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An investigation of serum irisin levels and inflammatory markers in fibromyalgia syndrome

Rumeysa Samanci,[1] Sarfinaz Ataoglu,[1] Mustafa Ozsahin,[1] Handan Ankarali,[2] Ozlem Admis[3]

[1]Department of Physical Medicine and Rehabilitation, University of Duzce Faculty of Medicine, Duzce, Turkey

[2]Department of Biostatistics and Medical Informatics, University of Istanbul Medeniyet Faculty of Medicine, Istanbul, Turkey

[3]Department of Biochemistry, University of Duzce Faculty of Medicine, Duzce, Turkey

ABSTRACT

OBJECTIVE: In the present study, we aimed to compare serum irisin levels in patients with fibromyalgia syndrome (FMS) and healthy control subjects and also investigate the relationship between irisin, disease activity and inflammation markers in patients.

METHODS: A total of 84 women, including 48 patients who were diagnosed with FMS and 36 healthy controls, were included in this study. The demographic characteristics of the patients and control group were recorded. VAS for pain and the Fibromyalgia Impact Questionnaire for the assessment of the physical function of the patients, SF36 was used for quality of life, and accompanying Beck Depression Inventory to assess depression was used. Blood samples were taken for analysis that irisin, and inflammatory markers of the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), high-sensitivity C-reactive protein (hs-CRP) and neutrophil/lymphocyte ratio (NLO). Serum irisin levels were determined using the Enzyme-Linked Immunosorbent Assay (ELISA) method.

RESULTS: Serum irisin level of the patients with FMS had no significant differences compared with the healthy control group. When we compared the values of ESR, CRP, hsCRP, NLO with FMS patients and healthy controls, there was no significant difference found between them ($p>0.05$). There was no significant correlation between inflammatory markers and level of serum irisin ($p>0.05$). In patients, there was no significant correlation between inflammatory markers and level of serum irisin ($p>0.05$).

CONCLUSION: Irisin, which is a myokine, was determined to have no significant role in the pathogenesis of FMS. Irisin had no association with disease activity and inflammatory markers. Also, the inflammation hypothesis was not supported, which suggested in FMS.

Keywords: Disease activity; fibromyalgia syndrome; irisin; inflammation.

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Fibromyalgia syndrome (FMS) is one of the most frequently encountered diseases of the modern age, which adversely affects the quality of life, especially during daily activities. FMS is also known as chronic pain syndrome, chronic fatigue syndrome or muscle rheumatism, is a chronic pain syndrome characterized by diffuse muscle pain and weakness [1].

It has been suggested that muscle tissue and its functions may be impaired in FMS, but as a result of studies, nonspecific changes have been identified [2]. Some studies have suggested that myokines, such as interleukin-6 (IL-6), may have a role in FMS [3, 4]. Irisin is a new myokine defined as a muscular factor. Irisin which promotes browning of adipose tissue, and has been suggested to mediate the beneficial effects of exercise has not been previously examined in FMS progressing with diffuse muscle pain [5].

This study aims to compare the serum irisin levels of patients diagnosed with FMS and healthy controls and to investigate the relationship between irisin, disease activity and inflammatory markers.

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Correspondence: Dr. Handan ANKARALI. Istanbul Medeniyet Universitesi, Tip Fakultesi, Biyoistatistik ve Tip Bilisimi Anabilim Dali, Istanbul, Turkey.
Tel: +90 216 280 40 18 e-mail: handanankarali@gmail.com

MATERIALS AND METHODS

Research Type and Sampling

This research was planned as a cross-sectional type, and this study included 36 healthy women and 48 female patients aged between 18-60 years who were diagnosed according to 1990 American Rheumatology Association FMS classification criteria.

Participants were informed about this study and an informed consent form was obtained. After obtaining approval from the noninvasive health research ethics committee of Duzce University, blood samples were started to be collected.

Inclusion Criteria

Among participants aged 18-60 years, adult women who received the diagnosis of FMS, and healthy volunteers were included in this study.

Exclusion Criteria

Patients with BMI >30 kg/cm² were excluded from this study not to affect the levels of irisin by obesity factor. In addition, pregnant and nursing women, individuals under the age of 18 and over 60 years of age, past or present antidepressant drug users, patients with current or past history of major psychiatric disease, malignancy, cases with acute, subacute viral/bacterial infection, muscle disease, diabetes mellitus (DM) and endocrine system disease were not included in this study.

