Original Article
https://doi.org/10.9758/cpn.2021.19.4.677 pISSN 1738-1088 / eISSN 2093-4327
Clinical Psychopharmacology and Neuroscience 2021;19(4):677-682

Could Irisin Levels be Affected by Physical Activity in Patients with Schizophrenia?

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Objective: The aim of this study was to explore the effect of physical activity and metabolic parameters on irisin levels in patients with schizophrenia and healthy controls.
Methods: Ninety-six patients with schizophrenia and 63 healthy controls comprised the study population. The participants were separated into three groups: inactive, low activity, and sufficiently active according to International Physical Activity Questionnaire short form (IPAQ-SF). We measured irisin levels using Enzyme linked immunosorbent assay. We also calculated exercise levels by using the IPAQ-SF for each individual. The independent samples *t* test was used in the data analysis to compare irisin levels according to the activity levels of the patients with schizophrenia and controls.
Results: The levels of irisin were higher in the healthy controls ($p < 0.001$) compared to schizophrenia groups. When the activity levels of the schizophrenia and healthy control groups were compared, the irisin levels of the low activity and sufficiently active groups with schizophrenia were found to be lower than those of the low activity and sufficiently active groups in the healthy controls (respectively $p = 0.014$; $p < 0.001$).
Conclusion: Irisin levels could be affected by physical activity and these results must be supported with new studies.

KEY WORDS: Exercise; Schizophrenia; Biomarkers; Adipokines.

INTRODUCTION

Irisin is a recently defined myokine [1] with a structure of peptide formed by 112 amino-acids and it's release is induced by exercise [2]. Irisin is formed by proteolytic cleavage of fibronectin type 3 domain containing factor protein 5 (FNDC5) [1,3,4]. The formation of FNDC5 is promoted by physical activity in muscle and can be converted to irisin by transcriptional co-activator peroxisome proliferator-activated receptor (PPAR)-gamma coactivator 1-alpha (PGC1α) [1].

As shown in the literature irisin has also central effects [5]. It is found that irisin has a role in neurogenesis and a protective role against neuronal damage caused by oxidative stress [6]. Irisin and FNDC5 enhance neuronal BDNF expression [7]. Also, irisin is thought to be involved in neuronal proliferation via the STAT3 signaling pathway [8-10]. By reducing the secretion of proinflammatory cytokine-like tumor necrosis factor (TNF)-alpha and interleukin (IL)-6, and by suppressing reactive oxygen species inflammatory signal in ischemia, irisin mediates neuroprotection of physical exercise in cerebral ischemia via the Akt and ERK1/2 signaling pathways against neuronal damage [11]. All these effects of irisin suggest that it should be considered a hormone worth investigating for neuropsychiatric disorders. For example, irisin may play a role in depression by actuating the expression of BDNF through the PGC1α/FNDC5 pathway [9]. Irisin promotes important processes in the nervous system, especially in the presence of neurodegenerative disorders including schizophrenia known to be linked with diminished neurogenesis [7,8,11,12].

Thus, we aimed to explore the irisin levels in patients with schizophrenia and healthy controls. Our hypothesis was that irisin levels would be lower in patients with

Received: August 22, 2020 / **Revised:** November 5, 2020
Accepted: November 8, 2020
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schizophrenia compared with healthy controls and irisin levels of patients with insufficient activity levels would be lower than patients with sufficient or low activity levels.

METHODS

This study population consisted of 96 patients who were diagnosed as schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders 5th edition criteria and 63 healthy controls. Mental retardation, pregnancy, malignancy, known inflammatory disease or use of immunosuppressive agents were regarded as exclusion criteria. The ethics committee of Dışkapı Training and Research Hospital approved the study (Date: 2017; No: 39/27). Signed approval for every sample was also obtained either from the patients themselves or their first-degree relatives.

We calculated exercise levels by using the International Physical Activity Questionnaire-short form (IPAQ-SF). The participants were separated into three groups: inactive, low intensity activity, sufficiently active. At the same time, The Brief Psychiatric Rating Scale (BPRS) was used to evaluate the symptom severity of patients with schizophrenia. Laboratory tests including complete lipid parameters, fasting blood glucose, glycated hemoglobin, and insulin measurements were performed on blood samples from every subject. The waist circumferences of the subjects were measured. Body mass index (BMI) values were noted for each subject.

IPAQ-SF: IPAQ-SF was used to measure the physical activity of the participants over the last week. IPAQ-SF consists of 7 questions and the scores of each question are added at the end. As a result, IPAQ-SF gives the activity level in MET*minute/week, and participants are separated into three groups concurring to their activity levels, as described earlier [13]. The validity and reliability study of the Turkish form of the scale was shown by Saglam *et al.* [14].

