Psychiatry and Behavioral Sciences 2024;14-1:40-47

Doi: 10.5455/PBS.20230914073554

ORIGINAL RESEARCH

Investigation of Irisin Levels in Patients with Major Depressive Disorder

Burak Okumuş[1], Meltem Pusuroğlu[2], Mehmet Baltacıoğlu[2], İlkay Bahçeci[3], Bülent Bahçeci[2]

[1] *Usak Training and Research Hospital, Department of Psychiatry, Usak, Türkiye*

[2] *Recep Tayyip Erdogan University, Medical School, Department of Psychiatry, Rize, Türkiye*

[3] *Recep Tayyip Erdogan University, Medical School, Department of Medical Microbiology, Rize, Türkiye*

Abstract

Objective: Major depressive disorder (MDD) is a common psychiatric disorder. Irisin, produced by proteolysis of FNDC5, is thought to be an exercise-induced hormone that may play a critical role in inducing antidepressant-like effects. Our study aimed to investigate the relationship between irisin and newly diagnosed MDD patients.

Methods: This cross-sectional study included 85 first-time diagnosed MDD patients and 81 healthy controls. Patients were diagnosed with MDD using the Structured Clinical Interview Questionnaire for DSM-IV Axis I and II Disorders (SCID-I, II) and the Hamilton Depression Scale (HAM-D). After an overnight fast, 5 ml of peripheral blood was drawn and serum irisin levels were measured.

Results: When the effects of age and gender variables were controlled, no statistically significant difference in irisin levels was found between the groups. ($F=1.832$, $p=0.178$). When the effects of age, gender and body mass index variables were controlled and a partial correlation was made between irisin and HAMD scores, a significant negative correlation was found between irisin and HAMD scores ($p<0.001$, $r=-0.523$). The correlation analysis showed a statistically significant negative relationship between age and irisin levels ($p=0.008$, $r=-0.205$). However, when the effects of other variables were controlled and a partial correlation was made, no statistically significant relationship was found ($p=0.610$, $r=-0.207$).

Conclusion: Our results indicate that irisin levels are associated with the severity of depression. Further studies are needed on the use of irisin as a potential biomarker for predicting clinical course and treatment response in patients with severe MDD.

Keywords: Major Depressive Disorder, Irisin, Etiopathogenesis

INTRODUCTION

Major depressive disorder (MDD) is a multifactorial and common psychiatric disorder that caused by biological, psychological, and social factors. The etiology of MDD remains unclear despite many extensive studies. There are many studies in the literature investigating the unpredictable variation in the clinical presentation of MDD. An important area that draws attention among the studies that emphasize differences is the study on the biological basis of MDD. Studies on the biological basis of MDD have found that clinical differences may be closely related to endocrine, inflammatory, and neural circuits (1, 2).

Irisin is an autocrine, paracrine, and endocrine hormone that is reported to be 100% similar in humans and mice (3). It occurs as a result of the proteolysis of a protein called fibronectin type III domain 5 (FNDC5) in the circulation. FNDC5 gene expression is directly related to peroxisome proliferator-activated receptor-γ and coactivator-1α, which are important parts of the muscle layer stimulated by exercise (4, 5). FNDC5 in the brain; Purkinje cells in the cerebellum are important regulators of brain-derived neurotrophic factor (BDNF) released from the hypothalamus and hippocampus. It has been shown that increasing FNDC5 levels positively affects cortical neuron survival (6).

Corresponding Author: Burak Okumuş, **E-mail:** okumusband@gmail.com

Citation: Okumuş B, Pusuroğlu M, Baltacıoğlu M, Bahçeci İ, Bahçeci B. Investigation of Irisin Levels in Patients with Major Depressive Disorder. Psychiatry and Behavioral Sciences 2024;14-1:40-47. Doi: 10.5455/PBS.20230914073554

Received: Sep 17, 2023 **Accepted:** Jan 05, 2024

Content of this journal is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

Preclinical research has provided the first evidence of a link between irisin and depression. Preclinical studies suggest that irisin is an exercise-induced hormone that may play a critical role in antidepressant-like effects in rats (7). One study found that four weeks of moderate-intensity exercise in adult female mice increased hippocampal FNDC5/irisin levels and had an antidepressant-like effect in these mice (8). In another preclinical study, centrally administered irisin reduced depression-like symptoms in mice through an increase in BDNF levels. (9). The antidepressant effect of irisin was reported to be observed following systemic administration (10). Another animal model of depression has shown that irisin induces significant changes in monoamine levels in many hypothalamic nuclei involved in feeding behaviour and vegetative functions, as well as in subcortical nuclei associated with neuropsychiatric disorders (11). A recent study reports that irisin may mediate the effect of esketamine on depressive behaviour (12).

