# ŞİZOFRENİ HASTALARINDA GÖZÜN ARKA SEGMENT YAPILARININ DEĞERLENDİRİLMESİ

# Evaluation of Posterior Ocular Structures in Patients with Schizophrenia

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Geliş tarihi/Received: 17.05.2019
Kabul tarihi/Accepted: 04.07.2019
**DOI:** 10.16919/bozoktip.566862

Bozok Tıp Derg 2019;9(3):108-114
Bozok Med J 2019;9(3):108-114

## ÖZET

**Amaç:** Bu çalışmada, şizofreni hastalığının gözün arka segment yapılarından retina sinir lifi tabakası (RSLT), santral makülar kalınlık (SMK), koroidal kalınlık (KK) ve lamina kribroza (LK) ölçümleri üzerine etkisinin değerlendirilmesi amaçlanmıştır.

**Gereç ve Yöntemler:** Çalışmaya şizofrenisi bulunan 35 hasta ve 35 sağlıklı katılımcı dahil edilmiştir. Her hastanın yalnızca sağ gözü çalışılmıştır. Fourier domain optik koherens tomografi (OKT) ile her kadrandan RSLT kalınlığı, KK, SMK, LK kalınlığı ve LK derinliği (LKD) ölçümleri yapılmıştır ve her değer gruplar arasında karşılaştırılmıştır.

**Bulgular:** Gruplar arasında ortalama yaş ve cinsiyet dağılımları benzerdi (p=0.528 ve p=0.299). Ortalama, superior, inferior, nazal ve temporal RSLT kalınlıkları şizofrenisi bulunan hastalarda, kontrollere göre anlamlı olarak düşüktü (sırasıyla; p<0.001, p<0.001, p=0.001, p=0.002 ve p<0.001). Fovea altı ve çevresindeki ortalama KK ölçümleri gruplar arasında anlamlı farklılık göstermiyordu (fovea altı; p=0.676, 1.5 mm nazal; p=0.632, 3 mm nazal; p=1.000, 1.5 mm temporal; p=0.811, 3 mm temporal; p=0.145). Ortalama SMK gruplar arasında benzerdi (p=0.678). LK kalınlığı ve LKD, gruplar arasında istatistiksel açıdan anlamlı farklılık göstermiyordu (p=0.816 ve p=0.161).

**Sonuçlar:** Tüm kadranlardaki RSLT kalınlıkları şizofreni hastalarında kontrol grubuna göre anlamlı şekilde düşüktü. Fakat SMK, fovea altı ve çevresi KK, LK kalınlığı ve LKD ölçümlerinde gruplar arasında anlamlı fark yoktu. Bu bulgular şizofreni hastalarında nöron kayıplarının görüntülenmesinde, RSLT kalınlığının değerlendirildiği OKT'nin kullanılabileceğini gösterdi.

**Anahtar kelimeler:** *Şizofreni; Retina sinir lifi tabakası; Koroidal kalınlık; Lamina kribroza kalınlığı; Makülar kalınlık*

## ABSTRACT

**Purpose:** We aimed to evaluate the effects of schizophrenia on posterior ocular structures including the retinal nerve fiber layer (RNFL), central macular thickness (CMT), choroidal thickness (CT) and lamina cribrosa (LC) measurements.

**Methods:** A total of 35 patients with schizophrenia and 35 healthy individuals were enrolled. Only the right eye of each participant was tested. RNFL thickness in all quadrants, CT, CMT, LC thickness, and LC depth (LCD) measurements were performed using Fourier domain optic coherence tomography (OCT), and each variable was compared between groups.

**Results:** The mean age and sex distributions were similar between groups (p=0.528 and p=0.299, respectively). The average, superior, inferior, nasal, and temporal RNFL thicknesses were significantly lower in schizophrenia patients than in controls (p<0.001, p<0.001, p=0.001, p=0.002 and p<0.001, respectively). The mean subfoveal and perifoveal CT were not significantly different between the groups (subfoveal; p=0.676, 1.5 mm nasal; p=0.632, 3 mm nasal; p=1.000, 1.5 mm temporal; p=0.811, 3 mm temporal; p=0.145). The mean CMT was similar among the groups (p=0.678). LC thickness and LCD were not statistically significant between groups (p=0.816 and p=0.161).

**Conclusions:** We demonstrated that RNFL thicknesses in all quadrants were significantly lower in schizophrenia patients than in control subjects. However, there were no significant differences in the CMT, perifoveal and subfoveal CT, LC thickness, and LCD between the groups. These results suggest that OCT can be used to image neuronal loss by evaluating the RNFL in patients with schizophrenia.

