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Evaluation of the effect of obesity on fibromyalgia in premenopausal female patients

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Abstract

Obesity is a chronic disease whose prevalence is increasing all over the world. The relationship between obesity and some rheumatic diseases such as Fibromyalgia Syndrome (FMS) has recently attracted attention. In this study, we investigated the effect of obesity on FMS in premenopausal female patients. Anamnesis, physical examination and laboratory data obtained from 103 female patients who were divided into two groups as obese and non-obese according to body mass index (BMI) were statistically analyzed in terms of FMS. 25.2% of the women participating in the study were diagnosed with FMS, and the mean age of the cases was 33.42 (± 10.41), the mean weight was 79.65 (± 19.91), and the mean BMI was 30.52 (± 7.75). The mean age of the obese was higher 38.48 (± 8.95) and the incidence of obesity was significantly higher with age ($p < 0.001$). The frequency of FMS ($p = 0.001$), Fibromyalgia Impact Questionnaire results ($p = 0.001$) and tender point numbers in the Widespread Pain Index Scale ($p < 0.001$) were significantly higher in the obese group. There was no statistically significant difference between the obese and non-obese groups in terms of marital status, occupation, smoking history and education levels. Obesity prevalence is increasing all over the world and the results of the present study reveal FMS complications are getting worse by obesity. Therefore, prevention and medical treatment of obesity, can positively affect many parameters in the body and reduce the incidence of FMS.

Keywords: Fibromyalgia syndrome, obesity, premenopause, woman

Introduction

Obesity is a chronic disease with many complications and its prevalence is increasing worldwide [1]. Although parameters such as clinical, etiological, body mass index (BMI) or the number of fat cell/ volume increase can be used in the classification of obesity, BMI is the most widely and practically used parameter. This index is found by dividing the body weight by the square of the height (kg/m^2) [1].

Fibromyalgia Syndrome (FMS) is one of the chronic pain syndromes defined by pain in certain parts of the body and the severity of this pain [2]. FMS is most common in the age range of 40-60 years and is 9-10 times more common in women. Its prevalence is reported to be 2-8% [2,3]. Obesity can be seen together with certain rheumatic diseases, and some publications have recently come to the fore regarding the coexistence of FMS and obesity [2,3]. In this study, we investigated the effect of obesity on FMS in premenopausal female patients.

Materials and Methods

Ethical Approval

This study was carried out in Bolu Abant İzzet Baysal University, Faculty of Medicine, Training and Research Hospital, Department of Internal Medicine. Our study was approved by the Ethics Committee of Bolu Abant Izzet Baysal University Faculty of Medicine (no:199). All patients were given detailed information about the study and written informed consent was obtained from the patients.

Data Collection

This study was carried out in Bolu Abant İzzet Baysal University,

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Faculty of Medicine, Training and Research Hospital, Department of Internal Medicine. Patients who were followed up at the Internal Medicine outpatient clinic for at least 3 months between 01.09.2019 - 01.12.2019 and diagnosed with obesity according to clinical and biochemical parameters were included in the study. 52 people diagnosed with obesity constituted the patient group, and 51 healthy individuals without any disease constituted the control group.

The questionnaire was applied to the participants by face-to-face interview method. The laboratory values of the participants were obtained retrospectively from the hospital data processing system. BMIs were determined using the height and body weights of the participants. In line with the recommendations of the World Health Organization, those with a BMI below 30 were considered non-obese, and individuals 30 and above were considered obese, and all cases were divided into two groups in this way.

The patients' age, height, weight, marital status, occupational status, education level, smoking history, presence of concomitant chronic disease and regular drug use were questioned. Pregnant, lactating, under 18 years of age, postmenopausal female patients, male patients, patients with chronic diseases such as infectious, inflammatory, haematological, neoplastic, rheumatic, psychiatric disease, history of bariatric operation, organ transplantation, current obesity treatment, ovulation induction, hormone replacement therapy, were excluded from the study.

American College of Rheumatology (ACR) 2015 classification criteria and Fibromyalgia Impact Questionnaire (FIQ)

The questionnaire used in the study was prepared by the researcher based on the literature. The first part consists of socio-demographic characteristics and patient's laboratory parameters, the second part consists of the Widespread Pain Index scale (WPI), and the third part consists of the Fibromyalgia Impact Questionnaire (FIQ). The diagnosis of FMS was made according to the ACR criteria based on the questioning of regional pain points and somatic symptoms [4].

