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Neuroserpin, Tissue Plasminogen Activator, Brain-Derived Neurotrophic Factor and Interleukin-6 Serum Levels in Patients with Bipolar Disorder

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ABSTRACT

Introduction: Numerous hypotheses have been proposed for the pathophysiology of bipolar disorder (BD). This study aimed to evaluate serum neuroserpin (NSP), tissue plasminogen activator (tPA), interleukin-6 (IL-6), brain-derived neurotrophic factor (BDNF), high-sensitivity C-reactive protein (hsCRP), and sedimentation levels in patients with BD, based on the inflammatory and fibrinolytic system hypothesis, to understand the etiopathogenesis of BD. The second aim of our study was to determine the risk of developing BD type 1 by examining the relationship between tPA and NSP in patients diagnosed with BD type 1.

Methods: The study included 80 euthymic outpatients with BD type 1 and 80 healthy controls (HC). Individuals with a Hamilton Depression Rating Scale (HAM-D) score of less than 7 and a Young Mania Rating Scale (YMRS) score of less than 4 who did not show any symptoms of mania, depression, or hypomania for the last 6 months were included in the study. In both groups, serum levels of NSP, tPA, IL-6, BDNF, hsCRP, and sedimentation were measured.

Results: Compared to the healthy control group, the NSP and tPA levels were lower in the BD group ($p<0.001$). We found no linear relationship when we analyzed the relationship between tPA and NSP by excluding other variables. (p: 0.027)

Conclusion: These findings suggest that tPA and NSP may serve as potential biomarkers for the euthymic period of BD type 1. These biomarkers may provide guidance in understanding the pathophysiology of bipolar disorder.

Keywords: Brain-derived neurotrophic factor, bipolar disorder, fibrinolytic system, neuroserpin, tissue plasminogen activator

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INTRODUCTION

Bipolar disorder (BD) is a persistent psychiatric disorder that affects approximately 1% of the population and is characterized by mood episodes (1). These episodes vary in frequency and severity, and are typically manifest as alternating depressive and manic periods (2). Bipolar disorder is often accompanied by a variety of medical and psychiatric comorbidities and can, as a result, cause severe impairments in a person's social, occupational, and family functioning (3).

Recent studies on the neurobiology of BD have shown that inflammatory processes have an essential impact on etiopathogenesis (4). Several studies have demonstrated increased levels of proinflammatory cytokines in the bloodstream during different episodes of BD (5). At the onset of an episode, these inflammatory mediators may play a protective role by limiting neuronal damage. However, when their activity persists over time –as observed in recurrent episodes– this regulatory balance is disrupted, resulting in a chronic proinflammatory state that contributes to neuronal injury (6). Specifically, elevations in interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-alpha) levels have been documented during manic episodes. While IL-6 levels tend to normalize following treatment with mood stabilizers, TNF-α levels often remain elevated (7). In mania, increased concentrations of proinflammatory cytokines such as IL-2, IL-6, IL-8, and Interferon-gamma (INF-gamma) are reported, while in depressive episodes, only IL-6 levels appear to be significantly elevated (8).

A hypothesis suggests that the fibrinolytic system might contribute to BD pathophysiology (9). The fibrinolytic system is an intricately regulated process that begins with tissue plasminogen activator (tPA) and culminates in the converting plasminogen to plasmin, its active form (10). Both plasmin and tPA are serine proteases whose activity is tightly controlled to limit plasmin's duration and magnitude (11). Plasminogen activator inhibitor (PAI-1) and neuroserpin (NSP) have been shown to serve as key inhibitors and regulators of tPA and plasmin, limiting tPA-mediated brain damage in acute ischemic stroke (12). In addition to promoting the procoagulant effect, PAI-1 contributes to the conversion of proBDNF to brain-derived neurotrophic factor (BDNF), another critical

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Highlights

- **Sedimentation, hsCRP, and smoking suggest an inflammatory role in BD.**
- **tPA and NSP may serve as potential biomarkers for the euthymic period of BD.**
- **NSP–tPA dynamics imply fibrinolytic involvement in BD etiopathogenesis.**

fibrinolytic system marker (13). proBDNF and BDNF have been shown to have opposite effects on neurogenesis, and patients with depression have been found to have high levels of proBDNF and decreased BDNF levels (14). Another study also found that the severity of mood symptoms and BDNF levels were inversely correlated in patients with BD (15). A meta-analysis has shown that both plasma and serum BDNF and tPA concentrations are lower in BD patients compared with HCs (16).