Clinical studies being carried out in special groups of patients have focused on a possible link between irisin and depression (13-15). These studies provide promising evidence that irisin may have beneficial effects on symptoms of depression (13-18). In addition, clinical studies of irisin have reported a significant negative correlation between irisin levels and depression scale scores (16-18). In a study including patients with MDD and bipolar affective disorder and healthy controls; there was no statistically significant difference in irisin levels between the groups, but there was a negative correlation between depression severity, number of depressive episodes, disease duration and irisin levels. These results may indicate that irisin may be affected by bipolar depression and unipolar depression (16). In a study examining the relationship between depression and serum irisin, adropin and preptin levels, it was found that these biomarker levels decreased in depression. However, this research suggests that the evaluation of these biomarkers may be more useful in a long-term follow-up study (19).

Preclinical and clinical research has shown that irisin can induce BDNF expression in the ventral tegmental area and hippocampus, and therefore irisin may play an important role in reducing symptoms of depression (6-10, 16, 20). There are also studies suggesting that irisin may act as an antidepressant by regulating energy metabolism in the prefrontal cortex (7). Therefore, the main purpose of this study is to determine the relationship between the first episode of MDD and the level of irisin.

Here are this study's hypotheses: 1. Irisin levels will be found to be lower in patients with MDD than in healthy controls. 2. There will be a negative correlation between symptom severity and irisin levels in the MDD group.

METHODS

The ethical committee of Recep Tayyip Erdogan University approved the protocol (Date: August 28, 2019/ No: 2019/135). The research group was recruited from 18 to 65 years old who applied to the Psychiatry Clinic of Recep Tayyip Erdogan University Training and Research Hospital between 2019 and 2020 and were diagnosed with MDD according to the DSM-4 criteria. The exclusion criteria for the MDD group were as follows: diagnoses of any neurological or chronic medical condition, previous medical treatment , chronic drug use, diagnoses of alcohol /substance – related disorder, being in a pregnancy and lactation period, body mass index (BMI) less than 18.5 and greater than 24.9 kg/m2, performing heavy work that requires muscle strength, performing heavy sports, having a situation that prevents them from being interviewed or using the scale, and being reluctant to participate in the study. All patients were fully informed about the study. Written informed consent was obtained from patients who met the inclusion and exclusion criteria and agreed to participate in the study. The power analysis of the study was performed using G-Power 3.1. The minimum number of samples required for a difference analysis with an effect size of 0.5, an alpha value of 0.05 and a power of 80% was calculated to be 64 for each group, for a total of 128 people (21). After adjustment for the possibility of missing data, a total of 166 samples (85 patients and 81 controls) were included in the study.

The sociodemographic data collection form and the Structured Clinical Interview Questionnaire for DSM-IV Axis I and II Disorders (SCID-I, II) were administered to the patients and control groups included in the study. In contrast to the control group, the Hamilton Depression Scale (HAM-D) was administered to the patient group. The HAM-D was developed to increase the diagnostic reliability of SCID-I, II interviews and to make DSM-IV axis I and II diagnoses, which include clinical psychopathological conditions, to ensure the comparability of the studies. Turkish adaptation and clinical studies of the semi-structured clinical interview scale SCID-I, II were made by Özkürkçigil et al. (1999) (22). The 17-item HAM-D was administered by an

interviewer to measure the severity of depression in the patient group. The HAM-D was developed by Hamilton in 1960. The Turkish validity and the reliability study was conducted by Akdemir et al. in 1996. The reliability of the Turkish version of the scale, Cronbach's alpha values were 0.75 and the Sperman-Brown reliability coefficient was 0.76 in the internal consistency study. The inter-rater reliability coefficient is between 0.86 and 0.98 (23).

Blood Sampling

Blood samples for the study were collected in 5 ml volumes in Vacusera yellow-capped gel plastic serum separator tubes from people who had rested for at least 15 minutes and were sitting in the morning after an overnight fast. After clotting, serum samples were collected by centrifugation at 3500 rpm for 15 minutes according to the manufacturer's recommendations. Serum was collected in two separate Eppendorf tubes of at least 1 cc each and stored at – 20°C until assayed. Lipemic and clotted blood were excluded from the study.

