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Optical Coherence Tomography Angiography in Schizophrenia

ABSTRACT

Objective: The aim of this study is to investigate the retinovascular structure of schizophrenia patients using optical coherence tomography angiography (OCTA).

Methods: 47 eyes of schizophrenia patients were compared with 50 eyes of demographically matched healthy controls in terms of OCTA measurements. Schizophrenia patients were evaluated in two groups as short-term (≤ 5years) and long-term (> 5years) according to the time elapsed after the diagnosis of schizophrenia.

Results: Schizophrenia patients showed overall thinning of retinal nerve fiber layer and macula, and lower vessel density (VD) compared to controls. The results were significant for thickness measurements of general macula and for VD in specific areas ($P < 0.05$); however, they were not significant for the RNFL measurements except the mean circumpapillary RNFL, which was noted to approach significance ($P = 0.055$). Long-term patients showed significantly lower VD in the whole and perifoveal region of superficial capillary plexus, the whole, perifoveal and foveal region of deep capillary plexus, and the whole area and the disc of radial peripapillary capillaries compared to short-term patients ($P = 0.014$, $P = 0.009$, $P = 0.011$, $P = 0.010$, $P = 0.011$, $P = 0.035$, $P = 0.030$).

Conclusions: These findings suggest that schizophrenia may be a neurodegenerative disease with progressive microvascular involvement over the years, and that OCTA has the potential to be a useful tool in detecting retinovascular changes in patients with schizophrenia.

Keywords: Schizophrenia, neuropathology, retinal-imaging, retinovascular

Introduction

Schizophrenia is a lifelong debilitating disorder affecting almost 1% of people in the world.[1] The diagnosis is made primarily based on the clinical judgment of psychiatrists considering the symptoms of the patients.[1] These symptoms are usually an admixture of mood, positive, negative, and cognitive signs, such as disorganized speech, delusions, and hallucinations that may mimic other neurological and metabolic or infectious disorders causing the diagnosis difficult to make.[2]

It is thought to be a multifactorial neurodegenerative disorder in which both genetic and environmental factors play a role.[1] However, because of difficulty in evaluating its pathogenesis at neurobiological level, the underlying mechanisms of this disorder still remain unclear.[3] The retina is considered as a window to the brain since both arise from the same embryological origin, the neuroectoderm.[4] It is a part of the central nervous system that derives from the same tissue as the brain in early development. It is an anatomical extension of the brain, and retinal changes may occur in parallel with inflammation and central nervous system degeneration.[5] Based on this fact, recently, investigations have been focused on retinal imaging studies that seek for potential signs of pathophysiology of schizophrenia.[6]

Optical coherence tomography (OCT) is an imaging technique that uses high-resolution slices to capture biological tissue layers. The delay time and intensity of infrared light that

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is transmitted to and reflected from different tissue layers are measured using this technique. It produces cross-sectional pictures of tissues similar to ultrasonography but with significantly better resolution. Its popularity grew quickly due to the fact that it is a noninvasive and quick way to assess the macular thickness (MT), macular volume (MV), foveal thickness, and retinal nerve fiber layer (RNFL). Several studies have reported quantitative measurements of the retina, allowing to evaluate possible changes in the cerebrovascular architecture of various neurodegenerative diseases, previously.[3] Recently, several studies with OCT, that identifies markers of brain pathology, have been performed to show retinal cytoarchitectural abnormalities in schizophrenia.[7] Other evidence for a vascular component involved in schizophrenia includes reduced cerebral blood flow, psychotic features in infections vascular disease (e.g., syphilis), and nail fold capillary bed abnormalities in patients with schizophrenia.[8]

Ascaso et al[9] showed a reduction in overall peripapillary RNFL thickness in 10 schizophrenia patients. In a subsequent study, Chu et al[10] did not replicate these findings but did detect a link between lower MV and increased severity of positive symptoms.[10]

In a study that focused on the link between the RNFL and the severity of the disease, the schizophrenia group was further separated into 3 categories: acute (<2 years of illness), chronic (2-10 years), and long-term chronic (more than 10 years of illness) (>10 years). The overall RNFL thickness was shown to be considerably lower in the chronic and long-term chronic schizophrenia group compared to controls and acute schizophrenia group.[11]

Since 2006, a new software called OCT angiography (OCTA) has been added to OCT devices to enable noninvasive visualization and measurement of both the neural and vascular structure of the retina at a microscopic level.[12]

