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The roles of Klotho and FGF-23 in bipolar manic episode

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Abstract. – OBJECTIVE: Bipolar disorder (manic episode) is an essential psychiatric disorder with unknown etiology, in which inflammation is considered to play a role. Klotho and FGF-23 are known to be associated with inflammation. Therefore, this study aimed to determine the link between Klotho and FGF-23 levels and bipolar disorder.

PATIENTS AND METHODS: In this study, 42 men with BD and 41 healthy controls were enrolled, followed up, and/or treated at the High-Security Forensic Psychiatry Clinic. Sociodemographic data form, Young Mania Rating Scale, and Hamilton Depression Rating Scale were applied to all participants.

RESULTS: Klotho and FGF-23 levels were significantly increased in patients with BD manic episodes. There was no correlation between Klotho and FGF-23 levels and clinical parameters. For Klotho and FGF-23, cutoff values of 69 and 1,646 yielded 67.4% sensitivity and 72.1% specificity and 81.4% sensitivity and 51.2% specificity, respectively.

CONCLUSIONS: Klotho and FGF-23 may play critical roles in the etiopathology of manic episodes and are potential candidate biomarkers for bipolar disorder. This relationship might contribute to the etiopathogenesis of the disease and determine its treatment. Anti-Klotho and anti-FGF-23 administration may be a future treatment for controlling the course of the disease.

Key Words:
Bipolar disorder, Inflammation, Klotho, FGF-23.

Introduction

Bipolar disorder (BD) is a mood disorder characterized by recurrent periods of hypomania, mania, and depression, with either complete well-being or subthreshold symptoms between these periods. BD often has a chronic course; its prevalence ranges between 0.5% and 4.3% in the population[1] and is similar in men and women[2]. The underlying mechanisms of this disease have not yet been fully elucidated, but recently, some proteins have been associated in literature with inflammatory processes in BD.

Klotho and fibroblast growth factor (FGF)-23 are members of the same protein family and are produced by ependymal cells of the choroid plexus, Purkinje cells, and hippocampal neurons in the brain[3]. Ahmadi et al[4] reported that the Klotho protein exerts neuroprotective effects by modulating oxidative stress. In addition, Klotho is involved in oxidative stress, anti-aging, fibrosis, memory, learning, and inflammation[5-7].

This protein family, especially Klotho, has recently been linked to several psychiatric disorders[8-10]. For example, Paroni et al[8] suggested that it has a role in major depression in the elderly, and another study reported that its levels are increased in patients with schizophrenia, albeit not statistically significant[9]. Another group of researchers[10] also recorded increased circulating Klotho levels in BD. However, Klotho and FGF-23 are proteins of the same cluster, and examining them together will complete the etiology of associated diseases.

FGF-23, mainly expressed by osteoblasts, is involved in the completion of neural development, and its deficiency leads to impaired cognitive functions[11]. In a postpartum depression study[12], it was reported that FGF-23 levels were significantly increased. A study[13] observed that lithium supplementation in depression controls the disease by increasing the amount of FGF-23. In addition, Li et al[14] reported a relationship between impulsivity and FGF-23.

Our hypothesis is to elucidate the inflammation process in the etiopathogenesis of bipolar disorder manic episodes. Klotho and FGF-23 levels, which

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play a role in inflammation and are measurable parameters in blood, may vary. We hope that determining this situation will facilitate the evaluation of manic episodes with blood analyses. To the best of our knowledge, there is only one study[10] in the literature investigating Klotho in BD, but Klotho and FGF-23 should be examined together as they are proteins of the same cluster. Despite our extensive literature search, we found no study investigating the relationship between Klotho and FGF-23 in BD. Therefore, this study aimed to determine the levels of circulating Klotho and FGF-23 in patients with BD and healthy controls using enzyme-linked immunosorbent assay (ELISA) and ascertain whether these proteins play a role in the etiopathology of the disease.

Patients and Methods

Participants

The study enrolled in a randomized manner 42 men diagnosed with BD manic episodes based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria. The patients who met the study criteria were followed up and/or treated at the High-Security Forensic Psychiatry Clinic of Fethi Sekin High-Security Forensic Psychiatry Hospital. All patients and controls comprised only men. The control group included 41 volunteers who visited our hospital for an annual routine check-up and had no history of any psychopathology, psychopathic, or systemic disorders according to the DSM-5 criteria and were enrolled in a randomized manner.

