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Original Article

Investigation of the role of irisin and FABP4 in iron deficiency anemia

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ABSTRACT

Objective: Anemia is defined as a condition in which the hemoglobin level is lower. Irisin (Ir) was a muscle-associated factor. Fatty acid-binding proteins (FABP) are involved in intracellular fatty acid transport. The study aimed to explore whether Ir and FABP4 levels might be linked to symptoms such as coldness, fatigue, and learning difficulties with Iron deficiency.

Material and Methods: Our study evaluated the effects of these three periods of iron deficiency, along with a control group, on serum and urine Ir, as well as FABP4 levels, both before and after iron treatment.

Results: In this study, median serum Ir levels exhibited statistically significant differences between the patient and control groups, with lower levels observed in the patient groups before treatment ($p=0.040$, $p<0.001$ and $p<0.001$). After treatment, a significant increase was noted in median serum Ir levels across all patient groups ($p=0.003$, $p=0.023$ and $p=0.014$).

Conclusion: In our study, we found that the feeling of coldness and decreased cognitive functions seen in iron deficiency may be related to serum Ir level.

Keywords: FABP4, Irisin, Iron deficiency, Iron deficiency anemia

INTRODUCTION

Anemia is clinically defined as a hemoglobin (Hb) level falling below two standard deviations from the mean for age. It is a widespread condition, particularly affecting infants and children globally. Iron deficiency (ID) is the most common cause of anemia. Globally in 2019, 21% of children aged 6–59 months had mild anaemia, 18% had moderate anemia, and 1% had severe anaemia (1). The World Health Organisation (WHO) estimates that 293 million pre-school-age and 305 million school-age children are anemic, and more than 50% are thought to be iron deficient (2). Iron deficiency significantly impacts physical growth, brain development, and early learning, with the most profound effects observed during infancy and preschool years. (3, 4). Iron plays a crucial role in myelin synthesis. Iron is required for myelin production from oligodendrocytes for maturation and function acquisition (5). ID has negative effects on brain development, myelination, and the development of major dopaminergic pathways. Persistent ID has lifelong effects on intelligence and learning functions. If low iron status is not corrected during developmental age, IQ scores may decrease by approximately 5-10 points (6, 7).

Irisin (Ir) was discovered in 2012 to be a muscle-associated factor involved in inducing the browning of white adipose tissue (WAT). Irisin-related pathways are known to be activated by peroxisome proliferator-activated receptor (PPARγ), peroxisome proliferator-activated receptor gamma coactivator 1-alpha coactivator (PGC-1α), and its release is increased by exercise. Irisin is a newly discovered peptide hormone released by proteolysis of FNDC5 protein in circulation (8, 9). Irisin is mainly responsible for the browning of WAT and the release of uncoupling protein-1 (UCP1). UCP1 exerts its effect by increasing total energy expenditure through thermogenesis (10). Irisin levels are thought to be determinant in fat storage and metabolic dysfunction (11).

Fatty acid binding proteins (FABPs) are chaperones involved in intracellular fatty acid transport, regulate lipid responses in cells, and are also linked to metabolic and inflammatory pathways.

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FABPs with a molecular weight of 14-15 kDa bind reversibly with high affinity to hydrophobic ligands such as saturated and unsaturated long-chain fatty acids, eicosanoids, and other fats. To date, nine FABP types have been identified (12, 13). FABP4 release is stimulated during adipocyte differentiation and by PPARγ receptor agonist transcription factors such as insulin, irisin, and fatty acids. Currently, FABP4 has been found to have roles in maintaining glucose homeostasis and energy storage systems. Irisin and FABP4 play a role in metabolic control. Irisin acts in metabolic control by providing thermogenesis with heat energy (14). Fatty acid binding protein-4 plays a role in metabolic events such as fatty acid storage, circulation, and glucose homeostasis, levels are increased in obese individuals (13, 15).