WPI was calculated as follows: Patients were questioned for 3 psychological symptoms (fatigue, not being able to wake up rested in the morning, cognitive symptoms) for one week. Those with no problems were scored as 0, those with mild or transient problems were scored as 1, those with moderate and significant problems were scored 2, and those with severe, widespread, persistent, and life-complicating problems were scored as 3 points. Afterwards, patients were questioned for 39 somatic symptoms for 3 months. Patients with 0 somatic symptoms had no symptoms (0 points), patients with 1-13 somatic symptoms were scored as few symptoms (1 point), patients with 14-26 somatic symptoms were scored as moderate symptoms (2 points), patients with 27-39 somatic symptoms were scored as multiple symptoms (3 points). The symptom severity scale (SS) score was calculated by summing the scores obtained from psychological and somatic symptoms. FMS was diagnosed in patients with symptoms for at least 3 months with WPI ≥ 7 and SS scale score ≥ 5 or WPI 3-6 and SS scale score ≥ 9.

All obese and healthy control group patients included in the study were evaluated for the presence of FMS and FIQ were applied. FIQ is a questionnaire created by Sarmer [5] and validated in 8 languages, including Turkish, and is freely available. High scores in the FIQ scoring indicate that the disease affects the person more. Scoring is done according to the following principles:

a) Items 1a-1k are related to the bodily disorder. The raw results between 0 and 3 in each item are summed and divided by 11. Since other items (between 4 and 10) are evaluated over 10 units, the result obtained is multiplied by 3.33 and normalized.

b) The low number in question number 2 means that the disorder is high. Therefore, the days when he feels bad should be taken into account. Therefore, the value marked by the patient is subtracted from 7. Since other items (between 4 and 10) are evaluated over 10 units, the result obtained is multiplied by 1.43 and normalized.

c) The high number in question 3 indicates that the disorder is high. Since the other items (between 4-10) are evaluated over 10 units, the result obtained is multiplied by 1.43 and normalized.

d) The values marked in questions 4 and 10 are noted. The total score can be obtained by adding the numbers of questions 1, 2, 5, 6, 7, 8, 9 and 10. The total score can be between 0-80. A score of 80 indicates high influence.

Statistical evaluation

Data were analyzed using the SPSS 21 (SPSS 21.0 for Windows, IBM, Chicago, USA) program. Descriptive data were noted as frequency, percentage, mean, standard deviation, median, minimum, and maximum values. Conformity to normal distribution was investigated by the Kolmogorov-Smirnov test. The Chi-square test was used to compare categorical data. For continuous data, the Pearson and Student t-test were used when the assumptions of conformity to the normal distribution were met, and the Spearman and Mann Whitney-U test was used when they were not met. The $p < 0.05$ level was considered statistically significant.

Results

General findings

In the study, the data of a group of 103 premenopausal female patients were evaluated. The participants included in the study were divided into two groups as obese and non-obese according to their BMI values. The obese patient group consisted of 52 (50.5%) and the non-obese patient group consisted of 51 (49.5%). The mean age of the women participating in the study was 33.42 (± 10.41), the mean weight was 79.65 (± 19.91), and the mean BMI was 30.52 (± 7.75). The youngest participant age was 18, while the oldest participant age was 56. While 26.2% (n=27) of the women participating in the study had a known disease, 73.8% (n=76) had no known disease.

There was a statistically significant difference between the ages of the obese and non-obese groups ($p < 0.001$), the mean age of the obese group was greater (38.48 ± 8.95), and obesity increased with age ($p < 0.001$). There was a statistically significant difference between the weight of the obese and non-obese groups ($p <$

0.001). There was no statistically significant difference between the obese and non-obese groups in terms of height, marital status, occupational distribution, smoking history and education level ($p > 0.05$).

Distribution of the cases according to the presence of type-2 diabetes mellitus, hypertension, hypothyroidism, drug use and vitamin-D replacement therapy

Of the women participating in the study, 13.6% (n=14) had a diagnosis of type 2 diabetes mellitus, 9.7% (n=7) had a diagnosis of hypertension, and 5.8% (n=6) had a diagnosis of hypothyroidism. In addition, 26.2% (n=27) of the women participating in the study were using regular medication and 1.9% (n=2) were taking vitamin-D replacement therapy.

