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The Role of Resolvin D1 in Indicating Chronic Inflammation and Axonal Damage in Bipolar Disorder: A Comparative Study of Manic and Depressive Episodes

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ABSTRACT

Introduction: Bipolar disorder (BD) is a chronic disorder associated with significant psychiatric morbidity and disability. Recent research has linked inflammatory processes to the pathology of BD. Resolvin D1 (RvD1), an anti-inflammatory molecule derived from eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), has been shown to inhibit apoptosis and neuroinflammation, and promote neurogenesis. This study aims to determine changes in serum RvD1 levels between acute episode and euthymic periods in patients with BD and their association with inflammatory and metabolic syndrome (MetS) parameters.

Methods: This prospective clinical study was conducted with patients diagnosed with BD-I according to SCID-5. Patients whose serum RvD1 levels were assessed during manic and depressive episodes in the previous study were invited to return to the study after at least 8 weeks, when they had reached the euthymic period. Blood samples for RvD1, C-reactive protein (CRP), and hemogram tests were collected during both acute episodes and remission periods.

Results: The study included 32 patients in manic episodes, 27 in depressive episodes, and 41 healthy controls, with no significant age difference among the groups. RvD1 levels decreased significantly from manic episodes to complete remission period (p=0.017, z=-2.391) during follow-up. The decrease from depression to remission was not statistically significant. Serum RvD1 levels in patients with depressive episodes in remission remained high in the control group (p=0.581, z=-0.553). During the follow-up period, white blood cell (p=0.009, z=-2.606) and neutrophil (p=0.007, z=-2.693) in mania period and CRP values in depression period (p=0.004, z=-2.880) were found to have decreased statistically.

Conclusions: The study indicates that serum RvD1 levels are elevated during manic and depressive episodes in BD patients compared to healthy controls and decrease significantly during the remission period in patients with manic episode. We propose the potential utility of RvD1 as a diagnostic marker for identifying manic and depressive states. We can assume that there is an inflammatory process in BD in which RvD1 also plays a role. Further research is needed to explore the therapeutic potential of targeting RvD1 pathways in BD treatment.

Keywords: Axonal degeneration, bipolar disorder, metabolic syndrome, neuroinflammation, resolvin D1

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INTRODUCTION

Bipolar disorder (BD) is a chronic disorder that significantly contributes to psychiatric morbidity, leading to notable psychosocial impairment and disability (1). Although neuroscientific research on the origins of BD has not yielded definitive conclusions, numerous studies have identified various inflammatory processes involved in its pathology (2).

The immune system is known to be dysregulated in psychiatric disorders (3). In particular, levels of the pro-inflammatory cytokines C-reactive protein (CRP) and interleukin-6 (IL-6) have been found to be higher in patients than in controls. It has been suggested that IL-8 may be a marker for various psychiatric disorders (4). In recent reviews, while the levels of proinflammatory cytokines IL-6 and tumor necrosis factor-alpha (TNF-α)

Highlights

- **Resolvin D1 could serve as a state marker for both manic and depressive episodes.**
- **Resolvin D1 appears to be a potential marker of chronic inflammation.**
- **Resolvin D1 may indicate axonal degeneration in bipolar disorder.**
- **Resolvin D1 may be used in monitoring disease progression and severity.**

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were found to be high in both depressive and manic episodes in BD, the opposite was reported for the anti-inflammatory IL-10 levels (5).

Resolvin D1 (RvD1) is a molecule synthesized from dietary eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in blood and peripheral tissues. RvD1 plays a role in inhibiting apoptosis and neuroinflammation, stimulating gene expression and neuronal activity, and promoting synaptogenesis and neurogenesis (6). Its anti-inflammatory activities are achieved by inhibiting pro-inflammatory cytokines and neutrophil trans-endothelial migration (7). Two mechanisms through which RvD1 initiates anti-inflammatory activity include PPAR-γ (peroxisome proliferator-activated receptor gamma) signaling and M2 markers produced by interleukin-4 (IL-4) in microglial cells. These effects are linked to the activation of PPAR-γ signaling pathways (8). Additionally, RvD1 has been shown to decrease levels of TNF-α and IL-1β while increasing IL-10 levels. It also suppresses neutrophil recruitment and the apoptotic activity induced by neutrophils (9).

Recently, there has been a growing body of research on resolvins in the field of neuropsychiatry. RvD1 and RvD2 receptor antagonists significantly reduced the simulated antidepressant effect of intracerebroventricular infusion of these molecules. The data suggest that the mechanistic target of the rapamycin complex 1 (mTORC1) signaling pathway may be how RvD1 and RvD2 enhance antidepressant activity (10).