Measured Characteristics

Demographic data (age, height, body weight, body mass index) of the individuals in both groups were recorded. Educational levels of the participants, history of surgical operation, drug use, exercise habits, smoking and alcohol use were questioned.

In the patient group, the duration of complaints in months was recorded. FMS symptoms diffuse pains, previous treatments and other concomitant diseases were evaluated. In addition, the patients were compared concerning serum irisin levels by dividing them into two groups according to the presence and absence of their symptoms and also as patients previously treated and newly diagnosed patients.

Depression level of the participants was evaluated using the Beck Depression Inventory (BDI), the quality of life with the Short Form 36 Health Survey Questionnaire (SF-36), pain with 10-point Visual Analogue Scale (VAS) and disease severity with Fibromyalgia Impact Questionnaire (FIQ).

As inflammatory markers, erythrocyte sedimentation rate (ESR), C-Reactive Protein (CRP), high- sensitivity CRP (h-sCRP), neutrophil/lymphocyte ratio (NLR) were examined in all individuals included in this study. In addition, thyroid function tests, measurements of 25-hydroxy vitamin D3, vitamin B12, hemogram and routine biochemistry tests were performed.

Venous blood samples were drawn into a three-gel barrier vacutainer tubes between 8.00-9.00 in the morning following a 12-hours of fasting. Blood samples were drawn into a tube for the measurement of inflammatory markers and routine tests and two other tubes were reserved for serum irisin tests (since hemolysed samples could affect the results of measurement, the third tube was used as a replacement tube). Blood samples were separated into their sera by centrifugation at 3500 rpm for four minutes. Then, they were divided into two portions, drawn into Eppendorf tubes and stored in the deep freezer, which cooled the samples down to – 20°C until the time of analysis. Samples were allowed to melt at room temperature before measurement. Serum irisin level was determined in one session using ELISA (The Enzyme-Linked Immunosorbent Assay) method using SunRed commercial kit, and the results were given in ng/ml.

Statistical Analysis

Descriptive statistics of the obtained data were expressed as mean±SD, numbers and percentages depending on the type of data. Shapiro-Wilk test was used to determine the fitness of data to the normal distribution of the quantitative characteristics and independent samples t-test or Mann-Whitney U test was used to compare the two groups according to their fitness to normal distribution.

The relationships between the quantitative variables were examined using the appropriate correlation coefficient. Pearson chi-square or Fisher-Freeman-Halton test was used to evaluate the relationships between groups and categorical variables. SPSS (v. 18) program was used in the calculations and $p<0.05$ was considered statistically significant.

RESULTS

The mean age of the FMS patients and the control group were 38.58±7.62, and 37.86±9.46 years, respectively. The mean BMIs were 25.02±3.24 kg/cm², and 24.44±2.86 kg/cm² in the FMS, and control groups, respectively. There was no statistically significant difference

between the groups concerning age and BMI. The duration of complaints in FMS patients was between 3-360 months (46.93±61.69). The average number of sensitive points (SPs) was 14.31. The VAS score was between 4 and 10 (6.12±1.57) points.

Occupation, educational and marital status of FMS patients and the control group are given in Table 1. The mean values of SF-36 and BDI scores and their mutual comparisons are given in Table 2.

When compared with the control group, FMS patients received significantly higher scores in all sub-dimensions of the SF-36 scale (p<0.01 for each), whereas their BDI scores were significantly lower (p=0.01). When the laboratory values of FMS patients and control group were examined, any statistically significant difference was not found between groups as for ESH, CRP, hs-CRP, NLR and serum irisin levels (p>0.05).

