Psychiatria Danubina, 2022; Vol. 34, No. 2, pp 273-278 https://doi.org/10.24869/psyd.2022.273 *Original paper*

SERUM CLAUDIN-5, BUT NOT ZONULIN, MAY BE ASSOCIATED WITH OBSESSIVE-COMPULSIVE DISORDER

Faruk Kılıç[1], Ümit Işık[2] & Duygu Kumbul Doğuç[3]

[1]*Department of Psychiatry, Süleyman Demirel University Medicine Faculty, Isparta, Turkey*
[2]*Department of Child and Adolescent Psychiatry, Süleyman Demirel University Medicine Faculty, Isparta, Turkey*
[3]*Department of Biochemistry, Süleyman Demirel University Medicine Faculty, Isparta, Turkey*

received: 6.11.2021; revised: 27.4.2022; accepted: 3.5.2022

SUMMARY

Background: *The aim of this research was to assess serum zonulin and claudin-5 concentrations to show whether or not their eventual changes in patients with obsessive-compulsive disorder (OCD) could have etiopathogenetic importance. There was no research in the literature assessing serum zonulin and claudin-5 levels in OCD to the best of our understanding.*

Subjects and methods: *In this study, we assumed that there may be a deterioration in serum zonulin and claudin-5 levels in OCD patients and this may affect the severity of the disease. Thirty-six OCD patients and 35 healthy controls were included in this study. The patients were administered Hamilton Depression Rating Scale (HDRS) and Yale-Brown Obsession Compulsion Scale (Y-BOCS) to determine the severity of depression and OCD, respectively. Venous blood samples were collected, and serum zonulin and claudin-5 levels were measured.*

Results: *The mean serum claudin-5 level was significantly higher without a significant difference between age, sex, and body mass index, whereas serum zonulin level was not different from the control group in OCD patients.*

Conclusions: *In conclusion, the current research indicates that claudin-5 is enhanced in OCD patients and this finding may contribute to the role of blood-brain barrier in the pathogenesis of OCD.*

Key words: *blood-brain barrier - claudin-5 - intestinal permeability – zonulin - obsessive-compulsive disorder*

* * * * *

INTRODUCTION

Obsessive-compulsive disorder (OCD), with an incidence of 2-3 percent throughout the world, is defined by intrusive unwanted thoughts, ideas, or pictures that are distressing and urge the patient to conduct ritualistic activities or mental acts to decrease this distress. It has been caused with significant impairment to the quality of life in both the patient and proximal family and friends (Kugler et al. 2013). Despite enormous information from genetic, neurobiological, neurochemical and neuroimaging research, its etiopathogenesis is obscure (Bandelow et al. 2017, Pauls 2010). Contemporary understanding shows that OCD's etiopathogenesis is multifactorial.

Zonulin, an endothelial stimulator of the growth factor of the receptor, has been shown to control the permeability of the intestine and the blood-brain barrier (BBB). It has earlier been involved in a loss of gastrointestinal tract barrier function, which allows macromolecules, including endotoxins, to move into the body and lead to an immune response (Fasano 2011). Zonulin has been studied as a peripheral marker of intestinal permeability in some inflammatory diseases (Sturgeon and Fasano 2016). It levels have been found to be high in obesity (Zak-Gołąb et al. 2013), diabetes mellitus (Zhang et al. 2014), multiple sclerosis (Camara-Lemarroy et al. 2019), sepsis (Klaus et al. 2013). Zonulin has also been studied in relation to some psychiatric disorders, such as autism spectrum disorder (ASD) (Esnafoglu et al. 2017), attention deficit hyperactivity disorder (ADHD) (Aydoğan Avşar et al. 2020, Özyurt et al. 2018), obsessive-compulsive disorder in children (Işık et al. 2020) schizophrenia (Barber et al. 2019, Usta et al. 2020), bipolar disorder (Kılıç et al. 2020), and suicide behaviour (Ohlsson et al. 2019). In addition to its effect on the intestine, zonulin also regulates the permeability BBB (Barber et al. 2019).

