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Iron transportation proteins Hepcidin and Ferroportin and alterations in depressive and anxiety disorders

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ABSTRACT

Objective: Iron element has critical roles such as myelin synthesis and neurotransmitter synthesis. Critical enzymes and proteins strictly control iron metabolism. Alterations in the enzyme activities could modify iron metabolism. Metabolic and endocrine changes may influence iron turnover in patients with major depression and anxiety disorders.

Materials and Methods: 30 patients with major depressive disorder (MDD), 30 with anxiety disorders (ADs) according to the DSM 5 criteria, and 30 healthy controls were included. Hamilton Depression and Anxiety Scales were the clinical evaluation tools. Blood samples were collected 12 hours of fasting. Hepcidin and Ferroportin levels were measured with ELISA method.

Results: Both Hepcidin and Ferroportin levels were lower in the MDD group compared to the ADs group, Hepcidin levels were found to be statistically significantly lower ($p= 0.014$). In addition, an inverse correlation was observed between the Hamilton Depression Scale score and Ferroportin levels ($r= -0.214$, $p<0.05$).

Conclusion: Decreased Hepcidin and Ferroportin levels indicate metabolic effects in patients with MDD and disruption of the feedback mechanism between the two proteins. Considering the long duration of the disease in the MDD group in our study, the treatment period was also thought to be prolonged and the use of antidepressants might affect negative feedback.

Keywords: Anxiety disorders, depressive disorder, Ferroportin, Hepcidin

INTRODUCTION

Major Depressive Disorder (MDD) affects more than 264 million people annually (1). The World Health Organization (WHO) has positioned MDD as the third cause of worldwide disease burden and predicted that it will rank first by 2030 (2). Similarly, it is known that anxiety disorders are also commonly seen and their frequency tends to increase (3). In anxiety disorders and MDD, emotional, cognitive, psychomotor, and somatic symptoms can be seen (4). The contribution of neuroendocrine and biochemical processes to clinical processes may lead to metabolic abnormalities that may affect the clinical course. For example, problems such as activation in the hypothalamic-pituitary-adrenal axis, inflammatory activation, and oxidative stress may become evident during depressive periods (5). All these processes together can lead to an increase in morbidity and mortality directly or indirectly, in anxiety disorders and MDD. Many studies have observed that the frequency of diseases such as cardiovascular diseases, diabetes mellitus, and cancer is increased in anxiety disorders and MDD, and occurs at an earlier age (6-8).

It is known that the iron element has critical roles in myelin synthesis, neurotransmitter synthesis, and oxygen transport; and these roles are affected by inflammation (9). Hepcidin is a peptide that plays an active role in iron metabolism and is synthesized from the liver. It plays a regulatory role in the iron release from liver storage, absorption of iron in the diet, and iron release from macrophages (10). Hepcidin performs this regulatory role through Ferroportin. Only one protein allows iron to get out from iron-transferring cells (enterocytes, hepatocyte macrophages), and this protein is called Ferroportin. In other words, Hepcidin reduces iron release into plasma by binding to Ferroportin and causing down-regulation of Ferroportin (11).

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An increase of IL-6, in cases of infection or inflammation, will cause an increase in Hepcidin synthesis, and an increase in iron-loaded macrophages by down-regulation of Ferroportin. This will lead to a decrease in plasma iron and hypoferremia within hours, and the pathogen entering the body will be unable to find iron for use (12). Also, it may cause the development of anemia due to inflammation by stimulating iron-restricted erythropoiesis (13). Similar changes occur in all iron metabolisms in conditions such as inflammation, mitochondrial disorders, and gene mutations. These changes also contribute to the progression of neurotoxic and neurodegenerative processes.

This study aims to evaluate the Ferroportin and Hepcidin levels in major depression and anxiety disorders. In the literature review, no clinical research was found that evaluated Hepcidin and Ferroportin levels in patients with anxiety disorders and/or major depression. It is thought that iron metabolism also plays a role in the multifactorial etiopathogenesis of the aforementioned diseases along with many metabolic disorders. Therefore, changes are possible in Hepcidin and Ferroportin levels and the balance of the feedback axis between them. In our study, we hypothesized that similar to the inflammatory response in patients with major depression and anxiety disorder, Hepcidin levels might be altered, and Ferroportin levels would subsequently be influenced.