Obesity and obesity-related diseases are increasing and have been linked to chronic low-grade inflammation in adipose tissue. Preventing metabolic disorders associated with obesity depends on a prompt inflammatory response and restoration of homeostasis in this tissue (11). A study showed that resolution agonists RvD1 and RvD2 increase adiponectin expression and secretion while reducing the release of pro-inflammatory adipokines/cytokines such as leptin, TNF-α, IL-6, and IL-1. This helps obese adipose tissue recover from its defective phenotype (12).

Bipolar disorder is characterized by high rates of diabetes, obesity, dyslipidemia, and metabolic syndrome (MetS) (13). The prevalence of diabetes, obesity, and MetS is higher in BD regardless of psychotropic medication use, contrary to the widely held belief that psychotropic medication promotes MetS (14). Metabolic and mental disorders are postulated to be two symptoms of the same multisystemic inflammatory disease (15). MetS is potentially related to variations in PPAR-γ levels, and dysregulation of immunological and metabolic regulatory factors is suggested by lower PPAR-γ activity and higher frequency of MetS in BD (16). In a previous study, we highlighted PPAR-γ as an important marker for patients with BD-depressive episodes and MetS (17).

In a recent study, serum RvD1 levels were compared between untreated first-episode adolescent patients with moderate to severe major depressive disorder and healthy adolescents. It was found that serum RvD1 levels were higher in patients and positively associated with the severity of depression. Additionally, RvD1 levels decreased after fluoxetine treatment, suggesting that RvD1 is a good discriminating molecule between depression and healthy adolescents (18).

In our previous study, we compared serum RvD1 levels in BD type-I manic, depressive, and euthymic patients with healthy controls. We found that serum RvD1 levels in patients with manic and depressive episodes were significantly higher compared to healthy individuals (19). In this prospective part of our study, we re-evaluated the serum RvD1 levels of patients during their euthymic period. Given the possible association of RvD1 with MetS parameters and inflammation, MetS parameters and hemograms of the patients were also monitored simultaneously. The aim of this study is to determine the changes in RvD1 levels, which have anti-inflammatory effects, between the episode and euthymic periods.

METHODS

Participants

This study employed a prospective clinical design. Patients hospitalized in the psychiatry clinics or attending the outpatient unit of Bakırköy Prof. Dr. Mazhar Osman Mental Health and Neurological Diseases Training and Research Hospital, who met the inclusion and exclusion criteria, were invited to participate. The previous study included 44 patients with manic episodes and 35 patients with depressive episodes, all aged 18–65 years with a diagnosis of BD-I (19). Additionally, 41 healthy volunteers, matched for age and smoking habits, were selected from our outpatient clinics as the control group. Samples taken during the acute episode were discussed in the previous article (19). In this study, patients with acute episodes were invited back to the study when they entered remission and serum samples were repeated during the euthymic period.

All participants underwent a clinical interview based on Structured Clinical Interview for DSM-5-Disorders (SCID-5) by a consensus between two senior psychiatrists. They were informed about the study and asked to read and sign the informed consent form. Data on the clinical characteristics of the patients were obtained through interviews with the patients and their significant others, as well as by reviewing their medical records. The clinician completed a sociodemographic data form for each participant.

During the follow-up period, patients with Young Mania Rating Scale (YMRS) ≤7 and 17-item Hamilton Depression Rating Scale (HDRS) ≤7 for at least 8 weeks were considered to be in complete remission, and their blood samples were re-evaluated. Of the initial participants, 32 patients with manic episodes and 27 patients with depressive episodes completed the study. Sixteen patients did not complete the study due to unwillingness to continue follow-up (n=14), inability to achieve complete remission (n=2), or death (n=1).

The healthy control group consisted of individuals visiting the outpatient clinic for mandatory psychiatric examinations prior to employment or adoption applications who did not have a diagnosis of psychiatric disorders in themselves or in their first-degree relatives, and who were matched according to age and smoking habits.

Inclusion criteria were being assessed in a manic or depressive episode with a diagnosis of BD-1 in the previous study and being in a euthymic period for at least 8 weeks after the episode for the current study, and giving written consent. Exclusion criteria were mental retardation, dementia, psychiatric disorders secondary to medical conditions, alcohol or substance use disorders, any condition affecting the central nervous system (CNS), a personal history of atypical headaches, head trauma, chronic lung disease, renal disease, chronic hepatitis, thyroid disease, active cancer, cerebrovascular disease, epilepsy, acute infection or allergy, and the use of medications such as omega-3, aspirin, or any other drugs with anti-inflammatory activity. Each participant provided written informed consent. The reason for including only male participants in the study is to reduce the risk of sex hormones potentially affecting inflammatory and metabolic markers. Estrogen and progesterone have been shown to decrease microglial TNF-α secretion (20). Additionally, menstrual alterations have been significantly correlated with affective symptoms in 65% of female patients with BD, suggesting a potential relationship between menstrual cycles and affective symptoms (21).