Previous studies of the retinal microvasculature in schizophrenia using conventional fundus photography found wider venules and abnormal venule and arteriole trajectories.[13,14] Optical coherence tomography angiography gives estimates of the total area containing blood vessels and the total length of blood vessels within prescribed regions of the retina, which are indicators that have not previously been reported in published studies on schizophrenia. However, apart from preliminary studies, a few OCTA studies on schizophrenia have been conducted before. Wierdak et al compared 24 patients with schizophrenia and healthy group using OCTA. They showed that the retinal microvascular dysfunction occurred in the macula in schizophrenia patients. The macular thickness in the whole vascular complex and in the fovea was significantly lower in schizophrenia patients.[15]

Patients with schizophrenia may have retinal vascular changes accompanying abnormalities in the neural retina. It is hypothesized that retinal microvascular density would be thinner in schizophrenia patients compared to healthy controls. In another study using OCTA and OCT, Silverstein et al showed retinal microvasculature density reductions and enlarged foveal avascular zones (FAZs), in both eyes in 28 schizophrenia or schizoaffective disorder patients. They concluded that these microvascular abnormalities were generally associated with thinning of retinal neural (macular and peripapillary nerve fiber layer) tissue.[16]

In the light of these studies, the aim of this study was to investigate the retinovascular structure of patients with schizophrenia using OCTA.

MAIN POINTS

- *Schizophrenia patients showed overall thinning of retinal nerve fiber layer, macula and lower vessel density (VD) compared to controls.*
- *The VD values ofretinal capillary plexuses (RCP) and superior capillary plexus (SCP) were measured smaller in long-term patients compared to short term schizophrenia patients.*
- *OCTA may be used for the development of biomarkers to monitor the disease progression in schizophrenia.*
- *Our findings support the theory that schizophrenia is a neurodegenerative disease with microvascular involvement that progresses over the years.*

Methods

This study was conducted in accordance with the Declaration of Helsinki, and approval was obtained from the Hatay Mustafa Kemal University Medical School Institutional Ethics Committee (April 11, 2019/24). Informed written consent was gathered from all subjects who participated in the study.

Patients with schizophrenia from psychiatry clinic between April 2019 and December 2020 were enrolled in the ophthalmology clinic. The schizophrenia patients were diagnosed based on the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders-fifth edition* by a psychiatrist.[17] The severity of schizophrenia was assessed with the Positive and Negative Syndrome Scale (PANSS). The items of the PANSS were rated on a 7-point scale (1 = absent, 2 = minimal, 3 = mild, 4 = moderate, 5 = moderate-severe, 6 = severe, and 7 = extreme). Thus, the range of possible PANSS total scores is from 30 to 210. The Cronbach's alpha was calculated as 0.95. This coefficient supports the internal consistency of the scale. This relatively high alpha coefficients were consistent with findings from other studies (0.70-0.89).[18,19] Also, the Clinical Global Impression-Severity Scale (CGI-S) was used for assessing global illness severity in the patient group.[20] The CGI-S rates the severity of the patient's illness on a 7-point scale ranging from "normal" 1 to "extremely ill" 7, according to the clinician's experience of patients suffering from the same. The CGI-S assesses the clinician's impression of the patient's current illness state.

Age- and sex-matched controls were selected from those who did not have any systemic or ocular disease. All subjects aged ≥18 were included in the study if they had visual acuity ≥20/25 and ocular refraction <2 diopters. Subjects with a history of pregnancy, substance use, systemic disease, ocular disease, and previous ocular trauma and intraocular surgery were excluded from the study.

All subjects underwent an ocular examination that consisted of intraocular pressure measurement by tonometry, best-corrected visual acuity testing with a Snellen chart, biomicroscopy of the anterior segment, funduscopy, and OCTA scanning performed after dilatation of pupils by the tropicamide 0.5% eye drop. Only right eyes were

scanned. All OCTA scans were taken by the same technician (E.K.) at the same interval of the day (10:00-12:30 AM). For each subject, 3 scans were performed from which the one with the highest quality was chosen to analyze.

The OCTA device has the AngioVue system with 2018.0.0.18 version (RTVue XR Avanti, Opto-Vue, Inc, Fremont, Calif, USA) that is equipped with the DualTrac™ Motion Correction technology.[21] It runs volumetric scans of 304 × 304 A-scans captured at each fixed position at 70000 A-scans per second using a light source at 840 nm wavelength and a bandwidth of 45 nm. Scans with a low-quality index (<8) or low signal strength index (<60), segmentation errors, and artifacts or opacities due to blinking or motion that lead to disruption in the view of retinal images are disqualified by the ophthalmologist.

