NÖRO PSİKİYATRİ ARŞİVİ
ARCHIVES OF NEUROPSYCHIATRY

RESEARCH ARTICLE

Arch Neuropsychiatry 2024;61:66–72
https://doi.org/10.29399/npa.28369

Vitamin D: An Overlooked Parameter in Studies of Depression Using Optic Coherence Tomography

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ABSTRACT

Introduction: The relationship between depression and inflammation and the resulting vascular/neuronal damage have been demonstrated in recent studies. In this study we aimed to investigate inflammation and the possible degeneration that can be caused by depression and accompanying vitamin D deficiency using a non-invasive imaging method of optical coherence tomography (OCT).

Methods: Twenty-four healthy controls and 42 drug free major depressive patients matched for age, sex and eye measurements were compared in terms of vitamin D, C Reactive Protein (CRP) and OCT parameters. The Hamilton Depression Rating Scale (HAM-D), The Clinical Global Impressions Scale (CGI) and Global Assessment of Functioning Scale (GAF) were used to assess disease severity.

Results: CRP level and choroidal thickness in the major depression group were significantly higher than the healthy controls. Vitamin D level and the ganglion cell layer (GCL) volume was significantly lower in the major depression group compared to healthy controls. Positive correlation was found between HAM-D and CRP in major depressive patients; a negative correlation was found between current attack duration and GCL volume. CGI was positively correlated with CRP and HAM-D. GAS was negatively correlated with CRP and HAM-D.

Conclusion: It has been shown that major depression might be an inflammatory disorder with possible degenerative processes observed with OCT and CRP measurements. But longitudinal follow up studies are needed to demonstrate a cause and effect relationship.

Keywords: C reactive protein, major depression, optical coherence tomography, vitamin D

Cite this article as: Özgedik Turhan N, Arısoy Ö, Ulaş F, Buğdaycı G, Altıntaş M. Vitamin D: An Overlooked Parameter in Studies of Depression Using Optic Coherence Tomography. Arch Neuropsychiatry 2024;61:66–72.

INTRODUCTION

Many biological, genetic, and psychosocial theories have been proposed concerning the etiology of major depression. Related studies in neurobiology started with neurotransmitter systems and focused on the hypothalamic-pituitary system, adrenal-thyroid systems, vitamin deficiencies, genetics, neural networks, neuroplasticity, and neuroimaging (1).

Recent studies have found that when sympathoadrenal system activation occurs with stress, there is an increase in the release of many mediators and proinflammatory cytokines, such as tumor necrosis factor-alpha, as a result of both the release of catecholamines and activation of the immune system. This increase destroys tryptophan and triggers depressive symptoms by decreasing serotonin synthesis from tryptophan. These events can also cause vascular/neurological damage (2).

Highlights

- **C Reactive Protein is increased in major depression.**
- **C Reactive Protein is positively correlated with depression severity and duration.**
- **Choroidal thickness is increased, ganglion cell layer volume is decreased in depression.**
- **Ganglion cell layer volume is negatively correlated with depression duration.**
- **Major depression seems to be an inflammatory and degenerative disease.**

Although no increased rate of vascular disease was found in depressed patients in epidemiological studies, the fact that increased deep white matter hyperintensities were found in a repetetive manner in patients with depression and the fact that a significantly increased ratio of atheromatous disease was found in the postmortem period in depressive patients compared to controls and the fact that higher rates of intercellular adhesion molecule-1 (ICAM-1) and vascular adhesion molecule -1 (VCAM-1) was found in the dorsolateral prefrontal cortices of depressed patients independent of confounding variables such as age and treatment indicates an increased risk of vascular disease in patients

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Received: 24.11.2022, **Accepted:** 16.03.2023, **Available Online Date:** 24.02.2024

with depression (3). A meta-analysis, examining structural magnetic resonance imaging studies performed to show atherosclerosis and neuronal damage that may be associated with inflammatory processes associated with depression, found a decrease in volume in the frontal cortex, orbitofrontal cortex, cingulate cortex, hippocampus, and striatum, as well as an increase in white matter hyperintensity in patients with depression (4).

Optical coherence tomography (OCT), a new imaging method called non-invasive tissue biopsy, enables the collection of tomographic sections of micron resolution from biological tissues. This technique allows images similar to those viewed under a microscope to be obtained without damaging the tissue. High-resolution cross-sectional images of the retina, choroid, anterior segment, optic nerve head, and retinal nerve fiber layer (RNFL) can be procured using OCT (5). The retina is made up of ten histologically distinct layers. The pigment epithelial layer, photoreceptor layer, outer limiting membrane, outer nuclear layer, outer plexiform layer, inner nuclear layer, inner plexiform layer (IPL), ganglion cell layer (GCL) composed of ganglion cell bodies and axons, the RNFL, and the inner limiting membrane are the layers from outside to inside (6). The volume and thickness of each layer can be measured with OCT. It is believed that the GCL reflects the ganglion cell body, and the IPL reflects the dendritic branching in the ganglion cells (7). Another important structure is the choroid which receives 85% of the ocular blood flow and is responsible for feeding the outer 2/3 of the retina (8).

