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RESEARCH

Serum irisin levels and symptom severity in women with fibromyalgia

Fibromiyaljili kadınlarda serum irisin düzeyleri ve semptom şiddeti

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Abstract

Purpose: The aim of this study was to investigate the relationship between irisin levels and clinical symptoms in patients diagnosed with fibromyalgia (FM) and to determine whether irisin could be used as a biomarker in the diagnosis of FM.

Materials and Methods: This prospective case–control study included 40 female patients with FM and 40 age-matched healthy female controls recruited between June and August 2024. Sociodemographic and clinical characteristics were recorded, and disease severity, anxiety, and depression were evaluated using the Fibromyalgia Impact Questionnaire, Beck Anxiety Inventory, and Beck Depression Inventory. Morning venous blood samples were obtained to assess routine laboratory parameters and serum irisin levels. Clinical and biochemical variables were statistically compared between the groups.

Results: Irisin levels were significantly higher in the case group (median 60.07) compared to the control group (median 17.56). A positive correlation was observed between irisin levels and FIQ scores, but no significant correlation was found between BDI or BAI scores.

Conclusion: Serum irisin levels were significantly elevated in patients with FM, suggesting a potential role for irisin in the pathophysiology of the disease. Irisin may serve as a promising biomarker for disease activity and discrimination of FM. Larger, multicenter, and longitudinal studies are needed to clarify its clinical utility and underlying mechanisms.

Keywords:. Fibromyalgia, irisin, biomarker

Öz

Amaç: Çalışmada, fibromiyalji (FM) tanısı konmuş hastalarda irisin düzeyleri ile klinik semptomlar arasındaki ilişkiyi araştırmayı ve irisinin FM tanısında biyomarker olarak kullanılıp kullanılamayacağının belirlenmesi amaçlkanmıştır.

Gereç ve Yöntem: Bu prospektif vaka-kontrol çalışması, Haziran ve Ağustos 2024 tarihleri arasında FM tanısı alan 40 kadın hasta ve yaşları eşleştirilmiş 40 sağlıklı kadın kontrol grubunu içermektedir. Sosyodemografik ve klinik özellikler kaydedilmiş, hastalık şiddeti, anksiyete ve depresyon ise Fibromiyalji Etki Anketi, Beck Anksiyete Envanteri ve Beck Depresyon Envanteri kullanılarak değerlendirilmiştir. Rutin laboratuvar parametrelerini ve serum irisin düzeylerini değerlendirmek için sabah venöz kan örnekleri alınmıştır. Klinik ve biyokimyasal değişkenler gruplar arasında istatistiksel olarak karşılaştırılmıştır.

Bulgular: Irisin düzeyleri, kontrol grubuna (ortanca 17,56) kıyasla vaka grubunda (ortanca 60,07) anlamlı olarak daha yüksekti. Irisin düzeyleri ile FIQ puanları arasında pozitif bir korelasyon gözlemlenirken, BDI veya BAI puanları ile anlamlı bir korelasyon bulunmadı.

Sonuç: FM hastalarında serum irisin düzeyleri önemli ölçüde yükselmiştir, bu da irisinin hastalığın patofizyolojisinde potansiyel bir rol oynadığını düşündürmektedir. Irisin, hastalık aktivitesi ve FM'nin ayırt edilmesinde umut verici bir biyomarker görevi görebilir. Klinik yararı ve altta yatan mekanizmalarını açıklığa kavuşturmak için daha büyük, çok merkezli ve uzun süreli çalışmalar gereklidir.

Anahtar kelimeler: Fibromiyalji, irisin, biyomarker

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INTRODUCTION

Fibromyalgia (FM) is a complex disease characterized by chronic widespread musculoskeletal pain, stiffness, fatigue, sleep disturbances, cognitive deficits, and psychological problems. The prevalence of FM varies between 2% and 4% worldwide, and it is more common in women[1,2]. Although its etiology and pathophysiology have not been fully elucidated, hormonal, immunological, psychological, and biochemical factors are thought to be involved[3]. The complex pathophysiology of FM and its clinical findings, which include both physical and neuropsychiatric symptoms, further complicate the treatment approach[4].

