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Research paper

The relation of optical coherence tomography findings with oxidative stress parameters in patients with bipolar disorder and unaffected first-degree relatives

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ABSTRACT

Background: We aimed to evaluate the optical coherence tomography(OCT) findings and oxidative stress parameters in patients with bipolar disorder(BD) and their unaffected first-degree relatives(FDRs) and to explore OCT findings and oxidative stress parameters as potential endophenotype candidates.
Methods: Fifty patients with BD, 40 FDRs of BD, and 50 healthy controls(HCs) were included. OCT was performed to measure peripapillary retinal nerve fiber layer(RNFL), ganglion cell layer(GCL), inner plexiform layer(IPL), central macular, and minimum foveal thicknesses(CMT and MFT), choroidal thickness(ChT). 4-hydroxy-2-nonenal(HNE), total thiol(TT), native thiol(NT), total oxidant status(TOS), total antioxidant status(TAS), disulfide (DIS) and oxidative stress index(OSI) were measured from serum samples.
Results: TOS was higher patients with BD and FDRs than HCs ($p < .001$ and $p = .012$, respectively). OSI, DIS, HNE levels were higher patients with BD and FDRs than HCs ($p < .001$). TAS, TT, NT levels were lower patients and FDRs than HCs ($p < .001$). MFT of patients was thinner than HCs ($p = .001$). CMT of patients was thinner than HCs ($p = .006$); the same trend was observed in FDRs but did not reach the statistical significance level ($p = .07$). The groups did not differ on RNFL and choroidal thickness or GCL and IPL volume.
Limitations: Evaluation of only a few retinal layers.
Conclusions: TOS, TAS, OSI, TT, NT, DIS, HNE can be useful endophenotype biomarkers in BD. Among the OCT findings, CMT was determined as the closest parameter to being an endophenotype biomarker. Our study corroborates that oxidative stress parameters are more effective than OCT findings in endophenotype studies.

1. Introduction

Bipolar disorder (BD) is a chronic episodic psychiatric disorder with a worldwide prevalence of 1%. BD causes severe impairment in social, occupational, cognitive functions of patients and deteriorates the quality of life (Cotrena et al., 2016).

The pathophysiology of BD is complex, multifactorial, and still not fully understood. BD is caused by genetic and environmental factors; characterized by multiple associations between disturbed brain development, neuroplasticity, and chronobiology, defects in apoptotic, immune-inflammatory, neurotransmitter, neurotrophin, and calcium-signaling pathways; oxidative and nitrosative stress; cellular bioenergetic; and membrane or vesicular transport (Sigitova et al., 2017). The creation of new hypotheses in this area promotes searching for new

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biomarkers for BD. New biomarkers facilitate diagnosing a disorder and follow-up of treatment and developing new hypotheses about causes and pathophysiology of BD.

Whether BD is a neurodegenerative disorder remains controversial. In recent years, evidence supporting neurodegeneration has been found, especially in neuroimaging studies (Kempton et al., 2008). The majority of these studies showed various structural changes such as enlargement of the lateral ventricles, reduced brain gray matter volume in the hippocampus, fusiform gyrus, cerebellar, and temporal lobe (Vita et al., 2009). Many of these changes have been demonstrated both in patients and unaffected first-degree relatives (FDRs) (Ladouceur et al., 2008).

The visual pathway has been the focus of many studies in the field of neurodegeneration. It is thought that the investigation of the retina, which is anatomically the first part of the visual pathway, may be a promising method in the early diagnosis of degenerative processes in the central nervous system (CNS). Nerve axons in the retina synapse with many brain regions such as the lateral geniculate nucleus, mesencephalon, pretectum, and hypothalamus. Therefore the retina is an extension of the CNS so that many researchers describe it as a "window to the brain" (Chu et al., 2012; Yeap et al., 2008). The fact that the retinal nerve fiber layer (RNFL) contains unmyelinated nerve axons and is embryologically an extension of the CNS makes RNFL an ideal structure for evaluating neurodegeneration (Hoon et al., 2014).

Optical coherence tomography (OCT), which enables rapid and noninvasive evaluation of retinal layers, is thought to be important in providing complementary, diagnostic, and prognostic information in BD and many other neurodegenerative diseases. OCT is a promising new technique for the detection of measurable retinal biomarkers in neuropsychiatric disorders. The first studies were carried out in diseases such as Multiple sclerosis, Alzheimer's dementia, Parkinson's disease, and retinal degeneration was shown to be in parallel with the disease's progression (Frohman et al., 2008; Lu et al., 2010; Roth et al., 2014). In recent years, OCT is increasingly used in evaluating retinal abnormalities in psychiatric disorders, especially schizophrenia and bipolar disorder. OCT studies in BD generally show a reduction in retinal layer thicknesses such as retinal nerve fiber layer (RNFL), ganglion cell layer (GCL), inner plexiform layer (IPL), and macula (Garcia-Martin et al., 2019; Kalenderoğlu et al., 2016; Khalil et al., 2017; Mehraban et al., 2016; Polo et al., 2019). However, considering that mood stabilizers and antipsychotic drugs in bipolar disorder may also affect retinal layer thickness, it will be difficult to interpret whether these changes are the cause or consequences of disease pathophysiology. For this reason, investigating retinal abnormalities in FDRs who have a similar genetic predisposition to patients but are not affected by the disease may be an essential guide for a better understanding of these findings and may provide an explanation of some neurodevelopmental problems.

