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Serum Klotho and FGF23 Levels in Patients with Schizophrenia

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ABSTRACT

Background: The aim of this study is to compare the serum levels of Klotho and fibroblast growth factor 23 in patients with schizophrenia, in whom etiopathogenesis inflammation plays an important role, with those of healthy control subjects and to investigate a possible correlation between these levels.

Methods: Forty male patients with schizophrenia and 40 healthy male control subjects who were followed up and/or treated at the High-Security Forensic Psychiatry Clinic participated in the study. Sociodemographic data form, the Positive and Negative Syndrome Scale, and the Clinical Global Impression Scale were collected from all subjects, and participants' fibroblast growth factor 23 and Klotho serum levels were measured by the enzyme-linked immunosorbent assay method.

Results: The serum levels of Klotho and fibroblast growth factor 23 were significantly higher in schizophrenia patients than in healthy controls ($P = .048$ and $P = .010$, respectively). A significant positive correlation was observed between serum levels of Klotho and fibroblast growth factor 23 in subjects ($r = 0.816$; $P < .001$).

Conclusion: Our study is the first to show significantly higher combined serum levels of fibroblast growth factor 23 and Klotho in patients with schizophrenia. The Klotho/fibroblast growth factor 23 pathway may play a role in the pathogenesis of schizophrenia. The involvement of Klotho and fibroblast growth factor 23 in inflammatory processes has the potential to provide alternative approaches to elucidate the etiopathogenesis and treatment of schizophrenia.

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INTRODUCTION

Schizophrenia is a psychiatric disorder that develops from childhood and is characterized by disturbances in cognition, emotion, perception, and behavior that impair patient functioning.[1] The prevalence is approximately 1%. There have been numerous attempts to clarify the etiopathogenesis of schizophrenia. Much of the research conducted to this end has focused on the inflammatory system[1] and, in this context, numerous biochemical markers associated with inflammation have been investigated. The accumulated evidence and meta-analyses have shown that inflammation and the load of proinflammatory cytokines increase in schizophrenia from the first episode of psychosis, regardless of treatment.[1,2] The interaction between cytokines and neurotransmitters contributes to the pathophysiology of schizophrenia. Chronic administration of interferon-α has been associated with decreased striatal dopamine release and anhedonia.[3] A higher risk of developing schizophrenia has been found in individuals exposed in utero to high levels of interleukins (IL)-8.[4] Animal studies suggest that high IL-6 levels in utero produce schizophrenia-like symptoms in the offspring, which have been shown to be reversible by anti-IL-6 antibodies.[5] Increased serum/plasma levels of prostaglandin E2, C-reactive protein, IL-1β, IL-6, IL-8, and tumor necrosis factor (TNF)-α are indicative of increased peripheral immune response in schizophrenia.[6] The anti-inflammatory celecoxib has been found to have significant effects on the positive and negative symptoms of the disease.[7] A meta-analysis of 59 studies found that total antioxidant levels were significantly lower and homocysteine, IL-6, and TNF-α levels were significantly higher in patients with first-attack schizophrenia than in controls.[8]