Analysis of The Irisin Levels

The irisin ELISA kit used was serum (Human Irisin assay kit, Elabscience, USA) and used the sandwich ELISA principle. A human irisin specific antibody is precoated on the micro ELISA plate provided in this kit. Standards and samples were added to the wells of the micro ELISA plate and combined with the specific antibody. Biotinylated detection antibody specific for human irisin and avidin-horseradish peroxidase (HRP) conjugate were then added sequentially to each microplate well and incubated. The free components were washed. Substrate solution was added to each well. Wells containing only human irisin, biotinylated detection antibody and avidin-HRP conjugate appeared blue. Stop solution was added. The enzyme-substrate reaction was stopped and the colour changed to yellow. The optical density (OD) was measured spectrophotometrically (Multiskan GO, Thermo Scientific, Waltham, MA, USA). The wavelength was 450 nm ± 2 nm. The OD value was measured by reference to the standard curve generated by the Titri ELISA software and is proportional to the concentration of human irisin. The absorbance values were then converted to irisin concentration using the standard curve. The detection range of the test was 15.63-1000 pg/mL and the sensitivity was 9.38 pg/mL.

Statistical Analysis

All data were analyzed using SPSS v18.0. Descriptive statistics were presented mean±standard deviation for the normally distributed variables. Categorical variables were reported as frequencies and percentages. The normal distribution of the data was assessed using histogram, Kolmogorov-Smirnov test, skewness and kurtosis values. For data with a normal distribution, the difference between groups was assessed by means of the independent samples t-test. Chi-square test was used for categorical data. ANCOVA was used to compare the groups' irisin levels, while age and gender were used as covariates. In order to assess the correlation in data that conform to a normal distribution, the Pearson correlation test was used and a partial correlation was made by controlling the effects of all variables. Statistical significance was $p<0.05$.

RESULTS

The study included 85 patients and 81 healthy controls. 64 (75.3%) of the patients are women and 21 (24.7%) are men. The average age is 40.28±12.23, with the youngest being 18 and the oldest being 65. The distribution rates for age and gender are different between the two groups ($p=0.017$ and $p<0.001$, respectively). The clinical and socio-demographic characteristics of the patient and control groups are shown in Table 1. ANCOVA was performed to compare irisin levels due to age and gender differences between the groups. As a result of the ANCOVA test, no statistically significant difference was found between the groups in terms of irisin levels ($F=1.832$, $p=0.178$) (Table 2). The relationship between irisin levels and clinical data was investigated in the patient group. A significant negative correlation was found between irisin levels and HAMD scores ($p<0.001$, $r=-0.429$). When the effects of age, gender and body mass index values were controlled and a partial correlation was made between irisin and HAM D, a negative significant relationship was found between the two variables ($p<0.001$, $r=-0.523$). Correlation analysis revealed a statistically significant negative relationship between age and irisin levels ($p=0.008$, $r=-0.205$). However, when a partial correlation was made, controlling for the effects of other variables, no statistically significant relationship was found ($p=0.610$, $r=-0.207$) (Table.4).

Table 1. Sociodemographic characteristics of groups

		MDD(n=85)		Control(n=81)		
		mean(SD)	min-max	mean(SD)	min-max	p
Age		40.28(12.23)	18-65	36.06(10.11)	20-56	**0.017***
BMI		20.8 (2.01)	18-24	21.18 (1.78)	18-24	0.194*
		n	%	n	%	
Gender	**Male**	21	24.7	42	51.85	**<0.001****
	Female	64	75.3	39	48.15	

*n: Number of cases; *:Independent Sample T Test, **: Chi-Square Test;*
MDD: Major Depressive Disorder, SD: Standard Deviation
Min: Minimum; Max: Maximum, p<0.05

Table 2. Difference in irisin levels between patients and control group

	Groups (n=166)					
	MDD (n=85)		control (n=81)		F	p
	mean(SD)	Adj means (SE)	mean (SD)	Adj means (SE)		
Irisin	82.88 (11.75)	84.47(1.77)	89.34 (14.74)	87.66(1.57)	1.832	0.178