Measurements

After fasting for at least eight hours, blood samples were collected from each participant into 10 cm^3 biochemistry tubes, and the blood serum was separated in the laboratory. Blood samples were collected at the same time in the morning as the assessment. RvD1, routine biochemical measures, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and hemogram tests were performed for each sample. Metabolic syndrome parameters, including high-density lipoprotein (HDL), triglycerides (TG), fasting blood glucose (FBG), waist circumference (WC), systolic and diastolic blood pressure, and body mass index (BMI), were measured during both the episode and remission periods. Statistical analysis was performed once the sample results were available.

The study was approved by the Clinical Ethics Committee of Dr. Sadi Konuk Training and Research Hospital with the protocol code 2018/245 and decision number 2018-14 on 06.08.2018.

Operation and calculation of RvD1

Venous blood samples were collected into specific tubes (131005 ml Vacutainer plastic SST gel tube, Code VT 367955 Becton Dickinson, Franklin Lakes, NJ) and transported to the laboratory at +4°C. The samples were centrifuged for five minutes at 4000 g, and the separated serum samples were transferred to sterile Eppendorf tubes and stored at -80°C until the study day. The Human Resolvin D1 ELISA Kit (SUNRED, 201-12-9313) was used to measure RvD1 levels in the serum samples according to the manufacturer's recommendations. This method relies on the colorimetric measurement of RvD1 levels via spectrophotometry, providing quantitative results for human serum samples.

Statistical analysis

Statistical analyses were performed using IBM IBM Statistical Package for Social Sciences (SPSS) program version 21.0 (IBM Corp., Armonk, 2012, NY, USA). Descriptive statistics were presented as means, standard deviations, medians, minimums, maximums, frequencies, and percentages. Pearson chi-square, Fisher's exact test, and McNemar's test were used to compare discrete variables. The Kolmogorov-Smirnov test evaluated the normality of continuous variables. Intergroup comparisons of continuous variables were performed using Kruskal-Wallis and Mann-Whitney U tests. When significant differences were found between three groups, post-hoc comparisons were conducted using the Mann-Whitney U test with Bonferroni correction. Dependent groups were analyzed using paired t-tests and Wilcoxon signed-rank tests for before-and-after comparisons.

The sample size in the study was calculated using the OpenEpi program. Previous relevant studies were reviewed, and an effect size of 0.5, power of 0.80, and alpha error value of 0.05 were accepted. The minimum sample size required for the tests applied to detect the difference between the BD-1 and healthy control groups was calculated to be 22 (11 in each group).

For baseline (symptomatic state) measurements, serum RvD1 levels were compared among study groups (patients with manic episodes, patients with depressive episodes, and controls) using Univariate Analyses of Covariance (ANCOVA) models, which included age, sex, BMI, and smoking status as covariates. For follow-up (remission state) measurements, the nonparametric Wilcoxon signed-rank test was used. The linear relationships between variables were evaluated using the Spearman correlation test.

Linear regression models were applied to identify associations between main findings and certain variables, including sociodemographic factors (age, smoking status), metabolic syndrome parameters (HDL, TG, FBG, WC, systolic and diastolic blood pressure, BMI), and daily doses of medications used by patients (Lithium [Li], valproic acid [VPA], carbamazepine [CBZ], lamotrigine (LTG), antidepressants [AD] and antipsychotics [AP]). A p-value of <0.05 was considered statistically significant.

RESULTS

Clinical characteristics

The study included 32 patients with BD-I in manic episodes, 27 patients in depressive episodes, and 41 healthy controls matched for age and smoking habits. The sample comprised only male participants. The mean age was 38.0±11.6 years for the manic group (n=32), 40.4±10.5 years for the depressive group (n=27), and 39.0±10.7 years for the control group (n=41). There was no statistically significant difference in age among the groups (p=0.703). The clinical characteristics of patients in the manic and depressive episodes are detailed in Table 1. Detailed sociodemographic and clinical data for all patients included in this cross-sectional study have been published in the previous publication (19).

In terms of smoking habits, 59.4% of patients in the manic episode group, 74.1% in the depressive episode group, and 63.4% in the healthy control group smoked. There was no statistically significant difference in smoking rates among the groups (p=0.480).

Regarding pharmacological treatments during the remission period following acute episodes, patients were on the antipsychotic drugs VPA, Li, CBZ, LTG, and AD. It was observed that 37.1% of patients with an acute depressive episode and 18.5% of patients in the post-depression group were on antidepressants. The pharmacological treatments during both the acute and remission periods are summarized in Table 2.

