatigue, as described clinically, is a subjective experience and may have both physical and cognitive components.[21,40] In this study, we have found that patients with FMS had higher fatigue scores than the control group, while there was no significant relationship between serum nesfatin-1 levels and the severity of fatigue.

Psychological factors are likely to play a role in the development of FMS symptoms and the predicted rate of comorbidity may be as high as 30 to 60%. Depression and anxiety are the most common comorbid psychiatric disorders in FMS.[5] Nesfatin-1 activates CRF neurons in the PVN that stimulate the HPA axis by stimulating stress-sensitive serotoninergic and noradrenergic neurons in the raphe nucleus and locus coeruleus. Dysfunctions of these regions are closely correlated with pathogenesis of depression and anxiety disorders.[32] Based on the disruption of the HPA axis, which plays an important role in the pathophysiology of FMS,[41] and findings that nesfatin-1 is distributed in stress-related brain regions such as the hypothalamus,[37] we thought nesfatine-1 may a play role in the pathophysiology of FMS and related symptoms such as depression and anxiety. Some studies suggest that nesfatin-1 induces anxiety or fear and probably depressive reactions, via activation of melanocortin pathways causing inhibition of gamma-aminobutyric acidergic neurons or hyperpolarization of neuropeptide Y neurons.[42,43] Nesfatin-1 might be related with the modulation of anxiety and depression. Limited data exist in the literature about the level of nesfatin-1 in patients with anxiety or depression,[15,34,44,45] and results from these studies are conflicting because of the marked heterogeneity of the study populations. On the other hand, this was not studied in FMS patients with anxiety and depression.

Our results showed that anxiety and depression scores were higher in FMS patients than in controls. When compared to the FMS patients without anxiety, serum nesfatin-1 concentration was significantly increased in FMS patients with anxiety. Also, we observed that serum nesfatin-1 levels were correlated with increased BAI score, positively in patients with FMS. Higher nesfatin-1 levels may be associated with anxiety independently from FMS. However, these anxious patients in our study had a mild anxiety score and correlation between anxious and unanxious FMS patients was weak ($p=0.027$). Further studies are required to clarify the causality and the mechanisms involved.

Patients with FMS showed a high frequency of sleep disturbances, an increased incidence of alpha electroencephalographic nonREMS, and clear abnormalities in sleep cycle organization.[4] Palagini et al.[46] have suggested that disturbed sleep is a key problem connecting pain and cognitive disturbances as a result of the activated stress system in FMS. Sleep is closely related to emotion states, and patients with sleep disorder often show psychological diseases that are often characterized by appetite and eating disorder. Current studies suggest that nesfatin-1 is associated with regulation of sleep and vigilance.[32] In a study, it was found that disturbance of nesfatin-1 signaling depressed the REMS.[16] It was also shown that deficiency of REMS decreases nesfatin-1 messenger ribonucleic acid and protein expression in the dorsolateral hypothalamus which is closely related to sleep-vigilance regulation, feeding, and depression.[17] In this study, we evaluated sleep quality and found significant sleep disturbance in FMS patients compared to healthy controls. Although serum nesfatin-1 levels were low in FMS patients, we could not find any relationship between nesfatin-1 and sleep disturbance. More clinical trials are needed to clarify this issue.

Although it is not often discussed, one of the remarkable comorbidities of FMS is a tendency to be overweight. Indeed, high rates of overweight patients with FMS (70-76%) have been reported

in the literature.[47] The power of this study is the attention given to matching of the BMIs of patients and controls. The median (min-max) of the patients and controls' BMI was 25 (range, 15-37) and 23 (range, 19-37), respectively. Due to nesfatin-1 being an anorexigenic peptide, results may be affected by body weight.[8] Although there was no difference in BMIs between FMS and control groups, we found significantly lower nesfatin-1 levels in FMS group. The low levels of nesfatin-1 in FMS patients suggest that nesfatin-1 may play a role in the pathophysiology of FMS independently from BMI.

This study has some limitations. Firstly, due to the cross-sectional design, we were unable to establish a causal relationship between FMS symptoms and nesfatin-1 level. Thus, further prospective investigations may provide supportive data to directly evaluate the relationships between pain, sleep, and overweight/obesity with an emphasis on metabolic processes by evaluating different hormones. Secondly, we could also have used the 2010/2016 ACR criteria for FMS diagnosis; however, the 1990 criteria were used for routine diagnosis in our clinic at the time of the study. Additionally, the study was conducted with a relatively small number of FMS patients who were all females. Therefore, the results cannot be generalized to all FMS patients. Future studies should include larger populations and both sexes.

In conclusion, according to our knowledge, this is the first study investigating the relationship between FMS and nesfatin-1 level and we believe that it will contribute to the clarification of the pathophysiology of FMS. We found that nesfatin-1 levels were significantly lower in FMS patients, but higher in FMS patients with anxiety symptoms than those without anxiety. According to the results of our study, we think that low serum nesfatin-1 level may have a potential role in the etiopathogenesis of FMS. However, our inability to find any correlation between nesfatin-1 and clinical scores except anxiety demonstrated that nesfatin-1 cannot be used as a parameter for the evaluation of disease activity and other clinical parameters in FMS. Therefore, larger-scale studies should be conducted to further investigate the correlation between FMS and level of nesfatin-1.

Declaration of conflicting interests

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