ANCOVA, MDD: Major Depressive Disorder Adjusted by gender and age, p<0.05

Table 3. Irisin level difference in between genders in patient group

	Female	Male	p
	mean(SD)	mean(SD)	
Irisin	82.70(12.31)	85.42(14.34)	0.441

Independent Sample T Test, p<0.05

Table 4. Relationship between irisin and clinical variables in patients group

	Irisin			
	r_1	p_1	r_2	p_2
HAM-D	-0.523	**<0.001**	-0.429	**<0.001**
BMI	0.061	0.589	-0.117	0.133
Age	-0.207	0.610	-0.205	**0.008**

r_1:partial correlation, r_2:pearson correlation, p<0.05
HAM-D: Hamilton Depression Scale; BMI: body mass index

DISCUSSION

There are many biomarkers being investigated for the diagnosis, treatment and clinical course of MDD. Despite its clinical importance, understanding the biological basis of MDD remains unclear due to common comorbidities and low specificity of biomarkers (1). The hormone irisin, which we believe may have a role in the biology of MDD, was the subject of this study. Our study was conducted with patients who had been diagnosed with first episode MDD. When the effects of age and gender variables were controlled, no statistically significant difference in irisin levels was found between the groups. Similarly, another study in the literature that included bipolar depression, unipolar depression and healthy controls found no statistically significant difference in irisin levels between the groups (16). Contrary to these findings, it has been reported that irisin levels in patients diagnosed with depression accompanying coronary heart disease are lower than in those without depression (17). In a 6-month follow-up study of patients diagnosed with post-stroke depression, serum irisin levels were found to be lower in patients with comorbid depression, and it was reported that decreased serum irisin levels were an independent predictor of the risk of developing post-stroke depression (24). In another study that included patients with MDD, a significant decrease in the serum levels of irisin was found (19). Serum irisin levels were

found to be lower in elderly patients with diabetes mellitus (DM) with depressive symptoms compared with controls in a study (25). It may be important to focus on the different factors that can affect irisin levels in the blood and to explain the differences found in these studies. There are many factors that affect irisin levels in the blood (26). Irisin is well distributed in many different tissues, including muscle and fatty tissue, as well as cerebrospinal fluid, cerebellum, thyroid, pineal gland, liver, pancreas, testicle, spleen, stomach, and fetus. Therefore, irisin levels; type 2 DM, DM-related kidney and eye complications, insulin resistance, thyroid disease, polycystic ovary syndrome, osteoporosis, Prader-Willi syndrome, neurodegenerative diseases, cancers, medications, obesity, fat metabolism, fat mass, lean muscle mass, BMI, waist circumference and waist-to-hip ratio (25, 27, 28). Our study examined participants' self-reports and health system records to exclude comorbidities. Differences in glucose and lipid metabolism may affect irisin levels (25, 27). In our study, the lipid profiles and biochemical parameters associated with glucose metabolism of the participants were not systematically controlled, which may explain the lack of difference in irisin levels between the groups. Furthermore, within the first year of seeking treatment, only 20% of people with bipolar disorder who have a depressive episode are diagnosed with bipolar disorder (29). It may not be possible to distinguish type I or II bipolar disorder from unipolar depression, especially in patients who present during a depressive episode and have no clear clue of mania or hypomania (30). It has been reported that unipolar depression is the most common misdiagnosis, especially in patients with type II bipolar disorder (29, 30). Therefore, an issue to be considered in terms of diagnosis is the fact that our study included first episode MDD.

One of the valuable findings of our study is that a statistically significant negative correlation was found between irisin levels and HAM-D scores when a partial correlation was made by controlling for the effects of age, gender and body mass index. Consistent with our study, many studies have shown that there is a statistically negative relationship between irisin and depression scores (16-19). Irisin levels were found to be negatively correlated with HAM-D scores in a study of bipolar depression patients, MDD patients and healthy controls. The same study reported that there was a negative correlation between irisin levels and the number of depressive episodes, the duration of the disease and the severity of the depressive episode (16). In a study of patients with MDD, serum irisin levels were found to be positively associated with quality of life and negatively associated with depression severity and functional impairment (19). The negative correlation observed between irisin levels and HAM-D scores may suggest that irisin levels have predictive value in assessing the severity of depression in patients with first-episode MDD. In this context, the severity of a depressive episode is associated with high relapse rates, chronicity and impaired functioning (31-33). Many patients have a 60% lifetime risk of recurrence after a first episode of MDD (31). The severity of the episode and the presence of recurrent relapses increase the risk of future episodes at higher rates (32). Evaluation of serum irisin levels in long-term follow-up may be more meaningful, according to a study of patients with MDD (19). Based on the literature, irisin levels may be a useful biomarker for predicting the clinical course of MDD (16, 32, 33). Further studies could investigate whether irisin can be used to help identify patients with MDD who are at risk of having poor treatment outcomes (33).

