# Investigation of Optic Disc and Retina Structures in Patients with Schizophrenia

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## ABSTRACT

**Purpose:** In this study, we aimed to compare the retinal thicknesses, the vascular density values optic disc and retina of patients with schizophrenia and healthy individuals using optical coherence tomography angiography (OCTA).

**Material and Methods:** The study included 48 patients with schizophrenia and 50 healthy controls of similar age and gender without any psychiatric disease or comorbidities. The OCTA scans of the patient and control groups were examined.

**Results:** In the schizophrenia group, the total, parafoveal, and perifoveal density values of the deep capillary plexus (DCP), optic disc total vascular density, peripapillary vascular density, subfoveal choroidal thickness, total retina parafovea thickness, total retina perifovea thickness, and outer retina perifovea thickness were statistically significantly lower (p<0.0001, p<0.0001, p<0.0001, p=0.01, p=0.04, p<0.0001, p=0.01, p=0.03, and p=0.04, respectively), while the foveal vascular density of the superficial capillary plexus (SCP) was statistically significantly higher (p=0.006) compared to the control group.

**Conclusion:** This study is the first study to find statistically significant differences between schizophrenia patients and the healthy controls in 5 different areas such as SCP vascular density, DCP vascular density, optic disc vascular density, retinal thickness and subfoveal choroidal thickness. The lower retinal and optic disc vascular density, retinal thickness and subfoveal choroidal thickness of patients with schizophrenia compared to healthy controls can be attributed to vascular damage. It is considered that inflammation, neurooxidative stress, and neurodegenerative changes play a role in the development of vascular damage.

**Key Words:** choroidal effusion, choroidal detachment, suprachoroidal hemorrhage, drainage

## INTRODUCTION

Schizophrenia is a chronic and serious psychiatric disorder characterized by hallucinations, delusions, restricted affect, difficulty assessing reality, and impairment in social and daily functioning [1]. Schizophrenia can lead to the loss of gray and white matter in the brain, resulting in cognitive deficits and reduced brain activity. In addition, the presence of visual disorders in this disease has highlighted the possibility of alterations in the retina [2, 3].

Optical coherence tomography angiography (OCTA) is a non-invasive imaging method that has recently been increasingly employed to visualize the optic disc and retinal vascular blood flow. The retina grows from the same neural tissue as the brain during embryonic development. These two structures have similar types of neurons, glial cells, neurotransmitters, and receptors. Previous studies have identified changes in retinal vascular blood flow using OCTA in patients with schizophrenia [4, 5].

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We hypothesize that patients with schizophrenia may have changes in posterior segment structures and posterior segment vascular densities, which can be detected using the OCTA device, and that these results can contribute to elucidating the vascular etiology of the disease. In this study, we aimed to compare the vascular density values and retinal thickness of patients with schizophrenia and healthy individuals using OCTA.

## MATERIAL AND METHODS

### Patient Selection

The study included 48 patients with chronic schizophrenia who were followed up in our psychiatry clinic and 50 healthy controls of similar age and gender without any psychiatric disease or comorbidities who presented to our clinic for a routine eye check-up. The patients were diagnosed with schizophrenia according to the criteria of the 5$^{th}$ edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). The diagnosis of schizophrenia was confirmed by a qualified and experienced psychiatrist using the Structured Diagnostic Clinical Interview for DSM-5. The patients had been followed up at the psychiatry clinic with a diagnosis of schizophrenia for at least two years. The average axial length of the eyes of patients with schizophrenia was measured as 22.78±0.89, and the average axial length of the eyes of patients in the control group was measured as 22.81±0.66, and no statistical difference was detected between the groups. The refraction values of schizophrenia patients and people in the control group were in the range of $-1< x <+1$, people with refraction values different from these values were not included in the study.