The roles of inflammatory processes and oxidative stress in the uncertain pathophysiology of BD are investigated as possible etiological factors (Bauer et al., 2014). Oxidative stress, which means increased reactive oxygen species (ROS), may play a role in the etiology of BD (Raffa et al., 2012). As part of the CNS, the retina is particularly susceptible to alterations of its microenvironment. In addition, the retina and especially the macula, is characterized by a state of physiological oxidative stress due to an elevated metabolism and high oxygen consumption. Thus, oxidative processes are critical factors in ocular pathologic conditions (Country, 2017).

Endophenotypes are disease-associated traits that are highly heritable, associated with the illness independent of the clinical state, and found in non-affected family members to a greater extent than in the general population. They mediate the path between the genotype and phenotypic expression and help to identify the illness-associated genes and understand the pathways from genes to the illness. An endophenotype may be biochemical, endocrinological, electrophysiological, neuroanatomical, or neurocognitive (Gottesman and Gould, 2003; Leboyer et al., 1998).

This study aimed in the first stage to investigate the OCT findings, which are thought to reflect central neurodegeneration in patients with BD, and to assess the relationship between the oxidative stress parameters and the OCT findings of patients with BD. In the second stage, our study aimed to explore whether OCT findings and oxidative stress parameters are potential endophenotype candidates.

2. Methods

2.1. Subjects

The sample consisted of 50 patients with bipolar disorder in remission, 40 unaffected first-degree relatives (siblings, parents, or children) of patients with bipolar disorder, and 50 healthy controls. Only patients who had a complete manic episode in the patient group were included in the study. The entire patient group was bipolar disorder type 1. FDRs comprised of 12 parents, 15 siblings and 13 adult offspring of bipolar disorder patients. All participants were recruited from Bezmialem Vakif University, Medical Faculty Department of Psychiatry outpatients clinic between May 2019 and January 2020. The age of participants ranged from 18 to 65 years old, and the groups were well-matched for age, gender, body mass index (BMI), and smoking status.

Patients were assessed using the Structured Diagnostic Interview for DSM-IV Axis 1 Disorders (SCID-I) by a trained psychiatrist. For the patient group, the severity of illness was assessed using the Hamilton Depression Rating Scale (HDRS) and the Young Mania Rating Scale (YMRS). Patients with HDRS < 7, YMRS < 12 were considered euthymic. Fasting blood samples were collected from the participants between 8–10 am. These blood samples were analyzed in the biochemistry laboratory of Bezmialem Vakif University Hospital. The 4-hydroxy-2-nonenal (HNE), total thiol (TT), native thiol (NT), total oxidant status (TOS), total antioxidant status (TAS) levels were measured, and glucose, triglyceride levels of the participants were determined to see the general metabolic status of the study sample. Disulfide (DIS) and oxidative stress index (OSI) were calculated with mathematical formulas. OCT measurements were performed in Bezmialem Vakif University, Department of Ophthalmology.

Ethical approval was granted by the Clinical Research Ethics Committee of Bezmialem Vakif University (No. 4/23- 20.02.2019), and this study was conducted according to principles in the Declaration of Helsinki. Written informed consent was obtained from all participants.

2.2. Exclusion criteria

Exclusion criteria for all participants were as follows: (a) Being younger than 18 and older than 65 years old (b) having a spherical equivalent of refractive error <-3D or $>+3$D (c) Alcohol and substance use disorders (d) Comorbid systemic diseases such as coronary artery disease, diabetes mellitus, hypertension, malignancy, hypothyroidism, hyperthyroidism, acute infection (e) Intellectual Disability (We excluded intellectual disability via a detailed clinical interview and review of past medical records.) (f) Any systemic or neurological disease that may affect the visual pathways (g) Neurodegenerative diseases and other neurological diseases (h) Any retinal or ocular pathology including glaucoma, cataracts, macular degeneration, uveitis, diabetic retinopathy, hypertensive retinopathy (i) Diagnosis of any major psychiatric disorder in SCID-I for non-BD groups (j) Those who do not give consent (k) Those who are illiterates (l) Those with a body mass index <18.5 kg/m^2 and >30 kg/m^2

2.3. Ophthalmological examination and OCT measurements

To exclude ophthalmological diseases that may affect the retinal layers, the participants received a detailed ophthalmological examination at the Bezmialem Vakıf University Ophthalmology Department. For this purpose, intraocular pressure measurement, best corrected visual