Distribution of cases according to FIQ questions and laboratory data

The FIQ questionnaire was applied to all the participants participating in the study. Participants were asked to give the following scores: 0-7 points for the question of how they felt in the last week, 0-6 points for the question of being unable to work, 0-10 points for the question of pain that interferes with working, 0-10 points for the pain level question, 0-10 points for the question of fatigue level, 0-10 points for the question of how they feel in the morning, 0-10 points for the morning stiffness question, 0-10 points for the nervous status question, 0-9 points for the depressive status question. The analysis of the responses received is given in Table 1. The analysis of the laboratory data of the cases is also given in Table 2.

Table 1. Analysis of the answers given by the cases to the FIQ questions

	Smallest	Largest	Average
Feeling well	0.00	7.00	4.55
Unable to work	0.00	6.00	1.24
Pain that interferes with working	0.00	10.00	3.12
Pain level	0.00	10.00	3.99
Fatigue level	0.00	10.00	5.42
How they feel in the morning	0.00	10.00	3.70
Morning stiffness	0.00	10.00	1.23
Nervous	0.00	10.00	4.89
Depressive	0.00	9.00	4.19

Table 2. Analysis of the laboratory data of the cases

	Smallest	Largest	Average
Fasting blood glucose	70.00	268.00	96.41 ± 26.58
HbA1c	5.00	10.40	5.83 ± 0.94
HOMA-IR*	0.53	29.00	3.22 ± 4.29
HDL-Cholesterol	28.00	197.00	54.49 ± 19.24
LDL-Cholesterol	35.00	228.00	109.39 ± 36.06
TG	33.00	467.00	121.51 ± 79.32
Total Cholesterol	119.00	330.00	186.42 ± 42.45
TSH	0.20	8.70	1.80 ± 1.30
Vitamin D	3.60	38.20	12.52 ± 6.62
Vitamin B12	137.00	546.00	308.62 ± 92.40
Phosphorus	2.40	4.60	3.63 ± 0.46
ALP	15.00	109.00	64.63 ± 19.08
Ferritin	1.65	59.00	18.87 ± 13.71
HGB	8.82	15.60	12.82 ± 1.31
HCT	28.70	46.40	39.17 ± 3.64
CRP	0.10	25.00	4.65 ± 5.46
Sedimentation	2.00	56.00	20.46 ± 11.44

*HOMA-IR: Homeostatic Model Assessment-Insulin Resistance

Analysis of cases according to the diagnosis of FMS, SS and FIQ scores and WPI

25.2% (n=26) of the women participating in the study were diagnosed with FMS. The mean SS score was 5.21 (± 2.75), the smallest SS score being 0.00 and the largest SS score being 11.00. The mean FIQ was 32.34 (± 16.51), the smallest score being 0.00 and the largest being 71.39.

The frequency of FMS was increased in obese women compared to the control group ($p < 0.001$). There was a statistically significant difference between the FIQ results of obese and non-obese women ($p = 0.001$), and the mean score of the obese group from the FIQ results was higher (37.19 ± 15.53). There was a statistically significant difference between the number of tender points in the WPI of obese and non-obese women ($p < 0.001$).

Analysis of laboratory data of obese and non-obese cases

There was a statistically significant difference between the two groups in terms of fasting blood glucose levels ($p < 0.001$). In addition, HbA1c ($p < 0.001$), HOMA-IR ($p < 0.001$), TSH ($p < 0.001$), PLT ($p < 0.001$), CRP ($p = 0.002$), sedimentation ($p < 0.001$), PTH ($p = 0.034$)), AST ($p < 0.001$), ALT ($p < 0.001$), Vitamin B12 ($p = 0.008$) and ALP ($p < 0.001$) levels differed statistically between the groups. The analysis of the laboratory data of the obese and non-obese groups is given in Table 3.