Another molecule which is an integral membrane protein that regulates the permeability of the BBB is claudin-5 from the claudin family. The BBB plays an important role in defending the central nervous system (CNS) via claudin-5, by restricting access to circulating solutes, macromolecules, and cells that could negatively affect neuronal activity (Fiorentino et al. 2016). Therefore, changes in claudin-5 functions can lead to the opening of the paracellular pathway and increase the permeability of the endothelial barrier of the brain (Greene et al. 2019). Dysfunctions of the claudin-5 have been associated with some neurodegenerative disorders such as Alzheimer's disease (Keaney et al. 2015), neuroinflammatory disorders such as multiple sclerosis (Mandel et al. 2012) as well as psychiatric disorders including depression (Menard et al. 2017; Sántha et al. 2016), ASD and schizophrenia (Fiorentino et al. 2016). OCD may be subject to the same conditions. Also, the claudin-5 gene is located within 22q11.2 chromosome (Greene et al. 2019). Individuals with the 22q11 deletion syndrome (22q11DS) have a 30-fold enhanced lifetime risk of developing schizophrenia and other neuropsychiatric conditions

(Murphy et al. 1999). Claudin-5 expression has been studied in schizophrenia, and the authors suggested that the disruption of BBB may be a modifying factor in schizophrenia development (Greene et al. 2018). Although OCD is common in 22q11DS (Gothelf et al. 2004), there is no study that has examined the relationship between adult patient with OCD and claudin-5. In our previous study, serum claudin-5 levels were found to be significantly higher in children with OCD patients whereas serum zonulin levels were not significantly different between the groups (Işık et al. 2020).

There was no research in the literature assessing serum zonulin and claudin-5 concentrations in OCD to the best of our understanding. In this study, we assumed that there may be a deterioration in serum zonulin and claudin-5 levels in OCD patients and this may affect the severity of the disease. Therefore, we conducted the current study to specifically measure serum zonulin and claudin-5 to see whether or not its eventual changes might have etiopathogenetic importance in patients with OCD.

SUBJECTS AND METHODS

The study consisted of 36 patients who applied to the University School of Medicine, Department of Psychiatry and were diagnosed with OCD according to DSM-IV-TR criteria. Available 35 healthy controls according to the exclusion criteria were chosen among the hospital staff members. Each topic underwent a physical examination and a psychiatric diagnostic assessment after giving written informed permission. DSM-IV-TR OCD diagnosis was created by a senior physician on the grounds of independent clinical interviews. After a full explanation of the research method, all subjects gave informed written permission. The research was carried out in compliance with the Helsinki Declaration. The study was reviewed and approved by the Ethics Committee at University Medical Faculty (date in 17/05/2019, protocol number 151).

Exclusion criteria can vary such as unstable physical condition, axis I comorbidity, presence of endocrinological disease, diabetes history or lipid disorder, pregnancy or lactating, substance abuse within the last 3 months, unstable metabolic parameters, diets which have effects on hematological and biochemical parameters, anti-biotic and anti-inflammatory drug usage.

Thirty-five healthy control subjects (17 women and 18 males) were selected from the hospital staff according to exclusion criteria. They did not have any psychiatric disorders in their present or lifetime history. In their first-degree families, they also had no history of significant mood disorder, dementia, and psychosis. They also had no history of any endocrinological disease, lactating or childbearing potential, substance abuse, known medical conditions that could influence changes in metabolic parameters, known history of diabetes or gastrointestinal disorder, use of anti-inflammatory and antibiotic agents, or clinically relevant abnormal laboratory testing.

The patients were administered Hamilton Depression Rating Scale (HDRS) (Hamilton 1960) and Yale-Brown Obsession Compulsion Scale (Y-BOCS) (Goodman et al. 1989) to determine the severity of depression and OCD, respectively.

Biochemical analysis

The patients and controls have fasted overnight. Venous blood samples were taken at 08.00-10.00 a.m. from the antecubital vein to determine the serum concentrations of zonulin and claudin-5. Venous blood samples of the patients included in the study were taken into biochemistry tubes and centrifuged at 3000 rpm for 10 minutes and the serum portion was obtained. The serum sample obtained was stored at -80°C until the working day.