The vessel density (VD) of retinal capillary plexuses (RCP) [both superior capillary plexus (SCP) and deep capillary plexuses (DCP)] was measured by using the assessment tool of VD. The AngioVue system analyzed the images of both b-scan and en-face scans. It automatically measured VD of the foveal, parafoveal, and perifoveal zones and the retinal thickness of macular sectors, which are calculated according to the ETDRS grid classification of diabetic retinopathy. Both macula and peripapillary thickness were measured. The device also measured the FAZ area.

The Angio DiscVue mode of the device also scanned the optic disc (4.5 × 4.5 mm) that allowed to calculate the mean peripapillary RNFL thickness (superior, temporal, inferior, nasal) and the VD of radial peripapillary capillaries (RPC) of the whole disc, inside the disc, and superior and inferior hemispheres of the peripapillary region.[22]

Statistical Analysis

Categorical variables were analyzed by Pearson's chi-square test. Normality of numeric variables was tested with the Shapiro–Wilk test. Mean differences between 2 groups with normally distributed were compared by Student's *t* test, whereas the Mann–Whitney *U* test was applied for comparisons of the non-normally distributed data. The relationship between 2 quantitative variables was analyzed by Pearson's correlation coefficient. Descriptive statistics were expressed as frequencies with percentages and mean (SD = Standard Deviation) for normal distributed variables and median (min-max) for non-normal distributed variables. All statistical analyses were performed by using Statistical Package for the Social Sciences (SPSS) version 21.0 (IBM SPSS Corp.; Armonk, NY, USA). $P < .05$ was considered as statistically significant. The effect size was calculated with Cohen's *d* method with G*Power® (Institute for Experimental Psychology in Dusseldorf, Germany) 3.1.9.2 program.

Results

Of the total 170 subjects enrolled, 22 were excluded because of having at least one of the exclusion criteria, 7 were excluded because of lack of cooperation while scanning of OCTA, 4 were excluded because of disqualification of OCTA scans that had low quality, low signal strength, artifacts, or opacities in the media due to mostly incompliance to the device while measuring. The final analysis included 97 eyes of 47 patients, 36 males (76.6%), 11 females (23.4%), and 50 age- and gender-matched healthy individuals, 35 males (70%), 15 females (30%). The mean age (±SD) of the patients and the controls were 34.74 (10.68) and 34.02 (10.30) years, respectively. No significant difference was found between groups in terms of age and gender ($P = .615$ and $P = .734$, respectively)

Patients with schizophrenia were further divided into 2 groups as short-term patients (≤5 years) and long-term (>5 years) patients according to the time elapsed after the diagnosis of schizophrenia. A total of 23 short-term patients, 14 males (60.9%) and 9 females (39.1%), and 24 long-term patients, 22 males and 2 females were included in this study. The mean age (± SD) of the short-term patients was found significantly smaller than that of the long-term patients (30.3 (8.98) years vs. 39 (10.60) years) ($d = 0.02$, $P = .004$)

The mean values of PANSS and CGI-S scoring in patients with schizophrenia were 94.02 (19.51) and 5.78 (0.83), respectively. The difference between short-term and long-term patients in terms of PANSS and CGI-S scoring was statistically found significant (101.17 (16.27) vs. 87.16 (20.20), $d = 0.76$, $P = .012$) (6.17 (0.71) vs. 5.41 (0.77), $d = 1.03$, $P = .002$).

The statistical comparisons of the mean values of the OCTA measurements of the schizophrenia patients and healthy controls are given in Tables 1 and 2. Compared to controls, all sectors of the patients' macula were found to be significantly thinner, but this difference was insignificant for the fovea which was also found thinner in the patients ($P < .05$ for all

and $P = .061$, respectively). Overall, RNFL measurements of all quadrants in patients were found to be smaller than controls, but this difference was shown to be statistically insignificant ($P > .05$ for all). On the other hand, *P* value was measured close to the significance only for the mean peripapillary retinal nerve fiber layer thickness ($P = .055$).