Schizophrenia patients use the drugs quetiapine, olanzapine, risperidone and aripiprazole. Of the 48 schizophrenia patients, 35 (72.92%) use double drug combinations and 13 (27.08%) use triple drug combinations.

The exclusion criteria were as follows: any eye pathology (e.g., glaucoma, uveitis, diabetic retinopathy), a history of eye surgery other than uncomplicated cataract surgery, and any systemic disease. After applying the exclusion criteria, 48 eyes of 48 patients and 50 eyes of 50 healthy individuals were included in the study.

Demographic characteristics and examination findings of the patient and control groups were obtained from their files. The findings of the full ophthalmological examination, biomicroscopy, and fundus examination were evaluated. The OCTA scans were examined. A spectral-domain OCTA (AngioVue; Optovue, Inc, Fremont, CA) device was used in OCTA imaging.

### OCTA Evaluation

The participants' OCTA measurements were made on a 6x6-mm HD Angio Retina and a 4.5x4.5-mm Angio Disc scale. Images with poor quality due to motion and other artifacts were not included in the study. Only images with signal quality higher than 8/10 were evaluated.

Foveal vascular density (FVD) was measured ina 1-mm circle centered on the fovea, parafoveal vascular density (PAFVD) in a circle between 1 mm and 3 mm, perifoveal vascular density (PEFVD) in a circle between 3 mm and 6 mm, and total vascular density (TVD) ina6-mm circle centered on the fovea, and these values were recorded as percentage density (Figure 1 and Figure 2).

Foveal avascular zone (FAZ) was automatically calculated using the automatic mode of the device. The device was also used to automatically determine outer retinal flow in an area with a central radius of 1 mm and an area of 3.142 mm$^2$in the outer retinal layer and choriocapillaris blood flow (CCA) in an area with a central radius of 1 mm and an area of 3.142 mm$^2$, and these values were recorded in mm$^2$.

Optic disc vascular density was accepted as the vascular density in a 4.5-mm diameter circle centered on the optic disc and recorded as a percentage. Retinal nerve fiber thickness was automatically measured by the device from a scanning circle with a diameter of 3.4 mm centered on the optic disc.

Retinal thicknesses were automatically measured by the device based on the distance between the internal limiting membrane and the retinal pigment epithelium in the foveal, parafoveal, and perifoveal regions.

Choroidal thickness measurements were made by two different observers from the subfoveal area in the Enhanced HD line section. The average of the measurements of the two observers was taken. The retinal pigment epithelium and sclerachoroidal junction were taken as the boundaries for the measurement of subfoveal choroidal thickness (SCT).