Inclusion criteria for the study: patients diagnosed with BD according to DSM-5 who were between the ages of 18 and 65 years, volunteered to participate in the study, were able to understand the scales used in the study, were literate, and did not have any chronic somatic disorders, inflammatory diseases, or immune disorders were eligible.

Exclusion criteria: mental retardation, alcohol and/or substance abuse, chronic somatic disorder and malignancy, presence of active infection, use of corticosteroids or any drugs affecting the immune system in the last six months, absence of rheumatologic disease diagnosis, illiteracy, and failure to fill out the written consent form.

Scales Used in the Study

Young Mania Rating Scale (YMRS)

It is a scale used to measure the severity and change of the manic state and filled in by the interviewer[15]. It is a Likert-type scale comprising a total of 11 items. Turkish validity and reliability study of YMRS was conducted by Karadağ et al[16].

Hamilton Depression Rating Scale (HAM-D)

The HAM-D developed by Hamilton is the most widely used clinician-administered depression assessment scale[17]. Turkish validity and reliability of the scale were performed by Akdemir et al[18].

Determination of Plasma Klotho and FGF-23 Levels

Venous blood samples from the left forearm vein were collected into heparinized tubes between 08.00 and 09.00 hours after overnight fasting. The blood samples were centrifuged at 3,000 rpm at 4°C for 10 min to remove plasma. Until analysis, the plasma specimens were stored at -80°C. A commercial ELISA kit [Human KL (Klotho); Catalog No: E-EL-H5451, Elabscience Biotechnology Inc., Houston, Texas; Human FGF-23 (Fibroblast Growth Factor 23); Catalog No: E-EL-H1116; Elabscience Biotechnology Inc., Houston, Texas] was used to measure plasma levels of KL and FGF-23 according to the manufacturer instructions. Plasma Klotho levels were recorded in ng/mL, and FGF-23 levels were recorded in pg/mL.

Ethical Considerations

After fully describing the study, all participants provided written informed consent according to the Helsinki Declaration. The local ethics committee approved the study (date: September 16, 2021; number: 2021/09-56).

Statistical Analysis

The data were analyzed in SPSS v. 24 (IBM Corp., Armonk, NY, USA). Kolmogorov-Smirnov test was used to determine whether the variables were normally distributed. The data were presented as mean and standard deviation and evaluated using descriptive statistics. Relationships between categorical data were assessed using the Chi-square test[19]. The patient and control groups' psychological outcomes and biochemical parameters were compared with the Student's *t*-test or the Mann-Whitney U test. The Spearman-Rank correlation coefficient was used to analyze the correlations between clinical features and plasma Klotho and FGF-23 levels. Multivariable logistic regression analysis was performed to predict manic episodes in bipolar disorder. *p*-values <0.05 (two-tailed) were considered significant. Receiver operating characteristic (ROC) curves were drawn to measure the diagnostic value of Klotho and FGF-23 levels.

Results

The study included 42 men with BD and 41 healthy controls with similar sociodemographic characteristics. Descriptive statistics regarding the sociodemographic data of the patients are given in Table I. There was no difference between the two groups in terms of age and body mass index (BMI) ($p > 0.05$).

In the patient group, 26 (61%) were married and 16 (38%) were single or widowed, whereas in the control group, 10 (24.4 %) participants were married and 31 (75.6 %) were single or widowed ($\chi^2 = 12.870$, $p = 0.002$). Twenty-five (59.5%) patients diagnosed with BD and 18 (44%) of the healthy controls were smokers ($\chi^2 = 2.028$, $p = 0.154$). The mean duration of diagnosis was 12.8 ± 8.3 years in the patient group. The mean YMRS score was 16.11 ± 9.27, and the mean HAM-D score was 7.88 ± 4.86.

The mean plasma Klotho level was 1.05 ± 0.75 ng/mL in the BD patient group and 0.51 ± 0.29 ng/mL in the control group. The plasma Klotho levels were significantly higher in patients with BD compared with healthy controls ($z = -3.767$, $p < 0.001$) (Table II, Figure 1).

The mean plasma FGF-23 level was found to be 45.86 ± 37.48 pg/mL in the patient group and 27.45 ± 25.26 pg/mL in the control group. We found a significant difference in FGF-23 levels between the patient and control groups ($z = -2.414$, $p = 0.016$) (Table II, Figure 1). There was no correlation between Klotho and FGF-23 levels and clinical parameters ($p > 0.05$). However, a positive correlation was found between Klotho and FGF-23 levels in the patient group ($r = 0.892$, $p < 0.001$).