In recent years, studies on the neuropsychiatric manifestations of FM (depression, anxiety, cognitive impairments) have revealed that the central nervous system and central pain modulation are affected in this syndrome. Central sensitization, hypothalamic-pituitary-adrenal (HPA) axis dysfunction, and neuroinflammation stand out as fundamental mechanisms underlying the neuropsychiatric and somatic symptoms of FM[5,6]. Cognitive impairments and depression, often described as "fibro-fog," are among the prominent symptoms of the disease in a large proportion of FM patients[7].

The search for biomarkers in FM is crucial for more objective diagnosis and monitoring of the disease[8]. Currently, the diagnosis of FM is largely based on clinical symptoms, and the development of biomarkers may be useful in confirming the diagnosis and monitoring disease activity[9]. In this context, it has been suggested that various biological factors, particularly adipokines and myokines, play a role in the pathophysiology of FM and could be considered potential biomarkers[10]. Irisin, an adipokine and myokine, offers new hope in the diagnosis and follow-up of FM, which is associated with musculoskeletal dysfunction, inflammation and metabolic disorders[11].

Irisin is a myokine that is a proteolytic product of the membrane protein fibronectin type III domain 5 in skeletal muscles. The release of irisin from muscle stimulates mitochondrial biogenesis, increasing the metabolic capacity of muscle cells. This leads to improvements in muscle performance and body composition[12]. Furthermore, irisin has been found to prevent muscle atrophy by regulating mitochondrial autophagy[13]. The secretion of irisin from muscle depends on several factors, the most important being exercise[14]. Irisin is also secreted by adipose tissue, thus belonging to both the myokine and adipokine families. Irisin is thought to act as an insulin-sensitizing hormone, regulate hepatic glucose and lipid metabolism, and protect against the development of insulin resistance and Type 2 diabetes[15,16]. It is known to have a positive effect on hyperglycemia in individuals with metabolic syndrome, facilitate glucose uptake by skeletal muscles, and protect individuals from metabolic diseases with regular exercise[17]. It is well known that obesity, metabolic syndrome, and diabetes mellitus are more prevalent among FM patients[18]. Insulin resistance is thought to be involved in the pathophysiology of FM by causing focal cerebral hypoperfusion[19]. Adipokines are also molecules involved in insulin resistance and glucose metabolism, and their roles in FM are being investigated[20].

There are limited studies investigating the relationship between irisin, an adipokine and myokine, and fibromyalgia (FM). Therefore, we aimed to evaluate serum irisin levels in patients with FM and examine their association with clinical symptom severity to determine the potential of irisin as a supportive biomarker for disease identification. We hypothesized that irisin levels would be altered in FM and correlate with disease burden. By comprehensively assessing irisin alongside clinical scales, biochemical parameters, and diagnostic performance, this study provides novel evidence that irisin may reflect underlying metabolic and inflammatory mechanisms and may contribute to a more objective, multiparametric assessment of FM.

MATERIALS AND METHODS

Sample

The study was conducted as a single-center study at Fethi Sekin City Hospital between June 1, 2024, and August 31, 2024, in the Internal Medicine and Physical Medicine and Rehabilitation outpatient clinics, and included 40 female patients and 40 healthy female volunteers. Inclusion criteria for patients were: age between 18 and 60, female gender, diagnosed with FM according to the ACR 2016 criteria [21], not previously diagnosed with FM, not receiving specific FM treatment, and not having a history of regular exercise in the last year. Exclusion criteria were; Patients with advanced cardiovascular, endocrine, metabolic, kidney, and liver disease; those

with a history of alcohol and substance abuse and dependence; those with a history of neurological disease; those with a history of inflammatory disease; and those with a history of malignancy.

Patients between the ages of 18 and 60 who were female, presenting to our hospital for yearly check-ups, and free of systemic or psychiatric symptoms were the requirements for inclusion in the control group. Similar to the FM group, individuals in the control group had also not participated in regular exercise during the previous year, ensuring comparable physical activity status between the groups. Those who had previously received psychiatric treatment, those with a history of alcohol or substance abuse within the last 6 months, and those with a Body Mass Index (BMI) > 30 were excluded from the study.