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Klotho is a protein first discovered in mice with multiorgan damage and shortened life expectancy, and its overexpression prolongs lifespan.[9] It is found primarily not only in the kidneys but also in the brain, skeletal muscle, pituitary gland, and adipose tissue and exerts cellular anti-aging effects by preventing oxidative stress-induced apoptosis in vascular cells.[9] Atherosclerosis, neurodegeneration, and cognitive impairment have been found in Klotho-deficient mice.[10,11] Klotho protects cells from oxidative stress by regulating the activities of multiple ion channels and various growth factors through pathways that are not yet fully elucidated.[12] Klotho functions as a humoral factor that regulates the activity of multiple cell surface glycoproteins, including ion channels and growth factor receptors such as growth hormone/insulin-like growth factor-1 (GH/IGF-1). To our knowledge, Klotho functions as a glucuronidase that activates the TRPV5 calcium ion channel to increase Ca2+ flux, which contributes to the homeostatic control of calcium.[12] By inhibiting the insulin/IGF-1 pathway, it activates mammalian forkhead box O (FOXO) transcription factors (FOXOs). Activated FOXOs bind directly to promoters of antioxidant enzymes, thus supporting the antioxidant system.[13] It rescues oligodendrocyte progenitors and astrocytes from TNF-α and glutamate cytotoxicity. In addition, it reduces nitric oxide release in endothelia in response to acetylcholine. It reduces the cellular senescence phenotype in fibroblasts and vascular endothelial cells via p53/p21.[14] Because of its protective properties in oxidative stress, the abundant expression of Klotho in Purkinje cells and some brain regions such as cortex, hippocampus, and medulla, and its detectability in cerebrospinal fluid, this protein is also the subject of research in psychiatry.[15,16] It is known from psychiatric research that low levels of Klotho are associated with major depressive symptoms and chronic stress.[17] In a recent study comparing patients with depression to healthy controls, no difference in Klotho serum levels was found.[18] The authors interpreted this to mean that peripheral Klotho serum levels do not adequately reflect Klotho levels in the central nervous system.[18] Because Klotho in the central nervous system originates from the brain and not from the bloodstream,[19] they pointed to the possibility of a link between Klotho and affective disorders that should be investigated.[18] In their study investigating inflammatory pathways in the pathophysiology of bipolar disorder, Barbosa et al[20] detected significantly higher plasma levels of Klotho in patients diagnosed with bipolar disorder than in the control group. In another study using the same mechanism, Xiong et al[21] found that plasma levels of Klotho were higher in patients with schizophrenia compared with healthy controls. In a study based on the interaction of Klotho with the GH/IGF-1 axis, it was found that serum levels of Klotho were lower in patients with anorexia nervosa compared with healthy controls.[22]

Klotho protein not only regulates ion channels and growth factor receptor activity but also acts as an important co-receptor for fibroblast growth factor 23 (FGF23).[23] Fibroblast growth factor 23, one of the fibroblast growth factors, is a phosphatonin of osseous origin that is produced not only in osteoblasts but also in muscle and brain tissue. It is an essential growth factor, especially for the maturation of catecholaminergic neurons, synaptogenesis, and neurogenesis.[23] As a cofactor, Klotho is involved in the signaling pathway of FGF23 and plays an important regulatory role in the homeostasis of phosphate, calcium, and vitamin D.[24] To date, the function of Klotho/FGF23 has been studied mainly in chronic renal and cardiovascular diseases, and it has been suggested that high levels of FGF23 and Klotho reduce the development of atherosclerosis through an anti-inflammatory effect.[25,26] Currently, Klotho as an antioxidant is also reported to prevent the toxicity caused by high peripheral FGF23 levels; however, Klotho alone is not sufficient to reverse the toxic effect, and cooperation between FGF23 and Klotho is required.[27] On the other hand, in other studies, high FGF23 levels have been associated with high mortality in patients with chronic renal failure on dialysis treatment.[26] In psychiatry, FGF23 has been shown to correlate with impulsive behavior in humans,[27] focusing on its effect on neurogenesis,[23] and lithium has been reported to increase FGF23 formation in the treatment of major depression.[28] Looking at vitamin D pathways beyond the antioxidant–oxidant balance, one can also speculate that the relationship between Klotho and FGF23 may be important in psychiatric disorders. This is because vitamin D, which is closely associated with psychiatric disorders, is responsible for releasing neurotrophic factors necessary for neuronal differentiation and exerts a calcium-mediated neuroprotective effect.[29] Patients with schizophrenia, depressive disorders, and other affective disorders were found to have significantly lower vitamin D levels than healthy controls, and the results were associated with these psychiatric disorders. The authors reported that their results might be related to the inhibitory effect of vitamin D on proinflammatory cytokines.[30,31]

Despite the central expression of FGF23 and Klotho proteins, the function of the FGF23/Klotho axis in psychiatric disorders remains unknown. However, we have more extensive and evidence-based information on the

MAIN POINTS

- Klotho levels in the serum of schizophrenia patients were significantly higher than in healthy controls
- Serum fibroblast growth factor 23 (FGF23) levels in schizophrenia patients were significantly higher than in healthy control subjects
- A significant positive correlation was observed between the serum Klotho and FGF23 levels of the subjects
- The Klotho/FGF23 pathway may play a role in the pathogenesis of schizophrenia.

role of both proteins in inflammatory processes. Now that we know the role of inflammation in the etiopathogenesis of schizophrenia, to our knowledge, there is no study reporting FGF23 and Klotho levels in schizophrenia and examining the relationship between these 2 proteins in these patients. In this study, serum FGF23 and Klotho levels of healthy control subjects were compared with those of schizophrenia patients, and the possible relationship between FGF23, Klotho, and schizophrenia symptoms was investigated.