MDD is a common condition, especially among older adults. MDD is also considered a risk factor for dementia. Understanding the molecular links between MDD and dementia is crucial to understanding common disease mechanisms (15). Reduced levels of brain-derived neurotrophic factor (BDNF) and neuroinflammation are known to play an important role in the pathophysiology of MDD and dementia (15, 28, 34). Irisin has been shown to improve cognitive function by increasing BDNF levels in animal models of Alzheimer's disease (34). It has been found that there is a decrease in cerebrospinal fluid irisin and BDNF levels in depression in elderly dementia patients, and the same study emphasised that irisin may be a common molecule linking depression and dementia (15). Our study found a statistically significant negative relationship between age and irisin levels. However, when the effects of other variables were controlled and a partial correlation was made, no statistically significant relationship was found. It is well known that the interaction between depression and dementia is a complex (15, 28, 34). Irisin may be affected by many comorbid conditions and factors (25, 27, 28). New research needs to be conducted in this context; it may focus on the relationship of the accumulated irisin literature to dementia and depression.

There are studies suggesting that the antidepressant effect of exercise may be explained by the increase in irisin levels during exercise (35-40). However, there has been no clear evidence as to what the relationship may be with the type of exercise (41). For this reason, cases

who did heavy work and/or sports that required muscle strength were not included in our study. This is one of the strenghts of our study. On the other hand, one of the most common clinical symptoms of MDD is a decrease in psychomotor activity, which may increase depending on the severity of the depressive episode (42). In this respect, psychomotor retardation, which may increase with the severity of the depressive episode, may have explained the negative relationship between HAM-D scores and irisin levels. Clinical studies have reported a relationship between depression scores and irisin levels similar to our study (16-19). A study of patients with MDD, bipolar depression and healthy controls found that levels did not differ between groups. The study emphasized that statistically insignificant results between groups may occur because irisin is affected by physical activity (16). Although we included cases who did not do heavy work or exercise in the study, we did not objectively measure the physical activity levels of the participants. The level of irisin can be determined more clearly in studies in which psychomotor activity is monitored objectively.

The effort to find an answer to the research question of our study was hypothesized on the basis of the theoretical foundations obtained from the literature. However, it should be noted that this study has several limitations. For example, it was not possible to establish appropriate assessment groups specific to the subtypes resulting from the heterogeneity of MDD. Therefore, it may not be appropriate to generalize the results to MDD subtypes. The inclusion of patients who did not exercise, had a normal body mass index, and were diagnosed with first – episode MDD may be a strength of our study. In addition, the inclusion of patients under the age of 65 years who had not previously received psychiatric treatment and who had no comorbidities to exclude the treatment burden of comorbid conditions is a strength of the study. Given the limitations of the studies that have evaluated the relationship between MDD and irisin, it is believed that this study makes a contribution to the literature.

CONCLUSIONS

In conclusion, our study evaluated the relationship between the hormone irisin, which is reported to play a role in the maturation of neurons and is effective in its pathophysiology, and MDD. The statistically significant negative relationship between depression severity and irisin levels is noteworthy. This may provide important information about the clinical course and severity of MDD. The severity of a depressive episode is associated with chronicity and functional impairment. In this context, further studies of irisin hormone may be promising in predicting the severity, treatment resistance, or clinical course of MDD. According to our study, the fact that irisin levels in first-episode MDD patients do not show a statistically significant difference compared to healthy controls can be explained by the fact that irisin levels decrease more as the number of recurrent MDD episodes increases. Therefore, conducting new studies with the assumption that the rate of decline in irisin level measurements in recurrent MDD episodes can provide an idea of the prognosis or severity of the disease may add promising data to the literature. Further studies in this area may contribute to the biological understanding of MDD.

Acknowledgements: *We would like to thank the participants in our study for their dedicated work.*
Funding: *The authors received no financial support for the research.*
Conflicts of interest: *This study does not have any form of conflict of interest.*
Ethics Committee Approval: *This study was approved by Ethics Committee of Recep Tayyip Erdoğan University (Decision date: August 28, 2019/ No: 2019/135)*
Peer-review: *Externally peer-reviewed.*
Author Contributions:
Research idea: BB, BO.
Design of the study: BB, BO.
Acquisition of data for the study: BB, BO.
Analysis of data for the study: BB, BO, IB
Interpretation of data for the study: BB, BO, IB, MP, MB.
Drafting the manuscript: BB, BO, IB, MP, MB.
Revising it critically for important intellectual content: BB, BO, IB, MP, MB.
Final approval of the version to be published: BB, BO, IB, MP, MB.