For the FM group, a total of 95 patients were initially assessed for eligibility. Of these, 8 were excluded due to incomplete data, 3 due to advanced cardiovascular disease, 15 due to endocrine or metabolic disorders, 9 due to renal or hepatic disease, 4 due to alcohol use, 12 due to a history of neurological disease, and 4 due to inflammatory disease. After applying the exclusion criteria, 40 patients met the eligibility requirements and were included in the final analysis.

Procedure

This study was approved by the Firat University Ethics Committee (date: 21.03.2024, no: 2024/05-33) and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

All clinical evaluations, physical examinations, and data collection procedures were performed by specialist physicians, while all psychometric assessments (BAI, BDI, and FIQ) were administered and evaluated by a psychiatrist.

Following completion of the Sociodemographic and Clinical Data Form and the Fibromyalgia Impact Questionnaire (FIQ), each participant was assessed by a specialist in internal medicine, physical medicine, and/or rehabilitation before being sent to a psychiatrist. The Beck Anxiety Inventory (BAI) and Beck Depression Inventory (BDI) were used, and a psychiatrist conducted structured interviews that lasted at least half an hour in accordance with the Diagnostic and Statistical Manual of Mental Disorders (DSM-5).

Clinical variables and blood biomarker analysis

After at least eight hours of fasting, blood samples were taken from each participant between 8:00 and 9:00 AM. Using an automated analyzer (Beckman AU 5800, Brea, CA, USA), routine biochemistry analysis was carried out. 3 mL of EDTA-anticoagulated whole blood (automated hematology analyzer, Beckman Coulter DXH 800, Brea, CA, USA) was used for standard hemogram assays.

Irisin test principle

In this study, serum samples were collected and then transported under cold-chain conditions to the authorized distributor's laboratory, where all biochemical analyses were performed. Irisin concentrations were measured using a commercial human Irisin ELISA kit (Elabscience, Wuhan, China; Catalog No: E-EL-H6120), based on the sandwich ELISA principle. The assay provided a measurement range of 0.78–50 ng/mL and a sensitivity (LOD) of 0.47 ng/mL, as reported by the manufacturer. The intra-assay and inter-assay coefficients of variation were <10% and <12%, respectively. All serum samples were stored at −80°C prior to analysis and were subjected to only a single freeze–thaw cycle. Measurements were performed using a BIO-TEK ELx800 microplate reader and an ELx50 automated strip washer.

Measures

Sociodemographic and Clinical Data Form

Authors created this semi-structured form, which uses clinical information to identify the individual, including residence, length of sickness, and comorbidities.

Beck Anxiety Inventory (BAI)

This 21-item self-report questionnaire measures the severity of anxiety symptoms. Each item is rated on a 4-point Likert scale (0–3), with total scores ranging from 0 to 63; higher scores indicate greater anxiety levels. It was developed by Beck et al. [22]. The Turkish version has demonstrated good validity and reliability, with high internal consistency, as reported by Ulusoy et al. [23].

Beck Depression Inventory (BDI)

The BDI is a 21-item self-report scale designed to assess the severity and frequency of depressive symptoms. Items are scored on a 4-point scale, with total scores ranging from 0 to 63, and higher scores

indicating more severe depression. It was developed by Beck et al. [24], and its Turkish adaptation has shown satisfactory validity and reliability [25].

Fibromyalgia Impact Questionnaire (FIQ)

The FIQ is a disease-specific instrument developed to evaluate functional status, physical functioning, and health-related quality of life in patients with FM. It includes multiple items assessing pain, fatigue, sleep, and daily activities, with total scores ranging from 0 to 100; higher scores indicate greater disease impact. The Turkish version has demonstrated acceptable validity and reliability, as reported by Sarmer et al. [26,27].

Statistical analysis

SPSS (Statistical Package for the Social Sciences; SPSS Inc., Chicago, IL) version 22 was the software used for the analyses. Using the Pearson chi-square test, categorical factors including smoking, alcohol consumption, marital status, and educational attainment were compared. For continuous variables, descriptive statistics are displayed using the median and interquartile range (25th-75th percentile values); for categorical variables, frequencies (n) and percentages (%) are used. Continuous variables' conformance to a normal distribution was evaluated using the Kolmogorov-Smirnov test, skewness-kurtosis, and histogram displays.