While OCT has recently begun to be used in psychiatric diseases, studies on depression using OCT are limited. Researchers found that choroidal thickness was increased in patients with first-episode depression compared to those with recurrent depression, which supports the supposition that acute depression is an inflammatory process. The GCL and IPL volumes of patients with recurrent depression were also reported to be significantly reduced compared to patients with first-episode depression (9). In another study, a negative correlation was found between the duration of the last depressive episode and nasal RNFL thickness and ganglion cell IPL thickness (10). No difference between right and left eye OCT measurements between major depressive patients and healthy controls was found (11). However, none of these studies investigated the effect of vitamin D on inflammatory/degenerative processes in depression using OCT.

Vitamin D, which is thought to be involved in the etiopathogenesis of depression, regulates protective neurotrophins and neuromediators in the central nervous system by binding to vitamin D receptors, especially in neurons, glial cells, and retinal endothelial cells in the brain. It provides anti-inflammatory/antiangiogenic/antioxidant effects and also activates tryptophan hydroxylase 2, which is responsible for serotonin synthesis in the brain (12,13). The relationship between vitamin D deficiency and depression is based on these facts.

The relationship between vitamin D deficiency and vascular damage has been discussed in several recent studies in which vitamin D deficiency, which is involved in the etiology of major depression, was evaluated with OCT. In one of these studies, the macular ganglion cell complex (GCC) and RNFL were examined using OCT to demonstrate vascular damage in patients with early-stage diabetic retinopathy with and without vitamin D deficiency, and there was a significant decrease in GCC in patients with vitamin D deficiency compared to those without, but no significant difference was found in terms of RNFL (14). In another study, Uro et al. showed a decrease in ganglion cell thickness in patients with vitamin D deficiency (15).

However, no study in the literature uses OCT to examine RNFL thickness in patients with major depression with or without vitamin D deficiency. In this study, we aimed to investigate the possible inflammation and degeneration associated with depression and vitamin D deficiency using the OCT method by comparing unmedicated major depressive patients with and without vitamin D defficiency with healthy controls. We hypothesized that patients with vitamin D deficiency would have more inflammation, more severe depression, less RNFL thickness measured by OCT, and increased choroidal thickness due to inflammation-related vascular blood flow.

METHODS

Participants

Bolu Abant İzzet Baysal University Ethics Committee approved this study with its decision dated 6.3.2017, numbered 56, and it complied with the Helsinki Declaration. In addition, it was supported by the Scientific Research Project Commission of Bolu Abant İzzet Baysal University. Patients 18–60 years of age diagnosed with major depression according to DSM-IV diagnostic criteria, who applied to Bolu Abant İzzet Baysal University Medical Faculty Psychiatry Polyclinics between March 2017 and March 2018, were included in this study. Controls consisted of healthy volunteers, hospital staff, and relatives of patients hospitalized in other departments. All participants voluntarily signed an informed consent form. Exclusion criteria included Axis 1 disorder other than major depression, head trauma with loss of consciousness, uncontrolled hypertension that may affect the vascular system in the eye, diabetes, a history of coronary heart disease, a systemic disease affecting the eye, an ophthalmological or neurological disease affecting the visual pathways, cataracts, and leukoma. Conditions affecting the OCT examination, including vitreous hemorrhage, those with ±5 spherical, ±3 cylindrical refractive errors, and those with a history of inflammatory disease in the last two weeks or a history of anti-inflammatory drug use were also excluded from the study. Of 46 patients with major depression, two were excluded because of urinary tract infections and two due to strabismus in OCT measurements. Two of 26 healthy controls were excluded due to strabismus in OCT measurements. Thus, the patient group consisted of 42 people, and the healthy control group included 24 people who met the research criteria. Both the patient and control groups were evaluated with the Structured Clinical Interview Inventory (SCID) for the Diagnostic and Statistical Manual of Mental Disorders (DSM), and the diagnosis of major depression in the patient group was made according to DSM-IV diagnostic criteria.

Scales

Participants were assessed to determine the severity of depression and anxiety and their level of functionality.

Hamilton Depression Rating Scale (HAM-D): Developed by Hamilton in 1960 (16), translated to Turkish by Akdemir et al. (1996) (17), is a clinician-evaluated scale scored as 0–13: no depression, 14–27: mild depression, 28–41: moderate depression, and 42–53: severe depression.

Hamilton Anxiety Rating Scale (HAM-A): Developed by Hamilton in 1959 (18) with Turkish validity and reliability confirmed by Yazici et al. (1998) (19), is a clinician-evaluated scale with an inter-rater reliability coefficient of 0.72: scored as 0–5: no anxiety, 6–14: minor anxiety, and ≥15: major anxiety.

Global Assessment Scale (GAS): Functionality for the current or past period using a score from 1to 100 (20).

Clinical Global Impression Scale (CGI): The severity of the disease and the extent to which the patient responds to treatment is evaluated on a scale of 1 to 7 points (1: normal, not ill, 2: borderline, 3: mildly ill, 4: moderately ill, 5: significantly ill, 6: severely ill, and 7: most severe) (21).