REFERENCES

[1] Otte C, Gold SM, Penninx BW, Pariante CM, Etkin A, Fava M, Mohr DC, Schatzberg AF. Major depressive disorder. Nature Reviews Disease Primers 2016;2:1–20. DOI: 10.1038/nrdp.2016.65.

[2] Fang Y, Mao R. Introduction. In: Fang Y, editor. Depressive Disorders: Mechanisms, Measurement and Management. 1st ed. Springer Nature Singapore Pte Ltd.; 2019. p. 1–19. DOI: 10.1007/978-981-32-9271-0.

[3] İnci A, Aypak S. Irisin and its metabolic effects: Review. Turkiye Klinikleri Journal of Endocrinology. 2016;11(1):15–21. DOI: 10.5336/endocrin.2016-49995. (Turkish).

[4] Aydin S. Three new players in energy regulation: Preptin, adropin and irisin. Peptides. 2014;56:94–110. DOI: 10.1016/j.peptides.2014.03.021.

[5] Boström P, Wu J, Jedrychowski MP, Korde A, Ye L, Lo JC, Rasbach KA, Boström EA, Choi JH, Long JZ, Kajimura S, Zingaretti

MC, Vind BF, Tu H, Cinti S, Højlund K, Gygi SP & Spiegelman BM. A PGC1-α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. Nature. 2012;481(7382):463–468. DOI: 10.1038/nature10777.

[6] Young MF, Valaris S, Wrann CD. A role for FNDC5/Irisin in the beneficial effects of exercise on the brain and in neurodegenerative diseases. Progress in Cardiovascular Diseases. 2019;62(2):172–178. DOI: 10.1016/j.pcad.2019.02.007.

[7] Wang S, Pan J. Irisin ameliorates depressive-like behaviors in rats by regulating energy metabolism. Biochemical and Biophysical Research Communications. 2016;474(1):22–28. DOI: 10.1016/j.bbrc.2016.04.047.

[8] Gruhn K, Siteneski A, Camargo A, Freitas AE, Olescowicz G, Brocardo PS, Rodrigues ALS. Physical exercise stimulates hippocampal mTORC1 and FNDC5/irisin signaling pathway in mice: Possible implication for its antidepressant effect. Behavioural Brain Research. 2021;400:113040. DOI: 10.1016/j.bbr.2020.113040.

[9] Siteneski A, Cunha MP, Lieberknecht V, Pazini FL, Gruhn K, Brocardo PS, Rodrigues ALS. Central irisin administration affords antidepressant-like effect and modulates neuroplasticity-related genes in the hippocampus and prefrontal cortex of mice. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2018;84:294-303. DOI: 10.1016/j.pnpbp.2018.03.004.

[10] Pignataro P, Dicarlo M, Zerlotin R, Storlino G, Oranger A, Sanesi L, Lovero R, Buccoliero C, Mori G, Colaianni G, Colucci S, Grano M. Antidepressant Effect of Intermittent Long-Term Systemic Administration of Irisin in Mice. International Journal of Molecular Sciences. 2022;23(14):7596. DOI: 10.3390/ijms23147596.

[11] Yardimci A, Ertugrul NU, Ozgen A, Ozbeg G, Ozdede MR, Ercan EC, Canpolat S. Effects of chronic irisin treatment on brain monoamine levels in the hypothalamic and subcortical nuclei of adult male and female rats: An HPLC-ECD study. Neuroscience Letter. 2023;806:137245. DOI: 10.1016/j.neulet.2023.137245.

[12] Hu N, Chen X, Chen C, Liu X, Yi P, Xu T, Jia J, Feng J, Zhang C, Wang X. Exploring the role of esketamine in alleviating depressive symptoms in mice via the PGC-1α/irisin/ERK1/2 signaling pathway. Scientific Reports. 2023;13(1):16611. DOI: 10.1038/s41598.023.43684-9.

[13] Bilek F, Cetisli-Korkmaz N, Ercan Z, Deniz G, Demir CF. Aerobic exercise increases irisin serum levels and improves depression and fatigue in patients with relapsing remitting multiple sclerosis: A randomized controlled trial. Multiple Sclerosis and Related Disorders. 2022;61:103742. DOI: 10.1016/j.msard.2022.103742.