Table 3. Analysis of obese and non-obese cases according to laboratory data

	BMI		
	<30	≥30	P-value
Fasting blood glucose	87.68 ± 8.29	104 ± 34.56	< 0.001
HbA1c	5.4 ± 0.31	6.2 ± 1.17	< 0.001
HOMA-IR	1.68 ± 0.78	4.74 ± 5.6	< 0.001
Vitamin D	12.04 ± 5.3	13.00 ± 7.6	0.982
TSH	1.67 ± 0.94	1.93 ± 1.57	< 0.001
HGB	12.91 ± 1.44	12.73 ± 1.18	0.260
PLT	265.39 ± 40.04	307.17 ± 82.75	< 0.001
CRP	3.00 ± 4.06	6.2 ± 6.17	0.002
Sedimentation	15.39 ± 9.41	25.44 ± 11.14	< 0.001
PTH*	65.50 ± 18.27	81.37 ± 40.66	0.034
AST	16.11 ± 3.56	19.96 ± 6.27	< 0.001
ALT	14.19 ± 6.52	20.61 ± 10.06	< 0.001
ALP	57.29 ± 18.52	71.82 ± 16.89	< 0.001
LDL-Cholesterol	105.80 ± 40.29	112.90 ± 31.37	0.248
HDL-Cholesterol	55.86 ± 14.30	53.15 ± 23.16	0.144
Total Cholesterol	180.19 ± 42.63	192.53 ± 41.77	0.066
Vitamin B12	332.88 ± 86.17	284.82 ± 92.89	0.008
HCT	27.41 ± 16.22	37.19 ± 15.53	0.676

*PTH: Parathormone

Analysis of cases according to age, FIQ total score, BMI, and Vitamin-D values

There was a statistically positive and weak correlation between age and FIQ total score ($p = 0.001$, $r = 0.310$). There was a statistically positive and moderate correlation between age and BMI ($p < 0.001$, $r = 0.556$). There was a weak statistically positive correlation between age and Vitamin D ($p = 0.038$, $r = 0.205$). There was a statistically significant difference between obesity and the FIQ total score ($p = 0.002$), and the mean of the total score from the FIQ was higher for those who were obese (37.19).

Analysis of cases in terms of FIQ total score, HbA1c, ALP, Vitamin D, sedimentation, and BMI

There was a statistically significant and positive moderate correlation between HbA1c level and FIQ total score ($p < 0.001$, $r = 0.402$). A statistically significant and positive weak correlation was found between ALP level and FIQ total score ($p = 0.030$, $r = 0.289$). There was a statistically significant and positive moderate correlation between vitamin D level and FIQ total score ($p = 0.001$, $r = 0.333$). A statistically significant and positive weak correlation was found between the sedimentation level and the FIQ total score

($p < 0.001$, $r = 0.277$). There was a statistically significant and positive weak correlation between BMI and FIQ total score ($p < 0.001$, $r = 0.300$).

Distribution of those with and without FMS according to BMI and FIQ total scores

There was a statistically significant difference between the BMIs of those who were diagnosed with FMS and those who did not ($p = 0.001$). There was a statistically significant difference between the total scores of those who were diagnosed with FMS and those who did not ($p = 0.001$), and those who were diagnosed with FMS had a higher mean total score from the FIQ (42.03). The presence of the known chronic disease did not affect the diagnosis of FMS ($p = 0.541$). There was no statistically significant difference between the presence of hypothyroidism and the presence of FMS ($p = 0.638$). There was no statistically significant difference between the diagnosis of FMS and ALP ($p = 0.190$), Vitamin B12 ($p = 0.981$), HGB ($p = 0.150$), HbA1c ($p = 0.328$), age ($p = 0.378$).

Discussion

Obesity is characterized by excessive fat deposition in adipose tissue. It is a complex disease with increasing frequency. It is known that musculoskeletal complaints and physical dysfunction are observed more frequently in obese patients compared to individuals with normal weight [4,5]. Obesity has been associated with some rheumatic diseases, and the most prominent relationship has been defined for knee osteoarthritis [6]. There are data that obesity, which is associated with musculoskeletal diseases such as carpal tunnel syndrome [7] and chronic low back pain [8], may be associated with FMS [9]. Better knowledge of the pathogenesis of FMS, the etiology of which is unknown, and which significantly affects the quality of life of patients, may enable more effective intervention in the disease [10]. Therefore, in our study, the relationship between obesity and FMS was tried to be clarified.

In our study, the frequency of FMS in obese patients was significantly higher than in the control group. Similarly, obese patients had higher FIQ scores than non-obese patients ($p = 0.001$). In addition, in our study, it was observed that the WPI total score increased as the increase in BMI continued. Considering that the prevalence of FMS is reported to be 3.6-5.6% in the general female population in our country [11,12]. Our findings show that there is a relationship between obesity and FMS. There are studies in the literature that support our findings. In these studies, the frequency of obesity was mostly evaluated in FMS patients [14-18], and the frequency of FMS in obese patients [9,13] was investigated in a few studies.