Recent studies have highlighted the interaction between the fibrinolytic and inflammatory systems in regulating physiological processes such as growth factor activation, cytokine production, cell differentiation, proliferation, and migration. This system is also involved in the etiology of chronic diseases such as systemic lupus erythematosus and ulcerative colitis (17).

A review of the literature reveals that studies on the fibrinolytic system have predominantly focused on schizophrenia and depression (18), while research addressing BD remains limited. Furthermore, there appears to be no study to date that investigates the interaction between the inflammatory and fibrinolytic systems in the context of BD.

This study aims to contribute to understanding the pathogenesis of BD by exploring the relationship between the inflammatory and fibrinolytic systems. Specifically, it compares biomarkers, including NSP, tPA, BDNF, hsCRP, and sedimentation levels between BD patients and HCs. The second aim of our study is to determine the risk of BD by examining the relationship between tPA and NSP in patients diagnosed with BD type 1.

METHODS

Euthymic patients diagnosed with BD type 1, aged between 18 and 65 years, who presented at the Health Sciences University Dışkapı Training and Research Hospital Psychiatry Polyclinic between May 2019 and May 2020 were included in this study with their informed consent. The diagnosis was based on the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) criteria. All participants provided informed consent, and their clinical history was evaluated by two experienced clinicians before inclusion. The diagnosis was confirmed using the Structured Clinical Interview for DSM-5 (SCID-5). Young Mania Rating Scale (YMRS) and Hamilton Depression Rating Scale (HAM-D) were used to evaluate the patient's current clinical status and determine whether they were in the period of exacerbation or remission. Inclusion criteria required that participants had a HAM-D score of <7 and a YMRS score of <4, with no signs of mania, depression, or hypomania in the previous six months.

Blood samples (5 cc) were collected after 12 hours of fasting at 8:00 am and stored at -20°C after centrifugation. Complete blood count, sedimentation rate and high sensitivity C-reactive protein (hsCRP) levels were measured. Body mass index (BMI) was calculated by measuring height and weight. The healthy control group consisted of 80 healthy volunteers who visited the Family Medicine Outpatient Clinic of the same hospital. These individuals were age– and gender-matched to the BD group and had no history of psychiatric or neurological disorders. Blood samples were also collected from the healthy control group, and biochemical analyses were performed to measure BDNF, tPA, NSP, and IL-6 levels.

Exclusion Criteria: Patients were excluded if they had a history of organic mental disorders (such as delirium, dementia, or intellectual disability), other psychiatric comorbidities (such as alcohol or substance use disorder, obsessive compulsive disorder, attention deficit hyperactivity disorder), were pregnant or breastfeeding, had any known unregulated systemic, inflammatory, or metabolic diseases (Diabetic patients with HbA1c values above 6 despite treatment, hypertension patients with blood pressure above 130/80 mmHg despite treatment), or were using immunosuppressive therapies.

Data Collection Tools

• **Sociodemographic Data Form:** This form was developed by the researchers to assess demographic and clinical variables, including age, marital status, education level, occupation, history of psychiatric illness, history of medical illness, family history of psychiatric and medical conditions, duration since diagnosis, current psychiatric and non-psychiatric medications, number of depressive and manic episodes, number of hospitalizations, and components of metabolic syndrome.

• **Hamilton Depression Rating Scale (HAM-D):** This scale assesses depression severity through 17 items rated on a 3-to 5-point scale. Scores are classified as mild (16–25), moderate (26–40), and severe (≥40) depression (19). Akdemir et al. (19) established the Turkish version's validity and reliability (19).