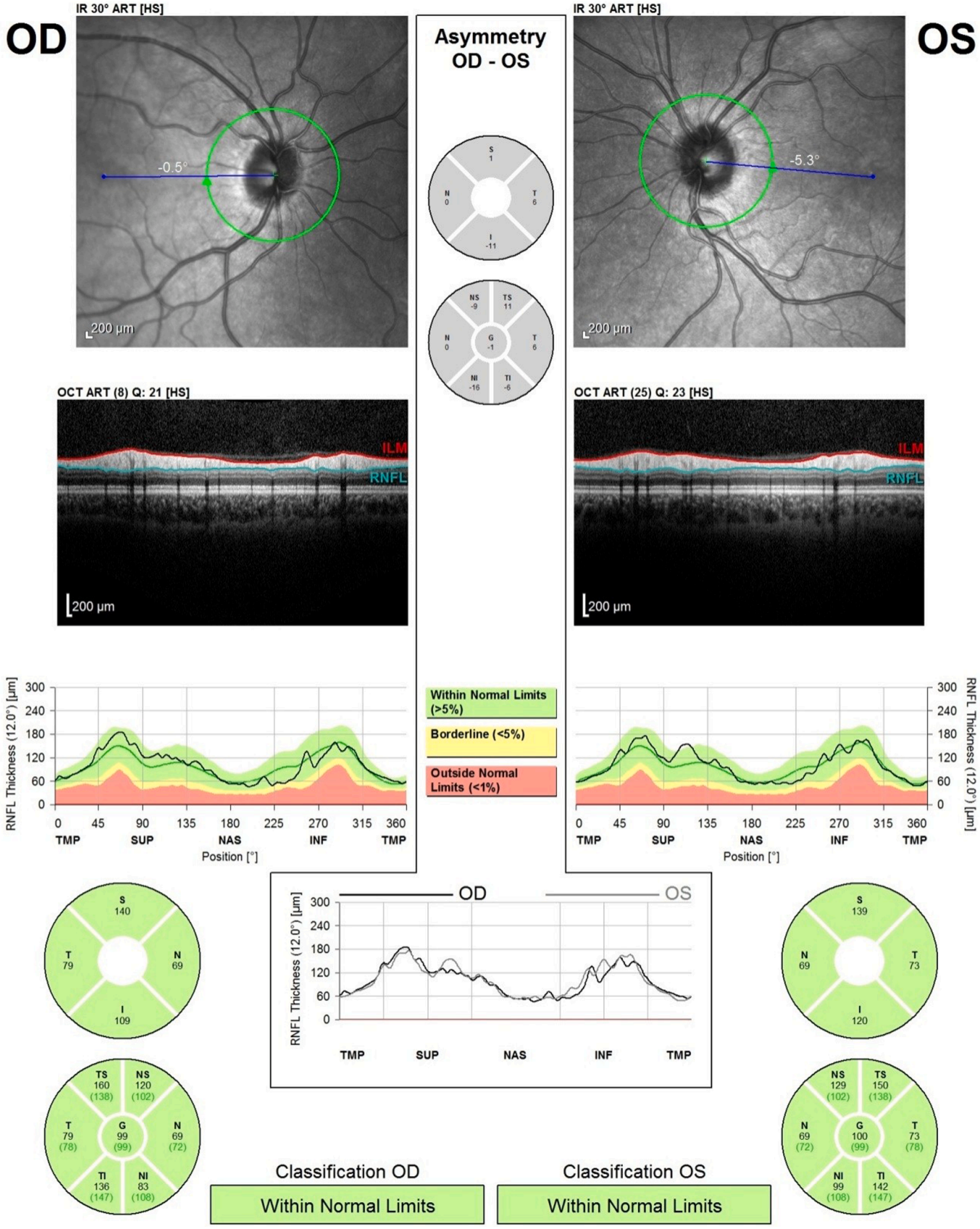

Fig. 1. Measurement of RNFL by SD-OCT. A. Circular scans centred on the optic disk are acquired. B. An image demonstrating RNFL. C. RNFL thickness map. D. The images are automatically into seven segments: superotemporal, temporal, inferotemporal, inferonasal, nasal, superonasal and global.

acuity, biomicroscopic anterior and posterior segment examination, and retina examinations were performed. Ocular OCT imaging of the participants was performed with the Spectralis SD-OCT (software version 5.3. Heidelberg Engineering, Heidelberg, Germany) device. OCT measurements were made between 10–12 am. All OCT imagings were done by the same experienced technician, performed with pupil dilation.

For RNFL thickness measurement, circular scans with 360º 3.4 mm diameter centered on the optic disk were performed. The imaged RNFL was automatically divided into superotemporal, temporal, inferotemporal, inferonasal, nasal, and superonasal segments using Heidelberg Eye Explorer software (version 1.0.10.0; Heidelberg Engineering) Fig. 1.

Macular SD-OCT imaging was performed using a posterior pole analysis protocol (61 B-scan lines at 25° × 30° macular area centered on the fovea). The device's automatic segmentation feature was used to determine the ganglion cell layer and inner plexiform layer. Volumetric measurements were used for the global evaluation of the aforementioned layers in the 6 mm macular area. Centralization and segmentation errors in the images were emended by the masked ophthalmologist (FK). The minimum foveal thickness (MFT) and central macular thickness (CMT) were also calculated automatically by the device.

The region from the Bruch membrane to the choroidoscleral interface was defined as the choroid. Choroidal imaging was performed with the Spectralis OCT device EDI (enhanced depth imaging) OCT mode. Measurement of subfoveal choroidal thickness was performed with the aid of a caliper integrated into the OCT deviceby two experienced masked ophthalmologists (FK, MHÖ).

2.4. Determination of oxidative stress parameters

2.4.1. Blood sample collection

After 12 h of fasting, blood was collected from all volunteers from the cubital vein to gel biochemistry tubes for laboratory analysis. The blood was centrifuged at 3000 xrpm for 10 min to separate the serum. All serums were aliquoted and stored at -80°C until further biochemistry analysis.

2.4.2. Determination of 4-hydroxy-2-nonenal levels

Serum 4-hydroxy-2-nonenal (Bioassay Technology Laboratory, Shangai-China-E1978Hu) levels were read with commercially purchased ELISA kits and photometric methods to 450 nm wavelength multi-plate reader (Thermo Scientific Varioskan Flash Multimode Reader). Results are given in ng / L.