The ability of various parameters to predict bipolarity was investigated using ROC analysis, and cutoff values were determined. For Klotho, a cutoff value of 69 yielded a sensitivity of 67.4% and a specificity of 72.1%, indicating Klotho was a good predictor. For FGF-23, a cutoff value of 1,646 yielded a sensitivity of 81.4% and a specificity of 51.2%, meaning that FGF-23 was also a good predictor (Table III, Figure 2).

Table I. Demographic and clinical characteristics of patients with manic episode bipolar disorder and healthy controls.

	Bipolar disorder (manic episode) (n = 42)	Control (n = 41)	t/χ^2	p
Age (years)	38.47±10.71	40.31±14.87	-0.648[a]	0.519
Marital status				
Single/Married/Divorced	26/12/4	10/27/4	12.870[b]	0.002*
Education				
Primary/High school/University	30/9/3	29/9/3	0.005[b]	0.998
Employment				
Employed/Unemployed	14/28	24/17	5.309[b]	0.021*
Smoking				
Smoker/Nonsmoker	25/17	18/23	2.028[b]	0.154
BMI	25.72±4.98	27.65±4.07	-1.930[a]	0.057
History of suicide attempt				
Yes/No	9/33			
Duration of illness (year)	12.8±8.3			
YMRS	16.11±9.27			
HAM-D	7.88±4.86			
CGI	8.30±2.0			

*$p < 0.05$, **$p < 0.001$; BMI: Body Mass Index; YMRS: Young Mania Rating Scale: HAM-D: Hamilton Depression Rating Scale; CGI: Clinical Global Impression. [a]Student's *t*-test; [b]Chi-square test.

Table II. Plasma Klotho and FGF-23 levels of patients with bipolar disorder manic episode and healthy controls.

	Bipolar disorder (manic episode) (n = 42)	Control (n = 41)	Z	p
Klotho (ng/mL)	1.05±0.75	0.51±0.29	-3.767	<0.001**
FGF-23 (pg/mL)	45.86±37.48	27.45±25.26	-2.414	0.016*

[a]Mann-Whitney U test used; FGF-23: Fibroblast Growth Factor-23. *$p < 0.05$, **$p < 0.001$.