• **Young Mania Rating Scale (YMRS):** The YMRS is used to measure the severity of manic episodes, consisting of 11 items. Seven of these items are rated on a five-point Likert scale, and four are rated on a nine-point scale. The total score ranges from 0 to 44, with the Turkish version validated by Karadağ et al. (21).

Biochemical Analysis

After blood collection, samples were processed using BD Vacutainer SST II Advance serum separator tubes. The samples were centrifuged at 1500 g for 10 minutes and stored at -20°C. The frozen samples were thawed to room temperature on the analysis day, vortexed, and processed according to the specifications of ELISA kits.

Kits Used for Biochemical Analysis

- IL-6: DIA source IL-6 ELISA Kit (DIA source ImmunoAssays S. A., Belgium) 190206/1
- BDNF: Human Brain-Derived Neurotrophic Factor ELISA Kit (Sunred Biotechnology, Shanghai, China) 201–12–1303
- NSP: Human Neuroserpin (NSP) ELISA Kit (Sunred Biotechnology, Shanghai, China) 201–12–4383
- tPA: Human Tissue Plasminogen Activator (tPA) ELISA Kit (Sunred Biotechnology, Shanghai, China) 201–12–6854

Ethical information

Before starting this study, permission was obtained from the ethics committee of the Scientific Research Committee of Health Sciences University Dışkapı Training and Research Hospital (Decision date: June 11, 2018 Decision number: 51/19). All stages of the study were carried out according to the provisions of the Declaration of Helsinki as revised in Edinburgh 2000. Informed consent was obtained from all participants. The authors thank all the study participants and clinical staff who helped with this article.

Statistical Analysis

Data was analyzed using IBM Statistical Package for Social Sciences (SPSS) program version 23.0 software and R (version 4.2.2). The Shapiro-Wilk test was used to check the normality of data distributions. Descriptive statistics were presented as mean ± standard deviation, median, and range for continuous variables and percentages for categorical variables. For non-normally distributed variables, differences between groups were assessed using the Mann-Whitney U test. Spearman's correlation coefficient was used to analyze the relationships between variables, and partial correlations were calculated by controlling for confounding variables. The Chi-square and Fisher's exact tests were applied for categorical data analysis. The impact of hsCRP, NSP and tPA on the groups was assessed using binary logistic regression. The interaction plot of tPA and NSP was generated with R. A p-value of <0.05 was considered statistically significant.

RESULTS

The comparisons of employment status, smoking status, income level and years of education of the BD and healthy control groups and the duration of illness, number of depressive periods, number of hospitalizations, treatment information and number of manic periods of the BD group are shown in Table 1. A statistically significant difference was determined between the BD and healthy control groups in terms of employment, smoking status, and income level (p<0.001, p=0.006, and p=0.007, respectively) (Table 1).

There were statistically significant differences in waist circumference, body mass index, hip circumference, and weight between the BD and healthy control groups (p<0.001, p<0.001, p=0.005, and p=0.007, respectively) (Table 2).

While the mean values of hsCRP, NSP, sedimentation and tPA variables showed statistically significant differences between the BD and healthy control groups (p<0.05), no significant differences were found for other variables (Table 3).

Logistic regression analysis applied in line with the basic analysis is presented to determine the predictors of BD presence (Table 4). A 1-unit increase in cigarette use (borderline significant) increased the probability of having BD by 3.6%, a 1-unit increase in BMI increased the probability of having BD by 6.2%, and a 1-unit increase in hsCRP increased the probability of having BD by 22.5%.