MATERIAL and METHODs

Ethics committee approval was obtained from the Afyonkarahisar Health Sciences University (AFSU), Clinical Research Ethics Committee in 03.01.2020 with the number 2020/51. Written informed consent was prepared according to the principles of the Declaration of Helsinki before the study obtained from all participants included in the study. A total of 84 patients, aged between 18-65, who were admitted to the AFSU Faculty of Medicine, Department of Psychiatry Outpatient Clinic consecutively between 01.02.2020 and 01.08.2020, and who were diagnosed with major depression or anxiety disorder according to DSM-5, and were receiving outpatient treatment were included in the study. However, according to the exclusion criteria, 13 people were excluded from the study due to acute infection and 11 people due to anemia. The study was completed with the remaining 60 patients and 30 healthy controls who voluntarily agreed to participate.

Exclusion criteria

- Severe organ failure,
- Alcohol/substance usagewithin last 3 months,
- Use of antioxidants,
- Active infection or have had any infectious disease within last 1 month,
- BMI lower than 18.5 or higher than 24.9,
- Chronic systemic disease (cardiologic, endocrinologic, allergic, genetic, neurologic),
- Received iron replacement therapy within last 3 months,
- Have had severe bleeding that caused significant blood loss within last 3 months, women with menstrual irregularities and excessive bleeding,
- A history of head trauma or brain surgery,
- Had a psychiatric diagnosis other than major depression or anxiety disorder according to DSM-5,
- Pregnancy
- The patien who did not accept participation after reading the detailed explanation of information form.

In addition to the above-mentioned exclusion criteria, subjects in the control group were also excluded if they or a first-degree relative had an axis 1 disorder according to the DSM-5 diagnostic criteria.

The patients diagnosed with major depression or anxiety disorder and the healthy control group included in the study applied Hamilton Depression Rating Scale (14, 15), Hamilton Anxiety Rating Scale (16, 17), and sociodemographic data form, after the clinical interview structured according to SCID-5 was performed in order to determine the clinical status.

Biochemical Measurement Processes

The blood samples required for the study were taken from the antecubital vein in the morning after 12-hour fasting. Complete blood count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), bilirubin, direct bilirubin, indirect bilirubin, albumin, total protein, serum iron, total iron-binding capacity, unsaturated iron-binding capacity (UIBC), ferritin values were measured from the blood samples. For the analysis of Hepcidin and Ferroportin levels: serum samples obtained by centrifugation for 5 minutes at 3220 g of blood taken, were stored in special boxes at -80 °C. and analyzed collectively. When the analyses were performed, the samples were thawed appropriately and reached room temperature in the laboratory of the biochemistry department of the university where the authors were working. In all samples, serum Hepcidin and Ferroportin levels were studied together at the same time. Hepcidin and Ferroportin measurements in serum were made with SunRed branded Human Hepcidin and Ferroportin Elisa kits (Jufengyuan Road, Baoshan District, Shanghai, China). Absorbance reading was performed on ChemWell 2910 branded ELISA reader device. (Awareness Technology, Inc. Martin Hwy. Palm City, USA). Results were reported in ng/ml.

Statistical analysis

The data were analyzed with the IBM SPSS® 25.0 (Armonk, NY, USA) package program. Continuous variables were controlled with the Shapiro-Wilks Test for distribution characteristics. Variables that fit to the Gaussian distribution characteristics were analyzed with parametric tests, whereas variables violating the normal distribution characteristics were analyzed with non-parametric tests. Difference analysis of numerical variables between groups was performed with Kruskal Wallis H Test.

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Mann-Whitney U Test (with Bonferroni correction) was used for the post-hoc analyzes. The relationship between continuous variables was analyzed by Pearson Correlation Analysis. In the correlation analysis, the power interpretation was made as follows: weak:0.0-0.24; medium: 0.25-0.49; strong: 0.50-0.74; very strong: 0.75-1.0 (18). Hepcidin markers were determined by linear regression analysis. Statistical differences were considered significant at the level of $p < 0.05$.

RESULTs

The study was completed with a total of 90 participants, including 30 patients with major depression, 30 patients with anxiety disorder, and 30 healthy volunteers. The clinical and sociodemographic data are presented in **Table 1**.