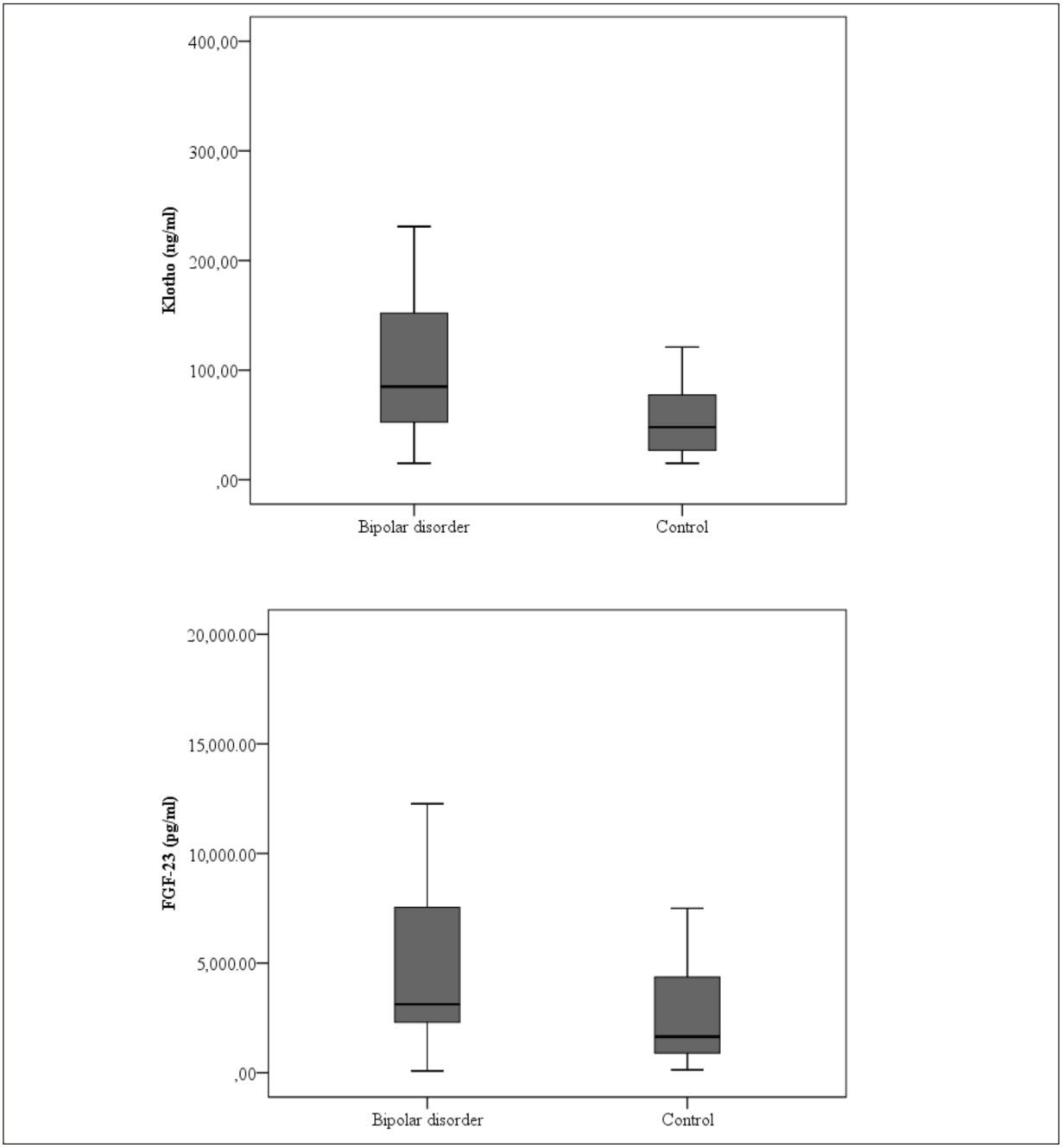

Figure 1. Klotho and FGF-23 levels in bipolar disorder.

In the logistic regression analysis, Klotho value [OR = 1.056 (95% C.I.: 1.27-1.087)] and FGF-23 value [OR = 0.998 (95% C.I.: 0.997-0.999)] predicted manic episode in bipolar disorder.

Discussion

The results obtained in this study showed that in the patient group with manic episodes, there were more single people than married people. Previous studies[20] have also reported that patients with BD are frequently single. In this respect, our sample is consistent with literature. Furthermore, 28 of the 42 patients with BD manic episodes were unemployed. Cloutier et al[20] reported a link between unemployment and BD, and this finding agrees with the data obtained in the present study.

When the Klotho levels of patients with BD manic episodes and healthy controls were

compared, the stories were significantly higher in the patient group. A previous study by Barbosa et al[10] measured Klotho levels in 40 patients diagnosed with BD type 1 and 30 healthy controls. It was shown that the stories were increased in patients with manic episodes during both remission and attack periods compared with the control group. In patients with schizophrenia, another psychiatric disease, Klotho levels of the patient group were significantly higher than those of the healthy control group. It was suggested that Klotho may play a role in the pathogenesis of schizophrenia and that high Klotho levels may positively affect cognitive functions in schizophrenia[21]. Another study[22] evaluated several inflammatory biomarkers in 245 patients with unipolar depression and 59 patients with BD depressive episodes. The Klotho protein level was found to be higher in BD depressive episodes compared with the control group. Therefore, the results obtained in the present study and previous findings imply a direct relationship between Klotho and psychiatric disorders[22,23]. In contrast to these findings, Sartorius et al[24] compared the Klotho levels of 53 patients with major depressive disorder and 39 healthy controls and found no significant difference between the two groups. The authors reasoned that the peripheral sample may not reliably reflect the Klotho level in the central nervous system.

In this study, FGF-23, a member of the same cluster and coexpressed with Klotho, was also evaluated and elevated in the patient group. Turner et al[25] examined the relationship between FGF-23 levels and depression and found that FGF-23 levels increased in depression. In many psychiatric diseases, overexpression of FGF-23 has been shown[26] to cause hypophosphatemia, leading to decreased memory and impairment in learning. Dysregulation of several fibroblast growth factor systems, including FGF-23, has been reported[27] in the frontal cortical regions of the brains of patients with major depressive disorder. In a study[12] involving 169 women with postpartum depression, FGF-23 levels were found to be elevated, and it was reported that inflammation played a role in postpartum mental health. It was suggested[14] that high levels of circulating FGF-23 in the depressive episode of BD may be associated with poor cognitive performance. In addition, the FGF-23 level in the cerebrospinal fluid was found[28] to be related to impulsive behaviors. The observation that Klotho deficient mice also lacked FGF-23 and exhibited a similar