The Mann-Whitney U test was used to compare age, irisin levels, BMI and all blood parameters, as they did not show a normal distribution. Due to statistically significant baseline differences between the groups in demographic (age, marital status) and clinical (folic acid, blood pressure) characteristics, the potential confounding effect of these variables on irisin levels was controlled for using Analysis of Covariance (ANCOVA). In this analysis, these four variables, which constituted the baseline inter-group differences, were included in the model as covariates.

The relationship between irisin levels and the parameters was assessed separately for each group using Spearman's correlation analysis. The Spearman correlation test was used to examine the association between irisin, age, and BMI. The Spearman correlation test was also used to assess the association between irisin in the case group and the BDI, BAI, and FIQ measures. To control for the false discovery rate (FDR) arising from multiple correlation analyses between irisin and biochemical or clinical parameters, p-values were adjusted using the Benjamini-Hochberg procedure.

Age, BMI, BDI, BAI, irisin, insulin, glucose, HbA1c, HomaIR, vitamin D, vitamin B12, folic acid, ferritin, TSH, and free T4 levels were all examined to see if they predicted FIQ scores using a linear regression model. Receiver Operating Characteristic (ROC) analysis was performed to evaluate the diagnostic performance of serum irisin levels in distinguishing patients with Fibromyalgia (FM) from healthy controls. The area under the curve obtained in the ROC analysis was presented alongside its 95% confidence interval. For all analyses, a significance level of $p<0.05$ was used.

The post-hoc power analysis was conducted using the serum irisin values as the primary reference, which were compared between the two groups using the Mann-Whitney U test. The substantial difference between the FM group (Median = 60.07 ng/mL) and the control group (Median = 17.56 ng/mL) corresponds to a large effect size (Cohen's ~ 1.31). At a significance level of $\alpha = 0.05$ and with a total sample size of 80 participants (n = 40 per group), the calculated statistical power (1 - β) was found to exceed 99%. These metrics demonstrate that the study was robustly powered to detect significant differences in circulating irisin, thereby confirming the statistical reliability of the observed inter-group variances.

RESULTS

There were 80 participants in the study: 40 women in the control group and 40 in the case group. The case group's median age was 40.50 (IQR = 30.25 - 51.50), whereas the control group's median age was 30.50 (IQR = 25.25 - 44.50) ($p>0.05$). Although individuals with a BMI >30 were excluded from the control group, no BMI criteria were applied in the selection of FM patients. Nevertheless, the BMI distribution of the FM group included in our study was naturally found to be similar to that of the control group ($p>0.05$). In the case group, 35 people (87.5%) were unmarried, compared to 26 people (65%) in the control group ($p = 0.018$). The groups' use of alcohol and cigarettes was comparable, and most of them reported not smoking ($p>0.05$). Regarding educational status, there was no difference between the groups ($p>0.05$). Table 1 displays comparisons of the groups' sociodemographic information.

Table 1. Comparison of sociodemographic data of groups

Variables		Case group (n=40)	Control group (n=40)	p value
Age (Mean±IQR)		40.50 (30.25 – 51.50)	30.50 (25.25 – 44.50)	0.053a
BMI (Mean±IQR)		25.00 (23.33 – 25.71)	23.68 (20.61 – 25.86)	0.105a
Sex n (%)	Woman	40 (100%)	40 (100%)	
Marital Status n (%)	Single	35 (87.5%)	26 (65%)	0.018b
	Married	5 (12.5%)	14 (35%)	
Education Status n (%)	Primary education	14 (35%)	15 (37.5%)	0.888b
	High School	13 (32.5%)	11 (27.5%)	
	University	13 (32.5%)	14 (35%)	
Alcohol use n (%)	Yes	34 (85%)	36 (90%)	0.499b
	No	6 (15%)	4 (10%)	
Cigarette smoking n (%)	Yes	31 (77.5%)	28 (70%)	0.446b
	No	9 (22.5%)	12 (30%)	