Iron deficiency anemia (IDA) patients tend to experience heightened sensitivity to cold compared to individuals with sufficient iron levels. While there are various theories regarding this phenomenon, the precise underlying cause remains unclear. The currently accepted view is that IDA results in impaired thermoregulation due to insufficiency of the thermoregulatory center, both in mice and humans. At the tissue level, ID is considered to impair the appropriate physiological response to cold because of impaired neurological control of the sympathetic nervous system (16). In addition, ID is thought to affect the ability of the endocrine system to respond to heat production and thermogenic tissues in response to cold (17). Thermogenesis capacity is impaired in ID. Brown adipose tissue (BAT) is a specialized form of adipose tissue characterized by multilocular fat droplets, high mitochondrial density, and abundant sympathetic innervation. After sympathetic stimulation in response to cold, the blood flow to BAT increases (18). Irisin browns WAT, while UCP-1 is released to release heat energy. We thought that the impaired thermogenesis capacity in ID may be due to the concomitant Ir deficiency. Iron deficiency is known to cause a variety of symptoms, but the etiology of these symptoms may not be fully understood. The study's objective is to explore whether Ir and FABP4 levels might be linked to symptoms such as feeling cold, fatigue, learning difficulties, and others in individuals with ID.

MATERIALS and METHODS

The study was conducted by the Department of Pediatric Hematology Oncology and the Department of Biochemistry, Faculty of Medicine, Fırat University. Ethical approval for this study was obtained from the Ethics Committee of Fırat University (02/ 24.03.2015), and informed consent was secured from all participants or their caregivers. This study evaluated ID across three stages, analyzing their effects on serum and urine levels of Ir and FABP4. The diagnosis of the 3 periods of ID was made according to the following laboratory values (19, 20).

1. ***Iron deficiency:*** In ID anemia is not seen, and iron stores are decreased. Serum iron, Hb, serum iron binding capacity (SIBC), and transferrin saturation (TS) are normal, but the ferritin level is <12 ng/mL.
2. ***Latentiron deficiency without anemia (LID):*** There is no anemia, iron stores are depleted and Hb is at the lower limit. Erythrocyte distribution volume and SIBC level increase, serum iron levels decrease, TS is <16% and ferritin level is <12 mL.
3. ***Iron deficiency anemia:*** Hypochrome microcytic anemia has developed. Hb and serum iron decrease, TS is <16% and ferritin level is <12 ng/mL.

In our study, a total of 60 patients from these 3 periods (20 patients diagnosed with ID, 20 patients diagnosed with LID, and 20 patients diagnosed with IDA) were included. In the control group, there were 20 patients with normal iron parameters and no iron deficiency or anemia. Oral iron treatment was started after the diagnosis of ID, LID, and IDA. Patients were administered iron treatment in the form of ferrous iron (Ferro Sanol®) at a dosage of 3-6 mg/kg/day, given 2-3 times daily for 3 months. Blood and urine samples were collected from individuals receiving iron treatment, both immediately before the initiation of the treatment and 3 months later. Additionally, samples were collected from the control group once for comparison. For the diagnosis of IDA, standard diagnostic procedures were followed for all patients presenting for diagnosis and treatment. This included obtaining a complete blood count (CBC), peripheral smear, reticulocyte count, serum iron levels, SIBC, and ferritin levels, as routinely performed in clinical practice. These tests collectively help in assessing various parameters related to red blood cell production, iron levels, and iron storage, aiding in the accurate diagnosis and treatment of iron deficiency anemia. Serum and urine Ir and FABP4 levels were analyzed in the patient group before and after treatment. In the control group, only serum and urine Ir and FABP4 levels were analyzed at baseline. Samples were studied as described in the manufacturer's catalog (Human (irisin) catalog no: 201-12-5328, Human (FABP4) catalog no: 201-12-2037 and manufactured at Awareness Technology, Inc. Palm City, Florida, USA). At the end of the study, the samples were read at 450 nanometres with a ChroMate microplate (ChroMate 4300 Florida, USA) reader.