Fig. 1 is the interaction graph of tPA and NSP created using logistic regression analysis. The column shows the risk of BD, and the row shows

Table 1. Demographic and clinic characteristics of the groups

	Bipolar disorder (n=80)	Healthy control (n=80)	p
Age (years); median (min-max)	39.50(20–63)	38(19–64)	0.364*
Gender (female); n (%)	40(50%)	40(50%)	1.000**
Marital status (married); n (%)	44(55%)	50(62.5%)	0.335**
Work status (working); n (%)	24(30%)	53(66.25%)	**<0.001****
Cigarette (packs/year); mean ± SD	8.35±11.86	3.86±7.471	**0.006*****
Income (yes); n (%)	35(43.75%)	62(77.5%)	**0.007****
Education time (years); mean ± SD	10.41±3.74	11.16±4.20	0.174***
Diseaase duration, years; mean ± SD	13.06±8.10	–	
Number of depressive episodes; mean ± SD	4.10±3.22	–	
Number of manic episodes; mean ± SD	4.23±2.79	–	
Number of hospitalizations; mean ± SD	2.13±2.48	–	
Antipsychotic chlorpromazine equivalent dose; mean ± SD	422.61±203.13		
Psychotropics used			
Lithium; n (%)	36(28.8%)		
Valproate; n (%)	32(25.6%)		
Quetiapine; n (%)	41(51.2%)		
Olanzapine; n (%)	12(15%)		
Aripiprazole; n (%)	10(12.4%)		
Risperidone; n (%)	6(7.5%)		
Paliperidone; n (%)	1(1.2%)		

Min: minimum; Max: maximum; mean ± SD: mean ± standard deviation; *: Mann-Whitney U test; **: Chi-square test; ***: Student's t-test; bold values indicate p-value of <0.05.

Table 2. Physical characteristics of the groups

	Bipolar disorder (n=80) Mean ± SD (n=80)	Healthy control (n=80) Mean ± SD (n=80)	p
Waist circumference (cm)	101.63±10.56	90.31±13.28	**<0.001**
BMI (kg/m²)	30.16±5.09	27.33±5.75	**<0.001**
Height (m)	1.67±0.09	1.68±0.09	0.303
Hip circumference (cm)	110.5±10.10	105.35±13.08	**0.005**
Weight (kg)	84.33±15.21	77.25±15.34	**0.007**

Descriptive statistics are given as mean ± standard deviation; BMI: body mass index; Mean ± SD: mean ± standard deviation; cm: santimetre; kg: kilogram; m: metre; Student's t-test was used; Bold values indicate p-value of <0.05.

Table 3. Biochemical values of bipolar and healthy control groups

	Bipolar disorder Mean ± SD	Healthy control Mean ± SD	p
NSP (pg/ml)	35.12±30.83	56.03±36.39	**<0.001**
tPA (pg/ml)	6.05±5.34	9.87±7.33	**<0.001**
BDNF (pg/ml)	1.29±1.56	2.22±2.24	0.236
IL-6 (pg/ml)	13.92±17.73	15.50±28.21	0.820
Lymp (mcL)	2.38±0.86	2.50±0.57	0.062
Neu (mcL)	4.22±1.52	4.03±1.25	0.711
Neu/Lymp	2.02±1.19	1.67±0.59	0.253
Neu/Plt	0.01±0.01	0.01±0.01	0.133
hsCRP (mg/L)	3.06±2.85	1.85±1.44	**0.004**
Plt (mcL)	249.23±50.09	267.80±60.40	**0.036**
Sedim (mm)	7.66±6.56	5.37±3.78	**0.035**

NSP: neuroserpin; tPA: tissue plasminogen activator; BDNF: brain-derived neurotrophic factor; IL-6: interleukin-6; Neu: neutrophil; Plt: platelet; hsCRP: high-sensitivity C reactive protein; Mean ± SD: mean standard deviation, Lymp: lymphocyte; Sedim: sedimentation; pg/ml: picogram/milliliter; mcL: microliter; mg/L: milligram/liter; mm: millimeter; Student's t-test was used; bold values indicate p-value of <0.05.

Table 4. Investigation of the effects of interaction values of hsCRP, BMI, cigarette packs/year, NSP and TPA in patient and healthy control groups

	B	S. E.	Wald	P	OR
Cigarette packs/year	-0.036	0.019	3.800	0.051	0.964
BMI	-0.064	0.032	3.885	**0.049**	0.938
hsCRP	-0.242	0.093	6.687	**0.010**	0.785
tPA*NSP	0.001	0.000	4.875	**0.027**	1.001

OR: odds ratio; BMI: body mass index; hsCRP: high-sensitivity C reactive protein; NSP: neuroserpin; tPA: tissue plasminogen activator; logistic regression analysis interaction table; bold values indicate p-value of <0.05.