[14] Tang XQ, Liao RY, Zheng LJ, Yang LL, Ma ZL, Yi C, Liu J, Liu JC, Kuang YJ, Cai HA, Huang L. Aerobic exercise reverses the NF-κB/NLRP3 inflammasome/5-HT pathway by upregulating irisin to alleviate post-stroke depression. Annals of Translational Medicine. 2022;10(24):1350. DOI: 10.21037/atm-22-5443.

[15] Gonçalves RA, Sudo FK, Lourenco MV, Drummond C, Assunção N, Vanderborght B, Ferreira DDP, Ribeiro FC, Pamplona FA, Tovar-Moll F, Mattos P, Ferreira ST, De Felice FG. Cerebrospinal fluid irisin and lipoxin A4 are reduced in elderly Brazilian individuals with depression: Insight into shared mechanisms between depression and dementia. Alzheimer's & Dementia: The Journal of the Alzheimer's Association. 2023;19(6):2595-2604. DOI: 10.1002/alz.12893.

[16] Erzin G, Yüksel RN, Usta MB, Topçuoğlu C, Örsel S. Assessment of irisin levels in patients with bipolar depression and unipolar depression. Annals of Clinical and Analytical Medicine. 2020;11(6):583–586. DOI: 10.4328/ACAM.20283.

[17] Han W, Zhang C, Wang H, Yang M, Guo Y, Li G, Zhang H, Wang C, Chen D, Geng C, Jiang P. Alterations of irisin, adropin, preptin and BDNF concentrations in coronary heart disease patients comorbid with depression. Annals of Translational Medicine. 2019;7(14):298. DOI: 10.21037/atm.2019.05.77.

[18] Mucher P, Batmyagmar D, Perkmann T, Repl M, Radakovics A, Ponocny-Seliger E, Lukas I, Fritzer-Szekeres M, Lehrner J, Knogler T, Tscholakoff D, Fondi M, Wagner OF, Winker R, Haslacher H. Basal myokine levels are associated with quality of life and depressed mood in older adults. Psychophysiology. 2021; 58:e13799. DOI: 10.1111/psyp.13799.

[19] Cicek MA, Tuygar Okutucu F, Ozturk N. Irisin, adropin, and preptin as biomarkers of energy dysregulation in depressive disorder. Current Medical Research and Opinion. 2023;39(9):1263-1270. DOI: 10.1080/03007.995.2023.2247317.

[20] Papp C, Pak K, Erdei T, Juhasz B, Seres I, Szentpéteri A, Kardos L, Szilasi M, Gesztelyi R, Zsuga J. Alteration of the irisin-brain-derived neurotrophic factor axis contributes to disturbance of mood in COPD patients. International Journal of Chronic Obstructive Pulmonary Disease. 2017;12:2023-2033. DOI: 10.2147/COPD.S135701.

[21] Cohen J. (1988). Statistical power analysis for the behavioral sciences. New York, NY: Routledge Academic.

[22] Corapcioglu A, Aydemir O, Yildiz M, Esen A, Koroglu E. Structured clinical interview for DSM-IV (SCID-I) Turkce formu. Hekimler Yayın Birliği; 1999. (Turkish).

[23] Akdemir A, Örsel S, Dağ İ, Ark. V. Hamilton depresyon derecelendirme ölçeği'nin geçerliği, güvenilirliği ve klinikte kullanımı. Psikiyatri Psikoloji Psikofarmakoloji Dergisi. 1996;4:251-259. (Turkish).

[24] Tu WJ, Qiu HC, Liu Q, Li X, Zhao JZ, Zeng X. Decreased level of irisin, a skeletal muscle cell-derived myokine, is associated with post-stroke depression in the ischemic stroke population. Journal of Neuroinflammation. 2018;15(133):1–10. DOI: 10.1186/s12974.018.1177-6.

[25] Gorska-Ciebiada M, Ciebiada M. Association between serum irisin and leptin levels and risk of depressive symptoms in the diabetic elderly population. Journal of Clinical Medicine. 2023;12(13):4283. DOI: 10.3390/jcm12134283.

[26] Munoz IYM, Del Socorro Camarillo Romero E, De Jesus Garduno Garcia J. Irisin a novel metabolic biomarker: Present knowledge and future directions. International Journal of Endocrinology. 2018;(7816806). DOI: 10.1155/2018/7816806.