[a]Mann-Whitney U test ; [b]Chi-square test; BMI: Body mass index, Median (IQR): Median and interquartile range

In the case group, the median irisin level was 60.07 (IQR = 21.56 - 101.84), whereas in the control group, it was 17.56 (IQR = 12.76 - 22.33). The case group's irisin levels were substantially greater than those of the control group ($p<0.001$). The two groups' arterial blood pressure, hemogram, and biochemistry readings were contrasted. It was discovered that the case group had significantly lower diastolic and systolic arterial blood pressures than the control group. WBC, hemoglobin, platelets, neutrophils, lymphocytes, monocytes, and sedimentation levels were found to be comparable between the groups. It was discovered that the case group's CRP readings were noticeably greater than those of the control group. While creatinine levels in the control group were significantly higher than those in the case group, the case group's levels of AST, HbA1c, ferritin, and folic acid were significantly higher than those in the control group. The groups' levels of insulin, glucose, HomaIR, ALT, urea, vitamin D, vitamin B12, TSH, and free T4 were comparable. Table 2 shows a comparison of the blood parameters for each group.

As significant baseline differences were identified between the groups regarding age, marital status, folic acid, and blood pressure parameters, these variables were controlled for as potential covariates using ANCOVA. It was determined that even after adjustment for these covariates, the difference in irisin levels between the groups retained its high statistical significance ($p<0.001$ for all covariance comparisons).

In the correlation analysis, performed separately for each group, the Benjamini-Hochberg False Discovery Rate (FDR) correction was applied to adjust for multiple comparisons. Following this adjustment, no significant correlations were detected between irisin and other parameters within the control group. However, within the case group, irisin levels demonstrated a significant positive correlation with ALT (rho=0.512, adjusted p=0.007). The correlation between irisin and the FIQ score, which was noted prior to correction, did not retain statistical significance after adjustment (rho=0.417, adjusted p=0.053). No significant correlations were observed between irisin and the remaining variables within the case group. Table 3 displays the correlation data for the case group.

Table 2. Comparison of blood parameters of groups

Parameters	Case group (n=40) (Mean±IQR)	Control group (n=40) (Mean±IQR)	p value
İrisin, ng/mL	60.07 (21.56 – 101.84)	17.56 (12.76 – 22.33)	<0.001
Systolic BP, mmHg	110 (100 – 124.5)	127 (116.5 – 135.75)	<0.001
Diastolic BP, mmHg	72 (68.5 – 80)	80.5 (78 – 85)	0.005
White blood cell, 109/L	6.05 (5.02 – 7.77)	6.5 (5.35 – 7.67)	0.596
Hemoglobin, g/dL	13.20 (12.30 – 13.90)	13.35 (12.6 – 13.9)	0.806
Platelet, 109/L	290.50 (244.75 – 343.75)	280.5 (230 – 322.75)	0.544
Neutrophil, 109/L	3.41 (2.77 – 4.38)	3.7 (2.91 – 4.86)	0.551
Lymphocyte, 109/L	2.02 (1.49 – 2.52)	1.92 (1.58 – 2.44)	0.889
Monocyte, 109/L	0.50 (0.41 – 0.57)	0.45 (0.38 – 0.55)	0.279
Sedimentation, mm/h	8 (4.25 – 15.75)	8.5 (5 – 11)	0.349
CRP, mg/L	2.45 (1.14 – 5.17)	1.28 (0.73 – 2.87)	0.031
Ferritin, µg/L	16.5 (6 – 34.75)	8 (5 – 17)	0.031
Fasting blood glucose, mg/dL	87 (82.25 – 93.75)	89 (84.25 – 93)	0.479
Insulin, µIU/mL	8.85 (6.17 – 12.59)	7.79 (5.26 – 12.07)	0.532
Homa-IR	1.82 (1.45 – 2.68)	1.63 (1.1 – 2.57)	0.630
HbA1c, %	5.60 (5.40 – 5.77)	5.4 (5.12 – 5.6)	0.002
AST, IU/L	19 (17 – 23.75)	17 (15 – 18)	<0.001
ALT, IU/L	15 (12 – 20)	14 (11 – 21)	0.515
Urea, mg/dL	23.5 (20 – 30)	22 (20 – 30.75)	0.802
Creatinine, mg/dL	0.59 (0.53 – 0.66)	0.63 (0.59 – 0.69)	0.022
Vitamin D, µg/L	15.5 (10.25 – 24)	14 (11 – 16)	0.221
Vitamin B12, ng/L	182.5 (145 – 285)	173.5 (150 – 222)	0.299
Folic acid, µg/L	8.14 (5.95 – 10.92)	6.61 (5.55 – 7.7)	0.002
TSH, µIU/mL	1.61 (1.28 – 2.46)	1.74 (1.2 – 2.59)	0.795
Free T4, ng/dL	0.82 (0.77 – 0.89)	0.83 (0.74 – 0.86)	0.736