Determination of serum zonulin and claudin-5

The levels of human Claudin-5 and human Zonulin were determined by using commercial enzyme-linked immunosorbent assay (ELISA) kits [E-lab science Catalog No: SEF295Hu (Wuhan-China), E-lab science Catalog No: E-EL-H5560 (Wuhan-China) respectively]. The samples were 5-fold diluted at the beginning of the assays. To determine the levels of mentioned parameters in patient samples, a standard concentration-optic density graphic is used and the results were multiplied by 5 claudin-5 assay included 7 point calibrators as 31.25 pg/ml, 62.5 pg/ml, 125 pg/ml, 250 pg/ml, 500 pg/ml, 1000 pg/ml and 2000 pg/ml. Similarly human Zonulin included 7 point calibrators as 0.78 ng/ml, 1.57 ng/ml, 3.13 ng/ml, 6.25 ng/ml, 12.5 ng/ml, 25 ng/ml, 50 ng/ml.

Statistical analysis

Our data were analyzed on the IBM SPSS Statistics software (ver. 18; IBM Corp., Armonk, NY, USA). Data were displayed as mean, normal deviation and proportion, and assessed using descriptive analysis. Relationship assessment on numerical data was conducted using the correlation test and using the chi-square test for categorical data. Depending on the sample numbers of the groups to be compared and on the homogeneous distribution, parametric or non-parametric comparisons were selected. When required, analysis of covariance (ANCOVA) was used to control for covariates. Age, sex, BMI-adjusted covariance Analysis (General Linear Model) for zonulin and claudin-5 parameters.

RESULTS

No difference in demographic variables was found between groups. The demographic data are shown in Table 1. In regard to smoking status, no difference was found between groups, with thirteen in the patient group versus eleven in control ones ($p>0.05$). The mean Y-BOCS and HRDS scores were 20.3±7.8 and 14.2±5.6 in OCD patients, respectively.

Table 1. Demographic and clinical characteristics of patients with OCD and controls

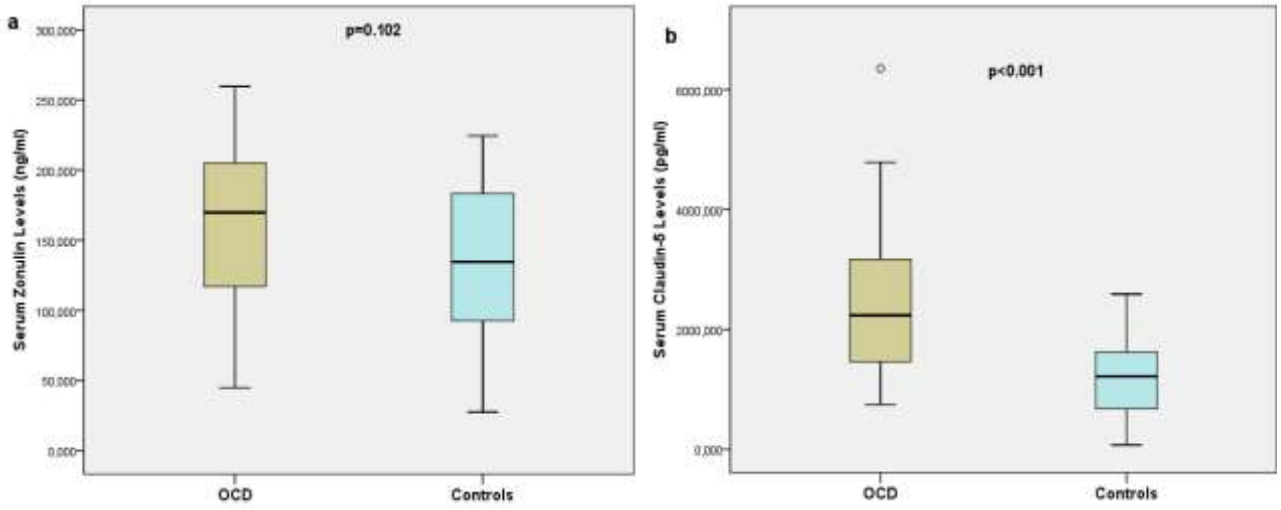
	OCD (n=36)	Control (n=35)	t/z/x^2	p
Age (years)	31±9.4	34.1±5.7	-1.848[b]	0.064
Sex			0.680[c]	0.410
Female	21	17		
Male	15	18		
Marital status			6.390[c]	*0.011*
Single	21	10		
Married	15	25		
Education			1.778[c]	0.411
Primary	5	7		
High	12	15		
University	19	13		
Smoking			0.174[c]	0.677
Yes	13	11		
No	23	31		
BMI	24.8±3.1	25.1±3.3	-0.414[a]	0.680
Duration of illness (year)	10.5±9			
Duration of drug use (year)	4.3±5			
History of suicide attempt				
Yes	5			
No	31			
Y-BOCS	20.3±7.8			
HDRS	14.2±5.6			