In general, VD values of both RCP and RPC measured were smaller in schizophrenia patients compared to the healthy controls. These differences reached to a statistically significant level at certain areas: SCP measurements at the whole area and perifoveal area were $d = 0.18$, $P = .015$ and $d = 0.76$, $P = .016$, respectively; DCP measurements at the whole area and the perifoveal area were $d = 0.40$, $P = .049$ and $d = 0.43$, $P = .041$, respectively; RPC measurements at the whole area, peripapillary disc, and the superior hemisphere of the peripapillary disc were $d = 0.50$, $P = .028$; $d = 0.42$, $P = .046$; and $d = 0.36$, $P = .015$, respectively; RPC measurements involving small vessels at the whole area and the superior hemisphere of the peripapillary disc were $d = 0.44$, $P = .034$ and $d = 0.45$, $P = .03$, respectively. There was no statistical significance in terms of FAZ area between groups ($P = .855$).

The statistical comparisons of the mean values of the OCTA measurements of short-term and long-term schizophrenia patients are given in Tables 3 and 4. No statistically significant difference was determined between groups of schizophrenia patients in terms of RNFL and macular thickness measurements although these parameters were found generally reduced in long-term patients (*P* values > .05 for all).

In general, the VD values of RCP and RPC measured were also smaller in long-term patients compared to short-term patients. These measurements were found significant for the SCP in the whole area and the perifoveal area ($d = 0.75$, $P = .014$ and $d = 0.80$, $P = .009$, respectively); for DCP in the whole area, foveal, and perifoveal areas, $d = 0.69$, $P = .011$; $d = 0.78$, $P = .010$; $d = 0.64$, $P = .011$, respectively; and

for the small vessels of RPC at the whole area and inside disc, $d = 0.64$, $P = .035$ and $d = 0.65$, $P = .030$, respectively. There was no statistical significance in terms of FAZ area between groups ($P = .222$).

Pearson correlation coefficients were calculated to determine the association between PANSS, CGI-S, duration of illness, macular and RNFL thickness measurements, VD and FAZ area measurements. Higher CGI-S scores result in higher perifoveal macular thickness in the superior and inferior hemispheres and high VD of all vessels inside disc (respectively, $r = 0.289$, $r = 0.306$, $r = 0.326$; $P < .05$) (Tables 5 and 6).

Higher duration of illness appears to be associated with a lower VD of SCP in the whole image and perifovea, lower DCP in the whole image and perifovea, and lower thickness of nasal perifovea (respectively, $r = -0.372$, $r = -0.384$, $r = -0.326$, $r = -0.311$, $r = -0.315$; $P < .05$).

There was a moderately negative correlation between disease duration and the VD of all vessels of the whole disc and the VD of the small vessels inside disc (respectively, $r = -0.401$, $r = -0.490$; $P < .05$) (Table 6).

Discussion

The retina is suggested as an early precursor of microangiopathies where neurodegeneration and neuroinflammation can be observed noninvasively in both brain and systemic diseases.[12] Additionally, because it has the same embryonic origin as the brain, the retina is considered as a mirror that reflects cerebral changes.[3,4] Based on these facts, using OCTA, this study aimed to investigate the retinovascular structure of patients with schizophrenia. The macula and RNFL thickness of schizophrenia patients were found to be thinner in all sectors compared to healthy controls, and these were found statistically significant for macular thickness and very close to significance for the mean peripapillary RNFL. Furthermore, schizophrenia patients generally showed lower VD of RPC and RCP than healthy controls, which were found statistically significant in certain areas. Finally, although there was no significant difference in macular and RNFL thickness between short-term and long-term schizophrenia patients, long-term patients generally showed lower VD of RPC and RCP than short-term patients for whom these measurements were statistically significant in certain areas.

Optical coherence tomography angiography has been used in investigations to quantify the potential retinal biomarkers of neurovascular changes and progression signs of various neurodegenerative disorders such as Alzheimer's disease.[3] However, in the literature, there are only preliminary pilot studies with smaller sample sizes and different measurement parameters that used OCTA in schizophrenia patients. Asanad et al[23] not only reported a significant increase in VD of SVP in the central macula but also reported a significant reduction in SVP perfusion density in the temporal peripapillary area in the schizophrenia patients compared to controls.[23]

There are various studies showing abnormal findings in vasculature of schizophrenia patients implicating that microvascular dysfunction may have a role in the etiology of schizophrenia.[8] Bannai et al[24] published a study that showed the swept-source OCTA analysis results of VD, diameter, length, and tortuosity of retinal superficial vascular