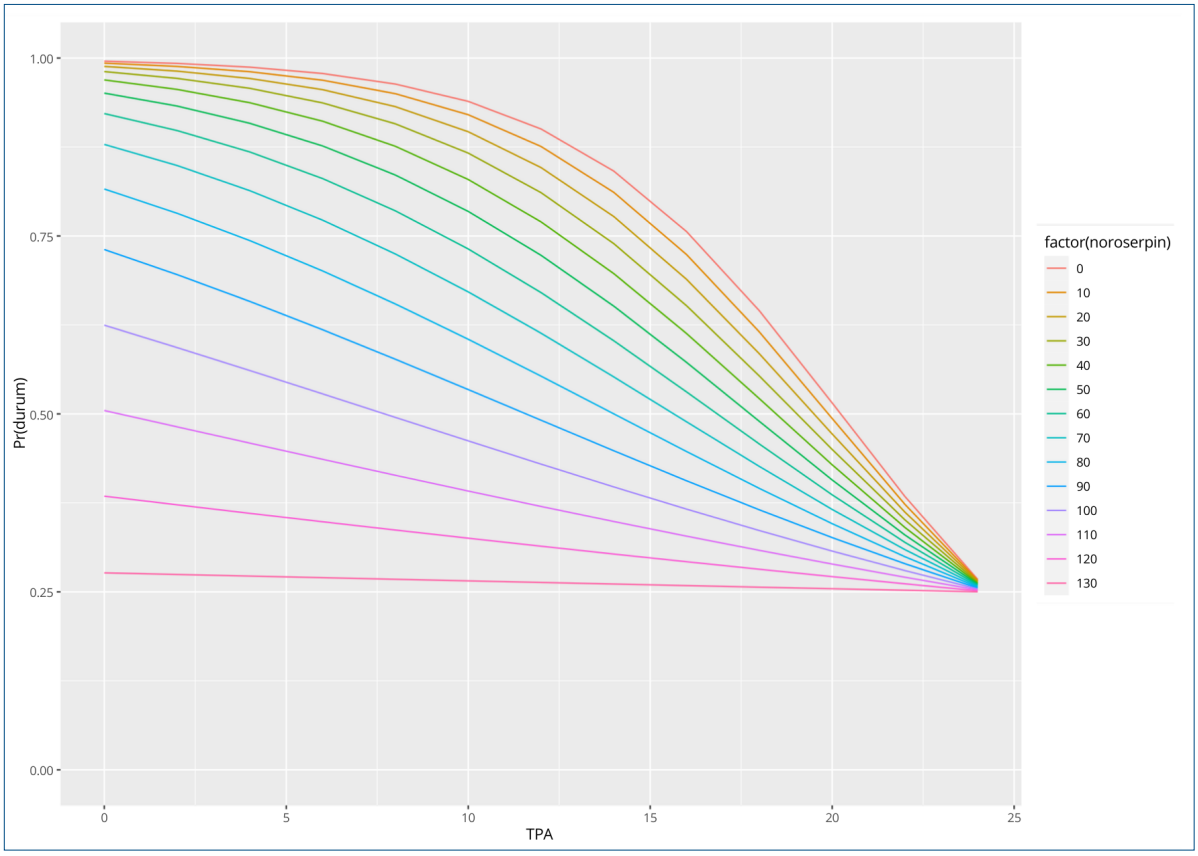

Figure 1. Examination of the tPA and NSP interaction graph using logistic regression analysis (NSP, neuroserpin; tPA, tissue plasminogen activator).