Eye Examination and OCT Measurements

After the scale applications, all participants were directed to the Department of Ophthalmology for eye examinations with OCT performed by Dr. Fatih Ulaş and Dr. Melek Altıntaş Gülner. Optical coherence tomography recordings were performed with the Spectralis® OCT device (Heidelberg Engineering, Heidelberg, Germany) loaded with 5.3 software without changing the values of the rapid macular thickness measurement modes. Right eye measurements were taken in 20 of 24 healthy controls, and left eye measurements were taken in two individuals due to ±3 cylindrical refractive errors in the right eye and ±5 spherical refractive errors in 2 subjects.

Blood Samples

To determine participants' vitamin D and C reactive protein (CRP) levels, blood samples (5–10 cc) were taken on an empty stomach in morning, and measurements were made on the same day. A vitamin D level <20 ng/mL was accepted as vitamin D Defficiency.

Statistical Analysis

Before initiating the study, the sample size was determined using G Power 3.1 (22). The effect size was accepted as d=0.40, the statistical significance as α=0.05, and the power (1–β) as 80%. The sample size was calculated to be 66 for a three-group comparison with one-way analysis of variance (ANOVA), thus we aimed to recruit 22 people for each group. Comparisons were analyzed with the chi-square test when the data were categorical and the continuous variables were analyzed for normal distribution with the Kolmogrov-Smirnoff test. The normally distributed continuous variables were compared in three groups with one-way ANOVA, and non-normally distributed variables were compared with the Kruskal–Wallis ANOVA. Posthoc Bonferroni correction was done to differentiate the groups from each other. After the Kruskal–Wallis-H test, Mann-Whitney U tests were performed for pairwise comparisons. The P-value was divided into three for multiple statistical correction since a post hoc three paired comparisons were done, and the significance level was accepted as p<0.016. Comparisons between the two groups were made with the Student's t-test when the data were normally distributed and the Mann-Whitney U test when they were not. The relationships between clinical variables and OCT parameters were examined by Spearman correlation analysis. Since the correlation of 16 parameters was examined, multiple statistical corrections were made, the P-value was divided by 16, and the significance level was accepted as p<0.003. Finally, in the linear regression analysis, attack duration, vitamin D level, and HAM-D score were evaluated as independent variables to understand what determines the CRP level in the whole sample.

RESULTS

Sociodemographic Data

In terms of age and gender, the depressed patients and healthy control groups were statistically comparable. Patients with serious depression had considerably lower levels of education than healthy controls, were more likely to be unemployed, and lived alone to a greater extent (p<0.05) (Table 1).

CRP and Vitamin D

The CRP level was statistically significantly higher in patients with major depression than in the healthy control group (p<0.001). Vitamin D levels of the patients with major depression were found to be statistically significantly lower than those of the healthy control group (p<0.001) (Table 2). When patients with major depression with and without vitamin D deficiency were compared to healthy controls, the CRP level of the healthy control group was found to be statistically significantly lower than that of major depressive patients with and without vitamin D deficiency (p<0.001), but no statistically significant difference was found between the major depression groups with and without vitamin D deficiency (p=0.26).

OCT Data

The nasal choroidal thickness (EDI. N) value of patients with major depression was significantly higher that of the healthy control group (p=0.03). The GCL volume value was statistically significantly lower in the major depression group than in the healthy control group (p=0.03) (Table 2). There was no significant difference between the three groups in terms of central choroidal thickness (EDI. C), temporal choroidal thickness (EDI. T), EDI. N, central retinal thickness (RET. C), temporal retinal thickness (RET. T), nasal retinal thickness (RET. N), global retinal nerve fiber layer (GRNFL), GCL, GCL volume, and IPL parameters (Table 3).

Correlations

Current attack duration was negatively correlated with vitamin D (p=0.002), positively correlated with CRP (p<0.001), positively correlated with disease duration (p<0.001), and negatively correlated with GCL volume (p=0.003). Total disease duration was negatively correlated with vitamin D (p=0.003) and positively correlated with CRP (p<0.001). Clinical global impression scale was positively correlated with CRP (p<0.001). The HAM-D total score, which indicates the severity of the disease, was negatively correlated with vitamin D (p=0.001) and positively correlated with CRP (p=0.002). The GAS value indicating functionality was negatively correlated with disease duration (p<0.001), negatively correlated with HAM-D (p<0.001), and negatively correlated with CRP (p<0.001) (Table 4).

Regression Analysis

In the linear regression analysis performed to understand what determines the CRP level in the whole sample, attack duration, vitamin D level, and HAM-D score were taken as independent variables, and the model is valid (F=6.28, p<0.001), and explains 24% of the variance (R^2=0.24). From the independent variables, attack duration significantly predicted the CRP level positively (B=0.01, p=0.02). In contrast, the vitamin D level predicted the CRP level negatively (B=-0.01, p=0.05) (Table 5).