Mann-Whitney U test; Median (IQR): Median and interquartile range, CRP: C-reactive protein, HOMA-IR: Homeostasis Model Assessment of Insulin Resistance, HbA1c: Hemoglobin A1c, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, TSH: Thyroid-stimulating hormone

Table 3. Correlation between irisin values and scale scores of the case group

Variables	Levels of the irisin	
	Spearman Rho	p value
Beck depression inventory	-0.030	0.856
Beck anxiety inventory	0.167	0.303
Fibromyalgia Impact Questionnaire	0.417	0.007

Spearman correlation test used

Receiver Operating Characteristic (ROC) analysis was performed to evaluate the diagnostic performance of serum irisin levels in distinguishing patients with Fibromyalgia (FM) from healthy controls. The analysis yielded an AUC of 0.821 (95% CI: 0.718–0.923, p<0.001). A cut-off value of 29.71 ng/mL was identified, providing 70% sensitivity and 98% specificity (Figure 1).

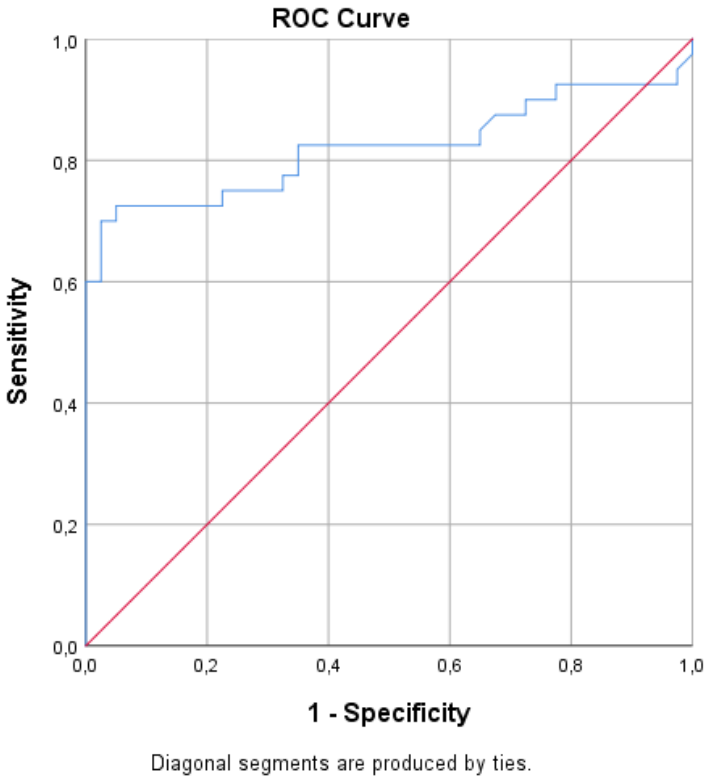

Figure 1. Area under the curve was 0.821 (p<0.001). The cut-off value of 29.71 ng/ml for irisin level was found to have 70% sensitivity and 98% specificity.

Age, BMI, BDI, BAI, irisin, insulin, glucose, HbA1c, HomaIR, vitamin D, vitamin B12, folic acid, ferritin, TSH, and free T4 levels were all analyzed in the linear regression model to see if they predicted FIQ scores in the case group. The results showed no significant impacts (p>0.05).