BPRS: BPRS was used to evaluate the symptom severity of patients with schizophrenia. There are 18 questions in total and 0 to 6 scoring for each question. It is a semi-structured scale used to evaluate psychotic, depressive symptoms, mannerism and posture, motor slowdown in schizophrenia, and other psychotic disorders [15]. The validity and reliability study of the Turkish form of the scale has been demonstrated [16].

Blood Sampling

After a 12-hour night fast, 5-milliliter (ml) samples of fasting blood were obtained by the participants. Blood samples were isolated from sera within 30 to 60 minutes of collection and stored at −80°C until required for analysis. On the same day, IPAQ-SF was measured for each participant and BPRS was measured for each patient.

Irisin Analysis

Levels of serum irisin were specified using enzyme-linked immunosorbent assay kits (2019; BioVendor, Bmo, Czech Republic) (Cat. No.: RAG018R, Lot No: X18-047) for quantitative determination in humans. The in-work CV% values were 4.863% and 6.748% for 0.678 μg/ml and 1.539 μg/ml concentrates, respectively, and the CV% values between the runs were 9.673% and 8.027% for 0.532 μg/ml and 1.145 μg/ml concentrates, respectively. The sensitivities were 1 ng/ml with a measurement range of 0.001−5 μg/ml and reference range 0.2−2 μg/ml.

Statistical Analysis

IBM SPSS ver. 23.0 (IBM Co., Armonk, NY, USA) was used to perform statistical analyses. Independent sample t test was used to analyze irisin levels, blood lipid values, and other metabolic parameters. The normality of data distribution before the analysis was evaluated using the Levene test. The normality of data distribution before the analysis was evaluated using the Levene test. Two-way independent ANOVA (2 participant groups X 3 activity groups) was used to compare the groups. Tukey's test was used for paired comparisons. Pearson correlation coefficient was used for variables with normal distribution and Spearman correlation coefficient was used for variables without normal distribution. The level of statistical significance was determined as $p < 0.05$.

RESULTS

The schizophrenia group constituted 64 (66.7%) males and 32 (33.3%) females. The control group included 41 (65.1%) males and 22 (34.9%) females. In the schizophrenia group, 26% of the patients were working, 60.4% were not working, 2.1% were students, and 11.5% were retired. In the control group, 42.9% were working, 36.5% were not working, 7.9% were students, and 12.7% were retired. In the schizophrenia group, 41.7% were smokers

and 58.3% were non-smokers. In the control group, 38.1% were smokers and 61.9% were non-smokers. No significant difference was shown between the two groups with regard to smoking ($p > 0.05$).

The mean and standard deviations BMI for the schizophrenia and control groups were 26.75 ± 5.40 kg/m^2 and 26.89 ± 3.16 kg/m^2 respectively (Table 1). According to the IFAQ-SF scores, 45.8% of the schizophrenia group was not physically active, 38.5% had low activity, and 15.6% were sufficiently physically active. It was found that 38.1% of the control group was not physically active, 38.1% had low physical activity, and 23.8% had sufficient physical activity. There was no significant difference with respect to the IFAQ-SF in either group ($p > 0.05$). The comparison of the laboratory finding and IFAQ-SF scores between the schizophrenia and control groups in the Table 2.

No significant relationship was found between irisin and sex, comorbidities, smoking in the schizophrenia group ($p = 0.904$, $p = 0.882$, $p = 0.170$). There was no significant correlation between irisin and duration of disease, BPRS total score in schizophrenia ($p = 0.257$, $p = 0.986$). Irisin levels were higher in the healthy control group ($p < 0.001$). In the control group, a negative correlation was found between irisin and BMI (r = −0.25, $p = 0.048$), and there was a positive correlation between irisin and activity levels (r = 0.5, $p = 0.001$).

When we divide the control group and the schizophrenia group into three according to their activity levels and compare each group with the control group; in the low-activity schizophrenia group, the irisin level is lower than in the low-activity control group; In the sufficient-active schizophrenia group, the level of irisin was found lower than the level of irisin in the sufficient-active control group ($p = 0.014$; $p < 0.001$) (Table 3).