After the blood samples of the participants were collected, the frozen blood was thawed and the Hepcidin and Ferroportin levels were assessed (**Table 2**). When the groups were compared, Hepcidin levels in MDD patients were found to be significantly lower than in patients with an anxiety disorder (p=0.014). However, no statistically significant difference was observed between MDD and healthy controls or between anxiety disorder and healthy controls. It was determined that there was no difference between the groups in terms of Hepcidin and other iron metabolism parameters (serum Fe, total Fe binding, UIBC, ferritin). It was also determined that there was no difference in terms of complete blood count values and AST, ALP, LDH, bilirubin, direct bilirubin, indirect bilirubin, total protein levels, while a statistically significant difference was determined between ALT, GGT, and albumin levels.

It was observed that ALT and GGT levels in patients with anxiety disorder were significantly lower than in patients with major depression (ALT p= 0.011) (GGT p= 0.001). The albumin values, also known as negative phase reactants, showed that albumin levels in healthy controls were higher than in both major depression patients (p= 0.009) and anxiety disorder patients (p= 0.004).

In the correlation analysis, it was found that there was a weak inverse correlation between age and Hepcidin (r=-0.241), Ferroportin (r=-0.217), and albumin (r= -0.231). In terms of the clinical scales, there was a weak inverse (r=-0.240) correlation between the HAM-A and albumin, and a moderate inverse correlation (r=-0.289) between HAM-D and albumin. A moderate inverse correlation was observed between both two scales and ferritin levels. Also, an inverse correlation was observed between HAM-D and Ferroportin, but the strength of this correlation was weak (r= -0.214) (Table 3). According to the study data, the strongest correlation was found between Hepcidin and Ferroportin (r=0.635). A moderate linear correlation was observed between albumin and ferritin (r=0.292) and between ferritin and serum iron (r=0.398) (**Table 3**).

In the linear regression analysis, it was found that the predictors of Hepcidin level were direct bilirubin (B=-466.01, p=0.032) and MCV (B=4.91, p=0.039) in the MDD group, albumin (B=165.00, p=0.019) in the anxiety disorder group, and serum iron level in the healthy control group (B= -1.11, p= 0.026) (**Table 4**).

Table 1. Sociodemographic and clinical characteristics of all the groups

		MDD (%)	Anxiety Disorders n (%)	Healthy Controls n (%)	p
Age (mean±sd)		38.80±13.11	36.30±15.3	31.57±8.4	0.082
Gender	Female	25 (83.3)	23 (76.7)	13 (43.3)	
	Male	5 (16.7)	7 (23.3)	17 (56.7)	0.002*
Marital Status	Single/Divorced	7 (23.3)	10 (33.3)	19 (63.3)	
	Married	23 (76.7)	20 (66.7)	11 (36.7)	0.004*
Level of education	Uneducated	5 (16.7)	2 (6.7)	0	
	5 years of education	5 (16.7)	4 (13.3)	1 (3.3)	<0.001**
	8 years of education	10 (33.3)	5 (16.7)	0	
	12 years of education	4 (13.3)	11 (36.7)	5 (16.7)	
	University graduate	6 (20)	8 (26.7)	24 (80)	
Employment status	Employed	6 (20)	10 (33.3)	23 (76.7)	
	Unemployed/Retired	24 (80)	20 (66.7)	7 (23.3)	<0.001**
Smoking status	Smoker	9 (30)	7 (23.3)	13 (43.3)	
	Non-smoker	21 (70)	23 (76.7)	17 (56.7)	0.241
Suicide history	No	25 (83.3)	28 (93.3)	30 (100)	
	Yes	5 (16.7)	2 (6.7)	0	0.053
Illness duration (months) (mean±sd)		29.89±30.37	16.67±20.69	-	0.056
HAM-A (mean±sd)		15.53±4.95	22.20±8.42	2.73±3.43	<0.001** p†:0.002* p‡:<0.001** p¶:<0.001**
HDRS (mean±sd)		18.30±4.96	11.97±5.31	1.07±1.57	<0.001** p†:<0.001** p‡:<0.001** p¶:<0.001**