Moderately significant negative correlations were found between BDI and both physical functioning (r=-0.476, p=0.001) and FIQ (r=-0.397, p=0.005): FIQ with pain (r=-0.535, p=0.001), and general health status (r=-0.536; p=0.001); BDI with general health status (r=-0.592, p=0.001), and vitality (r=-0.521, p=0.001); social functioning with FIQ (r=-0.448, p=0.001), and BDI (r=-0.449, p=0.001), mental health and FIQ (r=-

Table 1. Comparison of occupational educational and marital status of the patient and control groups

	Patient (n=48)	Control (n=36)	p
Occupation			
Housewife			
n	30	10	0.009
%		62.5	27.8
Manual worker			
n	15	22	
%	31.3	61.1	
Desk worker			
n	3	3	
%	6.3	8.3	
Retiree			
n	0	1	
%	0	2.8	
Education			
Illiterate			
n	0	2	0.038
%	0	5.6	
Primary and Secondary			
n	35	17	
%	72.9	47.2	
Lycée			
n	8	7	
%	16.7	19.4	
Higher education			
n	5	10	
%	10.4	27.8	
Marital status			
Single			
n	2	5	0.432
%	4.2	13.9	
Married			
n	42	28	
%	87.5	77.8	
Divorced			
n	2	2	
%	4.2	5.6	
Dead spouse			
n	1	1	
%	2.1	2.8	
Estranged			
n	1	0	
%	2.1	0	

Table 2. Comparison of FMS and control groups concerning SF-36 and BDI scores

SF-36 Alt Sub-dimensions	Mean	SD	p
Physical functioning			
FMS	18.87	4.45	<0.001
Control	24.15	3.82	
Physical role difficulty			
FMS	5.12	1.29	0.004
Control	6.18	1.68	
Pain			
FMS	5.61	1.76	<0.001
Control	8.28	1.83	
General health			
FMS	12.72	4.05	<0.001
Control	16.44	3.70	
Vitality			
FMS	10.58	3.53	<0.001
Control	14.39	2.80	
Social functioning			
FMS	6.31	1.82	<0.001
Control	7.93	1.88	
Emotional role difficulty			
FMS	4.16	1.20	0.046
Control	4.75	1.27	
Mental well-being			
FMS	16.66	5.10	<0.001
Control	20.87	3.25	
BDI			
FMS	20.14	10.52	<0.001
Control	9.36	4.52	

SS: Standard deviation.

Table 3. In the FMS group correlations between SF-36 sub-dimension scores and FIQ, BDI, VAS scores, SP, CRP, hs-CRP, ESR, NLO, and serum irisin levels

SF-36 Sub-dimensions	FIQ	BDI	VAS	SP	CRP	Hs-CRP	ESR	NLR	Irisin
Physical functioning									
r	-0.397	-0.456	-0.235	-0.396	0.104	0.094	0.094	0.159	-0.384
p	0.005	0.001	0.108	0.005	0.481	0.543	0.525	0.279	0.007
Physical role difficulty									
r	-0.054	-0.224	-0.122	-0.287	0.201	0.146	0.051	0.064	-0.384
p	0.718	0.126	0.410	0.050	0.172	0.343	0.729	0.667	0.007
Pain									
r	-0.535	-0.386	-0.173	-0.265	-0.117	0.015	-0.009	0.137	0.023
p	0.000	0.007	0.238	0.068	0.427	0.921	0.954	0.352	0.878
General well-being									
r	-0.536	-0.592	-0.181	-0.278	0.118	0.168	0.005	0.034	-0.069
p	0.000	0.000	0.219	0.055	0.423	0.275	0.972	0.820	0.642
Vitality									
r	-0.338	-0.521	-0.044	-0.180	0.155	0.135	-0.043	0.137	0.068
p	0.019	0.000	0.764	0.222	0.294	0.382	0.772	0.354	0.646
Social functioning									
r	-0.448	-0.449	-0.061	-0.260	0.137	0.235	0.082	0.038	-0.137
p	0.001	0.001	0.680	0.074	0.354	0.125	0.580	0.798	0.353
Emotional role difficulty									
r	-0.182	-0.266	-0.150	-0.288	0.240	0.267	0.372	0.091	-0.008
p	0.215	0.067	0.310	0.047	0.100	0.079	0.009	0.536	0.958
Mental well-being									
r	-0.477	-0.730	-0.059	-0.121	0.077	0.142	-0.011	0.062	0.020
p	0.001	0.000	0.690	0.413	0.601	0.359	0.941	0.673	0.891

FIQ: Fibromyalgia Impact Questionnaire; BDI: Beck Depression Inventory; VAS: Visual Analogue Scale; CRP: C-Reactive Protein; Hs-CRP: High-sensitivity C-Reactive Protein; ESR: Erythrocyte Sedimentation Rate; NLR: Neutrophil/Lymphocyte Ratio.