When the patients with schizophrenia were divided into two groups as for that use of clozapine, we did not find

Table 1. Demographic findings of samples

Variable	Schizophrenia (n = 96)	Controls (n = 63)	p value
Sex (female)	32 (33.3)	22 (34.9)	0.84
Age	41.5 ± 10.8	41.7 ± 13.0	0.93
Drug therapy			
Clozapine use	30 (31.3)	NA	-
Other antipsychotic use	66 (68.7)	NA	-
Numberof hospitalizations	2.1 ± 2.2	NA	-
The duration of illness	14.8 ± 8.5	NA	-
Smoking (smoker)	40 (41.7)	24 (38.1)	0.66
BMI (kg/m^2)	26.7 ± 5.4	26.9 ± 3.2	0.84
BPRS score	21.6 ± 8.2	NA	

Values are presented as number (%) or mean ± standard deviation.
BMI, body mass index; BPRS, Brief Psychiatric Rating Scale; NA, not applicable.

Table 3. Irisin levels according to patient's activity levels

Variable	Schizophrenia	Control	p value
Non-active (μg/ml)	3.7 ± 0.8	4.0 ± 0.7	0.172
Low active (μg/ml)	3.9 ± 0.9	4.4 ± 0.5	0.014
Sufficiently active (μg/ml)	3.9 ± 0.6	4.7 ± 0.3	< 0.001

Values are presented as mean ± standard deviation.
Independent samples t test was used in the data analysis.

Table 2. Laboratory findings

Variable	Schizophrenia (n = 96)	Controls (n = 63)	p value
Irisin (μg/ml)	3.8 ± 0.8	4.3 ± 0.6	< 0.001
Fasting blood glucose (mg/dl)	88 (52−151)	84 (58−151)	0.12
HbA1c (%)	5.6 ± 0.5	5.6 ± 0.5	0.97
HOMA-IR	1.83 (0.19−19.78)	1.38 (0.15−5.87)	0.20
Insulin (mU/L)	7.66 (1.07−80.92)	7.63 (1.94−22.43)	0.37
Waist circumference (cm)	99.0 ± 15.2	99.4 ± 11.6	0.87
HDL (mg/dl)	44.1 ± 8.8	46.8 ± 11.1	0.12
LDL (mg/dl)	139.5 ± 36.8	132.2 ± 32.8	0.19
Total cholesterol (mg/dl)	198.9 ± 44.9	189.4 ± 42.1	0.19
Triglyceride (mg/dl)	159 (42−479)	123 (39−620)	0.05
IPAQ-SF (MET*minute/week)	610 (0−7,550)	670 (0−9,600)	0.24

Values are presented as mean ± standard deviation or median (minimum [min]−maximum [max]).
HOMA-IR, homeostasis model assessment of insulin resistance; HDL, high-density lipoprotein; LDL, low-density lipoprotein; IPAQ-SF, International Physical Activity Questionnaire-short form.
Independent samples t test and Mann−Whitney U test were used in the data analysis.

any difference between patients using clozapine and using other antipsychotics in terms of irisin ($p = 0.5$).

When the levels of physical activity and irisin were compared with Two-way Independent ANOVA, irisin levels were found to be statistically different in schizophrenia + control and activity groups (2 schizophrenia-control group X 3 activity groups). In this respect, irisin levels were lower in the inactive group than in those with low or sufficient activity ($F = 6.49$, $p = 0.001$). However, no significant difference was determined when the relationship between the irisin level and activity levels in schizophrenia but irisin levels were found to be statistically different in the control and activity groups. In this respect, irisin levels were lower in the inactive group than in those with low or sufficient activity (respectively $p = 0.006$; $p = 0.001$).

There was not any correlation between IFAQ-SF and irisin levels in schizophrenia ($p = 0.28$, $r = 0.11$) while there was a significant correlation in the control group ($p = 0.001$, spearman's rho = 0.471).

DISCUSSION

According to our knowledge, this is the first study to investigate the relation of irisin levels and physical activity in patients with schizophrenia. Previously, we found no differences between non-obese and nondiabetic patients with schizophrenia and controls in terms of irisin. The result of the earlier study was explained by having a small sample size and not including some metabolic parameters [17]. In the present study, we evaluated parameters that might affect levels of irisin such as physical activity levels and metabolic parameters.

In our previous study, the correlation between positive and negative syndrome scale and irisin levels were not found to be statistically significant [17]. Similarly, in this study, there was no significant correlation between irisin levels, duration of disease and BPRS total score in patients with schizophrenia. In this study, there was no difference between schizophrenia and control groups in terms of metabolic syndrome parameters and physical activity levels in the last seven days, which have been shown to affect irisin levels in previous studies. Levels of irisin, however, were found to be lower in the schizophrenia group compared to controls. In the study that measured the level of irisin in the first episode schizophrenia, the irisin level was found higher in the schizophrenia group than the control group. In the same study, the role of physical activity on the level of irisin was not investigated [18]. According to our study, physical activity may have an effect on the change in the level of irisin in the schizophrenia group. In the literature, it was found that irisin can protect neurons against oxidative damage and mitigate diabetes-induced oxidative/nitrative stresses by reducing production of superoxide and peroxynitrite, and increasing production of antioxidant enzymes including glutathione peroxidase, catalase and superoxide dismutase [18-20]. Decreasing levels of irisin in schizophrenia might be one of the reasons behind the deterioration of oxidative processes in schizophrenia.