BMI: Body Mass Index; Y-BOCS: Yale-Brown Obsession Compulsion Scales; HDRS: Hamilton Depression Rating Scala;
[a] Student t test; [b] Mann-Whitney U test; [c] Chi square test

Table 2. Serum Zonulin and Claudin-5 levels of patients with OCD and controls

	OCD (n=36)	Control (n=35)	t/z	p	ANCOVA		
					F(1.66)	p	h_p^2
Zonulin (ng/ml)	157.5±60	134.6±56.2	1.655	0.102[a]	2.217	0.141	0.032
Claudin-5 (pg/ml)	2425.9±1181.9	1195.1±672.9	-4.715	*<0.001*[b]	25.886	*<0.001*	0.282

[a] Student t test; [b] Mann–Whitney U test; Analysis of covariance (ANCOVA) was used after adjusted for age, sex, and Body Mass Index for comparisons between two groups.



OCD: Obsessive-Compulsive Disorder

Figure 1. Box plots representing the distribution of Serum a) Zonulin and b) Claudin-5 levels in OCD patients and controls

There were no statistically significant differences between the groups with respect to body mass index (BMI) (24.8±3.1 in the patient group and 25.1±3.3 in controls) ($p>0.05$). The mean zonulin levels were 157.5±60 ng/ml for the patient group and 134.6±56.2 ng/ml for the control group ($p=0.102$). By using ANCOVA, no significant difference in the mean zonulin values maintained even after controlling for age, sex and BMI ($F=2.217$, $h_p^2=0.032$, $p=0.141$). By using ANCOVA, significant difference in the mean claudin-5 levels maintained even after controlling for age, sex and BMI ($F=25.886$, $h_p^2=0.282$, $p<0.001$) (Table 2, Figure 1).

In regard to gender, when comparing female to men levels of zonulin in the patient groups, significant difference determined. The mean zonulin level was higher in women than men in OCD patients (191±34.3 versus 110.7±57.5; in female and men, respectively; $p<0.001$).

Spearman correlation analysis showed that changes in zonulin or claudin-5 did not correlate with any of the parameters detected ($p>0.05$). There were no correlations between Y-BOCS scores and zonulin or claudin-5 levels in the patient groups ($p>0.05$). In addition, zonulin or claudin-5 levels were not correlated to the duration of illness, and age ($p>0.05$).

DISCUSSION

The findings of this study clearly show that the mean serum claudin-5 level was significantly higher without a significant difference between age, sex, and BMI, whereas serum zonulin level was not different from the control group in OCD patients. The finding that we found increased claudin-5 levels in OCD broadens our understanding of the pathogenesis of OCD. There was no research in OCD assessing its association with zonulin or claudin-5.