0.477, p=0.001),whereas a strong negative correlation was detected between mental health and BDI (r=-0.730, p=0.01) (Table 3).

According to the BDI scores of the FMS group, any depressive findings were not detected in 29.2% (n=14) of the patients, while mild (41.7%: n=20), and severe (29.2%; n=14) depression was observed in the indicated number of patients. In FMS patients, any significant correlation was not detected between BDI scores and parameters of VAS scores, SP, CRP, hs-CRP, NLR and ESR. However, a moderately positive correlation was observed between BDI and FIQ scores (r=0.448, p=0.001).

Thirty (62.5%) FMS patients and 63.9% (n=23) of the control group were exercising without any statistically significant difference between the two groups concerning exercise habits. Any significant difference was not seen between exercise and non-exercise groups as for serum irisin levels.

The mean FIQ score of the FMS patients was 56.23±18.06. There was no significant correlation between FIQ scores and HN, CRP, hs-CRP, NLR, ESR (correlation coefficient for each: r<0.20). However, a weakly moderate positive relationship was detected between VAS and these parameters (r=-0.320, p=0.028). In addition, any significant correlation was not found between serum irisin levels and BMI, FIQ, BDI, VAS, HN, CRP, hs-CRP, NLR, ESR (r<0.20).

In FMS patients, fatigue was observed in 85.4%, restless sleep in 70.8%, morning stiffness in 72.9%, headache in 85.4%, irritable bowel syndrome in 85.4%, Raynaud-like syndrome in 29.2%, and paresthesia in 83.3%., sicca-like symptoms in 62.5%, depression in 50%, anxiety in 87.5%, irritable bladder in 54.2%, concentration problems, and memory disorder in 83.3%, and dysmenorrhea in 43.8% of the cases There was no difference between patients with and without these symptoms as for serum irisin levels (Table 4).

TABLE 4. Correlation between irisin levels and patients with and without FMS symptoms

FMS symptoms	Irisin		
	Mean	SD	P
Fatigue			
No	58.28	50.64	0.909
Yes	68.59	65.83	
Restless sleep			
No	66.00	66.58	0.717
Yes	67.53	63.18	
Morning stiffness			
No	63.94	58.58	0.799
Yes	68.25	65.98	
Headache			
No	104.30	81.30	0.249
Yes	60.73	58.81	
Irritable bowel syndrome			
No	41.29	38.77	0.287
Yes	71.49	66.12	
Raynaud-like phenomenon			
No	66.32	68.57	0.229
Yes	68.93	51.23	
Paresthesia			
No	81.64	81.69	0.860
Yes	64.17	60.04	
Sicca-like symptoms			
No	78.77	76.41	0.360
Yes	60.07	54.51	
Depression			
No	54.65	55.71	0.170
Yes	79.51	69.33	
Anxiety			
No	57.45	45.43	0.939
Yes	68.46	65.96	
Irritable bladder			
No	57.34	58.96	0.169
Yes	75.33	67.08	
Concentration and memory disorders			
No	54.72	48.97	0.881
Yes	69.56	66.24	
Dysmenorrhea			
No	64.53	61.58	0.868
Yes	70.37	67.22	

*SD: standard deviation.

Twenty-three FMS patients were receiving treatment, while 25 patients had newly diagnosed FMS. Any statistically significant difference was not found between the mean serum irisin values of the treated and non-treated patients. Any statistically significant difference was not detected between patients without depression and patients with mild and severe depression as for serum irisin levels ($p>0.05$).

DISCUSSION

In recent years, inflammatory cytokines have been implicated in the pathogenesis of FMS. The substance-P substance, which is an inflammatory transmitter in cerebrospinal fluid, was found to be higher in FMS [6, 7]. The hypothesis suggesting that cytokines are effective in FMS is based on induction of hypersensitivity to pain by IL-6 whose secretions are stimulated by substance-P and increase in sympathetic pain by IL-8 In addition, proinflammatory cytokines, such as IL-1, tumor necrosis factor-α (TNF-α), may trigger other characteristic symptoms, such as stress, sleep disturbance, fatigue, and depression [9-11].