DISCUSSION

This study, investigating the value of irisin as a biomarker in FM and its relationship with symptom severity, found that serum irisin levels were significantly higher in women with FM compared to healthy controls. In contrast to previous studies mainly focusing on group comparisons, the present study also examined the relationship between irisin levels and symptom severity scores. This finding suggests that irisin may be related to the etiopathogenesis of FM and therefore could be considered a potential biomarker candidate. To our knowledge, this is the first study to investigate the relationship between irisin levels and symptom severity, anxiety, and depression in FM.

Mitochondrial dysfunction and oxidative stress are thought to be among the factors triggering the development of FM and are also associated with the

course of the disease[28]. Irisin is an important molecule that protects skeletal muscle cells from oxidative stress damage and prevents muscle atrophy by regulating mitochondrial autophagy[29]. Mitochondrial dysfunction leads to a decrease in intracellular energy production, free radical accumulation, and the triggering of an inflammatory response. Irisin is also known to exhibit anti-inflammatory functions by increasing anti-inflammatory cytokine production while decreasing pro-inflammatory cytokine production and reducing macrophage proliferation[30]. In our study, the significantly higher irisin levels in FM patients compared to healthy individuals may indicate a possible adaptive response. This increase could reflect a secondary change associated with inflammatory or metabolic alterations rather than a primary pathogenic mechanism. Another possibility is that increased irisin levels are a consequence of the musculoskeletal disorders and changes in energy metabolism observed in FM. Samancı et al. [10] observed similar irisin levels in patient and control groups in their study. These conflicting findings suggest that the biological functions of the iris may be influenced by factors such as disease stage, individual physical activity level, and degree of systemic inflammation. Additionally, variables such as exercise habits, dietary patterns, menopausal status, and circadian rhythm may influence circulating irisin levels and should be taken into account when interpreting the results.

The high prevalence of obesity, insulin resistance, and metabolic syndrome in individuals with FM indirectly supports the association of the adipokine irisin with this disease. Although no significant difference was found between the groups in insulin and glucose levels in our study, the positive correlation of irisin levels with metabolic and inflammatory indicators such as HbA1c and ferritin suggests that irisin may be an indicator of metabolic stress. Uslu et al.[31] linked low asprosin levels to FM in their study examining asprosin levels in FM. Paiva et al.[32] observed no difference between patients and controls in their study examining adiponectin and leptin levels in FM. This suggests that some adipokines may play a role in the pathophysiological processes in FM, but different factors (disease duration, activity level) should be considered for this effect to be reflected in biomarker levels.

Myokines have been shown to have effects not only on peripheral tissues but also on the central nervous system, playing a role in processes such as hippocampal neurogenesis, neurotrophin levels, and cognitive/mood regulation. Recent experimental studies have demonstrated that the hormone irisin supports neurogenesis and enhances synaptic plasticity by increasing Brain-Derived Neurotrophic Factor (BDNF) expression in the hippocampus. Furthermore, irisin suppresses microglial activity, reducing neuroinflammatory processes and thus preventing the development of central sensitization[33]. FM is thought to be associated with increased BDNF levels[34]. This interaction suggests a potential Irisin-BDNF axis in the pathophysiology of FM. It is well-documented that circulating irisin can cross the blood-brain barrier and induce the expression of BDNF in the hippocampus and other brain regions[35]. While BDNF is neuroprotective, its chronic elevation is frequently observed in FM patients and is implicated in the strengthening of nociceptive pathways a phenomenon known as central sensitization. Therefore, the significantly elevated serum irisin levels found in our study may not only be a compensatory metabolic response but could also be mechanically linked to the central pathophysiology of the disease. By stimulating BDNF production, high levels of irisin might inadvertently fuel maladaptive neuroplasticity and central sensitization, thereby acting as a bridge between peripheral muscle dysfunction and the maintenance of chronic widespread pain.

It is known that irisin levels increase with exercise. The recommendation of exercise as the primary non-pharmacological approach to treating FM supports the potential therapeutic role of irisin. Dos Santos et al.[36] found that irisin levels increased after 6 weeks of Whole-Body Vibration Training in FM patients. Increased irisin levels through exercise may improve muscle function, increase mitochondrial activity, and reduce systemic inflammation. This suggests that irisin levels are not only an indicator of disease pathophysiology but also a target for intervention. However, because exercise frequency and intensity were not evaluated in this study, their potential contribution cannot be excluded.