The mean age of the women in our study was 33.42 ± 10.41 years. The reason for the low mean age may be that the study was conducted on premenopausal women. 26.2% of the participants had a known disease and 13.6% of them had type 2 diabetes mellitus, 9.7% had hypertension and 5.7% had hypothyroidism. All those with the known diseases were obese. While 25.2% of the women participating in the study were diagnosed with FMS, 74.8% did not. In addition, it was observed that the BMI increased as the average age of the women participating in the study increased. There are studies have shown that BMI increases with increasing age [19,20]. For example, in the study conducted by Ulas et al., it is stated that BMI increases with age [21]. In the study conducted by Gunes et al, no relationship was found between age and obesity [22].

Results supporting the relationship between obesity and FMS have been reported previously in the literature. In a study conducted by Arreghini et al. [9], 130 Italian obese patients were evaluated, and the frequency of FMS was stated as 27.7%. In a study by Mork et al., 15,990 women without FMS were followed for 11 years. FMS was developed in 380 patients during the study period. In this large-scale study, it was stated that BMI is a risk factor for FMS, and the risk of FMS increased by 60-70% in overweight or obese patients [23]. In a study conducted by Saber et al, 5.15% of 194 patients who underwent gastric bypass for weight loss had FMS, and the BMI scores of these FMS patients decreased from 49.4% to 29.7% after surgery. It has also been reported that there is a decrease in the dose of medical treatment [13]. Although there was a decrease in FMS symptoms with the regression of obesity, the frequency of FMS reported in this study was lower than in our study. Possible reasons for this may be that the diagnosis of FMS was obtained retrospectively in this study and the obese patients included in the study were selected from the patients who had gastric bypass surgery.

There were also studies evaluating the prevalence of obesity in FMS patients. In the study conducted by Gota et al., the prevalence of obesity was reported as 43.8% in 224 FMS patients [14]. Again, in this study, it was reported that obese FMS patients had higher depression scores and lower quality of life compared to normal-weight patients, and obese patients received more medical treatment for FMS. In the study conducted by Kocyigit et al., 124 FMS patients were divided into three groups according to BMI. In the study, it was reported that the severity of pain and disease activity were higher in obese FMS patients, BMI and FIQ scores were correlated, and the number of tender points tended to be higher in obese patients [24]. These findings support our results. In a study conducted by Bennett et al., 2,596 patients with FMS were evaluated and a BMI of >30 was found in 43% of the patients [15]. In a study by Neumann et al., 100 FMS patients were evaluated, and it was stated that 45% of the patients were obese [16]. Again, in this study, it was reported that BMI and quality of life were negatively correlated, and pain sensitivity was higher in obese FMS patients.

In a study conducted by Okifuji et al., it was stated that approximately 50% of 38 FMS patients were obese and 21% were overweight [17]. In addition, BMI in FMS patients was associated with sleep disorders in this study. In a study conducted by Yunus et al., 211 female patients with FMS were evaluated and it was reported that 32.2% of the patients were obese and their quality of life was negatively correlated with BMI [18]. Obesity and FMS have similar clinical features such as increased pain sensitivity, decreased sleep and quality of life [25]. In the light of these findings, it can be said that in parallel with the increase in the frequency of FMS in obese patients, the prevalence of obesity in FMS patients is also high and there may be a bidirectional relationship between obesity and FMS.

The first theory to explain the relationship between obesity and FMS is insufficient physical activity. FMS is an important cause of disability [26] and reduces physical functions and activity. Sleep disorders observed in FMS have also been associated with

obesity [27]. Obesity shortens the duration of sleep and reduces its quality [27]. In addition, obesity and FMS share similar psychological mechanisms. FMS and mood disorders such as depression are closely related. In addition, mood disorders are also affected by weight disorders. Both conditions are characterized by central monoaminergic system disorders [28]. Another proposed mechanism is related to thyroid dysfunction. The frequency of autoimmune thyroid disease in FMS patients has been reported to be approximately 30% [29]. In another study, thyroid autoimmunity was reported as 41% in women with postmenopausal FMS. Again, according to this study, thyroid dysfunction negatively affects the basal metabolic rates of patients, and as a result, weight gain occurs in patients with thyroid dysfunction [30].