RvD1 measurement in acute and remission period

The initial mean RvD1 levels were 23.93±34.13 ng/ml in the manic episode group (n=44), 11.51±4.14 ng/ml in the depressive episode group (n=34), and 8.16±4.43 ng/ml in the control group (n=41). The mean serum RvD1 values for the current prospective study are presented in Table 1. Initial RvD1 measurements are shown in Figure 1, part A.

The mean RvD1 levels during the remission period were 11.43±7.15 ng/ml in the post-mania group (n=32) and 12.60±6.98 ng/ml in the post-depressive group (n=27). Follow-up RvD1 measurements are depicted in Figure 1, Part B.

A significant difference was observed between the initial acute episode RvD1 levels and the remission period levels in the mania group (p=0.017, z=-2.391, n=32). However, there was no significant difference between the first and second RvD1 measurements in the depression group (p=0.581, z=-0.553, n=27). Follow-up comparison values are shown in Figure 1, part C. Pairwise comparisons of serum RvD1 levels between groups are displayed in Table 3.

Correlations of RvD1

Acute correlates of RvD1 were discussed in the previous study (17). There was a significant correlation between the initial RvD1 measurement and daily doses of AP (p <0.001, r=0.382) and VPA (p=0.001, r=0.309).

Significant positive, weak-to-moderate correlations were found between the second RvD1 measurement and the YMRS total score (p=0.025, r=0.292) and HDRS total score (p=0.009, r=0.336). There were also significant correlations between the second RvD1 measurement and daily doses of AP (p=0.032, r=0.215) and Li (p=0.001, r=0.315), as well as HDL (p=0.04, r=-0.206) and TG (p=0.009, r=0.262). No statistically significant associations were found between RvD1 and MetS or inflammatory

Table 1. Clinical characteristics of the patients

	Mania (n=32)		Depression (n=27)		
	Mean ± SD	Median (min. – max.)	Mean ± SD	Median (min. – max.)	p / z (test statistic)
Age (years)	38.0±11.6	37 (18–62)	40.4±10.5	39 (21–64)	0.703 $^{\beta}$ z=0.704
Age of disorder onset (years)	26.1±9.1	23 (16–52)	23.3±7.3	21 (14–38)	0.251 ^{m} z=-1.147
Initial treatment age (Years)	26.4±8.9	24 (16–52)	25.7±8.8	25 (14–44)	0.696 ^{m} z=-0.390
Total number of episodes	6.3±4.4	5 (1–19)	9.9±6.7	7 (2–27)	**0.012** $^{\alpha *}$ **z=-2.504**
Number of manic episodes	4.7±3.2	4 (1–16)	4.1±4.1	3 (1–19)	0.120 ^{m} z=-1.553
Number of depressive episodes	1.4±1.2	1 (0–4)	4.7±3.3	4 (1–13)	**<0.001** $^{m **}$ z=-3.903
Number of hypomanic episodes	2.0±1.3	1 (1–4)	2.2±1.7	2 (1–7)	0.876 ^{m} z=-0.156
Number of mixed episodes	1.7±1.2	1 (1–3)	1.3±0.6	1 (1–2)	0.659 ^{m} z=-0.441
Total number of hospitalizations	4.5±3.9	3 (1–17)	4.4±4.5	3 (0–20)	0.832 ^{m} z=-0.213
Duration of disorder (Years)	11.6±9.6	9 (0–40)	16.6±9.8	16 (3–39)	**0.014** $^{m *}$ **z=-2.451**
Mean levels of serum RvD1 (ng/ml)	27.94±38.46	11.9 (2.7–162.9)	11.52±4.04	11.2 (4.6–17.2)	**0.014** $^{m *}$ **z=-2.451**

m: Mann-Whitney U test; min: minimum; max: maximum; ng/ml: nanograms per milliliter; SD: standard deviation; β: Kruskal-Wallis test (comparison with control group); *: <0.05; **: <0.001

Table 2. Pharmacological treatments received by patients in acute episode and complete remission

	Mania (n=44) % – mean ± SD	Post-mania remission (n=32) % – mean ± SD	Depression (n=34) % – mean ± SD	Post-depression remission (n=27) % – mean ± SD
Antipsychotic (mg/day) *	11.6% 140.81±413.63	87.5% 491.7±371.0	94% 498.6±446.8	85.1% 547±414.5
Valproic Acid (mg/day)	4.5% 56.81±268.84	53.1% 1323.5±439.8	28.6% 371.42±631.20	25.9% 1214.2±267.2
Lithium (mg/day)	2.2% 27.27±180.90	50% 1050±289.8	62.9% 702.85±586.35	66.6% 1250±212.1
Carbamazepine (mg/day)	-	-	2.9% 11.42±67.61	3.7% 400
Lamotrigine (mg/day)	-	-	17.1% 16.42±49.23	22.2% 187.5±54.1

mg/day: milligram per day; SD: standard deviation, *: mean antipsychotic dose was obtained as 100 mg chlorpromazine equivalent dose.

parameters during the remission period. Acute period correlations are available in a previous publication (19).