When examined in terms of biochemical parameters, CRP, AST, HbA1c, ferritin, and folic acid levels were found to be significantly higher in the FM group compared to the control group. High CRP indicates the presence of low-grade inflammation accompanying FM. This result is consistent with the literature[37]. High HbA1c indicates a relationship

between FM and glycemic dysregulation. Consistent with our study, HbA1c levels have been observed to be higher in FM compared to controls in many studies[38,39]. Normally, low levels of ferritin, folate, vitamin B12, and vitamin D are known to be associated with FM[40,41]. In our study, we believed that the higher ferritin and folate levels observed in the FM group were due to patients turning to vitamin supplements due to their chronic pain.

However, linear regression analysis revealed that age, BMI, glucose metabolism parameters, vitamin levels, and thyroid hormones, including irisin, did not significantly predict FIQ scores. This result reflects the multifactorial nature of FM and suggests that symptom severity cannot be explained by a single biomarker. While a significant correlation was found between irisin and FIQ scores, this association alone did not reach independent predictive value, suggesting that irisin levels reflect only one aspect of symptom burden. Nevertheless, this finding provides important clues that irisin may play a role in the biological processes specific to FM and warrants its evaluation in conjunction with broader biomarker panels in future studies. Further research with larger, well-controlled, and longitudinally designed cohorts would help clarify these relationships.

The ROC analysis demonstrated high diagnostic accuracy, particularly regarding specificity (98% at a cut-off of 29.71 ng/mL). This suggests that serum irisin has significant potential as a supportive diagnostic biomarker. While it may not yet replace current clinical criteria as a standalone screening tool, incorporating irisin measurement into a multimodal assessment could reduce diagnostic uncertainty. Specifically, elevated irisin levels could help rule in the diagnosis of FM with high confidence when clinical presentation is ambiguous.

Future studies should focus on larger, multicenter, and longitudinal cohorts to clarify the temporal relationship between irisin and disease activity, investigate mechanistic pathways linking irisin to central sensitization and mitochondrial dysfunction, and evaluate irisin in combination with other biomarkers to establish reliable, multiparametric diagnostic and prognostic tools for FM.

This study has some limitations. Firstly, the fact that the sample consisted solely of females limits the generalizability of the findings to male FM patients. Because FM is a syndrome influenced by gender-related hormonal and psychosocial factors, gender comparisons would be beneficial in future studies. Furthermore, the cross-sectional design of the study makes it difficult to determine whether changes in irisin levels are a cause or effect. Longitudinal follow-up studies could provide stronger evidence to assess the effect of irisin on FM symptoms over time. Another important limitation is the potential influence of unmeasured confounding variables on circulating irisin levels. Factors such as habitual physical activity, dietary habits, menopausal status, circadian rhythm, and previous use of vitamin or nutritional supplements could have affected serum irisin concentrations. Although these variables were not systematically controlled or recorded in the present study, they may partly explain inter-individual variability in irisin levels. Future studies should aim to include these parameters as covariates or perform stratified analyses to better clarify their effects. Second, the sample size is modest and replication in larger, prospectively powered cohorts is warranted. Third, because of sample size constraints, the number of covariates included in multivariable models was limited to avoid overfitting. Despite these limitations, the study provides useful preliminary data to guide future definitive studies on irisin in fibromyalgia. Finally, the relatively small sample size (n = 80) may have limited the statistical power of the analyses, particularly for regression models including multiple predictors; therefore, these findings should be interpreted with caution.

In conclusion, this study demonstrates increased irisin levels in FM, highlighting the potential role of irisin in the complex pathophysiology of this syndrome. However, for the data to be more clinically relevant, future studies with larger sample sizes, a mechanism-focused, multicentric, and longitudinal design are necessary. Furthermore, evaluating myokines such as irisin in multiparameter models, along with other biomarkers, may contribute to the identification of biological subtypes of FM and the development of more targeted treatment strategies.

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