Patients who were not included in the study; Patients with chronic infection, Patients who developed an allergic reaction with iron therapy or had a history of such a reaction, Patients who used any iron preparation before the study,Patients using vitamins.

Statistical analysis:

All data were analyzed using SPSS version 22.0 (IBM, Chicago, IL, USA). Median and interquartile range (IQR) values were given for non-normally distributed variables. Wilcoxon test was used for the comparison of ranks, Mann-Whitney U test was used for the comparison of two independent groups, and chi-square test was used for comparison of percentages.

Kruskal-Wallis test was used for the comparison of more than two independent groups when the data did not meet the assumptions of normality. A value of p<0.050 was considered statistically significant.

RESULTS

Female gender accounts for 41 patients, representing 51.25%. It is appropriate to give the genders of the patient and control groups separately. There is no statistically significant difference in terms of age and gender between the groups. Demographic characteristics of the patients are shown in Table I. The anthropometric measurements of the patients before and after treatment are given in Table II. Post-treatment comparisons revealed significant increases in Hb, hematocrit, and ferritin levels across all patient groups (Table III). The median serum Ir levels in our study revealed statistically significant differences between the patient groups (ID, LID, IDA) and the control group, with lower levels observed in the patient groups before treatment (p=0.040, p<0.001 and p<0.001, respectively) (Table IV). A statistically significant increase was found in the median serum Ir levels in all patient groups after treatment (p=0.003, p=0.002 and p=0.014). When urine Ir levels were analyzed, an increase in urine Ir levels was found in the ID and IDA groups and a decrease in the LID group after treatment, but these changes were not statistically significant (p=0.057, p=0.314 and p=0.387, respectively) (Table IV).

In our study, there was no statistically significant difference between the groups in serum FABP4 levels of the patients before and after treatment (p=0.423) (Table IV). After treatment, an increase was found in the mean serum FABP4 levels in the ID and LID groups, whereas a decrease was found in the IDA group, but these changes were not statistically significant (p= 0.681, p=0.709, and p= 0.514, respectively) (Table IV). In our study, there was no statistically significant difference between the groups in urinary FABP4 levels before and after treatment (p= 0.083, p=0.247, and p=0.135, respectively).

DISCUSSION

Iron deficiency anemia is an important public health problem in developing countries. The etiology of some of the symptoms seen in ID has not been elucidated. Especially within the scope of our study, we hypothesized that the sensation of coldness in IDA may be linked to decreased Ir levels, based on its known role in thermogenesis through WAT browning (21, 22). Irisin and FABP4 are peptide-structured hormones involved in both energy metabolism and thermoregulation processes (17). As known, iron acts as a cofactor in the enzymes required for energy metabolism, participating in thermoregulation processes. Therefore, we believe that there may be a connection between iron and these two hormones.

In our study, we found that the basal serum Ir levels of ID, LID, and IDA groups were statistically low compared to the control group (p<0.050). Ir, which is known to be synthesized in almost all biological tissues, leads to heat energy production instead of ATP synthesis by increasing UCP-1 proteins (9). An increase in the amount of Ir in biological fluids may be associated with

Table I: Demographic characteristics of the patients

	Control	ID	LID	IDA	p
Age*	8.5 (3.5-13.5)	5.5 (2.5-14.5)	9 (2.5-14)	10.5 (3.75-15.5)	0.090*
Gender†					
Female	11 (55)	9 (45)	9 (45)	12 (60)	0.717†
Male	9 (45)	11 (55)	11 (55)	8 (40)	

:** *median (IQR),* **†:** *n(%),* **‡:** *Kruskal Wallis test,* **ǁ:** *Chi-square test,* ***ID: *Iron depletion,* ***LID:*** *Latent Iron Deficiency,* ***IDA:*** *Iron Deficiency Anemia*