The studies conducted on the relationship between irisin and activity have presented different results, an increase in the levels of irisin correlated with activity levels has been obtained in various studies [21]. Dinas *et al.* [22] studied the acute effect of irisin on physical activity, reporting that circulating irisin levels were found to be in positive correlation with activity levels in individuals with high weekly physical activity. The level of irisin was found to be statistically higher in the low active and sufficiently active groups than in the inactive group when all participants were evaluated in our study. This result is compatible with our hypothesis that irisin levels could be affected by activity levels. A positive correlation was obtained in terms of irisin and activity levels in healthy controls.

In this study, we found that irisin was affected both by activity and found to be lower in schizophrenia independent from activity and there was no difference between the inactive schizophrenia and inactive control groups in terms of irisin levels. In a study conducted on patients with ischemic stroke, serum irisin levels were lower in patients with depression than in those without depression, and this was thought to be due to the relationship between inflammation and irisin [23]. Relationship between irisin and inflammation is shown by the positive correlation between the negative acute phase reactant retinol binding protein-4 and the anti-inflammatory adiponectin and irisin [24]. Irisin can decrease secretion of inflammatory cytokines such as TNF, IL-6, and NF-κB with its anti-inflammatory properties [25]. The low levels of irisin in the schizophrenia group in our study could be a result of the presence of inflammatory processes in schizophrenia. It is shown in a previous study that irisin treatment significantly reduces the levels of proinflammatory markers like

nitrotyrosine, superoxide anion and 4-hydroxynonenal in peri-infarct brain tissues [26]. Related to these findings, irisin would find to be a therapeutic target to reduce inflammation in the brain of patients with schizophrenia in the future.

In another study including patients with Alzheimer's disease (AD), a neurodegenerative disease, it was found that increased irisin levels leads to improved cognition and AD pathogenesis [27]. In our study, we didn't evaluate cognitive function in both groups. Therefore, further studies can also evaluate irisin's effect on cognition in schizophrenia and healthy controls. The irisin level in patients with the first episode schizophrenia was found to be higher than the control group [17], the reason for this result may be due to an increase in the activity levels because of positive psychotic symptoms. Therefore, it is important to evaluate the level of physical activity while comparing irisin levels in the future studies.

Irisin is formed by proteolytic cleavage of FNDC5 as a result of the activation of the transcription coactivator 1 alpha of PPAR-gamma by physical activity [7]. Therefore, there is a relationship between PPAR-gamma and irisin. In another study that compared PPAR-gamma levels in patients with schizophrenia and healthy controls, the results showed that PPAR-gamma levels were lower in the schizophrenia group [28]. Also, irisin increases neuronal BDNF expression [7]. It has been reported in meta-analyses that BDNF levels were lower in schizophrenia groups when compared with control groups [29].

The relation between PGC-1α-FNDC5 and irisin-BDNF could be assumed as a pathway. Considering the relevant findings in the literature, it can be concluded that there may be a deterioration of schizophrenia in the PGC-1α-FNDC5/irisin-BDNF pathway. Our findings should be supported by studies evaluating this pathway as a whole.

Limitations

This situation can be evaluated more clearly in the future through longitudinal studies in which physical activity should be measured by wearable technology tools. The other limitation of this study is that the using antipsychotic can cause the alteration in levels of irisin. So, we need future studies which are planned with medication free patients with schizophrenia.

■ Acknowledgments

This study was supported by the Scientific Research Committee of the Dışkapı Training and Research Hospital (funding number: 66, Date: 2017).

■ Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

■ Author Contributions

Conceptualization: Gamze Erzin, Olga Güriz, Sibel Örsel. Data collection: Gamze Erzin, Olga Guriz. Formal analysis: Sibel Örsel. Funding acquisition: Gamze Erzin. Investigation: Gamze Erzin, Sibel Örsel. Methodology: Gamze Erzin, Olga Güriz, Ali Yalçındağ, Sibel Örsel. Project administration: Gamze Erzin, Sibel Örsel. Resources: Gamze Erzin. Supervision: Sibel Örsel, Akfer Kahıloğulları. Writing—original draft: Gamze Erzin, Ali Yalçındağ, Akfer Kahıloğulları, Sibel Örsel. Writing—review & editing: Gamze Erzin, Akfer Kahıloğulları, Sibel Örsel.

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