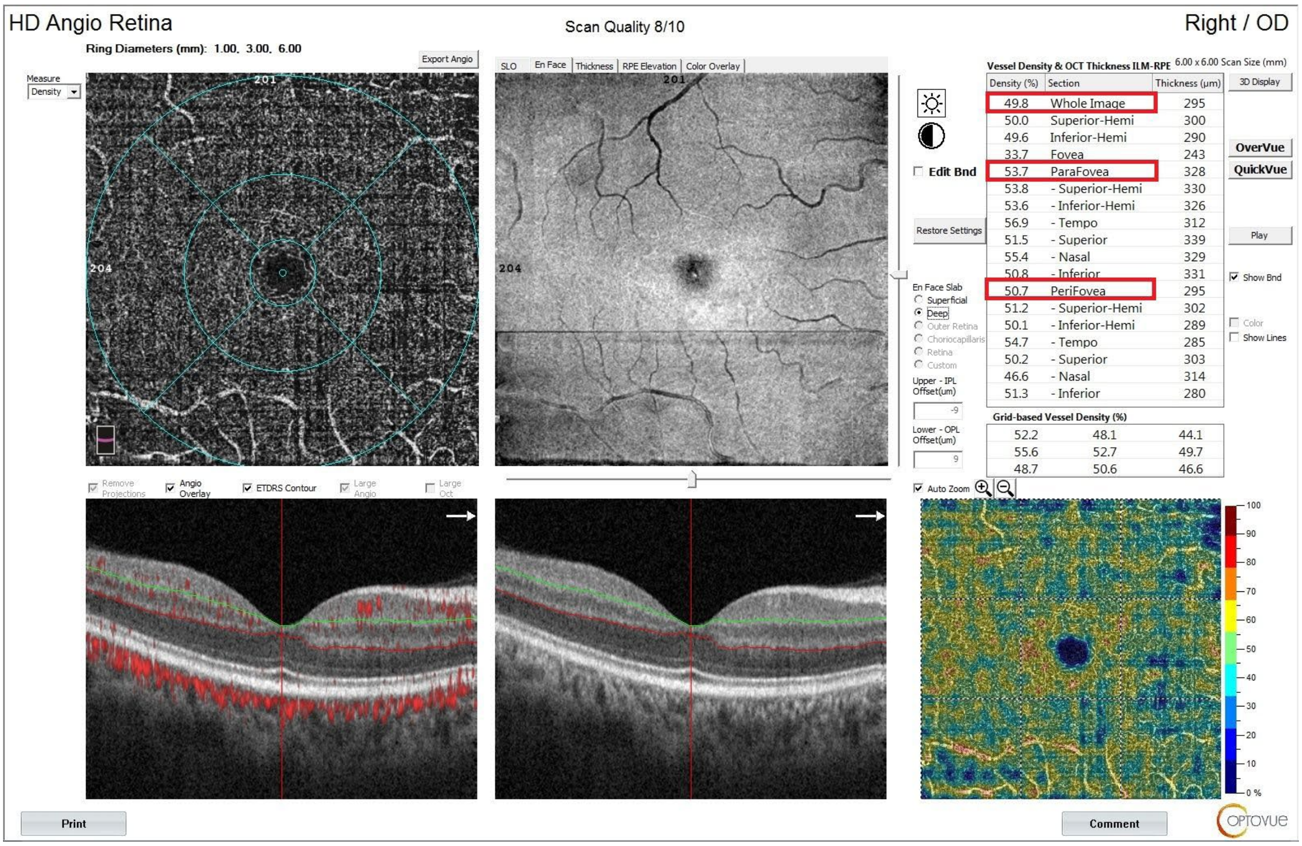


**Figure 1.** *Total vascular density, parafovea vascular density and perifovea vascular density values of the deep capillary plexus of the right eye of a schizophrenia patient*