DISCUSSION

Studies of major depression to demonstrate vascular damage and degeneration by a non-invasive imaging method of OCT are scarce. Thus, we intended to investigate depression, inflammation, and degeneration induced by vitamin D insufficiency using OCT, and this is the first study that attempted this. We found CRP levels to be significantly higher in patients with major depression compared to healthy controls, while vitamin D levels were significantly lower compared to healthy controls (Table 2). No significant difference was found between major depressive patients with or without vitamin D deficiency regarding CRP and disease severity. In terms of OCT parameters, there was a significant increase in nasal choroidal thickness determined by EDI. N in the major depressive group compared to the healthy control group and a decrease in the GCL volume, which is one of the retinal nerve parameters (Table 2).

Many studies have found an increase in CRP in patients with serious depression, which is consistent with our findings (23,24). In our study, attack duration, disease duration, and disease severity were positively correlated with CRP. These results are in line with another study's findings showing that inflammation increases with disease severity and duration (25).

Our finding of low vitamin D levels in patients with depression is consistent with both the literature and the results of our previous outpatient screening study (26,27). Many studies show that vitamin D deficiency increases the incidence of major depression and causes existing depression to be more severe (26). Similarly, in our study, a negative correlation was found between vitamin D levels and the severity of depression.

Table 1. Comparison of sociodemographic data of patients with major depression and healthy controls

Variable	Major Depression (n=42)	Healthy Controls (n=24)	X^2, t/z	P
Age, mean±standard deviation	30.95±9.97	30.63±5.43	-0.17[z]	0.86
Gender, n (%)				
Female	32 (76.2%)	13 (54.2%)	3.41[X2]	0.06
Male	10 (23.8%)	11 (45.8%)		
Education (years), mean±standard deviation	11.60±4.37	15.83±2.84	-3.79[z]	<0.01*
Non-working, n (%)	25 (59.5%)	3 (12.5%)	13.82[X2]	<0.01*
Living alone, n (%)	4 (9.5%)	8 (33.3%)	5.82[X2]	0.02*
Smoking, n (%)	14 (33.3%)	9 (37.5%)	0.11[X2]	0.73
HAM-D total	35.46±6.53	17.63±0.82	-6.72[z]	<0.01*
HAM-A total	19.85±7.48	0.78±0.73	-16.17[z]	<0.01*
CGI, mean±standard deviation	3.45±0.59	1.00±0.00	-7.10[z]	<0.01*
GAS, mean±standard deviation	58.95±6.97	96.50±1.61	33.36[z]	<0.01*
Current attack duration (months), mean±standard deviation	9.40±15.24	----	----	---
Disease duration (months), mean±standard deviation	36.90±48.66	----	----	---

*P<0.05, A Mann-Whitney U Test was applied to the variables that were not normally distributed, and z statistics[z] given. A Student's t-test was applied to normally distributed variables, and t statistics[t] given. Categorical variables were analyzed with chi-square and the x^2 statistic[x2] given.
CGI: Clinical Global Impression Scale; GAS: Global Assessment Scale; HAM-A: Hamilton Anxiety Rating Scale; HAM-D: Hamilton Depression Rating Scale.

Table 2. Comparison of patients with major depression and healthy controls in terms of CRP, Vitamin D, and OCT parameters

Variables, mean±standard deviation	Major Depression (n=42)	Healthy Controls (n=24)	X^2, t/z	P
CRP	0.79±0.98	0.10±0.02	-3.98[z]	**<0.001***
Vitamin D	21.26±16.89	30.46±8.76	2.90[z]	**<0.001***
EDI. C	323.69±75.79	319.50±72.58	-0.21[z]	0.82
EDI. T	288.07±73.15	296.13±84.17	0.40[t]	0.68
EDI. N	292.95±69.54	253.17±75.82	-2.16[t]	**0.03***
RET. C	217.61±11.86	223.58±17.27	1.65[t]	0.10
RET. T	323.95±18.45	330.29±20.27	1.29[z]	0.20
RET. N	352.76±20.60	359.33±25.86	1.13[z]	0.26
GRNFL	101.76±10.77	98.92±6.76	-1.31[t]	0.19
GCL	58.57±6.15	58.75±5.56	-0.43[z]	0.66
GCL volume	2.34±0.12	2.41±0.10	2.22[t]	**0.03***
IPL	45.83±5.10	47.13±4.89	1.00[t]	0.31
Axial	23.36±0.82	23.86±0.81	-1.20[t]	0.22
Spherical	-0.68±0.47	-0.89±0.67	-0.95[z]	0.34

*P<0.05, A Mann-Whitney U Test was applied to variables that were not normally distributed, and z statistics[z] given. A Student's t-test was applied to normally distributed variables, and t statistics[t] given.
CRP: C reactive protein; EDI. C: central choroidal thickness; EDI. N: nasal choroidal thickness; EDI. T: temporal choroidal thickness; GCL: ganglion cell layer; GRNFL: global retinal nerve fiber layer; IPL: inner plexiform layer; OCT: optical coherence tomography; RET. C: central retinal thickness; RET. N: nasal retinal thickness; RET. T: temporal retinal thickness.