HAM-A: Hamilton Anxiety Rating Scale, HDRS: Hamilton Depression Rating Scale
*p<0.05
**p<0.001
p†: MDD- Anxiety disorders
p‡: MDD– Healthy controls
p¶: Anxiety disorders – Healthy controls

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Table 2. Comparisons between the groups in respect of biochemistry examinations

	MDD	Anxiety Disorders	Healthy Controls	p
Hepcidin med.(Q_1-Q_3)	147.4 (98.7-175.7)	188.9 (134.5-302.4)	172.6 (124.4-292.4)	0.038* p†: 0.014* p‡: 0.079 p¶: 0.425
Hepcidin mean±s.d	156±76.1	226.4±117.9	210.9±108.4	
Ferroportin med.(Q_1-Q_3)	6.4 (4.2-9.2)	7.8 (6.2-13)	8.8 (5-15.7)	0.135
Ferroportin mean ±s.d	7.7±4.7	10.5±6.0	10.6±6.9	
ALT med.(Q_1-Q_3)	16 (12-20)	12 (10-15)	15 (12-25)	0.016* p†: 0.011* p‡: 0.717 p¶: 0.015*
ALT mean±s.d	20.5±23.2	14.6±10.5	19.9±12.4	
AST med.(Q_1-Q_3)	19.5 (15-23)	17 (15-21)	18 (16-22)	0.353 p†: 0.211 p‡: 0.836 p¶:0.219
AST mean±s.d	20.3±9.2	17.8±5.3	18.9±4.4	
GGT med.(Q_1-Q_3)	16 (14-25)	11 (9-16)	17.5 (10-32)	0.007** p†: 0.001** p‡: 0.882 p¶: 0.057
GGT mean±s.d	21.2±12.7	13.9±8.4	21.9±15.2	
Albumin med.(Q_1-Q_3)	4.7 (4.6-4.9)	4.6 (4.5-4.8)	4.9 (4.7-5.1)	0.005** p†: 0.379 p‡: 0.009** p¶: 0.004**
Albumin mean±s.d	4.7±0.2	4.7±0.3	4.9±0.3	

*p<0.05
**p<0.01
p†: MDD- Anxiety disorders
p‡: MDD– Healthy controls
p¶: Anxiety disorders – Healthy controls
ALT: Alanine aminotransferase, AST:Aspartate aminotransferase, GGT:Gamma glutamyl transferase

Table 3. Correlation analysis between biochemical data and clinical data

Pearson Correlation		Age	HAM-A	HDRS	Hepcidin	Ferroportin	Albumin	Ferritin
HAM-A	r	-.017						
	p	.874						
HDRS	r	.184	.612**					
	p	.083	<.001					
Hepcidin	r	-.241*	-.045	-.199				
	p	.022	.673	.060				
Ferroportin	r	-.217*	-.029	-.214*	.635**			
	p	.040	.787	.043	<.001			
Albumin	r	-.231*	-.240*	-.289**	.143	.177		
	p	.029	.023	.006	.179	.095		
Ferritin	r	.015	-.273**	-.275**	-.104	-.105	.292**	
	p	.887	.009	.009	.328	.324	.005	
Total Iron	r	-.065	-.091	-.109	-.028	.042	.184	.398**
	p	.543	.394	.308	.790	.697	.082	<.001

*p<0.05 ** p<0.01
HAM-A: Hamilton Anxiety Rating Scale, HDRS: Hamilton Depression Rating Scale, Pearson Correlation Test

Table 4. Evaluation of Hepcidin levels in groups with regression analysis

		Unstandardized Coefficients B	Unstandardized Coefficients SE	Standardized Coefficients Beta	t	p
MDD	D. Bil	-466.01	205.80	-0.37	-2.26	0.032
	MCV	4.91	2.26	0.35	2.17	0.039
Anxiety Disorder	Albumin	165.00	66.29	0.43	2.49	0.019
Healthy Control	Serum Fe level	-1.11	0.47	-0.41	-2.36	0.026

D. Bil: Direct bilirubin, MCV: Mean corpuscular volume
Linear Regression Analysis (Stepwise). Dependent Variable: hepsidin, Independent variables: All clinical and biochemical variables. Depression Group: F=5.41, p=0.011, Adjusted R2=0.23; Anxiety Group: F=6.20, p=0.019, Adjusted R2=0.16; Healthy Control group: F=5.56, p=0.026, Adjusted R2=0.17.
SE: Standard Error