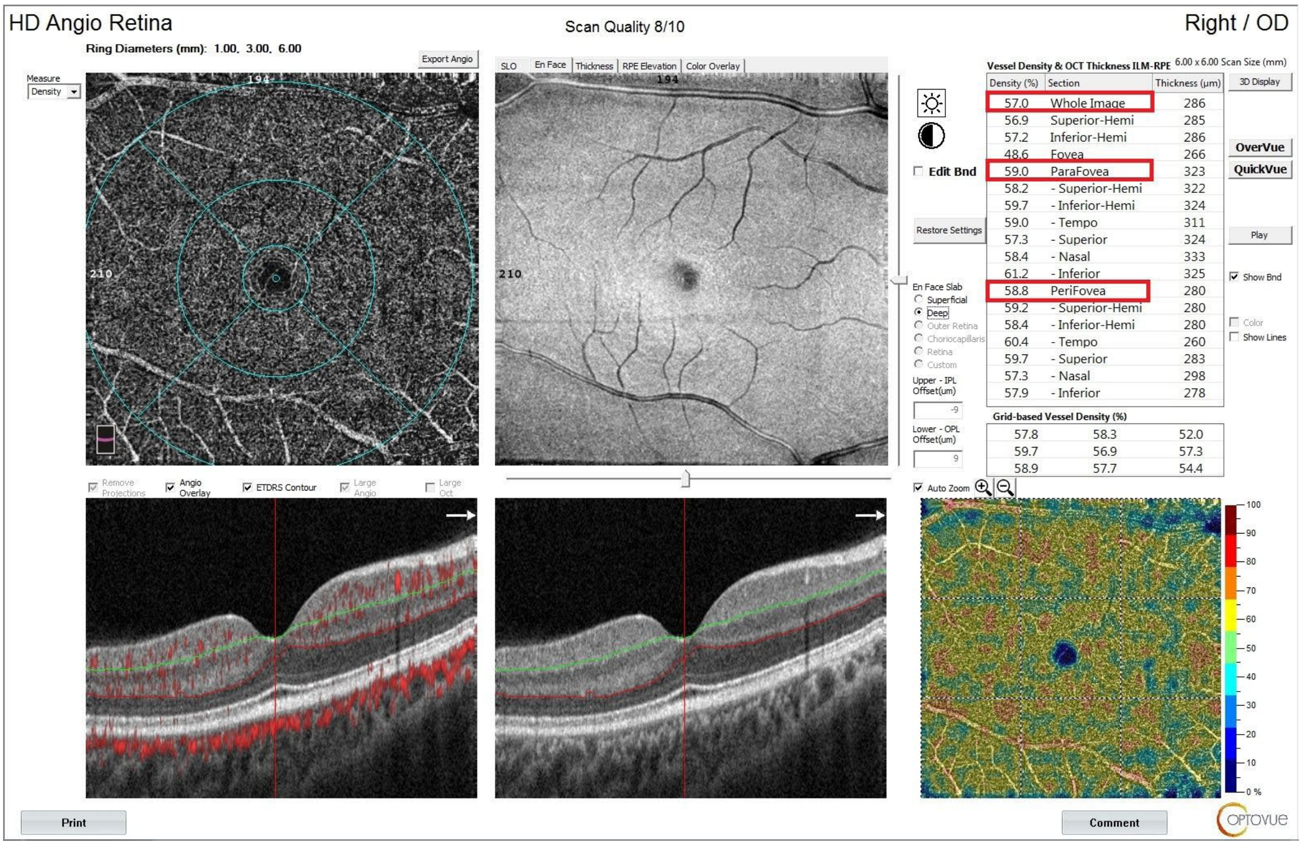


**Figure 2.** *Total vascular density, parafovea vascular density and perifovea vascular density values of the deep capillary plexus of the right eye of a healthy person*

## Statistical Analysis

In this study, all the data obtained from the study was analyzed using the Statistical Packages for the Social Sciences version 24.0 (SPSS Inc., Chicago, IL) package program. Descriptive statistics for numerical variables were given as mean standard deviation, median, minimum, and maximum values. The suitability of numerical variables for a normal distribution was evaluated with the Shapiro-Wilk test. The independent-samples t-test was used for the pairwise comparisons of data that conformed to the normal distribution, and the Mann-Whitney U test was used for the pairwise comparisons of data that did not conform to the normal distribution. The associations between the numerical values were assessed with the non-parametric Spearman correlation test. The results were evaluated within the 95% confidence interval, and $p<0.05$ was considered statistically significant. The required sample size for the study was determined in advance using G*Power 3.1 software. Power analysis was performed based on two-tailed t-test for independent samples. In the analysis, the effect size was accepted as medium level (Cohen's d = 0.5), alpha level as 0.05 and statistical power (1−β) as 0.80. In line with these criteria, it was calculated that at least 44 participants were needed for each group.

## Results

The mean age was calculated to be 35.91 ± 8.28 years for the 48 patients with schizophrenia and 35.02 ± 10.09 years for the 50 controls. The demographic characteristics of the patient and control groups are given in Table 1.