Table II: Demographic characteristics and anthropometric values of the patients before and after treatment

	Control*	ID*	LID*	IDA*
Age				
Before	8.5 (3.5-13.5)	5.5 (2.5-14.5)	9 (2.5-14)	10.5 (3.75-15.5)
Body weight (kg)				
Before	24.5 (13.25-44.5)	18.75 (14-45.75)	32.5 (12.2-56.2)	30 (13.25-52)
After		20.5 (14.6-46)	33 (13.75-56.25)	31.6 (14.72-52.5)
Height (cm)				
Before	124.5 (90.5-152.5)	111 (88-161.5)	139.5 (87.25-159.25)	140 (96.75-158.75)
After		113 (89.5-160.7)	141 (90.25-160.25)	142.5 (98.05-159)
Weight (percentile)				
Before	48 (35-56)	51 (10.25-73.25)	67 (19.25-79)	41 (17.75-57)
After		50 (12.75-77.5)	64.5 (25-80)	44.5 (27.5-60.5)
BMI (kg/m^2)				
Before	16.4 (15.55-18.7)	16.8 (15.27-18.15)	18.65 (14.37-20.37)	16.5 (14.37-20.37)
After		17.1 (15.52-21.12)	18.05 (15.97-18.22)	16.95(15.35-20.17)

:** *median (IQR),* ***ID: *Iron depletion,* ***LID:*** *Latent Iron Deficiency,* ***IDA:*** *Iron Deficiency Anemia*

Table III: Changes in laboratory values of the patients before and after treatment

	Control*	ID*	LID*	IDA*	p†
Hemoglobin (g/dL)					< 0.001‡
Before	13.25 (12.42-13.87)	12.5 (12.2-12.95)	12.6 (12.1-12.97)	9.4 (8.3-11)	0.001‖
After		12.9 (12.52-13.65)	13.25 (12.77-13.92)	12.5 (12-13.1)	< 0.001§
Hematocrit (%)					0.005‡
Before	39.55 (36.62-42.67)	36.9 (35.82-39.3)	37.85 (36.4-39.6)	30.35 (27.85-34.37)	0.002‖
After		38;95 (37-40.6)	40.05 (38.05-42.45)	38.1 (35.22-40)	< 0.001§
MCV (f/L)					0.066‡
Before	81 (78.25-87.5)	81.5 (78.25-85)	79 (77.4-83.4)	62 (59.2-70.3)	0.042‖
After		82.8 (78.5-87.25)	81.2 (79.47-83.75)	77.5 (73.7-82.5)	< 0.001§
RDW					0.053‡
Before	14.6 (13.55-16)	14.25 (13.25-16.65)	14.8 (14.2-16.3)	19 (16.92-21.92)	0.008‖
After		14.25 (12.97-15.2)	14.25 (12.97-15.2)	13.5 (12.62-14.15)	< 0.001§
Ferritin (ng/dL)					< 0.001‡
Before	36.5 (26.3-49.62)	8.5 (6.4-10.6)	9 (7.65-11)b.e	2.75 (1.47-6.6)	< 0.001‖
After		19 (15.22-32.25)	20 (17.85-38.05)	32 (18.92-48)	< 0.001§
Serum Iron (µg/dL)					0.896‡
Before	82 (71.5-119.5)	79 (74.25-105)	30.5 (18-39.5)	21 (16.25-28.5)	< 0.001‖
After		84 (73.25-89.5)	67.5 (57.5-74.75)	67 (56.5-87.5)	< 0.001§
SIBC (µg/dL)					< 0.001‡
Before	341 (314-376.75)	372 (339-389.75)	349 (327.75-404.5)	381.5 (343.75-421)	0.007‖
After		341 (314-376.75)	372 (339-389.75)	349 (327.75-404.5)	< 0.001§
Transferrin Saturation					0.117‡
Before	29 (22-37.5)	21 (19.02-28)	8.5 (5-11)	6.05 (5-7.97)	< 0.001‖
After		24.45 (21-29.7)	21.35 (17.07-28.82)	25.15 (20.4-28.75)	< 0.001§