2.4.3. Determination of total oxidant status

Serum TOS level was measured using a fully automatic photometric method developed by Erel (2005). The principle of the method is based on the oxidation of the ferrous ions into ferric ions by serum oxidants. Ferric ions formed in an acidic environment resulting from this oxidation take a visible color with xylenol orange. The resulting color density correlates with the level of oxidants in the serum.

2.4.4. Determination of total antioxidant status

Serum TAS level is a fully automatic colorimetric method developed by Erel (2004). The principle of the method is based on measuring the amount of OH^- radical. The ferrous ion of o-diasidine with H_2O_2 gives a Fenton-type reaction to produce the OH^- radical, and color change occurs due to o-diasidine. Serum antioxidants neutralize oxidants and prevent color change. This method determines the antioxidant capacityagainst oxidative free radical reactions initiated by OH^-.

2.4.5. Calculation of oxidative stress index

OSI value is the most important indicator of oxidative stress. The serum OSI value is calculated by dividing the TOS value by the TAS value. OSI (arbitrary unit) = TOS (μmol H_2O_2 eq/L)/TAS (mmol Trolox eq/L).

2.4.6. Determination of thiol/ disulfide homeostasis (TDH)

In order to measure thiol-disulfide homeostasis, a new indicator of oxidative stress, serum total thiol, native thiol, and disulfide levels were measured using the automated photometric method developed by Erel and Neselioglu (Erel and Neselioglu, 2014). This method is based on the reduction of dynamic bonds (-S-S-) in serum to native thiol groups (-SHHS-) by sodium borohydride ($NaBH_4$). Total thiol level is measured photometrically using Ellman reagent. The disulfide level is calculated by subtracting the native thiol level from the total thiol level and taking half of it.

2.5. Statistical analyzes

All analyzes were performed using the Statistical Package for Social Sciences (SPSS) version 22.0. After making descriptive statistics for all three groups, distribution characteristics of continuous variables were determined by the Kolmogorov Smirnov test. Regarding sociodemographic characteristics, groups were compared using the chi-square test for categorical variables, a one-way Analysis of Variance (ANOVA), or the Kruskal-Wallis test for continuous variables according to distribution characteristics. Group differences in OCT findings, oxidative stress biomarkers, and metabolic parameters were investigated using the one-way ANOVA test for normally distributed variables and the Kruskal-Wallis test for variables that did not show normal distribution. For variables showing significant differences between groups, paired comparisons were made using the post-hoc Bonferroni test. The effects of variables such as age, gender, BMI, and smoking status on oxidative stress levels among the groups were evaluated by Analysis of Covariance (ANCOVA) analysis. In addition, correlations between variables in the patient group were evaluated using the Pearson correlation test for those with normal distribution and the Spearman correlation test for those who did not show normal distribution. p< .05 was considered statistically significant for all

3. Results

3.1. Participant characteristics

Demographic and clinical characteristics of participants are presented in Table 1. The groups did not differ in age ($p = .59$), gender ($p = .44$), smoking status ($p = .24$), BMI ($p = .70$), triglyceride ($p = .07$), and glucose levels ($p = .22$).

In the group of patients with bipolar disorder; the age of onset was 26.06 ± 8.70 years, the mean disease duration was 13.06 ± 8.25years, the HDRS score was 1.16 ± 1.18, YMRS score was 0.02 ± 0.14, the median number of the lifetime depressive episodes were 3 (IQR = 2–5) the median number of the lifetime manic episodes were 2 (IQR = 1–3). Current treatment of patients were lithium only 24%, valproic acid only 18%, lithium and valproic acid 8%, antipsychotic only 4%, lithium and antipsychotic 18%, valproic acid and antipsychotic 24%, lamotrigine and antipsychotic 4%.

3.2. Oxidative stress parameters

Oxidative stress parameters of patients with bipolar disorder, unaffected first-degree relatives, and healthy controls are reported in Table 2. All parameters differed between groups significantly. According to post hoc pairwise comparison results, TOS was significantly higher in both patients and FDRs than HCs ($p < .001$ and $p = .012$, respectively). OSI, DIS, 4-Hydroxy-2-Nonenal (HNE) levels were significantly higher in both patients and FDRs than HCs ($p < .001$ for all pairwise comparisons). TAS, TT, NT levels were significantly lower in both patients and FDRs than HCs ($p < .001$ for all pairwise comparisons). Between group differences remained significant after controlling for age, gender, BMI, and smoking status (pack/day) for all dependent variables *($p < .001$ for all oxidative stress parameters; $F = 34.39, \eta^2 = .34$ for TOS; $F = 84.62, \eta^2 = .56$*

Table 1
Group characteristics.

	BD (n:50)	FDRs (n:40)	HCs (n:50)	p	Test statistics
Sociodemographics					
Gender (female %)	36 (% 72)	32 (% 80)	34 (% 68)	.44	χ^2 = 1.65
Age (years)	39.12 ± 10.19	40.67 ± 13.30	38.18 ± 11.02	.59	$F = 0.53$
Smoking status (smoker %)	15 (% 30)	6 (%15)	13 (% 26)	.24	χ^2=2.84
Smoking status (pack/day)	0.29 ± 0.47 (75.32)[1]	0.12 ± 0.30 (64.14)[1]	0.22 ± 0.40 (70.77)[1]	.23	H = 2.87
BMI (kg/m^2)	25.91 ± 2.81	25.86 ± 3.48	25.40 ± 3.40	.70	$F = 0.36$
Metabolic parameters					
Triglyceride (mg/dL)	121.98 ± 67.24 (80.53)[1]	102.93 ± 48.30 (68.24)[1]	98.84 ± 45.55 (62.28)[1]	.07	H = 5.24
Glucose (mg/dL)	92.60 ± 9.47	94.63 ± 15.58	90.58 ± 7.05	.22	$F = 1.54$
Clinical characteristics					
Age of onset (years)	26.06 ± 8.70				
Disease duration (years)	13.06 ± 8.25				
HDRS score	1.16 ± 1.18				
YMRS score	0.02 ± 0.14				
Number of depressive episodes	3.00/(2-5)				
Number of manic episodes	2.00/(1-3)				
Current treatment					
Lithium	12(% 24)				
Valproic acid	9(%18)				
Lithium+valproic acid	4(%8)				
Antipsychotic	2(%4)				
Lithium+antipsychotic	9(%18)				
Valproic acid+antipsychotic	12(% 24)				
Lamotrigine+antipsychotic	2(%4)				