Table 3. Comparison of major depression patients with and without vitamin D deficiency and healthy controls in terms of vitamin D, CRP, and OCT parameters

Variables, mean±standard deviation	**Major Depression without vitamin D Deficiency (n=22)**	**Major Depression with vitamin D Deficiency (n=20)**	**Healthy Controls (n=24)**	**F/K**	**P**	**Group difference**
Vitamin D	34.40±15.13	9.32±5.99	30.46±8.76	36.11[K]	**<0.001***	**1=3>2**
CRP	0.58±0.77	0.99±1.12	0.10±0.02	17.43[K]	**<0.001***	**1=2>3**
EDI. C	321.35±74.42	325.82±78.70	319.50±72.58	0.04[F]	0.95	1=2=3
EDI. T	292.10±88.37	284.41±57.88	296.13±84.17	0.13[F]	0.87	1=2=3
EDI. N	303.35±77.95	283.50±61.21	253.17±75.82	2.73[F]	0.07	1=2=3
GRNFL	100.45±11.56	102.95±10.11	98.92±6.76	1.03[F]	0.36	1=2=3
RET. C	216.37±12.21	218.68±11.72	223.58±17.27	1.48[F]	0.23	1=2=3
RET. T	323.90±13.39	324.00±22.42	330.29±20.27	0.82[K]	0.44	1=2=3
RET. N	352.85±18.52	352.68±22.77	359.33±25.86	0.63[K]	0.53	1=2=3
GCL	58.60±4.36	58.55±7.52	58.75±5.56	0.27[K]	0.87	1=2=3
GCLvolume	2.35±0.11	2.34±0.12	2.41±0.10	2.54[F]	0.08	1=2=3
IPL	47.20±5.24	44.59±4.76	47.13±4.89	1.97[F]	0.14	1=2=3
Axial	23.60±0.61	22.92±1.03	23.86±0.81	2.59[F]	0.09	1=2=3
Spheric	-0.84±0.26	-0.76±0.54	-0.89±0.67	1.74[F]	0.19	1=2=3

*P <0.05, A one-way ANOVA was applied to the normally distributed variables, and post hoc Bonferroni correction was made, F statistic given[F]. A Kruskal-Wallis test was applied to the non-normally distributed variables, and Kruskal-Wallis test statistic given[K]. P accepted as <0.016. Group 1: Major depression without vitamin D deficiency, Group 2: Major depression with vitamin D deficiency, Group 3: Healthy controls.
CRP: C reactive protein; EDI. C: central choroidal thickness; EDI. N: nasal choroidal thickness; EDI. T: temporal choroidal thickness; GCL: ganglion cell layer; GRNFL: global retinal nerve fiber layer; IPL: inner plexiform layer; OCT: optical coherence tomography; RET. C: central retinal thickness; RET. N: nasal retinal thickness; RET. T: temporal retinal thickness.

Table 4. Correlation of OCT and inflammation parameters with sociodemographic and clinical variables in the whole sample

	Disease duration	**CGI**	**HAM-D**	**Vitamin D**	**CRP**	**EDI. C**	**EDI. T**	**EDI. N**	**GRNFL**	**RET. C**	**RET. T**	**RET. N**	**GCL v**	**IPL**
Attack duration	r=0.80 **p<0.001**	r=0.73 **p<0.001**	r=0.35 **p<0.001**	r=-0.37 **p=0.002**	r=0.51 **p<0.001**	r=-0.01 p=0.91	r=-0.04 p=0.70	r=0.23 p=0.05	r=0.08 p=0.49	r=-0.16 p=0.20	r=-0.20 p=0.09	r=-0.28 p=0.01	r=-0.36 **p=0.003**	r=-0.16 p=0.19
Disease duration		r=0.77 **p<0.001**	r=0.73 **p<0.001**	r=-0.36 **p=0.003**	r=0.57 **p<0.001**	r=-0.11 p=0.34	r=-0.11 p=0.35	r=0.27 p=0.02	r=0.17 p=0.15	r=-0.09 p=0.43	r=-0.13 p=0.29	r=-0.14 p=0.26	r=-0.23 p=0.05	r=-0.09 p=0.43
CGI			r=0.86 **p<0.001**	r=-0.35 p=0.004	r=0.52 **p<0.001**	r=-0.07 p=0.54	r=-0.15 p=0.21	r=0.12 p=0.33	r=0.08 p=0.49	r=-0.12 p=0.30	r=-0.12 p=0.33	r=-0.07 p=0.57	r=-0.26 p=0.03	r=-0.10 p=0.42
GAS	r=-0.71 **p<0.001**	r=-0.94 **p<0.001**	r=– 0.84 **p<0.001**	r=0.32 p=0.007	r=-0.48 **p<0.001**	r=0.10 p=0.42	r=0.51 p=0.22	r=-0.13 p=0.28	r=-0.03 p=0.78	r=0.10 p=0.41	r=0.05 p=0.68	r=0.04 p=0.78	r=0.20 p=0.94	r=0.03 p=0.78
HAM-D				r=-0.39 **p=0.001**	r=0.38 **p=0.002**	r=-0.11 p=0.38	r=-0.10 p=0.40	r=0.07 p=0.56	r=0.13 p=0.30	r=-0.03 p=0.78	r=-0.01 p=0.91	r=-0.00 p=0.98	r=-0.17 p=0.17	r=-0.00 p=0.98

*p<0.003, Pearson's correlation was used for the related variables, and the correlation coefficient r given.
CGI: Clinical Global Impression Scale; CRP: C reactive protein; EDI. C: central choroidal thickness; EDI: N: nasal choroidal thickness; EDI: T: temporal choroidal thickness; GAS: Global Assessment Scale; GCL v: ganglion cell layer volume; GRNFL: global retinal nerve fiber layer; HAM-D: Hamilton Depression Rating Scale; IPL: inner plexiform layer; RET. C: central retinal thickness; RET. N: nasal retinal thickness; RET. T: temporal retinal thickness.