Table 2 presents the comparisons of the schizophrenia and control groups in terms of the vascular density

**Table 1.** *Demographic characteristics of the patients with schizophrenia and controls participating in the study*

| **Variable** | **Patients with schizophrenia** | **Controls** |
|---|---|---|
| Mean age | 35.91 ± 8.28 | 35.02 ± 10.09 |
| Female/male | 20/12 | 25/15 |
| Mean follow-up time (year) | 8.64 ± 1.83 | - |
| Total number of patients | 48 | 50 |

**Table 2.** *Comparison of the SCP and DCP vascular density values between the groups*

| Variables | **Group** | **Mean** | **SD** | **Min** | **Max** | **P** |
|---|---|---|---|---|---|---|
| **SCP total vascular density (%)** | Patient | 51.15 | 2.23 | 44.30 | 54 | 0.18* |
| | Control | 52.12 | 2.62 | 46.60 | 57.10 | |
| **SCP foveal vascular density (%)** | Patient Control | 23.03<br>19.62 | 4.56<br>2.68 | 16.80<br>5.80 | 33.80<br>31.80 | **0.006**** |
| **SCP parafoveal vascular density (%)** | Patient Control | 53.85<br>54.84 | 3.72<br>2.45 | 38.90<br>48 | 58.30<br>59 | 0.25* |
| **SCP perifoveal vascular density (%)** | Patient Control | 51.75<br>52.50 | 2.20<br>2.85 | 46.30<br>46.70 | 55.70<br>56.70 | 0.19** |
| **DCP total vascular density (%)** | Patient Control | 51.32<br>55.92 | 5.02<br>4.94 | 40<br>39.10 | 58.90<br>62.50 | **<0.0001*** |
| **DCP foveal vascular density (%)** | Patient Control | 38.06<br>38.14 | 5.45<br>6.58 | 28.70<br>26.20 | 48.60<br>51.10 | 0.15** |
| **DCP parafoveal vascular density (%)** | Patient Control | 54.53<br>58.21 | 4.41<br>4.17 | 44.30<br>41 | 60.30<br>62.30 | **<0.0001*** |
| **DCP perifoveal vascular density (%)** | Patient Control | 52.75<br>56.79 | 5.35<br>6.81 | 41.50<br>32.20 | 60.30<br>64.40 | **<0.0001*** |

**Bold values represent statistical significance.** SD: Standard deviation, Min: Minimum, Max: Maximum, SCP: Superficial capillary plexus, DCP: Deep capillary plexus *Mann-Whitney U test; **Student t-test values of the superficial capillary plexus (SCP) and deep capillary plexus (DCP). Accordingly, the mean DCP total, parafoveal, and perifoveal vascular density values were statistically significantly lower, while the SCP FVD value was statistically significantly higher in patients with schizophrenia than in the control group ($p < 0.0001$, $p < 0.0001$, $p < 0.0001$, and $p = 0.006$, respectively).

The comparisons of the FAZ, CCA, SCT, optic disc vascular density, and retinal nerve fiber layer thickness values between the patients with schizophrenia and controls are given in Table 3. The results revealed that the mean SCT and the total and peripapillary vascular density values of the optic disc were statistically significantly lower in patients with schizophrenia than in the control group ($p < 0.0001$, $p = 0.01$, and $p = 0.04$, respectively). However, there were no significant differences between the groups in terms of the mean values of FAZ, CCA, the inside-disc vascular density of the optic disc, or retinal nerve fiber layer thickness.

Table 4 shows the comparisons of retinal thicknesses between the study groups. The mean total retinal parafoveal thickness, total retinal perifoveal thickness, and outer retinal perifoveal thickness values were statistically significantly lower in patients with schizophrenia than in the control group ($p=0.01$, $p=0.03$, and $p=0.04$, respectively).