Table 5. NSP, BDNF, tPA, hsCRP, Sedim and IL-6 values according to the mood stabilizer type used in the bipolar group

	Lithium (n=36) Mean ± SD	Valproate (n=32) Mean ± SD	P
NSP (pg/ml)	28.81±24.67	39.63±33.77	0.298
BDNF (pg/ml)	0.99±1.16	1.66±2.06	**0.011**
tPA (pg/ml)	5.08±4.51	6.97±5.74	0.120
hsCRP (mg/L)	2.87±2.55	3.38±3.44	0.632
IL-6 (pg/ml)	12.67±13.78	13.50±20.04	0.873
Sedim (mm)	7.81±7.31	6.94±3.99	0.886

NSP: neuroserpin; BDNF: brain-derived neurotrophic factor; tPA: tissue plasminogen activator; hsCRP: high-sensitivity C-reactive protein; IL-6: interleukin-6; Sedim: sedimentation; Mean ± SD: mean standard deviation; pg/ml: picogram/milliliter; mg/L: milligram/liter; mm: millimeter; Student's t-test was used; bold values indicate p-value of <0.05.

the tPA level. Serum neuroserpin levels are shown in different colors in the graph. When the NSP value is 0, the risk of developing BD increases as the tPA value increases. When the maximum NSP value in the graph, which is 130, is considered, the risk of developing the disease is minimal, no matter how much the tPA value increases.

The comparisons between the NSP, BDNF, tPA, and IL-6 values according to the mood stabilizer type used in the BD group are shown in Table 5. Accordingly, while there was a statistically significant difference between the two groups in terms of BDNF levels (p=0.011), there was no statistically significant difference in terms of NSP, tPA, hsCRP, sedim and IL-6 levels (p>0.05).

DISCUSSION

In this study, we investigated serum levels of NSP, tPA, BDNF, IL-6, hsCRP, and sedimentation in patients diagnosed with bipolar disorder, aiming to contribute to understanding the neurobiological underpinnings of the disorder. Our findings revealed that NSP and tPA levels were significantly lower in the BD group compared to healthy controls, while hsCRP and sedimentation levels were elevated. No statistically significant differences were observed in IL-6 or BDNF levels between the groups. This is consistent with prior literature suggesting that serum BDNF levels tend to decrease during acute mood episodes but normalize during remission, particularly in the euthymic period (20).

Literature findings suggest that decreases in NSP and tPA are more commonly associated with acute episodes of BD (21). Our findings contribute to the literature by showing that reductions in NSP and tPA persist into the euthymic period, supporting their potential role as trait biomarkers. In a prior study, neuroserpin gene expression was significantly lower in both manic and euthymic BD patients than in healthy controls, with no difference between mood periods, implying a chronic alteration linked to the disorder itself (22). Similarly, tPA expression has been reported to be significantly reduced during both manic and depressive episodes compared to healthy controls, with only partial normalization observed during remission (23).

This study found no significant difference in BDNF levels between the BD and healthy control groups, which aligns with existing literature indicating that serum BDNF levels decrease during manic and depressive episodes but normalize in the euthymic period (20). The euthymic period in our study may explain the lack of difference in BDNF levels.

Changes in NSP and tPA expression have been linked to various diseases. tPA levels are reduced in Alzheimer's Disease (AD) compared to healthy controls (24), while systemic inflammatory diseases like rheumatoid arthritis show increased peripheral NSP levels with anti-inflammatory effects (25). High NSP expression limits tPA-induced neuroinflammation and reduces ischemic infarct size (26), and NSP plays a critical role in AD by forming a non-toxic complex with amyloid beta (27). Moreover NSP-BDNF-tPA share common neuroprotective pathways in the central nerve system (28). These findings support the neuroprotective roles of NSP and tPA in normal physiology (29), suggesting a positive correlation between them. The reduced levels of NSP and tPA during the euthymic period in our study underscore the involvement of neuroinflammatory processes in the pathophysiology of BD.