DISCUSSION

When the results were evaluated, it was determined that Hepcidin and Ferroportin levels were lower in the major depressive disorder group, and when compared to the anxiety group, Hepcidin levels were statistically significantly lower. In addition, when all participants were evaluated together, an inverse correlation was found between Ferroportin levels and the severity of depression. The regression analysis showed that the determinants of Hepcidin levels were direct bilirubin and MCV in the depression group. It was found that albumin levels in the anxiety disorder group and serum iron levels in the control group were negative determinants of Hepcidin levels.

Diet-related causes, vegetative symptoms of depression, neuroendocrine changes, inflammation, and oxidative stress may cause systemic metabolic effects in patients with MDD. The influence of nutrition and the biological systems of depression are highly related. In other words, nutrition can activate hormonal, neurotransmitter, and signaling pathways in the gut that modulate brain functions such as appetite, sleep, energy intake, neurogenesis, reward mechanisms, cognitive function, and mood (19). Exercise also has many known effects on metabolism. A study reported that Hepcidin levels increased after exercise, and iron metabolism was affected by exercise (20).

The relationship between sleep disorders and iron deficiency may also be involved (21). Therefore, symptoms such as sleep disturbance, appetite changes, and psychomotor retardation, which are expected to be seen in major depression, may be one of the factors affecting the metabolism of proteins that regulate iron metabolism. Besides, the effects of the drugs used are not yet known. A recent study found a relationship between chlorpromazine-equivalent doses of antipsychotic drugs and Ferroportin levels (22). These metabolic effects may have affected Hepcidin levels. The inverse relationship between the Ferroportin level and the severity of depression supports this view. Besides, Hepcidin is a protein that inhibits Ferroportin synthesis. The level of Hepcidin may also have decreased secondary to the low level of Ferroportin.

Some studies reported that Hepcidin levels were higher in Alzheimer's disease and attention deficit hyperactivity disorder (22, 23) and Ferroportin levels were lower in schizophrenia patients (24). These results provide evidence to iron turn over especially the Hepcidin - Ferroportin axis, may be impaired in psychiatric disorders.. This study is in line with this notion.

Age and gender are two crucial factors that affect iron metabolism. It is known that iron metabolism deteriorates with aging (25). Our study results show that age, Hepcidin, and Ferroportin levels are inversely correlated. However, in the gender evaluation, it was determined that there was no statistically significant difference in Hepcidin and Ferroportin levels. We inferred this result was due to the small sample size and gender distribution imbalance.

When the results were evaluated in aggregate, there was a difference between the depression group and the anxiety disorder group in terms of Hepcidin levels, while the healthy controls did not differ with both groups, which was attributed to the imbalance of gender distribution. As there is no significant difference in the sex ratios between the patient groups, the evaluations of this study between the patient groups are more valuable.

Limitations

The low number of samples, imbalance of gender distribution, and the study's cross-sectional nature are some of the limitations. Also, the fact that many of the patients included in the study were currently using antidepressants and that biomarkers have been studied from peripheral blood samples were limitations of our study. Without doubt, studies using CSF samples and imaging methods will help to enlighten the subject. Inflammation and vitamin D levels are shown to influence Hepcidin synthesis (26, 27). Future studies may analyze the interaction between inflammatory mechanisms and Hepcidin-Ferroportin levels.

CONCLUSION

The low levels of Hepcidin and Ferroportin both together in MDD indicate that the relationship between these two molecules is affected. Considering the long duration of the disease in the MDD group, it was thought that the treatment period was also prolonged and antidepressant use might have affected negative feedback. The inverse correlation between the severity of depression and Ferroportin is another important finding of this study. However, it is difficult to explain the causal relationship between depressive symptoms and Ferroportin. Large-scale follow-up studies on this subject will enlighten the subject. Experimental models may provide an opportunity to determine the secondary changes upon altered Hepcidin and Ferroportin levels.

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BKG, MIA: Revisions

Ethical approval: All procedures performed in studies involving human participants were in accordance with the institutional and/or national research committee's ethical standards and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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