Claudine proteins are a significant component in tight junctions that play a key role in the reactions in BBB to altering natural, physiological and pathological circumstances. The vital importance of claudin-5 was demonstrated by the experiment on mice (Braniste et al. 2014). In one study, claudin-5 knockout mice were found to have increased permeability of molecules that would damage the central nervous system of less than 800 daltons by impairing the BBB permeability. Also, claudin-5 knockout mice had died within 10 hours of birth (Nitta et al. 2003). Studies have shown the relationship between claudin-5 dysfunction and some diseases such as intracranial hemorrhage (Jiao et al. 2015), multipl sclerosis (Mandel et al. 2012), migraine (Yücel et al. 2016) and epilepsy (Rempe et al. 2018). In addition, there are some studies examining the relationship between claudin and psychiatric disorders. In one of these studies, Fiorentino et al. found that claudin-5 protein levels in cortex and cerebellum were increased compared to schizophrenia and healthy controls in individuals with postmortem autism. (Fiorentino et al. 2016). In another postmortem study by Nishiura et al. (2017) found that decreased claudin-5 protein level in frontal cortex in schizophrenia. In addition to these studies, we found high serum levels of claudin-5 in our study. Also, there was no correlation between disease symptom severity and claudin-5 level. We suppose that this result may cause a deterioration in the permeability of BBB and may lead to a new perspective on the pathogenesis of OCD. To our knowledge, this is the first study to investigate the circulating claudin-5 levels in OCD patients. Despite these contradictory results, it is difficult to draw conclusive conclusions about the role of claudin-5 in the pathogenesis of OCD.

In especially, zonulin emerges as a significant mediator of enhanced intestinal permeability in humans. Under the impact of environmental stimuli, zonulin is generated by human small intestinal epithelium (Fasano 2011). In addition to its effect on the intestine, zonulin also regulates the permeability BBB (Barber et al. 2019). In some psychiatric disorders such as ADHD (Aydoğan Avşar et al. 2020, Özyurt et al. 2018), ASD (Esnafoglu et al. 2017), schizophrenia (Barber et al. 2019, Usta et al. 2020), and depression (Stevens et al. 2018), zonulin levels have been studied, but to our knowledge, OCD has not been studied. Esnafoglu et al. (2017) reported that serum zonulin levels were significantly higher compared with the healthy controls. Barber et al. (2019) found that serum zonulin level was higher than serum cut off value in 98 schizophrenia patients. Moreover, the connection between zonulin concentrations and suicide behavior has lately been proved (Ohlsson et al. 2019). Our study results did not reveal a significant difference in serum zonulin levels between OCD patients and healthy control. In addition, there was no correlation between disease symptom severity and zonulin level in our study. Diet has a significant role to play in controlling gut permeability. Because nutritional factors have not been assessed as this study's restriction, we presume zonulin concentrations may be influenced.

With some constraints, the results observed in this research should be assessed. First, as the sample size was comparatively small, we cannot unable to generalize the results to all OCD patients. At this stage, however, we should stress the power of the research that included patients with OCD without any comorbidity. Second, we only examined zonulin and claudin-5, associated parameters could be evaluated. Third, our sample does not consist only of drug-naive OCD patients, all of patients had been using medication. However, various studies have shown that administration of antipsychotic drugs is associated with an increase in claudin-5 levels (Greene et al. 2018). Drug use may have affected biochemical parameters results. In addition, the diet and weight patterns of patients and controls were not the same. This is a limitation of our study, as weight and diet may affect the BBB.

CONCLUSION

In conclusion, the current research indicates that claudin-5 is enhanced in OCD patients and this finding may contribute to the role of BBB in the pathogenesis of OCD.

Acknowledgements:

The study was reviewed and approved by the Ethics Committee at University Medical Faculty (date in 17/05/2019, protocol number 151).

Conflict of interest: None to declare.

Contribution of individual authors:

Faruk Kiliç: study design, data collection, first draft.
Ümit Işik: study design, first draft, statistical analysis.
Duygu Kumbul Doğuç: study design.
All authors approval of the final version.