**Table 3.** *Comparison of the foveal avascular zone, choriocapillaris blood flow, subfoveal choroidal thickness, optic disc vascular density, and retinal nerve fiber layer thickness between the groups*

| Variables | Group | Mean | SD | Min | Max | P |
|---|---|---|---|---|---|---|
| **Foveal avascular zone** | Patient | 0.27 | 0.07 | 0.12 | 0.39 | 0.08* |
| **(mm²)** | Control | 0.28 | 0.09 | 0.12 | 0.49 | |
| **Choriocapillaris blood flow (mm²)** | Patient<br>Control | 2.12<br>2.09 | 0.12<br>0.14 | 1.94<br>1.58 | 2.39<br>2.37 | 0.40* |
| **Subfoveal choroidal thickness** (µm) | Patient<br>Control | 233.63<br>282.16 | 24.45<br>49.73 | 207<br>180 | 299<br>431 | **<0.0001*** |
| **Optic disc total vascular density (%)** | Patient<br>Control | 55.02<br>56.42 | 1.49<br>2.17 | 51.60<br>52.40 | 57.10<br>60.80 | **0.01**** |
| **Optic discinside-disc vascular density (%)** | Patient<br>Control | 59.45<br>60.06 | 3.67<br>2.79 | 52.50<br>51.10 | 65.60<br>65.20 | 0.52* |
| **Peripapillary vascular density (%)** | Patient<br>Control | 57.82<br>58.65 | 2.01<br>2.24 | 54.10<br>54 | 62.40<br>62.60 | **0.04**** |
| **Retinal nerve fiber layer thickness** (µm) | Patient<br>Control | 127.64<br>113.35 | 8.61<br>11.43 | 96<br>95 | 130<br>139 | 0.21** |

**Bold values represent statistical significance.** SD: Standard deviation, Min: Minimum, Max: Maximum *Mann-Whitney U test; **Student t-test

**Table 4.** *Comparison of retinal thicknesses between the groups*

| Variables | Group | Mean | SD | Min | Max | P |
|---|---|---|---|---|---|---|
| **Total retinal foveal thickness (μm)** | Patient<br>Control | 250.36<br>249.38 | 17.26<br>16.27 | 226<br>225 | 313<br>297 | 0.95* |
| **Total retinal parafoveal thickness (μm)** | Patient<br>Control | 310.50<br>316.58 | 10.40<br>11.13 | 292<br>294 | 332<br>340 | **0.01**** |
| **Total retinal perifoveal thickness (μm)** | Patient<br>Control | 284.31<br>289.22 | 11.97<br>8.42 | 262<br>273 | 307<br>309 | **0.03**** |
| **Inner retinal foveal thickness (μm)** | Patient<br>Control | 74.50<br>69.16 | 15.62<br>8.94 | 59<br>56 | 133<br>97 | 0.20* |
| **Inner retinal parafoveal thickness (μm)** | Patient<br>Control | 130.95<br>131.74 | 7.14<br>7.02 | 108<br>117 | 141<br>143 | 0.16* |
| **Inner retinal perifoveal thickness(μm)** | Patient<br>Control | 114.72<br>115.83 | 4.85<br>5.06 | 105<br>105 | 123<br>127 | 0.06** |
| **Outer retinal foveal thickness (μm)** | Patient<br>Control | 248.59<br>249.35 | 9.37<br>9.86 | 161<br>160 | 197<br>199 | 0.19* |
| **Outer retinal parafoveal thickness (μm)** | Patient<br>Control | 179.45<br>184.93 | 8.07<br>8.17 | 166<br>174 | 196<br>203 | 0.08* |
| **Outer retinal perifoveal thickness (μm)** | Patient<br>Control | 169.40<br>173.64 | 8.89<br>6.40 | 155<br>161 | 192<br>189 | **0.04**** |

**Bold values represent statistical significance.** SD: Standard deviation, Min: Minimum, Max: Maximum *Mann-Whitney U test; **Student t-test

## Discussion

Schizophrenia is a serious mental disorder that manifests symptoms across all domains of the mental state. The progression of the disease varies from one individual to another and can cause disability. According to the data from the World Health Organization, the frequency of schizophrenia is 0.85% in Europe and Asia [6]. In Turkey, the frequency of schizophrenia has been reported to be 0.89% [7]. While it is considered that there is no significant difference in the frequency and prevalence of schizophrenia between genders, current reports indicate a higher prevalence among men. Schizophrenia not only affects an individual's mental health but also disrupts the functioning of the nervous, endocrine, cardiovascular, and immune systems. Therefore, it has recently been acknowledged as a systemic disease, which has led some researchers to consider the possibility of discovering additional biomarkers for its diagnosis [8].