Data expressed in mean ± SD orn(%) ormedian/interquartilerange (q1-q3)
[1] Mean rank
BD: Bipolar disorder patients, FDRs: Unaffected first-degree relatives, HCs: Healthy controls
HDRS: Hamilton Depression Rating Scale, YMRS: Young Mania Rating Scale
BMI: Body mass index, F: ANOVA, χ^2: chi-square test, H: Kruskal-Wallis

Table 2
Comparison of oxidative stress parameters by study groups.

	BD	FDRs	HCs	P	F
TOS	16.32 ± 3.25	13.05 ± 2.27	11.52 ± 1.48	<.001[1]	49.67
TAS	0.77 ± 0.10	0.91 ± 0.19	1.24 ± 0.20	<.001[2]	104.51
OSI	21.60 ± 5.13	15.05 ± 4.35	9.53 ± 2.12	<.001[3]	111.13
TT	457.76 ± 31.74	507.11 ± 54.62	569.04 ± 43.44	<.001[2]	82.46
NT	298.56 ± 29.56	375.18 ± 48.42	462.18 ± 40.21	<.001[2]	215.02
DIS	79.60 ± 9.90	65.96 ± 8.63	53.43 ± 8.11	<.001[3]	107.30
HNE	201.69 ± 23.49	138.37 ± 21.16	76.60 ± 15.80	<.001[3]	472.39

Post-hoc Bonferroni test was used to explore pairwise differences.
[1] Post-hoc Bonferroni BD > FDRs (p< .001) BD > HCs (p< .001) FDRs > HCs (p = .012)
[2] Post-hoc Bonferroni BD < FDRs < HCs (p<.001 for all pairwise comparisons)
[3] Post-hoc Bonferroni BD > FDRs > HCs (p<.001 for all pairwise comparisons)
TOS: Total Oxidant Status
TAS: Total Antioxidant Status
OSI: Oxidative Stress Index
TT: Total Thiol
NT: Native Thiol
DIS: Disulfide
HNE: 4-Hydroxy-2-Nonenal
F: ANOVA
*Significant at p < .05

Table 3
Comparison of OCT measures by study groups (Right Eye).

	BD	FDRs	HCs	P	F
RNFL (μm)					
Global	101.68 ± 10.15	102.90 ± 9.30	103.06 ± 6.52	.70	0.36
Ts	137.80 ± 23.19	140.23 ± 16.97	141.78 ± 14.58	.60	0.57
T	74.86 ± 10.70	75.58 ± 10.82	74.76 ± 11.98	.94	0.07
Ti	149.28 ± 20.64	142.93 ± 22.16	148.52 ± 17.75	.28	1.28
Ns	102.50 ± 18.92	112.30 ± 19.77	108.92 ± 14.41	**.029**[1]	3.62
N	77.66 ± 13.35	77.28 ± 16.50	78.94 ± 11.43	.83	0.19
Ni	118.06 ± 23.82	120.28 ± 25.03	115.64 ± 15.18	.60	0.52
MFT (μm)	208.86 ± 13.44	214.40 ± 16.24	219.90 ± 15.79	**.002**[2]	6.66
CMT (μm)	256.30 ± 15.48	258.75 ± 22.40	267.28 ± 14.96	**.006**[3]	5.31
GCL Volume (mm^3)	1.14 ± 0.10	1.15 ± 0.10	1.17 ± 0.08	.41	0.91
IPL Volume (mm^3)	0.94 ± 0.07	0.96 ± 0.08	0.95 ± 0.06	.54	0.61
ChT (μm)	306.78 ± 82.64	288.33 ± 95.06	342.04 ± 70.04	**.008**[4]	5.04

[1] Post-hoc Bonferroni BD< FDRs (p = .03)
[2] Post-hoc Bonferroni BD< HCs (p = .001)
[3] Post-hoc Bonferroni BD< HCs (p = .006)
[4] Post-hoc Bonferroni FDRs< HCs (p = .008)
BD: Bipolar Disorder patients, FDRs: Unaffected first-degree relatives, HCs: Healthy Controls, RNFL: Retinal nevre fiber layer, Ts: Temporal superior, T: Temporal, Ti: Temporal inferior, Ns: Nasal superior, N: Nasal, Ni: Nasal inferior, MFT: Minimum Foveal thickness, CMT: Central macular thickness, GCL: Ganglion cell layer, IPL: Inner plexiform layer, ChT: Choroid thickness, F: ANOVA, *Significant at p < .05

for TAS; F = 81.20, η^2 = .55 for OSI; F = 68.27, η^2 = .51 for TT; F = 181.14, η^2 = .73 for NT; F = 92.88,η^2 = .59 for DIS; F = 404.68, η^2 = .86 for HNE)

3.3. OCT data

Optical coherence tomography findings of patients with bipolar disorder, unaffected first-degree relatives, and healthy controls are reported in Table 3. Comparisons were quite similar for both eyes; therefore, only measurements for right eyes were presented here and used for further analysis. However, results for left eyes were provided in Table 4.