Linear regression model for RvD1

A linear regression model, including age, BMI, smoking status, daily medication doses (Li, VPA, CBZ, LTG, AP), and MetS parameters (TG, HDL, FBG, WC, systolic and diastolic arterial pressure), revealed that the daily dosage of AP (β=0.025, t=4.949, p <0.001), VPA (β=0.013, t=2.631, p=0.01), and Li (β=-0.012, t=-2.686, p=0.009) significantly impacted RvD1 changes. None of the predictors significantly affected the second RvD1 measurement in this model (R^2=0.194, df=14, F=1.441, p=0.153).

Metabolic syndrome and inflammatory parameters

Metabolic syndrome parameters were compared between acute and remission periods, and between remission and control groups, as shown in Table 4. During follow-up, WBC (p=0.009, z=-2.606) and neutrophil counts (p=0.007, z=-2.693) significantly decreased in patients with mania when complete remission was achieved. No significant differences were observed in ESR (p=0.678, z=-0.416) and CRP levels (p=0.808, z=-0.243) between the manic episode and remission periods. In the depressive episode group, no significant differences were found in WBC (p=0.782, z=-0.276), ESR (p=0.193, z=-1.303), and neutrophil counts (p=0.130, z=-1.514) upon achieving remission. However, CRP

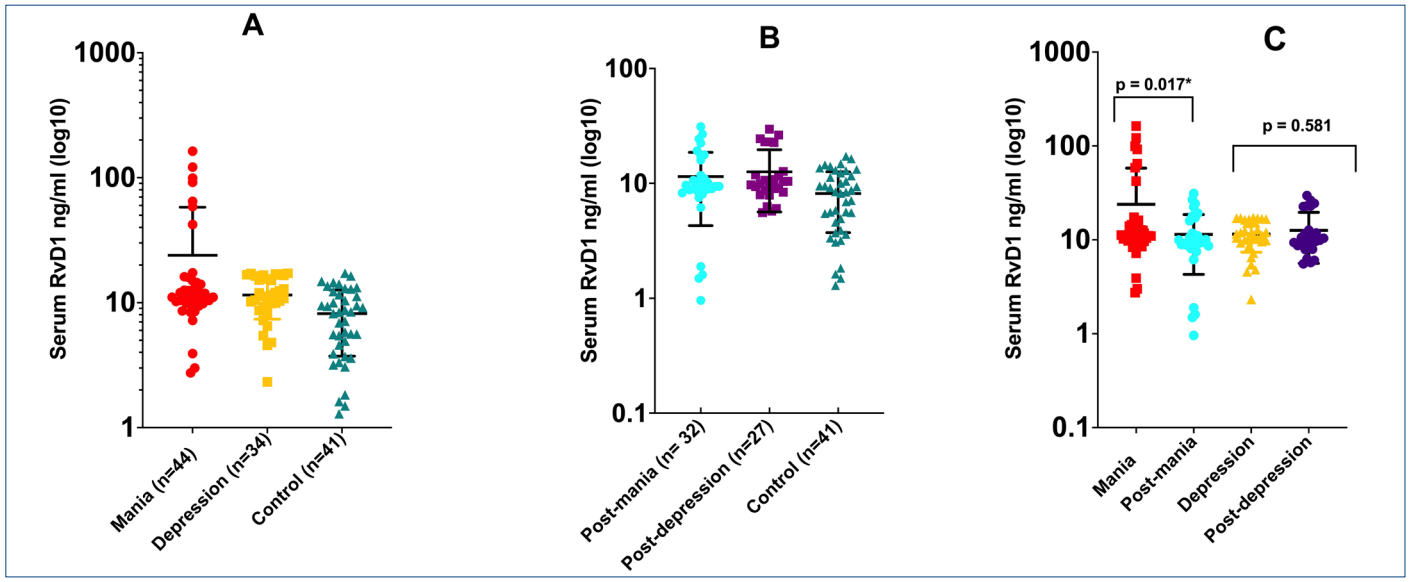

Figure 1. Part A: There was a statistically significant difference in the first measurement of RvD1 values between the three groups (p <0.001, z=15.719, df=2). RvD1 levels in the control group were significantly lower than those in the mania and depression groups (after Bonferroni correction adjusted p=0.001, z=27.731; p=0.008, z=23.843, respectively). This difference remained significant between the mania and control groups even after adjustment for age, sex, body mass index, and smoking status (p=0.003, F=6.263, df=2). There was no statistically significant difference between the RvD1 measurements in the mania and depression groups (p=1, z=3.888). The values in the table are plotted on a logarithmic scale. **Part B: When compared with the control group, a statistically significant difference was found between the groups in terms of the second RvD1 measurements (p=0.033, z=6.812, df=2)**. The serum RvD1 levels in the control group were significantly lower than those in the post-depression group (after Bonferroni correction adjusted p=0.044, z=17.521). This difference remained significant between the post-depression and control groups even after adjustment for age, sex, body mass index, and smoking status (p=0.021, F=4.049, df=2). There was no statistically significant difference between the patients in the post-mania and post-depression periods (p=1.000, z=-4.751) and the post-mania and control groups (p=0.186, z=12.770). The values in the table are plotted on a logarithmic scale. **Part C: There was a significant difference between the first measurement of the acute episode and the second measurement of RvD1 when they reached the remission period in the mania group (p=0.017, z=-2.391, n=32).** There was no significant difference between the first and second RvD1 measurements in the depression group (p=0.581, z=-0.553, n=27). The values in the table are plotted on a logarithmic scale.