**Keywords:** *Schizophrenia; Retinal nerve fiber layer; Choroidal thickness; Lamina cribrosa thickness; Macular thickness*

## INTRODUCTION

Schizophrenia is one of the most common mental diseases that affects over 24 million people worldwide (1). It is characterized by unorganized thought, delusions, hallucinations (auditory, visual, and others), cognitive deficits, and decreased ability to feel natural emotions (1). Many previous neuroimaging studies have reported that the brain volumes in patients with schizophrenia are progressively reduced during the disease process (2). Postmortem and other neuroimaging studies have also reported gray matter structural deficits in chronic schizophrenic patients (3). The retina originates from the neuroectoderm, providing the opportunity to noninvasively evaluate brain pathology in neurological disorders (3). This means that structural deficits in gray matter can be detected based on defects in the retinal nerve fiber layer (RNFL). Because the optic nerve is part of the central nervous system (CNS), RNFL thinning reflects axonal damage and is correlated with neurological changes (4). Ong et al. reported that neurodegeneration of the CNS during aging is related to RNFL thinning (5). Retinal ganglion cell (RGC) axons exit from the eye via the optic nerve and synapse at the lateral geniculate nucleus. This area may be particularly affected in schizophrenia patients, who may have impairments in the subcortical magnocellular and parvocellular visual pathways (6).

The RNFL and other retinal structures can be examined using optical coherence tomography (OCT), which is a non-contact and fast imaging method, which can be used to evaluate RNFL thicknesses in patients with schizophrenia. Recently, RNFL thickness, macular thickness, and volume were studied using OCT of schizophrenia patients (7, 8). However, the pathophysiology of optic nerve injury remains unclear in such patients. The lamina cribrosa (LC) is an important anatomical formation of the CNS. Kwun et al. reported that normal-tension glaucoma (low-tension glaucoma) is associated with damage to the optic nerve, despite low intraocular pressure being linked to pathological LC morphology and thickness (9). According to our theoretical predictions, LC morphology or thickness may be affected in patients with schizophrenia, whose brain volume is progressively reduced. For this reason, optic nerve damage may be caused by anatomical changes in the LC.

In this study, we objectively assessed the effects of schizophrenia on posterior ocular structures, including the RNFL, CMT, and CT, and changes in LC measurements during the disease period.

## MATERIALS AND METHODS

### Study population and design

This cross-sectional prospective study was conducted in the departments of psychiatry, neurology, and ophthalmology. All individuals that were examined agreed to participate in the study, and written informed consent was signed by each participant. This study complied with the Declaration of Helsinki and was approved by the local ethics committee.

The study investigated 35 patients with schizophrenia and 35 healthy volunteers. Group 1 was the patient group and group 2 was the control group. Participants of similar age and sex were enrolled in each group. Participants were recruited from the psychiatry department. Only the right eye of all individuals was evaluated.

### Inclusion criteria

The inclusion criteria were age 18–65 years old, a diagnosis of schizophrenia, and no exposure to electroconvulsive therapy. Diagnoses of schizophrenia were made according to the Diagnostic and Statistical Manual for Mental Disorders, Fifth Edition (DSM-V) criteria (10).

### Exclusion criteria

The ocular exclusion criteria for groups I and II included a history of ocular surgery (such as refractive surgery and cataract surgery) or eye injury, any eye disorders (e.g., cataract, uveitis, amblyopia, macular degeneration, diabetic retinopathy, and glaucoma), other retinal diseases, and a topical drug usage that could affect the posterior ocular structures. Psychiatric exclusion criteria included treatment with a psychotropic drug that affected ocular parameters, any neurological or other psychotic disorders, and exposure to electroconvulsive therapy. Participants who had a systemic disease that could affect retinal health other than schizophrenia, such as hypertension, and diabetes mellitus, were also excluded from the study.

**Patient assessment**

Each participant was subjected to a complete ophthalmic evaluation, including best-corrected visual acuity, refraction examination, biomicroscopy of the anterior segment, intraocular pressure (IOP) measurements using the Goldmann applanation tonometry, and a dilated fundus examination.

Group 1 consisted of patients with schizophrenia who had been using antipsychotic treatment for at least 2 years. All individuals in both groups were interviewed by two separate psychiatrists. All subjects were evaluated using Fourier domain OCT imaging. The RTVue-100 Fourier domain OCT system (Optovue, Fremont, CA, USA) was used to obtain retinal scans in the right eyes of participants. The working principles of this imaging system have been described in previous studies (11). The axial length (AL) was measured with the IOL Master 500 (Carl Zeiss Meditec, Jena, Germany).

**RNFL thickness measurements**

For RNFL thickness measurements, a 3-dimensional disc and an optic nerve head map of 4 mm diameter using the RTVue protocol was used (11). This protocol was composed of 12 radial scans and six concentric ring scans in a 3.45 mm square centered on the nerve head. For the macular thickness measurements, standard ganglion cell complex scans were used (12). All image qualities were checked with the signal strength index (SSI) using the RTVue-100 OCT. Only scans with an SSI>50 (good and very good quality scans) were included. After imaging, the average RNFL thickness, all quadrants RNFL thicknesses (superior, inferior, temporal, and nasal) and macular thickness were evaluated.