MATERIAL AND METHODS

Ethical Statement

After a detailed description of the study, all participants gave written informed consent according to the Declaration of Helsinki. The study was approved by Fırat University ethics committee (date: September 16, 2021, and number: 2021/09-28).

Power Analysis

The G-Power 3.1.9.2 program was used to determine the sample size. With an effect size of 0.915, a type 1 error rate of 0.03, and an accepted test power of 95%, it was determined that it would be appropriate to work with 36 patients and 36 controls (total of 72 participants). To be on the safe side, it was deemed appropriate to design a study with 80 participants.

Sample Group

Patient Group: Forty male patients diagnosed with schizophrenia according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), who were followed up and/or treated at the High-Security Forensic Psychiatry (HSFP) Clinic of the Elazığ Fethi Sekin City Hospital and who met the study criteria, participated in the study in a randomized manner.

Control Group: Forty healthy male control subjects who were admitted to the Psychiatric Clinic of the Elazığ Fethi Sekin City Hospital and had no history of psychiatric disorders and no systemic disorders according to DSM-5 criteria were randomly enrolled in the study.

Study Inclusion Criteria: Patients were eligible if they were diagnosed with schizophrenia according to DSM-5, were between 18 and 65 years of age, voluntarily participated in the study, could understand the scales used in the study, could read and write, and did not have chronic somatic disorders, inflammatory diseases, and immune diseases.

Criteria for Exclusion of Participants from the Study: Intellectual disability, alcohol and/or substance abuse, chronic somatic disorders and malignant diseases, use of antioxidants, presence of active infection, presence of immunological disease, use of corticosteroids or other drugs affecting the immune system in the last 6 months, illiteracy, and failure to provide written informed consent were the criteria for exclusion of participants from the study.

Procedure: The study was conducted in the HSFP Clinic of the Elazığ Fethi Sekin City Hospital after approval by the ethics committee. Interviews were conducted by a consultant psychiatrist and lasted at least 30 minutes. They were structured according to the DSM-5. After all participants signed written informed consent, we prepared the sociodemographic data form, and the psychiatrist administered the Positive and Negative Syndrome Scale (PANSS) and the Clinical Global Impression (CGI) Scale to all participants. On the day of the psychometric assessment, 5 mL of blood was drawn once from the antecubital vein into a biochemical tube using a 5-mL injector. After all samples were collected, FGF23 and Klotho levels were analyzed in the biochemical laboratory by the enzyme-linked immunosorbent assay (ELISA) method.

Determination of Serum Levels of Klotho and Fibroblst Growth Factor 23

Venous blood samples from the left forearm vein were placed in heparinized tubes between 08:00 AM and 09:00 PM after overnight fasting. Blood samples were centrifuged at 3000 rpm and 4°C for 10 minutes to remove plasma. Serum samples were stored at −80°C until analysis. A commercial ELISA kit [Human KL (Klotho); catalog number: E-EL-H5451; Elabscience Biotechnology Inc, Human FGF23 (Fibroblast Growth Factor 23); catalog number: E-EL-H1116; Elabscience Biotechnology Inc] was used to measure serum levels of KL and FGF23 according to the manufacturer's instructions. Serum levels of KL were expressed in ng/mL and those of FGF23 in pg/mL.

Scales Used in the Study

1) **Sociodemographic and Clinical Data Form:** A sociodemographic and clinical data form was used, which we prepared in accordance with the information obtained from clinical experiences in cases and reviewed references and considering the objectives of the study.
2) **Positive and Negative Symptom Scale (PANSS):** This is a 30-item scale to measure psychopathology related to the positive, negative, and general symptoms of schizophrenia. Of the 30 psychiatric parameters assessed by the PANSS, 7 are on the positive symptoms subscale, 7 are on the negative symptoms subscale, and the remaining 16 are on the general psychopathology subscale. Each item was assigned a score from 1 to 7. This resulted in a score range of 7-49 for the positive and negative subscales and 16-112 for the general psychopathology subscale.[32] Kostakoğlu et al[33] conducted the Turkish validity and reliability study of the scale. The Cronbach's alpha

value was 0.75 for the positive subscale, 0.77 for the negative subscale, and 0.71 for the general subscale.