Table III. ROC analysis of Klotho and FGF-23 levels in bipolar disorder

	Klotho	FGF-23
Cutoff value	> 69	> 1646
Sensitivity	67.4%	81.4%
Specificity	72.1%	51.2%
Positive predictive value	70.7%	62.5%
Negative predictive value	68.9%	73.3%
AUC (area under the curve)	0.721	0.625
AUC 95% confidence interval	0.613-0.812	0.514-0.727
AUC *p*-value	< 0.001	0.043

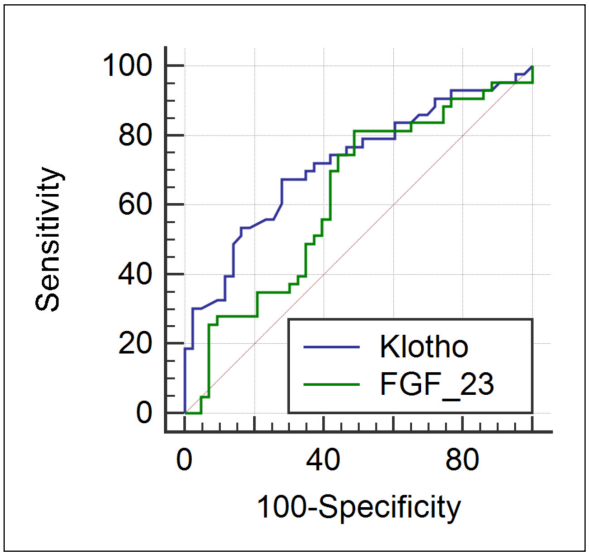

Figure 2. ROC curves of Klotho and FGF-23 in bipolar disorder.

phenotype, including increased plasma phosphate levels and a short life span, growth retardation, infertility, muscle atrophy, hypoglycemia, and renal vascular calcification[29,30], alludes that Klotho and FGF-23 may function via a common signaling pathway[31]. The present study also found a positive correlation between Klotho and FGF-23 levels in patients with BD manic episodes ($r = 0.892$, $p < 0.001$).

Kazgan Kılıçaslan et al[32] reported that Klotho and FGF-23 levels were higher in patients with schizophrenia compared with the control group, but there was no correlation between these two parameters.

In contrast, a negative correlation between Klotho and FGF-23 was reported[33] in patients with chronic kidney disease. Our findings differ, suggesting that these molecules may exhibit different disease correlations. The elevation in the present study's FGF-23 and Klotho levels also

reflects the relationship between the two molecules. Available data in literature suggest that these two molecules are probably synthesized and released stoichiometrically. Therefore, measuring a single molecule in manic episodes may provide clinicians with sufficient information about the course of the disease[33-35]. Klotho and FGF-23 are members of the same family, and they do not need to be studied together. However, studying these parameters together as an internal control may be helpful.

According to the ROC curve, Klotho had a specificity of 72.1% and a sensitivity of 67.4% with a cutoff value of 0.72, whereas FGF-23 had a specificity of 51.2% and a sensitivity of 81.4% with a cutoff value of 0.63. According to these data, it is believed that Klotho and FGF-23 may be additional parameters to psychiatric scales in diagnosing manic episodes.

Limitations

The limitations of this study include its cross-sectional design and the lack of evidence that the levels of the measured parameters reflect their levels in the brain. In addition, 78.6% of our patients were using psychiatric medications at the time of the study. Moreover, the study included people who had committed crimes in the forensic psychiatry service, and the results may vary in the patient group without impulsive behaviors. Longitudinal studies in patients not using psychiatric medications or in more homogeneous antipsychotic treatment groups are needed.

Conclusions

The results obtained in this study showed that Klotho and FGF-23 levels were higher in patients with BD manic episodes compared with the healthy control group. These parameters may play a role in the etiopathogenesis of BD, and comprehensive studies are required to elucidate this finding.

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Ethics Approval

The study was approved by the Fırat University Non-Interventional Clinical Research Ethics Committee (Approval No: 2021/09-56).

Informed Consent

Informed consent was obtained from all subjects involved in the study.

Availability of Data and Materials

The article's data will be shared upon reasonable request to the corresponding author.

Conflict of Interest

The authors declare no conflict of interest.

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