References

1. *Aydoğan Avşar P, Işık Ü, Aktepe E, Kılıç F, Doğuç DK, Büyükbayram Hİ: Serum zonulin and claudin-5 levels in children with attention-deficit/hyperactivity disorder. Int J Psychiatry Clin Pract 2021; 25:49-55*
2. *Bandelow B, Baldwin D, Abelli M, Bolea-Alamanac B, Bourin M, Chamberlain SR et al.: Biological markers for anxiety disorders, OCD and PTSD: A consensus statement. Part II: Neurochemistry, neurophysiology and neurocognition. World J Biol Psychiatry 2017; 18:162–214*
3. *Barber GS, Sturgeon C, Fasano A, Cascella NG, Eaton, WW, McMahon RP et al.: Elevated zonulin, a measure of tight-junction permeability, may be implicated in schizophrenia. Schizophr Res 2019; 211:111–112*
4. *Braniste V, Al-Asmakh M, Kowal C, Anuar F, Abbaspour A, Toth M et al.: The gut microbiota influences blood-brain barrier permeability in mice. Sci Transl Med 2014:6, 263ra158-263ra158*
5. *Camara-Lemarroy CR, Silva C, Greenfield J, Liu WQ, Metz LM, Yong VW. Biomarkers of intestinal barrier function in multiple sclerosis are associated with disease activity. Mult Scler J 2020: 26;1340-1350*
6. *Esnafoglu E, Cırrık S, Ayyıldız SN, Erdil A, Ertürk EY, Daglı A et al.: Increased Serum Zonulin Levels as an Intestinal Permeability Marker in Autistic Subjects. J Pediatr 2017; 188:240–244*
7. *Fasano A: Zonulin and Its Regulation of Intestinal Barrier Function: The Biological Door to Inflammation, Autoimmunity, and Cancer. Physiol Rev 2011; 91:151–175*
8. *Fiorentino M, Sapone A, Senger S, Camhi SS, Kadzielski SM, Buie TM et al.: Blood–brain barrier and intestinal epithelial barrier alterations in autism spectrum disorders. Mol Autism 2016; 7:49*
9. *Goodman WK, Price LH, Rasmussen SA, Mazure C, Fleischmann RL, Hill CL et al.: The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability. Arch. Gen. Psychiatry 1989; 46:1006–1011*
10. *Gothelf D, Presburger G, Zohar AH, Burg M, Nahmani A, Frydman M et al. Obsessive–compulsivedisorder in patients with velocardiofacial (22q11 deletion) syndrome. Am J Med Genet 2004;126B:99–105*
11. *Greene C, Kealy J, Humphries MM, Gong Y, Hou J, Hudson N et al. Dose-dependent expres-sion of claudin-5 is a modifying factor in schizophrenia. Mol Psychiatry 2018;23:2156–2166*
12. *Greene C, Hanley N, Campbell M: Claudin-5: gatekeeper of neurological function. Fluids Barriers CNS 2019; 16:3*
13. *Hamilton M: A rating scale for depression. J Neurol Neurosurg Psychiatry 1960; 23:56–62*
14. *Işık Ü, Aydoğan Avşar P, Aktepe E, Doğuç DK, Kılıç F, Büyükbayram Hİ: Serum zonulin and claudin-5 levels in children with obsessive–compulsive disorder. Nord J Psychiatry 2020; 74:346-351*
15. *Jiao X, He P, Li Y, Fan Z, Si M, Xie Q et al.: The Role of Circulating Tight Junction Proteins in Evaluating Blood Brain Barrier Disruption following Intracranial Hemorrhage. Dis Markers 2015; 1–12*
16. *Keaney J, Walsh DM, O'Malley T, Hudson N, Crosbie DE, Loftus T et al.: Autoregulated paracellular clearance of amyloid-β across the blood-brain barrier. Sci Adv 2015;1: e1500472*
17. *Kılıç F, Işık Ü, Demirdaş A, Doğuç DK, Bozkurt M: Serum zonulin and claudin-5 levels in patients with bipolar disorder. J Affect Disord 2020; 266:37–42*
18. *Klaus DA, Motal MC, Burger-Klepp U, Marschalek C, Schmidt EM, Lebherz-Eichinger D et al.: Increased plasma zonulin in patients with sepsis. Biochem Medica 2013; 23:107–111*
19. *Kugler BB, Lewin AB, Phares V, Geffken GR, Murphy TK, Storch EA: Quality of life in obsessive-compulsive disorder: The role of mediating variables. Psychiatry Res 2013; 206:43–49*
20. *Mandel I, Paperna T, Glass-Marmor L, Volkowich A, Badarny S, Schwartz I et al.: Tight junction proteins expression and modulation in immune cells and multiple sclerosis. J Cell Mol Med 2012; 16:765–775*
21. *Menard C, Pfau ML, Hodes GE, Kana V, Wang VX, Bouchard S et al.: Social stress induces neurovascular pathology promoting depression. Nat Neurosci 2017; 20:1752–1760*
22. *Murphy KC, Jones LA, Owen MJ. High rates of schizophrenia inadults with velo-cardio-facial syndrome. Arch Gen Psychiatry.1999;56:940–945*
23. *Nitta T, Hata M, Gotoh S, Seo Y, Sasaki H, Hashimoto N et al.: Size-selective loosening of the blood-brain barrier in claudin-5-deficient mice. J Cell Biol 2003; 161:653–660*
24. *Ohlsson L, Gustafsson A, Lavant E, Suneson K, Brundin L, Westrin Å et al.: Leaky gut biomarkers in depression and suicidal behavior. Acta Psychiatr Scand 2019; 139:185–193*
25. *Özyurt G, Öztürk Y, Appak YÇ, Arslan FD, Baran M, Karakoyun İ et al.: Increased zonulin is associated with hyperactivity and social dysfunctions in children with attention deficit hyperactivity disorder. Compr Psychiatry 2018; 87:138–142*
26. *Pauls DL: The genetics of obsessive-compulsive disorder: a review. Dialogues Clin Neurosci 2010; 12:149–163*