3) **Clinical Global Impression Scale (CGI):** It was developed to assess the course of all psychiatric disorders at any age for the purpose of clinical research. It was also developed to assess patients during clinical studies and monitor treatment-related changes at subsequent follow-ups. Severity levels on the scale were as follows: 1=normal, not at all ill, 2=borderline mentally ill, 3=mildly ill, 4=moderately ill, 5=markedly ill, 6=severely ill, and 7=among the most extremely ill patients.[34] The Cronbach's alpha value was 0.69-0.96.[35]

Statistical Analysis

Our data were analyzed using Statistical Package for the Social Sciences software 20 (IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test was used to determine the normal distribution of the variables. Data were shown as mean and standard deviation and analyzed using descriptive analysis. Relationships between categorical data were assessed using Pearson's Chi-square test. Fisher-Freeman-Halton test was used for 3 × c contingency tables. Psychological outcomes and biochemical parameters of the patient and control groups were compared by Student's *t*-test or Mann-Whitney *U*-test. Group differences in serum levels of Klotho and FGF23 were tested by independent analyses of covariance (ANCOVA) with age and body mass index (BMI) as covariates. Analyses of covariance effect sizes for all other group comparisons were recorded as partial eta-squared (ηp2; small ≥ 0.01, moderate ≥ 0.06, and large ≥ 0.14). Spearman's rank correlation coefficient was used to analyze correlations between clinical characteristics and serum levels of Klotho and FGF23. *P*-values < .05 (2-tailed) were considered significant.

RESULTS

The sociodemographic characteristics of the patient and control groups are summarized in Table 1.

About 82.5% (33) of patients were actively using psychotropic drugs, whereas 17.5% (7) were not. About 92.5% (37) of patients had a psychiatric treatment history, whereas 7.5% (3) had no psychiatric treatment history.

The mean positive PANSS score of the patients was 18.02 ± 4.9, the mean negative PANSS score was 16.10 ± 5.18, the mean PANSS general score was 33.52 ± 6.09, the mean PANSS total score was 67.37 ± 10.52, and the mean CGI score was 7.95 ± 1.83 (Table 1).

The mean serum Klotho level of the patients with schizophrenia was 0.76 ± 0.47 ng/mL, and the mean serum Klotho level of the control group was 0.58 ± 0.41 ng/mL, and a statistically significant difference was observed between them (*P* = .048) (Table 2). Even when an ANCOVA was performed by controlling for age and BMI as covariates,

Table 1. Demographic and Clinical Characteristics of Schizophrenia Patients and Control Subjects

	Schizophrenia Patients (n=40)	Control Subjects (n=40)	t/x^2	*P*
Age (years)	37.2 ± 11.1	37.4 ± 11.9	−0.097[a]	.923
Marital status				
Single/married	30 (75%)/10 (25%)	12 (30%)/28 (70%)	16.241[b]	<.001**
Education				
Primary school/high school/university	21 (52.5%)/10 (25%)/9 (22.5%)	26 (65%)/10 (25%)/4 (10%)	2.455[b]	.293
Working status				
Working/not working	16 (40%)/24 (60%)	22 (55%)/18 (45%)	1.805[b]	.179
Smoking				
Smoker/nonsmoker	28 (70%)/12 (30%)	18 (45%)/22 (55%)	5.115[b]	.024*
Alcohol use				
	6 (15%)/34 (85%)	0/40 (100%)	6.486[b]	.011*
BMI	27.5 ± 4.4	27.6 ± 4.1	−0.177[a]	.860
History of suicide attempts				
Yes/no	5 (12.5%)/35 (87.5%)	0/40 (100%)	5.333[b]	.021*
Duration of illness (year)	9.55 ± 7.46			
PANSS positive	18.02 ± 4.9			
PANSS negative	16.10 ± 5.18			
PANSS general	33.52 ± 6.09			
PANSS total	67.37 ± 10.52			
CGI	7.95 ± 1.83			

*$P < .05$, **$P < .001$; [a]Student's *t*-test; [b]Pearson's Chi-square test.
BMI, body mass index; PANSS, Positive and Negative Syndrome Scale; CGI, Clinical Global Impression.