Recent studies have explored the relationship between BD and inflammation, often focusing on lithium's immunomodulatory effects (30). Increased acute phase proteins, such as hsCRP, and proinflammatory cytokines like IL-6 are observed in manic and depressive BD episodes, activating neuroinflammatory pathways (31,32). Meta-analyses indicate that CRP increases during manic and depressive periods but normalizes in euthymia, while IL-6 remains elevated (33). In our study, sedimentation and hsCRP levels were higher in BD patients, but no significant difference was found in IL-6 levels (34). This could be due to factors such as BMI and smoking, which are associated with inflammation (35). Contrary to popular belief, obesity and metabolic syndrome are common in BD, regardless of psychotropic treatment, and are considered a reflection of the inflammatory process (36). Smoking is also known to suppress anti-inflammatory processes and increase the production of pro-inflammatory mediators (37). These data support our analysis examining the relationship between smoking, BMI and hsCRP with the risk of having BD. These predictors may increase the risk of having BD by contributing to inflammatory processes. Although inflammatory processes in BD have been associated with higher disease severity, higher risk of relapse, and poorer response to treatment, there are still issues that remain unclear about the link between BD and inflammation (38). Therefore, this study is important because it addresses inflammation and the fibrinolytic system, a possible related process in BD (39).

The study found no significant relationship between NSP levels and mood-regulatory drug use in BD patients. A recent study showed that valproate increases serpin levels, including NSP (40). The absence of a difference in our study could be due to the neuroprotective effects of both lithium and valproate (7). Future research measuring NSP levels before and after treatment may offer better insight into the effects of these drugs.

This study, in which we examined the relationship between tPA and NSP by excluding other variables, showed a complex non-linear relationship between them. This is a finding that supports the neuroprotective effect of NSP. These results suggest that tPA and NSP are components of a neuroprotective pathway and the relationship between them may be a predictive factor for the risk of disease development (41). Further studies evaluating other neuroprotective components will enable a better understanding of the pathogenesis of BD.

This study has several limitations. First, its cross-sectional design precludes any conclusions about causal relationships or the temporal dynamics of biomarker changes across different periods of bipolar disorder. Longitudinal studies tracking NSP and tPA levels throughout manic, depressive, and euthymic periods would provide more robust insights. Second, the sample was limited to patients in the euthymic period, which restricts the generalizability of the findings to other mood periods. Third, potential confounding factors such as BMI, smoking status, and metabolic parameters –known to influence inflammatory and fibrinolytic markers– could not be fully controlled despite statistical adjustments. Additionally, the impact of psychotropic medication on biomarker levels remains uncertain; although no significant differences were observed between mood stabilizer subgroups, treatment duration and dosage variability may have influenced the results. Finally, although the sample size was comparable to similar biomarker studies in psychiatric populations, larger multicenter studies are needed to confirm these findings and enhance their external validity.

As a result, the findings of this study suggest that NSP and tPA levels are significantly reduced in patients with bipolar disorder during the euthymic period, indicating their potential role as trait biomarkers independent of mood period. These alterations may reflect underlying disruptions in neuroprotective and fibrinolytic processes, contributing to the pathophysiology of bipolar disorder. Although no significant differences were found in BDNF and IL-6 levels, elevated hsCRP and sedimentation values support the presence of persistent low-grade inflammation even in remission. The observed non-linear interaction between NSP and tPA further underscores the complexity of their regulatory relationship and highlights the need for future studies exploring their mechanistic roles. Longitudinal and period-specific research with larger samples is warranted to clarify the clinical utility of these biomarkers and their potential as targets for therapeutic intervention.

Ethics Committee Approval: Before starting this study, permission was obtained from the ethics committee of the Scientific Research Committee of Health Sciences University Dışkapı Training and Research Hospital (Decision date: June 11, 2018 Decision number: 51/19).

Informed Consent: Patients were included in this study with their informed consent.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept- HK; Design- GE; Supervision- HK; Resource- HK; Materials- FNA; Data Collection and/or Processing- HÜ; Analysis and/or Interpretation- GÖ; Literature Search- HÜ; Writing- HÜ; Critical Reviews- GE.

Conflict of Interest: The authors declared that there is no conflict of interest.

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