In the one-way ANOVA test, no statistically significant difference was found between the groups in terms of GCL and IPL volumes, but the MFT, CMT, and ChT showed a significant difference between the groups.

There was no significant difference between the groups in the global RNFL measurements and regarding the segments, only the nasal superior RNFL quadrant of patients was significantly thinner than FDRs (p = .03). The minimum foveal thickness (MFT) of patients was significantly thinner than HCs (p = .001). Central macular thickness (CMT) was significantly thinner in patients than HCs (p = .006). CMT was thinner in FDRs than HCs, but this difference did not reach the statistical significance level (p = .07). The choroid thickness of FDRs was significantly thinner than HCs (p = .008)

Table 4
Comparison of OCT measures by study groups (Left Eye).

	BD	FDRs	HCs	P	F
RNFL (μm)					
Global	100.32 ± 10.46	102.65 ± 9.19	101.86 ± 8.12	.48	0.74
Ts	138.42 ± 23.40	139.80 ± 18.33	140.28 ± 16.73	.89	0.12
T	72.76 ± 11.80	71. ± 8.71	71.68 ± 10.22	.72	0.33
Ti	144.66 ± 24.11	147.28 ± 19.89	146.12 ± 20.58	.85	0.16
Ns	112.50 ± 18.72	121.68 ± 19.92	120.74 ± 17.53	**.02**[1]	3.90
N	73.12 ± 11.44	75.28 ± 12.97	76.52 ± 12.07	.37	1.00
Ni	115.84 ± 20.45	120.35 ± 23.63	117.00 ± 15.53	.55	0.60
MFT (μm)	208.86 ± 12.54	216.15 ± 16.46	220.96 ± 15.71	**.001**[2]	8.36
CMT (μm)	255.62 ± 16.13	259.50 ± 22.38	268.86 ± 16.36	**.001**[3]	6.94
GCL Volume (mm^3)	1.14 ± 0.09	1.16 ± 0.10	1.17 ± 0.09	.21	1.58
IPL Volume (mm^3)	0.96 ± 0.16	0.95 ± 0.07	0.96 ± 0.07	.79	0.24
ChT (μm)	303.40 ± ± 88.41	289.15 ± 89.89	360.16 ± 79.41	**.001**[4]	9.01

[1] Post-hoc Bonferroni BD< FDRs ($p = .047$)
[2] Post-hoc Bonferroni BD< HCs ($p < .001$)
[3] Post-hoc Bonferroni BD< HCs ($p = .001$)
[4] Post-hoc Bonferroni FDRs< HCs (p< .001), BD<HCs ($p = .004$)
BD: Bipolar Disorder patients, FDRs: Unaffected first-degree relatives, HCs: Healthy Controls, RNFL: Retinal nevre fiber layer, Ts: Temporal superior, T: Temporal, Ti: Temporal inferior, Ns: Nasal superior, N: Nasal, Ni: Nasal inferior, MFT: Minimum Foveal thickness, CMT: Central macular thickness, GCL: Ganglion cell layer, IPL: Inner plexiform layer, ChT: Choroid thickness, F: ANOVA, *Significant at p < .05

Table 5
Relationship of OCT data with oxidative stress parameters in the patient group.

	RNFL	GCL	IPL	ChT	CMT	MFT
TOS	$r = 0.15$	$r = 0.15$	$r = 0.22$	$r = 0.17$	$r = 0.10$	$r = -0.09$
	$p = .29$	$p = .32$	$p = .13$	$p = .25$	$p = .49$	$p = .56$
TAS	$r = 0.28$	$r = 0.26$	$r = 0.33$	$r = 0.01$	$r = 0.10$	$r = -0.06$
	$p = .05$	p=. 06	$p =$ **.02***	$p = .96$	$p = .48$	$p = .67$
OSI	$r = -0.01$	$r = 0.01$	$r = 0.02$	$r = 0.13$	$r = -0.02$	$r = -0.09$
	$p = p = .95$	$p = .96$	$p = .91$	$p = .36$	$p = .88$	$p = .55$
TT	$r = -0.06$	$r = -0.14$	$r = -0.14$	$r = 0.11$	$r = -0.27$	$r = -0.08$
	$p = .70$	$p = .35$	$p = .34$	$p = .45$	$p = .06$	$p = .58$
NT	$r = 0.01$	$r = -0.22$	$r = -0.11$	$r = 0.12$	$r = -0.27$	$r = -0.19$
	$p = .96$	$p = .13$	$p = .43$	$p = .41$	$p = .06$	$p = .18$
DIS	$r = -0.10$	$r = 0.11$	$r = -0.05$	$r = -0.01$	$r = -0.02$	$r = 0.16$
	$p = .48$	$p = .45$	$p = .72$	$p = .97$	$p = .87$	$p = .26$
HNE	$r = 0.06$	$r = 0.08$	$r = 0.08$	$r = -0.19$	$r = 0.004$	$r = 0.05$
	$p = .69$	$p = .58$	$p = .72$	$p = 0.20$	$p = .98$	p=.74

r= pearson correlation coefficient
*significant at p < .05
TOS: Total Oxidant Status
TAS: Total Antioxidant Status
OSI: Oxidative Stress Index
TT: Total Thiol
NT: Native Thiol
DIS: Disulfide
HNE: 4-Hydroxy-2-Nonenal
RNFL: Retinal nerve fiber layer
GCL: Ganglion cell layer
IPL: Inner plexiform layer
CMT: Central macular thickness
MFT: Minimum foveal thickness
ChT:Choroidal thickness

3.4. Relationship of OCT data with oxidative stress parameters

The correlation of OCT findings with oxidative stress parameters in the patient group is reported in Table 5. High TAS was associated with an increase in IPL volume (p = .02). Apart from that, there was no significant correlation between OCT findings and oxidative stress parameters.