**: median (IQR), †: Comparison between before and after treatment (Wilcoxon Test), ‡: ID (Iron depletion), ‖: LID (Latent Iron Deficiency), §: IDA (Iron Deficiency Anemia).*

increased heat production in the body. Ir is considered a hormone that regulates energy expenditure and promotes the conversion of WAT to BAT. In this context, elevated levels of Ir in biological fluids may contribute to increased thermogenesis and heat production in the body. There are factors outside the hypothalamus that influence thermogenesis in our body, and Ir is one of these pathways. Ir increases the expression of a protein called UCP1 in white fat cells. UCP1 stimulates thermogenesis by converting energy into heat in the mitochondria of the cell. This process redirects energy towards heat production rather than the normal function of energy storage in WAT. We observed decreased levels of Ir in cases of diminished iron, even in the absence of anemia. Furthermore, there was an elevation in serum Ir levels following iron therapy. Based on this mechanism, we hypothesized that increased cold sensitivity in individuals with iron deficiency (ID) might be associated with reduced irisin levels. In cases of ID, symptoms such as fatigue and weakness often emerge, leading to decreased physical activity and slower movements. This reduction in activity may be due to lower levels of irisin, a myokine predominantly secreted by skeletal muscles. Previous studies have demonstrated a positive correlation between physical activity and irisin levels. In the present study, an increase in irisin levels was observed following iron supplementation, suggesting that the improvement in fatigue and weakness associated with iron deficiency might be linked to this increase in irisin levels. This recovery process appears to support the normalization of physical activity in affected children. The treatment of iron deficiency not only alleviates these debilitating symptoms but also enhances energy levels, thereby supporting a more active and healthier lifestyle. Consequently, we propose that the treatment of iron deficiency, through increased physical activity, may indirectly lead to a rise in irisin levels via this mechanism.

In other studies, the correlations of Ir and FABP4 serum and urine levels with anthropometric measurements were analyzed. In our study, we observed no correlation between the levels of serum and urine Ir and FABP4 and gender, as well as anthropometric measurement data. Similarly, Liuliu et al. (23) and Moreno et al (24) found no relationship between Ir concentrations and gender. However, Al-Dalghri et al. (25) in a cohort study of 153 Saudi Arabian children found that circulating Ir levels in the blood were higher in girls than in boys. Siahanidou et al. (26) found no significant correlation between FABP4 levels and gender, body weight, height, and BMI, but Ibarretxe et al. (27) found high FABP4 levels in females in a study (25).

In our study, we also investigated urine samples to establish a potential link between Ir and ID using a simpler and non-invasive approach. However, we did not find any correlation between the levels of Ir in serum and urine samples. On the other hand, no difference was observed in the changes in urine depending on the treatment, and the possible reason for this was thought to be that there was no correlation between the circulating level of Ir and its excretion from urine.

As it is known, decreases in neurocognitive functions such as attention deficit, learning difficulties, behavioral disorders,