Xiao et al. investigated hs-CRP, ESR, IL-6, IL-8 levels in FMS patients. They found that hs-CRP levels were higher than healthy controls, while ESR, IL-6 and IL-8 levels were similar. They also found that hs-CRP levels in FMS patients were correlated with BMI, IL-6, IL-8, whereas any correlation was not detected between hs-CRP levels and age, gender, ethnicity and other clinical measurements. They suggested that inflammation may contribute to symptoms, particularly in some obese FMS patients, and that weight loss and treatment against inflammation may be useful in the treatment of patients with increased hs-CRP levels [3].

Toker et al. evaluated serum sialic acid, hs-CRP and ESR levels in 52 patients with FMS and 32 healthy individuals. They found significantly higher sialic acid, hs-CRP and ESR values in FMS patients when compared with controls. They suggested that an inflammatory component may play a role in the pathogenesis of FMS [9]. Ortega et al. found that serum cortisol, noradrenaline, IL-8, IFN-γ and CRP levels were significantly higher in FMS patients compared to the control group. After four months of exercise program, they found a significant decrease in the levels of all these inflammatory markers. They attributed this result to the anti-inflammatory effect of exercise and the effectiveness of cytokines in the regulation of hypothalamic pituitary adrenal axis.

Salemi et al. measured the levels of IL-1β, IL-6, TNF-α by investigating neurogenic inflammation in skin tissue samples of FMS patients. They found higher levels of IL-1β, IL-6, TNF-α in FMS patients compared to

the control group. They argued that inflammation might be effective in induction of the pain [4]. In this study, any significant difference was not found between FMS patients and healthy controls concerning CRP, hs-CRP, ESR levels, but cytokine levels were not evaluated.

In recent years, as an easily estimated and inexpensive indicator NLR is being used to investigate the severity of systemic inflammation in diseases, such as cardiovascular diseases, malignancies, and DM [12]. We have not read a study in the literature that investigated the level of NLR in FMS. However, NLR has been studied in some rheumatologic diseases. It was found that NLR levels increased [13, 14] in familial Mediterranean fever patients compared to healthy controls, while NLR levels were not different between healthy individuals and patients with ankylosing spondylitis [15, 16]. However, its higher levels were detected in patients with Behçet's disease relative to healthy controls [12, 17]. In this study, any difference was not found between FMS patients and healthy controls concerning NLR. In addition, any significant relationship was not found between NLR and clinical markers. These results do not support the presence of the inflammatory hypothesis proposed in FMS.

Impairment of muscle tissue and its functions have long been suggested in the etiopathogenesis of FMS. However, only nonspecific changes have been observed in muscles [2]. Some studies have suggested that myokines, such as IL-6, may have a role in the pathogenesis of FMS [3, 4]. Irisin is a newly discovered myokine and a proteolytic product of transmembrane protein FNDC [5].

Mao et al. investigated the relationship between radiographic severity and serum irisin levels in patients with knee osteoarthritis (OA) and found that synovial fluid and serum irisin levels of 215 knee OA patients were negatively correlated with disease severity. They noted a negative correlation between serum irisin and CRP levels. They hypothesized that irisin might be associated with the pathogenesis of knee OA by indirectly inhibiting inflammation [19].

Matsuo et al. demonstrated that TNF-α, IL-1b mediated formation of myotubes reduced FNDC5 protein expression in rats. They also found a negative correlation between circulating levels of TNF-α and irisin [20]. Park et al. found a positively significant correlation between CRP and irisin [21], while Stengel et al. could not see any relationship [22].

Most of the studies with irisin have focused on the relationship between metabolic diseases and exercise. Irisin is considered as a possible mediator facilitating the beneficial effects of physical exercise [23, 24]. In this study, any significant difference was not found between serum irisin levels in patients in exercise and non-exercise groups.

In some of the research studies, a negative [18, 25], but in others, a positive correlation [22, 26, 27] was detected between serum irisin levels and BMI. In addition, still, some other studies could not find a significant relationship between serum irisin levels and BMI 45. In this study, any significant relationship was not found between serum iris levels and BMI in FMS patients.

In conclusion, as an outcome of this study, any relationship between myokines and especially irisin and FMS was not seen. Besides, the inflammatory hypothesis proposed in FMS could not be supported. Further studies with more homogenous and larger patient groups are needed on the subject of irisin, which we have investigated in relation to FMS.

Ethics Committee Approval: Noninvasive Health Research Ethics Committee of Duzce University, Number: 2016/32, Date: 19.12.2016.

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