Table 1. Comparisons Between Patients and Controls in Terms of Macular and RNFL Thickness Measurements

Macular Thickness (μm)	Patients (n = 47)	Controls (n = 50)	*P*
Whole image	276.77 (9.45)	288.06 (11.13)	<.001*
Superior hemisphere	278.00 (9.62)	289.08 (10.97)	<.001*
Inferior hemisphere	275.45 (9.52)	286.96 (11.62)	<.001*
Fovea	243.94 (18.22)	251.12 (18.98)	.061*
ParaFovea	315.26 (12.97)	328.32 (12.67)	<.001*
-Superior hemisphere	316.21 (12.90)	328.96 (12.70)	<.001*
-Inferior hemisphere	314.21 (13.42)	327.72 (13.06)	<.001*
-Temporal	306.47 (12.38)	318.6 (12.76)	<.001*
-Superior	320.11 (13.34)	333.52 (13.30)	<.001*
-Nasal	318.19 (13.86)	331.14 (12.86)	<.001*
-Inferior	316.53 (14.14)	330.14 (13.48)	<.001*
Perifovea	275.57 (9.85)	285.8 (12.10)	<.001*
-Superior hemisphere	277.68 (9.57)	287.58 (11.87)	<.001*
-Inferior hemisphere	272.47 (9.87)	284.1 (12.63)	<.001*
-Temporal	261 (24-283)	273.5 (28-298)	<.001**
-Superior	276.11 (9.94)	286.82 (11.77)	<.001*
-Nasal	293.00 (14.00)	304.32 (14.27)	<.001*
-Inferior	267.64 (9.68)	279.38 (13.01)	<.001*
Peripapillary RNFL thickness (μm)			
Mean	107.89 (13.31)	112.46 (9.61)	.055*
Superior	130 (54-169)	135.5 (108-17)	.257**
Nasal	97.79 (16.91)	101.54 (12.80	.219*
Inferior	138 (69-177)	146 (15-188)	.182**
Temporal	71 (40-89)	74 (54-87)	.166*

RNFL, retinal nerve fiber layer. Normal distributed variable was given as mean (standard deviation), non-normal distributed variable was given as median (min-max).

Table 2. Comparisons Between Patients and Controls in Terms of Vessel Density and Foveal Avascular Zone Area Measurements

Vessel Density of Retinal Capillary Plexuses (%)		Patients (n = 47)	Controls (n = 50)	*P*
Superficial	Whole image	50.55 (2.69)	51.88 (2.58)	.015*
	Fovea	22.00 (5.58)	22.29 (7.02)	.825*
	Parafovea	54.3 (39-59.3)	55.1 (49.1-60.3)	.053**
	Perifovea	51.15 (2.69)	52.50 (2.72)	.016*
Deep	Whole image	53.17 (6.97)	55.87(6.36)	.049*
	Fovea	38.35 (6.34)	39.78(6.61)	.281*
	Parafovea	56.65 (5.41)	58.15(4.79)	.150*
	Perifovea	54.8 (37.9-63.2)	57.2 (35.3-65.2)	.041**
Vessel density of RPC (%)				
All vessels	Whole disc	55.8 (43.8-59.9)	56.7 (50.3-60.6)	.028**
	Inside disk	60.24 (4.30)	61.08 (3.57)	.296*
	Peripapillary	57.6 (44.4-63.4)	58.8 (51.7-63.6)	.046**
	-Superior hemisphere	57.2 (42.6-63.7)	59.2 (49.7-64.1)	.015**
	-Inferior hemisphere	57.26 (3.25)	58.28 (2.96)	.111*
Small vessels	Whole disc	48.44 (2.79)	49.55 (2.27)	.034*
	Inside disk	50.54 (4.69)	51.09 (3.64)	.521*
	Peripapillary	50.24 (3.33)	51.37 (2.99)	.082*
	-Superior hemisphere	49.81 (3.64)	51.34 (3.18)	.030*
	-Inferior hemisphere	50.7 (3.46)	51.36 (3.14)	.332*
	Foveal avascular zone (mm^2)	0.26 (0.08)	0.26 (0.09)	.085

Test RPC, radial peripapillary capillaries.
Normal distributed variable was given as mean (standard deviation), non-normal distributed variable was given as median(min-max).