4. Discussion

Bipolar disorder is a significant health problem and has serious social and economic consequences. Duration of untreated bipolar disorder (DUB) causes a negative impact on prognosis. Identifying the mechanisms that play a role in the etiology of the disease and defining the risk factors that contribute to the development of the disease at an early stage shorten the time between the onset and management of the bipolar disorder and affect the results positively.

4.1. Oxidative stress parameters

The relationship between BD and oxidative stress is still an important area of research. It is not entirely clear whether oxidative stress is increased due to bipolar disorder or bipolar disorder develops in high oxidative stress responses. While increased oxidative stress may predispose to developing the disease, it may also occur secondary to the neurodegenerative mechanisms in the disease process.

In our study, oxidative stress parameters such as TOS, OSI, DIS, HNE levels were significantly higher in both patients and FDRs than HCs. Antioxidant parameters such as TAS, TT, and NT levels were significantly lower in both patients and FDRs than HCs. When the covariance analysis was performed considering confounding factors such as age, gender, BMI, and smoking, the difference between the groups remained statistically significant for all these parameters. The findings of our study show that high oxidative stress and low antioxidant response may be an endophenotype candidate for bipolar disorder.

Scola et al. evaluated lipid peroxidation (lipid hydroperoxide, 4-hydroxy-2-nonenal, 8-isoprostane), protein oxidation (protein carbonyls), and inflammation (IL-1, IL-6, IL-10, IFNγ, TNFα) among four groups aged 9–20 years: high-risk children, ultra high-risk children, first-episode BD patients, and healthy controls. Lipid hydroperoxide levels, an early-stage lipid peroxidation parameter, showed a decreasing trend across the BD risk spectrum. In contrast, late-stage lipid peroxidation parameters (*4-hydroxy-2-nonenal*, 8 isoprostane), protein carbonyls, and inflammatory markers did not differ between the groups (Scola et al., 2016). In our study, oxidative stress parameters such as TOS, OSI, DIS, and *HNE* levels were significantly higher in both patients and FDRs than HCs, suggesting that these parameters may also be inherited endophenotypes. Also, antioxidant parameters such as TAS, TT, NT levels were significantly lower in both patients and FDRs than HCs, suggesting that these parameters may also be inherited endophenotypes. The relatively large sample size, exclusion of those with comorbid diseases, and the fact that BMI and smoking status did not differ between our groups may have been effective in the significant results of our study.

Although different results were obtained regarding antioxidants in many studies, most of them found a high level of oxidants in psychiatric diseases (Bayazit et al., 2017; Ercan et al., 2017; Ersoy et al., 2008; Selek et al., 2008; 2012; Talarowska et al., 2012; Uğur et al., 2018; Ustundag et al., 2006). In our study, both increased oxidant levels and decreased antioxidant levels were shown together in patients with BD. Increased oxidant levels are similar to other psychiatric diseases. The decrease in

antioxidant levels appears to be either a predisposing factor or a consequence of psychiatric disorders.

4.2. OCT data

Investigation of retinal layers with OCT in BD is one of the new fields, and there are not many studies in the literature. Researchers have generally focused on RNFL.

Multiple studies have shown that patients with BD have statistically significant thinning in global RNFL (Garcia-Martin et al., 2019; Kalenderoglu et al., 2016; Mehraban et al., 2016; Polo et al., 2019). Mehraban et al. showed thinning in the nasal RNFL quadrant in their study (Mehraban et al., 2016). Khalil et al. and Martin et al. denoted a thinning in the temporal RNFL quadrant (Garcia-Martin et al., 2019; Khalil et al., 2017). Our study found that only the nasal superior RNFL quadrant was significantly thinner in patients with BD than FDRs, and no statistically significant difference was found in the global and other RNFL quadrants. Unlike other studies, the global RNFL thickness did not differ between the groups, and this was explained by the high oxidative stress levels of the patients with BD could be suppressing the possible thinning of the vascularized retinal layers such as RNFL.

GCL and IPL in BD have been investigated by volume in some studies and thickness in others. In the study of Kalenderoğlu et al., there was a decrease in GCL volume in patients with BD compared to HCs (Kalenderoglu et al., 2016). In the study of Khalil et al., there was a decrease in the thickness of some GCL quadrants in patients with BD (Khalil et al., 2017). Martin et al. found a decrease in the thickness of some GCL and IPL quadrants in patients with BD (Garcia-Martin et al., 2019). In our study, instead of thicknesses, GCL and IPL volumes were assessed as like in the study by Kalenderoğlu et al.; however, we found no difference between the groups.

In the two studies investigating choroidal thickness in BD, no significant difference was found between patients and HCs (Kalenderoglu et al., 2016; Polo et al., 2019). In our study, a significant thinning in choroid was found only in the FDRs compared to HCs.