Table 2. Serum Levels of Klotho and FGF23 in Schizophrenia Patients and Control Subjects

	Schizophrenia Patients (n = 40) Median (Min-Max)	Control Subjects (n = 40) Median (Min-Max)	z^a	*P*
Serum Klotho (ng/mL)	0.585 (0.16-2.03)	0.480 (0.15-1.89)	−1.978	.048*
Serum FGF23 (pg/mL)	32.135 (4.95-137.88)	16.32 (1.34-170.18)	−2.593	.010*

[a]Mann-Whitney *U*-test; *$P < .05$.
FGF23, fibroblast growth factor 23.

significant differences remained in serum Klotho levels between the patient and control groups (F[1,76] = 4.518, $P = .037$, ηp2 = 0.056).

The serum FGF23 level of the patients with schizophrenia was significantly higher than the control group ($P = .010$) (Table 2). Even after performing ANCOVA by controlling for age and BMI as covariates, significant differences remained in serum FGF23 levels between the patient and control groups (F[1,76] = 8.419, $P = .005$, ηp2 = 0.100).

No correlation was detected between serum Klotho and FGF23 levels in schizophrenia patients and clinical parameters ($r = 0.044$; $P = .789$ and $r = -0.043$; $P = .792$, respectively).

A significant positive correlation was found between serum Klotho and FGF23 levels in the study ($r = 0.816$; $P < .001$).

DISCUSSION

In our study, significantly higher combined serum levels of FGF23 and Klotho were found for the first time in patients with schizophrenia compared to healthy controls. Considering that a high central Klotho level may correct synaptic deterioration and cognitive function, we sought to elucidate the underlying molecular mechanisms and investigate Klotho protein in schizophrenic patients.[21] This study also found that plasma Klotho level was higher in schizophrenia patients than healthy control subjects, which is consistent with our research findings. In addition, high Klotho levels were reported to be positively related to patients' cognitive performance. It has been suggested that Klotho may play a role in the pathogenesis of schizophrenia and that Klotho plasma levels may serve as a predictor of cognitive function in schizophrenia.[21] Another recent study demonstrated that Klotho serum levels were higher in patients with schizophrenia compared with healthy controls, but no significant difference was found between the 2 groups.[36] After genetic studies discovered that the variant KL-VS, a haplotype and variant of the human Klotho gene (KL), increases serum levels of Klotho in the heterozygous state,[37] a study showed that the variant KL-VS impairs cognitive function in patients with schizophrenia.[38] Because Klotho downregulates inflammatory cytokines and patients with bipolar disorder are prone to age-related disorders, Klotho has become a focus of interest, and researchers found that Klotho plasma levels are elevated in these patients.[20] Fibroblast growth factor 23 protein alone has not been studied in schizophrenia patients. However, because of the neuromodulatory effects of the FGF family and the ability of antidepressant therapies to alter central FGF expression, it has been suggested that these family members may represent a genetic predisposition to affective disorders, anxiety disorders, and substance abuse.[23] Most studies of peripheral FGF23 have focused on its association with cognitive function. In these studies, the association was based on the correlation between FGF23 and vitamin D3, because vitamin D3 is inhibited by the 1α-hydroxylase FGF23 (and its cofactor in this pathway, Klotho).[39,40] One of these studies failed to demonstrate an association between FGF23 and cognitive deterioration.[39] Another study found no evidence that high serum FGF23 levels were associated with cognitive impairment.[39] Apart from this, one study showed an association between peripheral FGF23 and mood regulation. Although there was no direct evidence for this, the authors emphasized that the effect here could be due to lithium-induced polyuria and dehydration.[28] However, there are also studies that individually report that FGF23 is lower in major depression.[41,42] Central FGF23 has been found to correlate with impulsive behavior in humans.[27] Despite our limited knowledge, we hypothesize that FGF23, a member of the FGF family, may be involved in the pathophysiology of schizophrenia in view of a potent neuroprotective and mood-regulating factor, FGF21.[43]

The proteins Klotho and FGF23, which are likely indicators of anti-inflammation and inflammatory balance, are relatively new proteins in psychiatry. To date, many studies have reported positive results of upregulation of Klotho and FGF23 levels.[11,17,23] In particular, these results are based on the fact that Klotho has antioxidant and anti-inflammatory effects, and both proteins have been associated with neurodevelopmental pathways in individual cases.[23,25,44] Schizophrenia is a complex disease with neurodevelopmental origins that progresses through neurodegenerative processes. Abnormal neurogenesis and neurodegeneration determine the course of schizophrenia.[44] Although the distribution of Santal Klotho in the central nervous system is not precisely known, it is known to have a positive effect on cognitive functions (learning, memory, executive function, processing speed, and working memory). These positive effects on cognitive functions are thought to be caused by a series of reactions, particularly in the hippocampus and/or cerebral cortex. The primary ones of these reactions are activation of phosphoinositide 3-kinases (PI3K/Akt) by co-release of Klotho with FGF23, Klotho's inhibition of insulin/IGF-1 signaling, and Klotho's activation of FOXO1, followed by