Table 5. Linear regression determining C reactive protein in the whole sample

	B	**Standard error**	**beta**	**t**	**P**
Attack duration	0.01	0 0.00	0.27	2.33	**0.02***
Vitamin D	-0.01	0.00	-0.23	-1.99	**0.05***
HAM-D total	0.01	0.01	0.16	1.39	0.16

*P<0.05
HAM-D: Hamilton Depression Rating Scale.

The negative correlation between vitamin D level and CRP (Table 4) may indirectly indicate that vitamin D deficiency contributes to inflammation. In addition, the fact that the attack duration, and the low vitamin D level predicted the CRP level in the regression analyses in the whole sample also supports the inflammation-increasing effect of vitamin D deficiency. Although inflammatory markers other than CRP could not be examined in our study, a negative correlation has been shown between vitamin D levels and inflammatory markers in various studies in the literature (28,29). The role of vitamin D on the immune system is to shift T helper 1 cells towards less pro-inflammatory T helper 2 cells (30), so the pro-inflammatory state that occurs in vitamin D deficiency which improves with vitamin D replacement may possibly have a negative effect on inflammation in the brain.

Many studies show that inflammation caused by chronic stress and high cortisol levels leads to severe depression and degenerative processes (31,32). Although many methods are used to show degenerative changes, very few studies examine the retina, which is accepted as an extension of the brain, or use the OCT method to try to show signs of deterioration. Although no significant difference was found between RNFL and IPL values between major depressive individuals and healthy control groups in our study using OCT, GCL volume, another retinal nerve parameter, was significantly lower in major depressive patients compared to the healthy control group (Table 2). In a similar study, no difference was found in terms of RNFL in major depression, but GCL volume and IPL values were found to be lower than that of healthy controls (9). In two other studies, no difference was found in RNFL values (10,11), which may be explained by the higher sensitivity of GCL and IPL measurements to degeneration. GCL and IPL measurements were more sensitive than RNFL to show deterioration during the attack period in patients with multiple sclerosis (33). In our study, although a decrease in GCL volume was found with major depression, which is thought to be an inflammatory disease like multiple sclerosis, a decrease was also expected in RNFL thickness, however, no difference was found, which may be due to including patients with major depression in acute attack. The indifference between the groups regarding RNFL might be explained by the possible edema occurring between the retinal layers due to increased inflammation detected in patients with acute major depressive episodes. In addition, it has been stated that retinal changes can be demonstrated with OCT when only 50% of retinal nerve fiber cells are lost with advancing age (34). Since our study group was composed of relatively young patients, and RNFL measures are affected by factors such as age, inflammation, and edema caused by neovascularization, there may not have been a difference in RNFL across the groups.

Our study found a negative correlation between current depressive episode duration and GCL volume. In the literature, similar to our research, Yildiz et al. also found a negative correlation between current attack duration and RNFL, GCL, and IPL (10). In our study, no significant correlation was found between HAM-D, which is the parameter measuring the severity of depression, and OCT parameters. However, a negative correlation was found between the functional GAS score and the duration of the disease, the severity of depression, and CRP (Table 4). In a study investigating the relation between depressive attack severity and OCT parameters, a negative correlation was found between Montgomery-Asberg Depression Scale (MADRS) scores and RNFL, GCL volume, and IPL in major depressive patients (11). In another study, a negative correlation was found between disease severity determined by CGI score and HAM-D, and GCL volume and IPL (9). All these data may indicate that the increase in the duration and severity of depression and the corresponding decrease in functionality contribute to the degenerative process, characterized by OCT parameters.

In our study, besides the retina, the choroid, a vascular network structure that provides nutrition to the retina, was also examined. A significant increase in nasal choroidal thickness determined by EDI. N was found in the major depressive group compared to the healthy control group (Table 2). Similar to our findings, Kalenderoğlu et al. discovered that the mean choroidal thickness was higher in patients with major depression than in healthy controls (9). It has been reported that cytokines such as interleukin (IL)-6, TNF-a, and IL-1β increase in patients with major depression and these cytokines increase the choroidal blood supply as an effect of inflammatory processes (35). The increase in choroidal thickness may also be due to the increased retinal blood flow due to inflammation to compensate for the axonal degeneration caused by depression.