Bennett et al. reported that IGF-1 levels decrease in the presence of obesity in FMS patients and that GH levels decrease after IGF-1 stimulation [31]. Disruption of GH and IGF-1 secretion has also been described for obesity [32]. Cuatrecasas et al. reported that low-dose subcutaneous GH reduced the symptoms and severity of FMS [33]. A positive correlation was observed between the patients' age, FIQ scores and BMI in our study. In the literature, it has been reported that advanced age is associated with quality of life and physical disability score in FMS patients [34]. In addition, there is a lot of evidence that BMI increases, and the frequency of obesity increases in advanced age [35]. In the light of these findings, it can be thought that obesity will increase the burden of disease in older adult FMS patients.

Tishler et al. reported that FMS is common in type 1 and type 2 diabetes mellitus patients in their study [36]. Again, in this study, it was stated that the prevalence of FMS in this disease group was associated with disease control. In addition, it has been stated that the HbA1c level is higher in both diabetes and FMS patients. In a cross-sectional study conducted by Lichtenstein et al., it was shown that the frequency of diabetes is higher in FMS patients [37]. A significant correlation between HbA1c and FIQ scores seen in our study is consistent with these findings.

It is known that many factors are effective in the pathogenesis of FMS. Among these factors, genetic, environmental and neurohormonal factors have been defined. There is also evidence that inflammation plays a role in the pathogenesis of FMS [38]. Cytokines, chemokines, lipid mediators, oxidative stress, and various plasma-derived factors have been implicated in the inflammatory state in FMS [38]. A significant correlation between sedimentation and FIQ scores in our study may indicate that inflammation may be effective in the pathogenesis of FMS. However, large-scale studies are needed to confirm this finding.

In our study, there was a positive correlation between FIQ and vitamin D levels. However, a negative correlation between FIQ and vitamin D levels was expected. In their study, Dogru et al. observed a significant improvement in FIQ scores after replacement in FMS patients with normal and low vitamin D levels [39]. Finding an inverse relationship in our study may be related to the application of the FIQ scale to both obese and control groups and the possible use of vitamin D replacement therapy in obese patients. In addition, no relationship was found between hypothyroidism and the presence of FMS in our study. However, there is evidence that hypothyroidism and FMS are related, and the frequency of hypothyroidism in patients with FMS and the frequency of FMS in patients with hypothyroidism is high [40]. Possible reasons for not showing such a relationship in our study may be the low number of patients. Therefore, future studies examining hypothyroidism and the FMS relationship is recommended.

Obesity also has effects on blood parameters. In our study, a positive correlation was found between ALT and AST values and BMI values in obese patients, and it was similar to Sonsuz's findings [41]. In the cases included in our study, ALP level does not affect whether or not to be diagnosed with FMS. In a study by Gurbuz et al., no significant difference was found in ALP values in patients with FMS [42]. In our study, there was no significant difference between groups in lipid profiles. This result is similar to the study of Kaya et al. [43].

In our study, no statistically significant difference was found between the obese and non-obese groups in terms of marital status, occupational distribution, smoking history and education level. The report published by Ozkahraman et al. [44] reported that low education, being married and not working actively are risk factors for obesity. Similarly, in a study conducted among healthcare professionals, BMI was found to be lower in smokers than in non-smokers [45]. Possible reasons for not showing these relationships in our study may be the low number of patients.

Our study had some limitations. First, the number of patients was small. Our study is a study that evaluates the frequency of FMS in a case-control design and is not a study in which the cause-effect relationship can be examined. Therefore, in the light of our findings, it can be said that there is a relationship between obesity and FMS, but it cannot be said that obesity causes FMS or that FMS causes obesity.

Conclusion

Our study indicates that the pathogenesis of obesity and FMS have similar commonalities. Considering obesity in the pathogenesis of FMS, in which many different factors are contributory, may have an important place in the treatment of FMS patients. Therefore, considering different treatment methods for obese FMS and non-obese FMS patients is essential in clinics.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
All authors declare no financial support.

Ethical approval
Our study was approved by the Ethics Committee of Bolu Abant İzzet Baysal University Faculty of Medicine (no:199).

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