[27] Leustean L, Preda C, Teodoriu L, Mihalache L, Arhire L, Ungureanu M-C. Role of irisin in endocrine and metabolic disorders—Possible new therapeutic agent?. Applied Sciences. 2021; 11(12):5579. DOI: 10.3390/app11125579.

[28] Colucci-D'Amato L, Speranza L, Volpicelli F. Neurotrophic factor BDNF, physiological functions and therapeutic potential in depression, neurodegeneration and brain cancer. International Journal of Molecular Sciences. 2020;21(20):7777. DOI: 10.3390/ijms21207777.

[29] Hirschfeld RM, Lewis L, Vornik LA. Perceptions and impact of bipolar disorder: how far have we really come? Results of the national depressive and manic-depressive association 2000 survey of individuals with bipolar disorder. The Journal of Clinical Psychiatry. 2003;64(2):161-174.

[30] Phillips ML, Kupfer DJ. Bipolar disorder diagnosis: challenges and future directions. Lancet. 2013;381(9878):1663-1671. DOI: 10.1016/S0140-6736(13)60989-7.

[31] Monroe SM, Harkness KL. Recurrence in major depression: A conceptual analysis. Psychological Review. 2011;118:655–674. DOI: 10.1037/a0025190.

[32] Lee AS. Better outcomes for depressive disorders?. Psychological Medicine. 2003;33:769–774. DOI: 10.1017/s003.329.170300802x.

[33] Malik S, Singh R, Arora G, Dangol A, Goyal S. Biomarkers of major depressive disorder: Knowing is half the battle. Clinical Psychopharmacology and Neuroscience : The Official Scientific Journal of The Korean College of Neuropsychopharmacology. 2021;19(1):12–25. DOI: 10.9758/cpn.2021.19.1.12.

[34] Peng J, Wu J. Effects of the FNDC5/Irisin on elderly dementia and cognitive impairment. Frontiers in Aging Neuroscience. 2022;14:863901. DOI: 10.3389/fnagi.2022.863901.

[35] Huh JY, Mougios V, Kabasakalis A, Fatouros I, Siopi A, Douroudos II, Filippaios A, Panagiotou G, Park KH, Mantzoros CS. Exercise-induced irisin secretion is independent of age or fitness level and increased irisin may directly modulate muscle metabolism through AMPK activation. Journal of Clinical Endocrinology and Metabolism. 2014;99:E2154 –E2161. DOI: 10.1210/jc.2014-1437.

[36] Gruhn K, Siteneski A, Camargo A, Freitas AE, Olescowicz G, Brocardo PS, Rodrigues ALS. Physical exercise stimulates hippocampal mTORC1 and FNDC5/irisin signaling pathway in mice: Possible implication for its antidepressant effect. Behavioural Brain Research. 2021;400. DOI: 10.1016/j.bbr.2020.113040.

[37] Mura G, Moro MF, Patten SB, Carta MG. Exercise as an add on strategy for the treatment of major depressive disorder: A systematic review. CNS Spectrums. 2013;19:496–508. DOI: 10.1017/S109.285.2913000953.

[38] Liu PZ, Nusslock R. Exercise mediated neurogenesis in the hippocampus via BDNF. Frontiers in Neuroscience. 2018;12:1–6. DOI: 10.3389/fnins.2018.00052.

[39] Rosa JM, Pazini FL, Olescowicz G, Camargo A, Moretti M, Gil-Mohapel J, Rodrigues ALS. Prophylactic effect of physical exercise on Aβ 1–40 induced depressive like behavior: Role of BDNF, mTOR signaling, cell proliferation and survival in the hippocampus. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2019;94. DOI: 10.1016/j.pnpbp.2019.109646.

[40] Bilek F, Cetisli-Korkmaz N, Ercan Z, Deniz G, Demir CF. Aerobic exercise increases irisin serum levels and improves depression and fatigue in patients with relapsing remitting multiple sclerosis: A randomized controlled trial. Multiple Sclerosis and Related Disorders. 2022;61:103742. DOI: 10.1016/j.msard.2022.103742.

[41] Fatouros IG. Is irisin the new player in exercise-induced adaptations or not? A 2017 update. Clinical Chemistry and Laboratory Medicine. 2018;56(4):525–548. DOI: 10.1515/cclm-2017-0674.

[42] Karamustafalıoğlu O, Gül IG. Depresyon. In: Karamustafalıoğlu O, editor. Temel ve Klinik Psikiyatri. Ankara: Murat Yılmaz; 2018. p. 313–339.