Whilst several correlations were discovered, no difference between subgroups was found. One reason for this may be the small sample size. This issue can be investigated further in studies with larger sample populations. Altough matching major depression and healthy control groups in terms of age, gender, and OCT parameters of spherical and axial equivalence is a strength of the study, the asymmetric female-male ratio of 32:10 in the patient group and 13:11 in the control group, is a limitation. In addition, the fact that the depressed patients were less educated and working less than the healthy controls may have put these groups under different stresses, leading to the development of a depressive state affected by exogenous rather than endogenous factors, which is another limitation of the study. Furthermore, although the findings may indicate a degenerative process they may have occurred due to a neurodevelopmental process as well. The cross-sectional design of the study makes it difficult to differentiate the degenerative process from a neurodevelopmental one and the cross-sectional design is also insufficient to demonstrate a cause-effect link in terms of OCT outcomes.

We aimed to show the relationship between depression and inflammation, the vascular and degenerative damage that may occur as a result, and the relationship between this damage and vitamin D using a non-invasive imaging method OCT. The decreased vitamin D levels which was correlated with increased CRP levels in major depressive patients compared to healthy controls and the increased CRP and choroidal thickness in the depressed group might show an increased inflammatory processes and blood supply accompanying inflammation in depression which are consistent with the findings of previous studies. The decreased GCL volume in major depressive individuals compared to healthy adults is also consistent with other studies showing possible degeneration; however, longitudinal follow-up studies are needed to reveal a causal relationship.

Ethics Committee Approval: Bolu Abant İzzet Baysal University Medical Faculty Ethics Committee approved this study with its decision dated 6.3.2017, numbered 56, and it complied with the Helsinki Declaration.

Informed Consent: Written informed consent was obtained from all participants.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept- NÖT, ÖA, FU; Design- NÖT, ÖA; Supervision- NÖT ÖA, FU, GB; Resource- NÖT, ÖA; Materials- NÖT, ÖA, GB; Data Collection and/or Processing- NÖT, MAG; Analysis and/or Interpretation- ÖA; Literature Search- NÖT; Writing- NÖT, ÖA; Critical Reviews- ÖA.

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

Financial Disclosure: It was supported by Abant İzzet Baysal University Scientific Research Project Commission.

REFERENCES

1. Dean J, Keshavan M. The neurobiology of depression: An integrated view. Asian J Psychiatr. 2017;27:101–111. [Crossref]
2. Maes M. The cytokine hypothesis of depression: inflammation, oxidative & nitrosative stress (IO&NS) and leaky gut as new targets for adjunctive treatments in depression. Neuro Endocrinol Lett. 2008;29(3):287–291.