27. *Rempe RG, Hartz AMS, Soldner ELB, Sokola BS, Alluri SR, Abner EL et al.: Matrix Metalloproteinase-Mediated Blood-Brain Barrier Dysfunction in Epilepsy. J Neurosci 2018; 38:4301–4315*
28. *Sántha P, Veszelka S, Hoyk Z, Mészáros M, Walter FR, Tóth AE et al.: Restraint Stress-Induced Morphological Changes at the Blood-Brain Barrier in Adult Rats. Front Mol Neurosci 2016; 8:88*
29. *Stevens BR, Goel R, Seungbum K, Richards EM, Holbert RC, Pepine CJ et al.: Increased human intestinal barrier permeability plasma biomarkers zonulin and FABP2 correlated with plasma LPS and altered gut microbiome in anxiety or depression. Gut 2018; 67:1555-1557*
30. *Sturgeon C, Fasano A: Zonulin, a regulator of epithelial and endothelial barrier functions, and its involvement in chronic inflammatory diseases. Tissue Barriers 2016; 4: e1251384*
31. *Usta A, Kılıç F, Demirdaş A, Işık Ü, Doğuç DK, Bozkurt M: Serum zonulin and claudin-5 levels in patients with schizophrenia. Eur Arch Psychiatry Clin Neurosci 2021; 271:767-773*
32. *Yücel M, Kotan D, Çiftçi GG, Çiftçi IH, Cikriklar HI: Serum levels of endocan, claudin-5 and cytokines in migraine. Eur Rev Med Pharmacol Sci 2016; 20:930–936*
33. *Zak-Gołąb A, Kocełak P, Aptekorz M, Zientara M, Juszczyk L, Martirosian G et al.: Gut microbiota, micro-inflammation, metabolic profile, and zonulin concentration in obese and normal weight subjects. Int J Endocrinol 2013, 674106*
34. *Zhang D, Zhang L, Zheng Y, Yue F, Russell RD, Zeng Y: Circulating zonulin levels in newly diagnosed Chinese type 2 diabetes patients. Diabetes Res Clin Pract 2014; 106:312–318*

Correspondence:
Assistant Professor Faruk Kılıç, MD
Department of Psychiatry, Süleyman Demirel University Medicine Faculty
Isparta, Turkey
E-mail: drfarukk33@hotmail.com