Table 3. Pairwise comparisons of the serum RvD1 levels between groups

	p	Test statistics
Mania vs depression $^{\alpha}$	1.000 ^{m}	23.843
Mania vs control $^{\alpha}$	**0.001** ^{m*}	**27.731**
Depression vs control $^{\alpha}$	**0.008** ^{m*}	**23.843**
Post-mania remission vs control $^{\alpha}$	0.186 ^{m}	12.770
Post-depression remission vs control $^{\alpha}$	**0.044** ^{m*}	**17.521**
Post-mania vs post-depression remission $^{\alpha}$	1.000 ^{m}	-4.751
Mania vs post-mania remission $^{\gamma}$	**0.017** $^{\gamma*}$	**-2.391**
Depression vs post-depression remission $^{\gamma}$	0.581 $^{\gamma}$	-0.553

m: Mann-Whitney U test; γ: Wilcoxon signed-rank test was used; *: <0.05.
Significance values have been adjusted by the Bonferroni correction for multiple tests.

Table 4. Mean values of metabolic syndrome parameters in patients with acute episode or remission period and control group

	Mania	Post-mania remission	p	Depression	Post-depression remission	p	Control	p
Systolic AP (mmHg)	117.0±8.8	123.4±11.8	0.078 ^{t} t=-2.939	116.4±9.1	123.0±9.5	0.001 ^{t} t=-3.631	119.3±10.6	0.203 $^{\alpha}$ F=9.972
Diastolic AP (mmHg)	73.7±7.0	76.4±10.3	0.156 ^{t} t=-1.376	76.0±6.2	76.7±8.1	0.646 ^{t} t=-0.465	75.6±7.0	0.847 $^{\alpha}$ F=0.166
FBG (mg/dl)	96.3±28.9	99.7±18.4	0.052 $^{\gamma}$ z=-1.946	96.4±19.4	99.9±14.9	0.151 ^{t} t=-1.480	93.1±23.7	0.013 $^{\beta}$ t. ist=8.662
WS (cm)	102.1±16.9	109.3±15.5	**<0.001** ^{t} t=-4.272	101.6±10.9	105.2±10.9	**0.007** ^{t} t=-2.944	96.4±11.1	**<0.001** $^{\alpha}$ F=9.972
HDL (mg/dl)	44.3±12.7	41.7±12.4	0.113 $^{\gamma}$ z=-1.584	37.9±11.4	37.7±9.5	0.647 $^{\gamma}$ z=-0.458	43.9±11.13	0.064 $^{\beta}$ t. ist=5.484
TG (mg/dl)	193.3±344.8	203.1±133.8	**0.006** $^{\gamma}$ z=-2.773	231.5±173.0	202.9±134.5	0.290 $^{\gamma}$ z=-1.057	138.1±66.1	**0.049** $^{\beta}$ t. ist=6.045
BMI (kg/m²)	27.2±6.7	28.5±6.4	**<0.001** ^{t} t=-3.241	27.4±3.3	28.0±2.8	0.124 ^{t} t=-1.588	26.0±3.4	**0.043** $^{\alpha}$ F=3.246

AP: arterial blood pressure; BMI: body-mass index; cm: centimeter; FBG: fasting blood glucose; HDL: high lipoprotein; mg/dl: milligrams per 100 millilitres; mmHg: millimeters of mercury; kg/m2:kilogram per square meter; TG: triglyceride; t: T test in dependent groups; t. ist: test statistic; WS: waist circumference; α: One-way ANOVA; β: Kruskal Wallis test; γ: Wilcoxon signed-rank test.
Kruskal-Wallis test was used between post-mania, post-depression and control groups.

levels significantly decreased during the follow-up period of depression (p=0.004, z=-2.880).