3. Thomas AJ, Ferrier IN, Kalaria RN, Woodward SA, Ballard C, Oakley A, et al. Elevation in late-life depression of intercellular adhesion molecule-1 expression in the dorsolateral prefrontal cortex. Am J Psychiatry. 2000;157(10):1682–1684. [Crossref]
4. Arnone D, McIntosh AM, Ebmeier KP, Munafò MR, Anderson IM. Magnetic resonance imaging studies in unipolar depression: systematic review and meta-regression analyses. Eur Neuropsychopharmacol. 2012;22(1):1–16. [Crossref]
5. Lee J, Rosen RB. Learning to read retinal OCT. Ophthalmology Management. 2015;19:4446–4448.
6. İnan S. Retina Anatomisi. KTD. 2014;15(3):355–359.
7. Gabriele ML, Wollstein G, Ishikawa H, Kagemann L, Xu J, Folio LS, Schuman JS. Optical coherence tomography: history, current status, and laboratory work. Invest Ophthalmol Vis Sci. 2011;52(5):2425–2436. [Crossref]
8. Nickla DL, Wallman J. The multifunctional choroid. Prog Retin Eye Res. 2010;29(2):144–168. [Crossref]
9. Kalenderoglu A, Çelik M, Sevgi-Karadag A, Egilmez OB. Optic coherence tomography shows inflammation and degeneration in major depressive disorder patients correlated with disease severity. J Affect Disord. 2016;204:159–165. [Crossref]
10. Yıldız M, Alim S, Batmaz S, Demir S, Songur E, Ortak H, et al. Duration of the depressive episode is correlated with ganglion cell inner plexifrom layer and nasal retinal fiber layer thicknesses: Optical coherence tomography findings in major depression. Psychiatry Res Neuroimaging. 2016;251:60–66. [Crossref]
11. Schönfeldt-Lecuona C, Schmidt A, Kregel T, Kassubek J, Dreyhaupt J, Freudenmann RW, et al. Retinal changes in patients with major depressive disorder - A controlled optical coherence tomography study. J Affect Disord. 2018;227:665–671. [Crossref]
12. Patrick RP, Ames BN. Vitamin D hormone regulates serotonin synthesis. Part 1: relevance for autism. FASEB J. 2014;28(6):2398–2413. [Crossref]
13. Józefowicz O, Rabe-Jabłoska J, Woniacka A, Strzelecki D. Analysis of vitamin D status in major depression. J Psychiatr Pract. 2014;20(5):329–337. [Crossref]
14. Gungor A, Ates O, Bilen H, Kocer I. Retinal nerve fiber layer thickness in early-stage diabetic retinopathy with vitamin D deficiency. Invest Ophthalmol Vis Sci. 2015;56(11):6433–6437. [Crossref]
15. Uro M, BO, Cherif M, Graffe A, Milea D, Annweiler C. Age-related vitamin D deficiency is associated with reduced macular ganglion cell complex: a cross-sectional high-definition optical coherence tomography study. PLoS One. 2015;10(6):e0130879. [Crossref]
16. Hamilton MA. Rating scale for depression. J Neurol Neurosurg Psychiatry 1960; 23:56-62
17. Akdemir A, Orsel S, Dag I. Reliability and validity of Turkish version of Hamilton Depression Scale. Journal of Psychiatry Psychology Psychopharmacology 1996; 4: 251-259. [Crossref]
18. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol 1959; 32:50-55
19. Yazici MK, Demir B, Tanriverdi N, Karaoglu E, Yolac P. Hamilton Anksiyete Değerlendirme Ölçeği, Değerlendiriciler Arası Güvenirlik ve Geçerlik çalışması. Türk Psikiyatri Dergisi 1998; 9(2):114-117
20. Endicott J, Spitzer RL. Psychiatric Rating Scales. In: Kaplan HI, Sadock BJ, editors. Comprehensive Textbook of Psychiatry. 5th ed. Baltimore, Maryland: Williams & Wilkins, 1989. pp.2391-2409.
21. Guy W. Clinical global impression (CGI). ECDEU Assessment Manual for Psychopharmacology. Rockville: US Dept Health, Education and Welfare publication (ADM); 1976.
22. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: A Flexible Statistical Power Analysis Program for the Social, Behavioral, and Biomedical Sciences. Behavior Research Methods 2007; 39: 175-191. http://dx.doi.org/10.3758/BF03193146
23. Chamberlain SR, Cavanagh J, de Boer P, Mondelli V, Jones DNC, Drevets WC, et al. Treatment-resistant depression and peripheral C-reactive protein. Br J Psychiatry. 2019;214(1):11–19. [Crossref]
24. Goyal S, Srivastava K, Kodange C, Bhat PS. Immunological changes in depression. Ind Psychiatry J. 2017;26(2):201–206. [Crossref]
25. Wium-Andersen MK, Orsted DD, Nordestgaard BG. Elevated C-reactive protein, depression, somatic diseases, and all-cause mortality: a mendelian randomization study. Biol Psychiatry. 2014;76(3):249–257. [Crossref]
26. Stefanowski B, Antosik-Wójciska AZ, wicicki Ł. The effect of vitamin D3 deficiency on the severity of depressive symptoms. Overview of current research. Psychiatr Pol. 2017;51(3):437–454. English, Polish. [Crossref]
27. Shin YC, Jung CH, Kim HJ, Kim EJ, Lim SW. The associations among vitamin D deficiency, C-reactive protein, and depressive symptoms. J Psychosom Res. 2016;90:98–104. [Crossref]
28. Eksioglu U, Atilgan HI, Yakin M, Yazihan N, Altiparmak UE, Yumusak N, et al. Antioxidant effects of vitamin D on lacrimal glands against high dose radioiodine-associated damage in an animal model. Cutan Ocul Toxicol. 2019;38(1):18–24. [Crossref]
29. Rodriguez AJ, Mousa A, Ebeling PR, Scott D, de Courten B. Effects of vitamin D supplementation on inflammatory markers in heart failure: a systematic review and meta-analysis of randomized controlled trials. Sci Rep. 2018;8(1):1169. [Crossref]
30. Grudet C, Malm J, Westrin A, Brundin L. Suicidal patients are deficient in vitamin D, associated with a pro-inflammatory status in the blood. Psychoneuroendocrinology. 2014;50:210–219. [Crossref]
31. Lebedeva A, Sundström A, Lindgren L, Stomby A, Aarsland D, Westman E, et al. Longitudinal relationships among depressive symptoms, cortisol, and brain atrophy in the neocortex and the hippocampus. Acta Psychiatr Scand. 2018;137(6):491–502. [Crossref]
32. Su L, Faluyi YO, Hong YT, Fryer TD, Mak E, Gabel S, et al. Neuroinflammatory and morphological changes in late-life depression: the NIMROD study. Br J Psychiatry. 2016;209(6):525–526. [Crossref]
33. González-López JJ, Rebolleda G, Leal M, Oblanca N, Muñoz-Negrete FJ, Costa-Frossard L, et al. Comparative diagnostic accuracy of ganglion cell-inner plexiform and retinal nerve fiber layer thickness measures by Cirrus and Spectralis optical coherence tomography in relapsing-remitting multiple sclerosis. Biomed Res Int. 2014;2014:128517. [Crossref]
34. Honrubia F, Calonge B. Evaluation of the nerve fiber layer and peripapillary atrophy in ocular hypertension. Int Ophthalmol. 1989;13(1-2):57–62. [Crossref]
35. Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK, et al. A meta-analysis of cytokines in major depression. Biol Psychiatry. 2010;67(5):446–457. [Crossref]