Table 3. Comparisons Between Short-Term and Long-Term Patients in Terms of Macular and RNFL Thickness Measurements

Macular Thickness (µm)	Short-term (n = 23)	Long-term (n = 24)	*P*
Whole image	278.39 (8.01)	275.21 (10.58)	.253*
Superior hemisphere	279.74 (8.36)	276.33 (10.6)	.229*
Inferior hemisphere	276.74 (7.92)	274.21 (10.86)	.368*
Fovea	244 (209-271)	241 (21- 308)	.766**
ParaFovea	316.83 (11.96)	313.75 (13.94)	.422*
-Superior hemisphere	318.04 (11.66)	314.46 (14.00)	.346*
-Inferior hemisphere	314 (291-337)	311.5 (294-350)	.233**
-Temporal	307.22 (11.04)	305.75 (13.75)	.689*
-Superior	322.3 (12.14)	318 (14.33)	.273*
-Nasal	319.91 (12.76)	316.54 (14.92)	.410*
-Inferior	317 (293-345)	312.5 (29- 354)	.229**
Perifovea	276.17 (7.49)	275 (11.82)	.688*
-Superior hemisphere	278.48 (7.36)	276.92 (11.41)	.582*
-Inferior hemisphere	273.87 (8.14)	271.13 (11.30)	.346*
-Temporal	260.7 (8.01)	261.92 (10.10)	.649*
-Superior	278.48 (8.03)	273.83 (11.17)	.110*
-Nasal	296.83 (10.07)	289.33 (16.32)	.066*
-Inferior	268.91 (8.40)	266.42 (10.79)	.382*
Peripapillary RNFL thickness (µm)			
Mean	111 (89-128)	105.5 (54-131)	.516**
Superior	132 (54-157)	127.5 (59-169)	.757**
Nasal	96 (79-128)	96 (5-133)	.283*
Inferior	140.52 (18.15)	137.5 (22.59)	.617*
Temporal	72.52 (7.76)	68.54 (11.76)	.180*

Test RNFL, retinal nerve fiber layer.
Normal distributed variable was given as mean (standard deviation), non-normal distributed variable was given as median (min-max).

Table 4. Comparisons Between Short-Term and Long-Term Patients with Respect to Vessel Density and Foveal Avascular Zone Area Measurements

Vessel Density of Retinal Capillary Plexuses (%)		Short-Term (n = 23)	Long-Term (n = 24)	*P*
Superficial	Whole image	51.52 (2.56)	49.62 (2.51)	.014*
	Fovea	23.41 (5.49)	20.65 (5.45)	.091*
	Parafovea	54.6 (44.8-59.3)	53.4 (39-57.8)	.885**
	Perifovea	52.18 (2.41)	50.17 (2.63)	.009*
Deep	Whole image	57 (40.2-63.2)	53 (37.9-63)	.011**
	Fovea	40.73 (6.05)	36.08 (5.86)	.010*
	Parafovea	57.97 (5.49)	55.38 (5.13)	.101*
	Perifovea	58.7 (45.1-65.9)	57.6 (45.8-63.8)	.011**
Vessel density of RPC (%)				
All vessels	Whole disc	56.7 (51.7-59.9)	55.3 (43.8-59.8)	.148**
	Inside disk	61.27 (4.27)	59.26 (4.17)	.111*
	Peripapillary	57.9 (52.-61.4)	56.7 (44.4-63.4)	.366*
	-Superior hemisphere	57.4 (53.8-60.8)	56.6 (42.6-63.7)	.430*
	-Inferior hemisphere	57.73 (2.44)	56.81 (3.88)	.335*
Small vessels	Whole disc	49.31 (1.70)	47.61 (3.37)	.035*
	Inside disk	52.05 (4.72)	49.10 (4.28)	.030*
	Peripapillary	50.84 (2.03)	49.65 (4.19)	.225*
	-Superior hemisphere	50.61 (2.18)	49.05 (4.55)	.145*
	-Inferior hemisphere	51.17 (2.66)	50.26 (4.10)	.377*
Foveal avascular zone (mm^2)		0.25 (0.08)	0.28 (0.08)	.331*

RPC, radial peripapillary capillaries.
Normal distributed variable was given as mean (standard deviation), non-normal distributed variable was given as median (min-max).