DISCUSSION

The key finding of this study is that RvD1 levels significantly decreased from the manic episode to the remission period during follow-up. However, the decrease observed from the depressive episode to the full remission period was not statistically significant.

The receptor formyl peptide receptor 2 (ALX/FPR2), associated with RvD1, plays a crucial role in neuronal growth. Inhibition of this receptor leads to reduced axon and dendrite lengths in hippocampal neurons. These receptors are prevalent in the central nervous system and are thought to influence learning, memory, balance, and nociception by mediating axonal and dendritic growth through substances like arachidonic acid/LXA4 or DHA/RvD1 (22). Patients with early Parkinson's disease have been found to exhibit lower natural levels of RvD1. In a rat model of Parkinson's disease, chronic and early treatment with RvD1 reduced inflammation, neuronal dysfunction, and motor issues (23). This highlights RvD1's potential neuroprotective effects. Additionally, a study examining axonal transport-related proteins in the prefrontal white matter of patients with BD and schizophrenia found significantly lower levels of these proteins in BD patients compared to healthy controls. This suggests a potential deficit of axonal proteins in the prefrontal white matter, indicating decreased axonal density or function in the CNS of BD patients (24). In the current study, it was hypothesized that elevated RvD1 levels during acute BD episodes and remission might indicate possible axonal degeneration. The increase in RvD1 during acute episodes suggests heightened degeneration, and the persistently high levels during remission, compared to the control group, indicate ongoing neurodegeneration.

RvD1 levels in the cerebrospinal fluid (CSF) are higher in patients with highly active multiple sclerosis (MS) compared to those with less active MS (25). The association between RvD1 and inflammatory disease activity was emphasized. In our previous article, we suggested that RvD1 may act as a "delayed resolver," increasing reactively in response to inflammation during episodes (19). Inflammation was categorized into two groups during the resolution phase. The mechanism that protects the central nervous system from chronic inflammatory diseases seems unable to prevent the dominance of these resolution agonists because the "early resolvers" tend to be low at the beginning of the resolution and increase gradually, while the "delayed resolvers" are initially detected at very high levels. In the current study, the persistently high RvD1 levels in both groups compared to the control group may indicate that RvD1 is a delayed resolver. This suggests the presence of a chronic inflammatory process in the etiopathogenesis of BD.

In a study conducted on familial Mediterranean fever (FMF) patients during both acute and remission periods, serum RvD1 levels were found to be higher in both periods compared to healthy controls, although levels decreased between the two periods (26). The fact that we obtained similar results in the present study emphasizes the important role of RvD1 in the etiology of chronic inflammatory diseases. Our study indicates that RvD1 is particularly insufficient during depressive episodes. Thus, RvD1 may be a potential therapeutic target for resolving chronic low-grade inflammation in BD.

Studies have shown that when inflammation is intense and inflammatory cells peak rapidly, the resolution of inflammation is swift; however, when inflammatory cells increase gradually, resolution is delayed (27). In our study, RvD1 levels were found to be higher during manic episodes compared to depressive periods. It is thought that RvD1 increased more in mania as a reactive response to more severe inflammation, whereas resolution was delayed in the depressive period, likely due to the gradual increase in low-level inflammation. Therefore, RvD1 remained high even during the complete remission period of depressed patients. Considering previous experimental animal model studies, we suggest that treatments targeting RvD1 may be particularly beneficial during depressive episodes.

Intracerebroventricular infusion of RvD1 and RvD2 in mice in a chronic unpredictable stress model has been observed to improve depressive-like behavior (28). The mechanistic target of rapamycin complex 1 (mTORC1), which is critical for the antidepressant effects of ketamine, is activated by the behavioral effects of RvD1, RvD2, and RvE1 (29). Previous studies have reported that RvD1 levels are higher in patients with depression compared to healthy individuals (19). In the present results, even when the depressive episode group entered the remission period, RvD1 levels did not decrease and remained significantly higher than those in the healthy control group. This may indicate that the depressive period, in particular, causes permanent inflammatory changes in BD, and that a therapeutic agent acting via RvD1 could reverse these effects. It suggests that manic and depressive episodes in BD may have different etiopathogenesis.