Macula and foveal thicknesses have been investigated in patients with schizophrenia in the literature. CMT was found to be decreased in patients with schizophrenia in the study of Lee et al., while Ascaso et al. found that the MFT was significantly reduced in the left eye (Ascaso et al., 2015; Lee et al., 2013). In our study, CMT was significantly thinner in patients with BD than HCs; also, CMT was thinner in FDRs than HCs, but this difference did not reach the statistical significance level. MFT was significantly thinner in patients with BD than HCs, and no significant difference was found between other groups in terms of MFT.

In order to avoid the confounding effect of metabolic disorders/conditions on retinal layer thicknesses, a priori decision was made to exclude participants with diabetes mellitus, coronary artery diseases, hypertension and a BMI over than 30 kg/m^2. So, patients are similar to HCs and it differs from the literature. This may be one reason why the global RNFL thickness and GCL, IPL volumes did not differ between our groups. The metabolic status of the patients was not evaluated in any of the previous OCT studies. In these patients, the risk of metabolic syndrome is higher than the normal population, and this may be affecting OCT findings (Acharya et al., 2017). Therefore, it is important to evaluate the metabolic status of participants in studies investigating OCT findings as biological markers.

Previous neuroimaging studies investigating endophenotype candidates for BD reported that patients might have healthy children with gray matter abnormalities (Ladouceur et al., 2008). Functional magnetic resonance imaging studies (fMRI) report changes in the lower frontal gyrus, medial prefrontal cortex, limbic areas, and amygdala activity in unaffected FDRs (Özerdem et al., 2016). In a study investigating OCT findings as an endophenotype in patients with schizophrenia, it was stated that IPL might be a useful endophenotype for genetic and early detection studies (Kurtulmus et al., 2020). Our findings suggest that CMT could be a useful endophenotype for BD, which needs to be investigated in further research.

4.3. Relationship of OCT data with oxidative stress parameters

Oxidative stress mechanisms play a role in the pathogenesis of psychiatric disorders. The brain is considered particularly vulnerable to oxidative damage because ofits lipid-rich structure, the presence of metal ions involved in redox reactions, and the deficiency of antioxidant defenses (Halliwell, 2006; Ng et al., 2008).

Oxidative stress causes changes in proteins and DNA structure, leading to inflammation, apoptotic cell death, and tissue damage. Many studies have shown a relationship between oxidative stress and neuronal degeneration. Oxidative stress plays a central role in mechanisms combining gene-environment interactions in neurodegenerative diseases. Oxidative stress-induced changes in white matter channels and gray matter volumes can be detected by diffusion tensor imaging (Parek et al., 2019). Based on this, our study investigating the relationship between OCT findings and oxidative stress levels found that a high total antioxidant statuswas associated with an increase in IPL volume. IPL volume was also inversely correlated with the number of manic episodes and the duration of the disease. According to these findings, IPL could be a marker associated with neurodegeneration.

The limitation of our study, only a few retinal layers were evaluated. This is the first study evaluating retinal layer alterations in unaffected first-degree relatives of BD. Given the study's exploratory nature, we only focused on the particular retinal layers that have been the most common focus of prior OCT studies, and most consistent results have been reported in patients with BD. Further studies evaluating deeper layers of the retina in both patients with bipolar disorder and their unaffected first-degree relatives would contribute to the literature. Another limitation of our study is that the female/male ratio in the sample is higher than in the literature.

In conclusion, our study focus on oxidative processes in the pathophysiology of bipolar disorder. One of the strengths of this study is that the differences between groups were disclosed independently of the effects of confounding factors such as body mass index and smoking. It was revealed that oxidative stress parameters TOS, OSI, DIS, HNE, and antioxidant parameters TT, NT, TAS could be strong endophenotype candidates in BD. Among the OCT findings MFT was significantly thinner in patients with BD than HCs. CMT was significantly thinner in patients with BD than HCs; also, CMT was thinner in FDRs than HCs, but this difference did not reach the statistical significance level. These data support the conclusion that OCT findings reflect central neurodegeneration. CMT was determined to be the closest parameter to be an endophenotypic candidate among OCT findings in our study. Further research is needed for this marker. With these findings, it was concluded that biochemical parameters are more valuable and effective in BD endophenotypic studies compared to OCT findings. If we can prove that neurodegeneration in bipolar disorder patients or unaffected first-degree relatives correlates with the OCT findings or oxidative stress parameters, we can benefit from them to show the magnitude of neurodegeneration in a shorter time, instead of longer neurocognitive tests in clinical practice. They allow high-risk group candidates to be identified early, followed closely, and shorten the duration of untreated bipolar disorder (DUB), which is thought to be associated with poor prognosis.

CRediT authorship contribution statement

Tezer Kilicarslan: Visualization, Writing – review & editing, Data curation, Formal analysis, Writing – original draft. **Ebru Sahan:** Visualization, Writing – review & editing, Writing – original draft. **Furkan Kirik:** Visualization, Writing – review & editing, Writing – original draft. **Eray Metin Guler:** Visualization, Writing – original draft. **Ayse Kurtulmus:** Visualization, Formal analysis, Writing – original draft. **Fatma Busra Parlakkaya Yildiz:** Data curation. **Mehmet Hakan Ozdemir:** .

Abdurrahim Kocyigit: . **Ismet Kirpinar:** Visualization, Writing – review & editing.

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