Koman-Wierdak et al. compared the OCTA findings of 24 eyes of 24 with schizophrenia and 30 eyes of 30 healthy individuals. They determined the mean DCP TVD value to be 43.66 ± 5.50%in patients with schizophrenia and 50.66 ± 4.26% in the control group, indicating a statistically significantly lower value in the former ($p<0.0001$) [9]. In a study undertaken by Kokacya et al., 47 eyes of 47 patients with schizophrenia and 50 eyes of 50 healthy individuals were compared using OCTA. The mean DCP TVD and PEFVD values were found to be 53.17 ± 6.97% and 54.80%, respectively, in the schizophrenia group and 55.87 ± 6.36% and 57.20%, respectively, in the control group. Accordingly, patients with schizophrenia had statistically significantly lower DCP TVD and PEFVD values compared to the controls ($p=0.04$ for both) [10]. Similarly, Silverstein et al., who evaluated 33 patients with schizophrenia and 38 healthy individuals, reported the mean TVD value to be statistically significantly lower in the schizophrenia group compared to the control group ($p=0.01$) [11]. In another study, Naghib et al. compared the OCTA results of 22 eyes of 22 patients with schizophrenia and 12 eyes of 22 healthy individuals. The authors determined that the mean FVD and PAFVD values were statistically significantly lower in patients with schizophrenia compared to the controls ($p = 0.03$ and $p = 0.01$, respectively) [12]. Consistent with the literature, in the current study, the TVD, PAFVD, and PEFVD values of the DCP were statistically significantly lower in patients with schizophrenia compared to the control group.

Kokacya et al. found that the mean optic disc total vascular density value was 55.80%, and the mean peripapillary vascular density value was 57.60% in patients with schizophrenia, while these values were 56.70% and 58.80%, respectively in the control group. The optic disc total vascular density and peripapillary vascular density values were noted to be statistically significantly lower in the schizophrenia group compared to the control group ($p=0.02$ and $p=0.04$, respectively) [10]. Similarly, in our study, the optic disc total vascular density and peripapillary vascular density values of the patients with schizophrenia were statistically significantly lower than those of the controls.

In the literature, some studies comparing schizophrenia patients and healthy individuals have different results for vascular density values than those mentioned above. Additionally, in different studies examining schizophrenia patients, different vascular density values may be found in schizophrenia patients. So, larger-scale studies are needed in the future.

Although vascular damage is considered to occur in patients with schizophrenia, the exact mechanism behind this phenomenon has not yet been fully clarified. It has been suggested that neurooxidative stress increases in schizophrenia, which is effective in the development of vascular damage. It is thought that the inflammatory process plays a role in schizophrenia, with higher levels of inflammatory cytokines observed in these patients than in healthy individuals. It has also been suggested that there is a neuroischemic vascular process in patients with schizophrenia and that neurodegenerative changes also contribute to this process. This increase in inflammation and neurooxidative stress has been proposed to cause microvascular damage. It has been considered that blood flow to the retinal vessels may decrease due to this microvascular damage [9, 12, 13]. It has also been claimed that the immune system is impaired in patients with schizophrenia, and antiangiogenic mechanisms areinvolved in this impairment. This situation can be inferred to disrupt the microvascular circulation of the retina and cause a decrease in the retinal vascular density value [14].