Chronic stress increases 5-lipoxygenase expression in the hippocampal region, leading to the production of cysteinyl leukotrienes, which induce depression through their receptors. Resolvins in the brain reduce depression caused by neuroinflammation, consistent with the beneficial effects of n-3 fatty acids in the diet of patients with depression (30). In animal models of type 1 diabetes mellitus, it has been reported that depression-like behaviors and elevated blood glucose levels due to inflammation caused by diabetes mellitus are reduced after hippocampal and prefrontal RvD5 administration (31). Higher response rates were seen in major depressive disorder (MDD) patients who were randomly assigned to receive EPA 4 g/day supplementation and those who showed a superior ability to stimulate the production of 18-hydroxyeicosapentaenoic acid (18-HEPE). Due to the inverse relationship between 18-HEPE and both systemic inflammation and depressive symptoms, the activation of the resolution of inflammation is highlighted as a potential mechanism in the treatment of MDD with omega-3 fatty acid supplementation (32). The association of RvD1 with TG and HDL suggests that omega-3 supplementation to increase RvD1 levels may be particularly useful in BD patients with lipid and glucose dysregulation.

Acute period RvD1 serum levels were measured in patients with aneurysmal subarachnoid hemorrhage (aSAH) and compared with a healthy control group. The lowest level was found on day 1 after aneurysm, while the highest level was observed on day 9 (33). Serum RvD1 is a predictive biomarker for aSAH; its decline post-aSAH is strongly associated with disease severity and independently predicts worse outcomes in individuals with aSAH (34). RvD1 was also positively correlated with the severity of depression in patients with MDD (18). Furthermore, our previous study found that RvD1 levels in remission are associated with YMRS and HAM-D scores, with YMRS scores indicating the severity of manic episodes. This suggests that RvD1 may be used as a serum marker to assess the severity of BD in the future.

The effect of lithium or quetiapine treatment on erythrocyte DHA levels in first-episode manic patients and controls was investigated. The findings suggest that the onset of manic symptoms is associated with selective erythrocyte DHA deficiencies and that changes in fatty acid status do not mediate the reduction of mood symptoms following therapy (35). Patients who had attempted suicide exhibited significantly higher DHA levels compared to controls, leading to the hypothesis that fewer suicide attempts might be linked to higher EPA and lithium levels (36). A post-mortem study revealed that drug-free bipolar patients had greater deficiencies in orbitofrontal cortex DHA and arachidonic

acid composition compared to those receiving mood-stabilizing or antipsychotic medications (37). In the present study, the significant positive correlation of RvD1 with antipsychotics and mood stabilizers during both acute and remission periods may indicate that the effects of BD treatments are partly mediated by RvD1.

One study found that CRP was higher compared to controls only in the manic episode and was suggested as a marker of the state (38). It has also been reported that CRP is higher in BD compared to healthy individuals, independent of mood, and that hs-CRP is a predictor of BD and BD manic episodes (39). It is believed that hs-CRP may predict response to treatment (40). As CRP decreased when the depressed group went into remission, we can suggest that CRP can be used to predict response to treatment.

Our study has some limitations. To prevent cyclical variations in hormones and consequently inflammatory markers, we exclusively recruited male participants. Estrogen and progesterone have been shown to decrease microglial TNF-α secretion (20). Estrogen fluctuation has been reported to be important in the etiology of BD (41). However, an all-male sample is not representative of the general population. Furthermore, our study's reliance on RvD1 as the sole marker limits the scope of our findings. Evaluating additional markers from the pro-inflammatory and lipid-resolving families could have provided a more comprehensive interpretation of the data. Another limitation is the drop-out rate and the small number of participants who completed the study. As resolvin is partially synthesized from omega-3 fatty acids, dietary intake of omega-3 may significantly influence resolvin levels. The lack of dietary habit documentation in our patients represents a limitation. Finally, age and smoking have unintended interactions on inflammatory processes. Therefore, we selected groups with similar mean ages and smoking rates to mitigate these effects (42).

Our findings suggest that RvD1 may serve as an indicator of both chronic inflammation and potential axonal degeneration in BD. We propose the potential utility of RvD1 as a diagnostic marker for identifying manic and depressive states. The observed correlation between RvD1 levels and disease severity during both acute episodes and remission periods indicates that this biomarker holds promise for monitoring disease progression and severity. Additionally, the prospect of exploring therapeutic interventions targeting RvD1, particularly in the context of depressive episodes, warrants further investigation in future research. Further research is warranted to explore the therapeutic implications of modulating RvD1 levels in managing BD-I. In addition, future studies are needed that examine patients' inflammatory parameters longitudinally, including both acute and remission periods.

Ethics Committee Approval: The study was approved by the Clinical Ethics Committee of Dr. Sadi Konuk Training and Research Hospital with the protocol code 2018/245 and decision number 2018-14 on 06.08.2018.

Informed Consent: They were informed about the study and asked to read and sign the informed consent form.

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