Table IV: Comparison of Ir and FABP4 levels before and after treatment

	Control*	ID*	LID*	IDA*	p†	p‡	p‖	p§	p¶
Serum									
Ir Before Treatment(ng/dL)	43.02 (32.88-60.02)	34.09 (32.19-38.10)	23.64 (20.35-33.65)	24.37 (19.53-29.83)	0.002	0.808	< 0.001	0.003**	0.040**
Ir After Treatment (ng/dL)		36.78 (32.38-41.44)	26.28 (20.56-32.89)	25.05 (22.32-32.19)	0.001	0.766	< 0.001	0.0023†,	< 0.001†,
Urine								0.014‡‡	< 0.001‡‡
Ir Before Treatment (ng/dL)	20.64 (18.93-26.98)	22.5 (20.44-25.16)	24.66 (24.12-26.61)	21.97 (19.9-23.13)	-	-	-	0.057**	-
Ir After Treatment (ng/dL)		25.72 (20.69-29.45)	24.28 (23.11-26.10)	22.91 (19.28-23.57)				0.314†,	
								0.387‡‡	
Serum								0.682**	0.808**
FABP4 Before Treatment (ng/dL)	21.64 (18.06-29.72)	20.02 (10.09-32.98)	12.81 (7.79-31.81)	26.5 (12.27-38.94)	o.433	0.068	0.181	0.709†,	0.607†,
FABP4 After Treatment(ng/dL)		22.35 (7.78-34.82)	12.99 (10.13-33.2)	18.83 (8.19-37.89)	0.579	0.204	0.570	0.514‡‡	0.194‡‡
Urine									
FABP4 Before Treatment (ng/dL)	10.44 (8.93-12.19)	12.79 (7.41-15.41)	11.5 (8.82-15.41)	13.74 (11.8-14.88)13.34 (11.36-13.93)	-	-	-	0.083**	-
FABP4 After Treatment (ng/dL)		14.43 (10.23-15.69)	12.18 (10.7-14.31)					0.247†,	
								0.135†,	

**: median (IQR), †: Comparison between ID and LID (Mann-Whitney U test), ‡: Comparison between LID and IDA (Mann-Whitney U test), ‖: Comparison between ID and IDA (Mann-Whitney U test), §: Comparison between before and after treatment (Wilcoxon Test), ¶: Comparison between control, **: ID (Iron depletion), †: LID (Latent Iron Deficiency), ‡‡: IDA (Iron Deficiency Anemia)*

decreased perceptual functions, and retardation in motor and mental development tests are observed in ID. Studies in school children have shown that learning and various developmental tests are impaired in ID with or without anemia, but learning difficulty may improve with iron treatment (28). In our study, it was thought that the decline in cognitive functions might be related to Ir, which is known to be released from all biological tissues. FNDC5/irisin has been shown as a new therapeutic factor that can improve cognition, learning, and memory function (29). FNDC5 has been found to reduce some factors that provide neuronal destruction, and it has also been found that FNDC5 administration with adenovirus increases neuroprotective factors (30, 31). Moon et al. (32) found that Ir at pharmacological concentrations increased STAT3 levels in H 19-7 hippocampal neuronal cells and STAT3 levels in mice, and low levels of Ir decreased differentiation in neuronal functions in mouse embryonic stem cells. Low levels of Ir in serum have been shown to reduce the level of FNDC5, an Ir precursor in the human brain. A direct relationship has been shown in hippocampal neurogenesis. Dun et al. (33) showed in another immunohistochemical study that Purkinje cells in rats and mice expressed Ir and also FNDC5 in recent days. It is known that the hippocampus is a critical region in learning and memory formation, and is a very important structure in spatial memory formation. According to our current knowledge, the cellular and molecular mechanisms of learning and memory formation are explained by long-term potentiation (LTP) in the hippocampus (34). Since Ir and hippocampus are especially related to learning, we think that decreased Ir level in ID may be related to the decrease in cognitive functions seen in ID. In addition, the fact that these symptoms are reversible with iron supplementation suggests that they may be directly related to the increased Ir level after iron treatment.

CONCLUSION

In our study, we found that the feeling of coldness and decreased cognitive functions seen in iron deficiency may be related to serum Ir level. Today, IDA is an important public health problem and affects many systems. Additional studies are needed to clarify the pathophysiology of its effects on different systems.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Firat University Ethics Committee (24.03.2015/02).

Contribution of the authors

Selmanoğlu A: Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study,

Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***Akarsu S:*** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***Aydın S:*** Constructing the hypothesis or idea of research and/or article, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study.

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Conflict of interest

The authors declare that there is no conflict of interest.

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