Asanad et al. found the SCP vascular density values to be higher in patients with schizophrenia compared to the control group [15]. Similarly, in our study, the patients with schizophrenia presented with a statistically significantly higher SCP FVD value than the controls, while the TVD, PAFVD, and PEFVD values of the DCP were found to be lower in the schizophrenia group. These results suggest that schizophrenia affects the deep vascular layer of the retina to a greater extent. One possible explanation for the higher vascular density in the SCP of patients with schizophrenia is the formation of a compensation mechanism against a low level in the DCP.

Koman-Wierdak et al. reported that the mean total retinal foveal thickness was 260.67 ± 24.28 μm in the schizophrenia group and 263.53 ± 15.37 μm in the control group. This parameter was found to have a statistically significantly lower value among the patients with schizophrenia compared to the controls ($p = 0.002$) [9]. In another study, Kokacya et al. determined the total retinal parafoveal and perifoveal thickness values to be 315.26 ± 12.97 μm and 275.57 ± 9.85 μm, respectively, for the patients with schizophrenia and 328.32 ± 12.67 μm and 285.80 ± 12.10 μm, respectively, for the controls, indicating statistically significantly lower values in the schizophrenia group ($p < 0.001$ for both). However, the authors did not find a statistically significant difference between the mean total retinal foveal thickness values of the two groups [10]. Naghib et al. found statistically significantly lower values for the total retinal foveal and parafoveal thicknesses in the schizophrenia group compared to the control group ($p=0.02$ and $p=0.01$, respectively) [12].

In the literature, retinal thickness in patients with schizophrenia has been reported to be significantly lower than in healthy controls [16-18]. Consistently, in our study, the SCT, total retinal parafoveal thickness, total retinal perifoveal thickness, and outer retinal perifoveal thickness values were found to be statistically significantly lower in the schizophrenia group compared to the control group.

The retina and the brain derive from the same neural tissue in embryonic development. These structures have similar types of neurons, glial cells, and receptors. There is also a connection between the retina and the brain in terms of visual function. The optic nerve transmits information from retinal ganglion cells to the lateral geniculate nucleus of the thalamus [19]. During this process, there is a very intense flow of neurotransmitter substances between the brain and the retina [19, 20]. A correlation has been found between the thinning of brain volume and the thinning of retinal layers in some neurodegenerative diseases. Previous research has established a correlation between decreased brain volume and retinal thickness in patients with multiple sclerosis [19]. An association has been shown between tissue loss in gray and white matter in patients with dementia and a decrease in retinal thickness [21]. Another study showed that the parafoveal ganglion cell complex thickness could be used as a primary marker in Parkinson's disease [22]. A different investigation evaluating psychotic patients found a volume decrease in Brodmann areas 17 and 18, which are the primary and secondary visual areas [23]. The decrease in retinal thickness in schizophrenia can be attributed to the neuroinflammation process. Furthermore, it can be suggested that fluid-electrolyte balance is disrupted due to decreased retinal blood flow, and atrophy and apoptosis may occur in photoreceptor cells [14, 18].

Concerning the limitations of the study, the number of patients was small. In addition, given the many variables of OCTA, the results may be purely coincidental. The medications used by the patient may also affect the OKTA results. However, this work has the potential to pave the way for future multicenter studies to elucidate the vascular pathogenesis of schizophrenia.

## Conclusion

This study is the first study to find statistically significant differences between schizophrenia patients and the healthy controls in 5 different areas such as SCP vascular density, DCP vascular density, optic disc vascular density, retinal thickness and subfoveal choroidal thickness. It is considered that the lower retinal and optic disc vascular density, retinal thickness and subfoveal choroidal thickness values of the patients with schizophrenia might be due to the development of vascular damage, in which inflammation, neurooxidative stress, and neurodegenerative changes play a role. This study has the potential to serve as a guide for future research on the vascular pathogenesis of schizophrenia.

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