plexus in schizophrenia patients. In contrast to Asanad et al. the authors only showed a significant increase in the superficial vessel diameter index. In total, 26 patients with schizophrenia and 21 controls were compared using swept-source OCTA. They found that schizophrenia patients demonstrated higher overall oculus dextrus (OD) superficial skeletonized vessel density (SVD), OD choriocapillaris VD compared to healthy controls. They also established correlations between symptoms and OCTA findings of patients, indicating that an increase in the superficial VD index was associated with worse negative symptoms, and a decreased vascular tortuosity was associated with poorer cognition. Early-course schizophrenia patients had significantly higher OD superficial VD and OD choriocapillaris SVD compared to matched healthy controls. They showed that higher bilateral superficial VD correlated with lower PANSS positive scores. These findings point to the occurrence of microvascular dysfunction in schizophrenia in its early stages. Higher measures were associated with worse symptom severity and functioning in early stages, and lower measures were associated with lower symptom severity and better functioning in later stages, supporting this hypothesis. However, despite all the differences, all OCTA studies with schizophrenia patients, including the current study, presented vascular changes in the retina, suggesting vascular involvement in the schizophrenia disease.

Increased visibility of small venule plexuses in the nail beds has been documented.[25] Using morphometric analysis and electron microscopy, Uranova et al[26] showed various abnormalities in the structure of capillaries along with microglia activation in the visual and prefontal cortex of schizophrenia patients. Furthermore, retinal microvascular abnormalities including narrower arterioles and wider venules were observed in schizophrenia patients by Appaji et al.[13] who used retinal images acquired by a non-mydriatic fundus camera. Additionally, wider retinal venules were shown in siblings of schizophrenia parents, which was suggested as a proxy marker for an increased risk for schizophrenia development.[27] In a longitudinal study, Meier et al[28] also demonstrated wider retinal venules in patients with schizophrenia compared to those in normal individuals. Besides, it was shown that the retinal venule widening was positively correlated with the extent of the psychotic symptoms both in childhood and adulthood, proposing that these findings could be associated with a chronic inadequate oxygen supply to the brain in schizophrenia patients. This proposal has been supported by some other neuroimaging studies that showed circulatory impairment.[29,30] For instance, Andreasen et al[29] used positron emission tomography (PET) to demonstrate a lower cerebral blood flow in multiple regions of the brain of unmedicated patients suffering from schizophrenia compared to healthy controls.[29] Using PET, Schultz et al[30] also demonstrated significantly decreased blood flow with increasing age in the bilateral parietal and frontal regions of schizophrenia patients.

These findings supported the neuroimaging studies that showed reduced brain volume in patients with schizophrenia over years.[31] In connection with these results, several studies have reported thinning of both the macula and RNFL in patients with schizophrenia.[32,33] Among them, there were also some studies that established a negative relationship between retinal thickness and the chronicity or symptoms of the disease.[34] In parallel with these studies, the present study similarly showed general thinning of the retina in schizophrenia patients compared to healthy controls, but it did not show a significant relationship between the chronicity of the disease and the OCTA measurements. Nevertheless, different results in the literature can be attributed to differences in sample sizes, antipsychotic or

Table 5. Correlation analysis of PANSS, CGI-S, Duration of Illness, Macular and RNFL Thickness Measurements

Macular Thickness (μm)	PANSS	CGI	Duration
Whole image	0.164	0.204	−0.198
Superior hemisphere	0.129	0.160	−0.206
Inferior hemisphere	0.187	0.229	−0.165
Fovea	−0.257	−0.203	−0.007
ParaFovea	0.041	0.029	−0.170
-Superior hemisphere	0.091	0.081	−0.199
-Inferior hemisphere	0.030	−0.008	−0.138
-Temporal	−0.017	0.006	−0.134
-Superior	0.096	0.096	−0.223
-Nasal	0.084	0.051	−0.180
-Inferior	0.016	−0.007	−0.150
Perifovea	0.124	0.134	−0.012
-Superior hemisphere	0.122	0.136	−0.037
-Inferior hemisphere	0.194	0.237	−0.157
-Temporal	0.005	0.044	0.045
-Superior	0.257	0.289*	−0.216
-Nasal	0.171	0.243	−0.315*
-Inferior	0.281	0.306*	−0.147
Peripapillary RNFL thickness (μm)			
Mean	0.120	0.243	−0.269
Superior	−0.020	0.030	−0.113
Nasal	0.113	0.270	−0.266
Inferior	0.157	0.239	−0.228
Temporal	0.168	0.232	−0.234

*$P < .05$ (n = 47). *r* was obtained from Pearson's correlation coefficient.
RNFL, retinal nerve fiber layer; PANSS, Positive and Negative Syndrome Scale; CGI-S, Clinical Global Impression-Severity Scale.