suppression of lipid oxidation. These reactions also include the triggering of long-term potentiation by Klotho and the increase in antioxidant expression of peroxiredoxin-2 (Prx-2) by Klotho via the N-methyl-D-aspartate receptor through the activation of Ca^{2+}-sensitive proteins.[13,14] Because Klotho positively affects neuronal function and is neuroprotective via an antioxidant mechanism, its levels decrease in neurodegenerative diseases.[21,45] For example, decreased Klotho levels, an increase in proinflammatory TNF-alpha, and a deterioration in cognitive function have been observed in the prefrontal cortices of nephrectomized rats. Klotho protects cells from TNF-alpha-induced cytotoxicity by inhibiting TNF-alpha, the product of central neurons.[14] Overexpressed Klotho has also been shown to significantly protect dopaminergic neurons from oxidative damage.[44] Given microglial activation leads to increases in proinflammatory cytokines and impaired astrocyte function in schizophrenia, the effects and pathways of Klotho are important.[46] Although Klotho exerts its effects through different pathways, the common conclusion is that it may be an effective treatment method for neurodegeneration.[14] Perhaps most importantly, the co-release of FGF23 and Klotho has been shown to affect neuronal morphology and synaptic density through activation of the PI3K/Akt pathway.[13]

Based on the available data, we cannot say whether the increase in serum levels of Klotho and FGF23 in the patients in our research results is a cause or consequence of the pathology. However, based on the literature, we can say that these high serum levels may be a consequence of pathology in schizophrenia, in which the oxidant load is high. This is because it has been observed in schizophrenia that the anti-inflammatory response also increases in response to increased peripheral proinflammatory activity.[1] Significantly higher levels of neuroinflammatory markers have been found in schizophrenia in both the acute and stable phases.[47] However, the higher levels of anti-inflammatory markers in schizophrenics in the first episode suggest a combined increase in both pathways.[2] The positive correlation between serum levels of FGF23 and Klotho in our study may be due to the 2 proteins working together and showing common effects. However, further studies on the cooperation of FGF23 and Klotho are warranted.

Our study has some limitations. Because our study is cross-sectional, we cannot generalize the results beyond the sample. Another aspect of our study is that we measured Klotho levels in peripheral serum; however, it is unclear how Klotho serum levels reflect Klotho protein concentration in the central nervous system. In addition, our sample consisted of a relatively specific group of male schizophrenic patients in the HSFP clinic, and the sample group was unstable, with an average PANSS score of 67.37, which may have affected the serum levels of FGF23 and Klotho, which are influenced by numerous pathophysiological factors.

The correlated serum levels of FGF23 and Klotho were significantly higher in schizophrenic patients than in control subjects. There is increasing evidence that abnormal inflammatory responses may be involved in the pathophysiology of schizophrenia. Given its role in both FGF signaling and neuronal development and intracellular communication, we suggest that FGF23 and Klotho may both play potential roles in the etiopathogenesis of schizophrenia. The interaction between Klotho and FGF23 is more complex than suggested in the current literature and needs further elucidation. Further studies are needed to investigate a possible causal relationship between FGF23 and Klotho in serum and schizophrenia, which our study failed to demonstrate. However, we believe that, as in our study, new approaches such as Klotho and FGF23 should gain importance day by day to elucidate a disease with complex pathogenesis such as schizophrenia and may even provide alternative substructures for therapeutic approaches in this disease.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Fırat University (Approval Number: 2021/09-28, Date: September 16, 2021).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – K.K.A., Y.S., S.E.B., A.M.; Design – K.K.A., Y.S., K.F., A.M.; Supervision – K.K.A.; Materials – K.K.A., S.E.B.; Data Collection and/or Processing – S.E.B., K.F.; Analysis and/or Interpretation – K.K.A., K.F.; Literature Review –K.K.A., Y.S.; Writing – K.K.A., A.M.; Critical Review – K.K.A., Y.S., S.E.B., K.F., A.M.

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