Table 6. Correlation Analysis of PANSS, CGI-S, Duration of Illness, Vessel Density, and Foveal Avascular Zone Area Measurements

Vessel density of retinal capillary plexuses (%)		PANSS	CGI-S	Duration
Superficial	Whole image	0.188	0.220	−0.372*
	Fovea	−0.110	−0.084	−0.172
	Parafovea	0.230	0.198	−0.231
	Perifovea	0.178	0.220	−0.384**
Deep	Whole image	0.271	0.271	−0.326*
	Fovea	0.103	0.080	−0.383**
	Parafovea	0.194	0.202	−0.217
	Perifovea	0.251	0.265	−0.311*
Vessel density of RPC (%)				
All vessels	Whole disc	0.012	0.228	−0.401**
	Inside disk	0.145	0.326*	−0.411**
	Peripapillary	−0.155	0.037	−0.232
	-Superior hemisphere	−0.144	0.036	−0.270
	-Inferior hemisphere	−0.161	0.032	−0.174
Small vessels	Whole disc	0.014	0.208	−0.414**
	Inside disk	0.237	0.350*	−0.490**
	Peripapillary	−0.166	0.006	−0.229
	-Superior hemisphere	−0.104	0.048	−0.324*
	-Inferior hemisphere	−0.234	−0.055	−0.102
Foveal avascular zone (mm^2)		0.070	0.119	0.085

**Correlation is significant at 0.001; *Correlation is significant at 0.05.
RPC, radial peripapillary capillaries; PANSS, Positive and Negative Syndrome Scale; CGI-S, Clinical Global Impression-Severity Scale.

antidepressant use doses, and the use of retinal imaging techniques with varying resolution and scan thickness.[6]

The present study also showed more VD in patients with short-term schizophrenia compared to patients with long-term schizophrenia. This result can be explained by the inflammatory hypothesis on the pathophysiology of schizophrenia. Lizano et al[35] reported an immunological and angiogenesis dysfunction in the early stages of schizophrenia, shifting the balance toward inflammation and anti-angiogenesis. Increased inflammatory agents were blamed for damaging microvascular structures leading to a reduction in cerebral blood flow that causes a failure in delivering sufficient energy and oxygen, which end up with an increased oxidative stress on neural tissues.[8] It has been suggested that oxidative stress along with immune system abnormalities play an important role in the etiology of psychiatric disorders including schizophrenia.[36]

In our study, only right eyes were scanned and assessed. This is the main limitation of the study. Compared to OCT scans, OCTA scans take longer time as more parameters are measured. This situation can make it difficult for schizophrenic patients to cooperate during OCTA scanning. The present study chose to use only the results of right eye for further analysis to decrease the complexity of the tables. Although there are some studies in which only one eye was selected[22,37] both eyes should be scanned, especially in the context of the brain asymmetry hypothesis in psychotic disorders. Besides, there can be differences between left and right eyes as it relates to retinal vasculature.[24] Also, the intra-scanner reliability between eyes is not exactly great for the RNFL.[38]

Another limitation of this study was the smaller-than-expected sample size due to disqualification of OCTA measurements, especially due to patients' non-compliance. Since the symptoms of schizophrenia may have appeared long before the patients were first examined, it could have been inaccurate to group patients according to the duration of the disease calculated from the date of diagnosis. Thirdly, chlorpromazine equivalent dose, as a measure of total amount of antipsychotic medication currently taken daily, was not included in the study. Besides, the evaluation of the retina without other supporting tools, including neuroimaging, pathology laboratory study, or electrophysiology, may have limited the study due to involvement of only a small part of the central nervous system, but not itself. Further, the OCTA studies in the literature with preliminary design and smaller sample sizes may have prevented appropriate comparisons.

Using OCTA, the present study investigated the retinovascular structure of schizophrenic patients that revealed OCTA findings that support the theory that schizophrenia is a neurodegenerative disease with microvascular involvement that progresses over the years. These results suggest that investigating the retinovascular structure of patients with schizophrenia using OCTA would be a helpful tool in the future for determining possible biomarkers of the pathogenesis and progression of the disease. Nevertheless, longitudinal studies with larger sample sizes with 2 eyes scanned are still needed to better understand the relationship between schizophrenia and the OCTA measurements.

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