**LC and CT measurements**

LC and choroid were also evaluated with high resolution imaging by RTVue-100 OCT, using the vitreoretinal and chorioretinal settings. This method has been described in previous studies (13).

For the LC thickness measurements, the chorioretinal option was used. A total of 1,024 A-scans were performed on a 6 mm horizontal line within 1.25 s. These scans passed through the center of the optic nerve head with nasal fixation. LC was identified as the area between the outer and inner lines of the hyperreflective region at the vertical center of the optic nerve head, and the perpendicular distance between these borders was considered the LC thickness. In the horizontal B-scans, three sections were selected (center, mid-superior, and mid-inferior regions) and all parameters were measured in each of these frames. Each measurement was performed as close as possible to the vertical center of the optic nerve head and perpendicular to the reference plane. If visualization was prevented by central retinal vessels, parameters were measured on the temporal side. Contrast settings were adjusted to obtain the clearest visualization of LC thicknesses.

Figure 1 shows the LC borders and Bruch's membrane opening (BMO) in the optic nerve head of OCT images of a schizophrenia patient and a normal control. The line connecting two end points of Bruch's membrane was defined as the BMO. The perpendicular distance from the BMO to the anterior margin of the LC was identified as the lamina cribrosa depth (LCD).

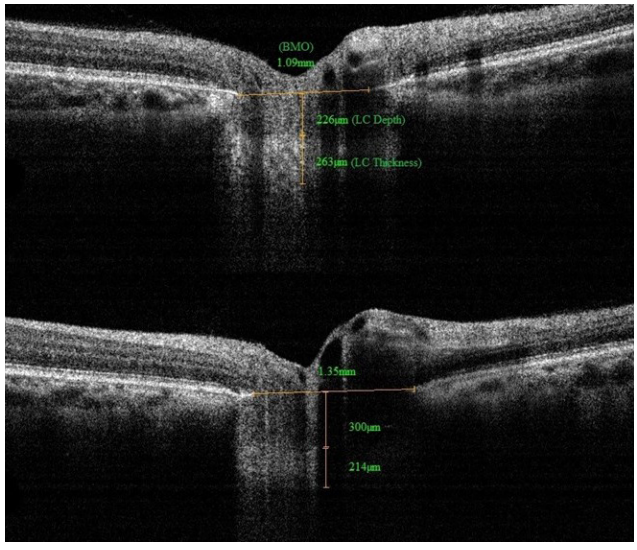


**Figure 1.** Measurements of the Bruch's membrane opening (BMO), lamina cribrosa (LC) thickness, and LC depth in healthy control (upper) and schizophrenia patient (bottom)

For the CT measurements, the enhanced depth imaging mode of RTVue OCT was used for evaluations (Figure 2). This technique has been described by Spaide et al. in a previous study (14). The subfoveal CT was the vertical distance between the base of the retinal pigment epithelium and the inner margin of the sclera under the center of the fovea. The CT was measured in the subfoveal area and at 1500 and 3000 µm both temporal and nasal to the center of the fovea. All of the measurements were performed by two independent specialists during two different periods, and the mean value was used for analyses.

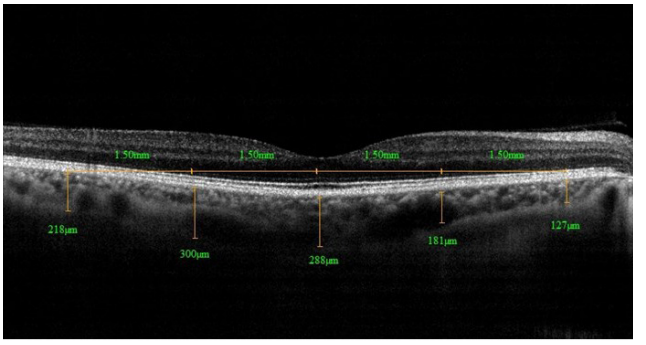


**Figure 2.** Measurements of the subfoveal and parafoveal choroidal thickness in patient with schizophrenia

### Statistical analyzes

All statistical analyses were performed using SPSS statistical software for Windows, version 25.0 (SPSS, Chicago, IL, USA). Descriptive statistics were used to calculated all data, which are reported as the mean ± SD or median ($1^{st}/3^{rd}$ quartiles), as appropriate. For each variable, the normality of the distribution of was checked using the Shapiro-Wilk normality test. The categorical parameters between the groups were compared using the chi-square test. An independent sample test was performed to compare variables between groups for normally distributed data, and the Mann-Whitney test was used to compare variables between both groups for nonparametric distributions. Pearson's correlation test was used to evaluate the relationships between the measured parameters. A value of $p<0.05$ was defined as statistically significant.

## RESULTS

This study included 35 patients with schizophrenia in group 1 and 35 normal controls in group 2. The baseline characteristics of the groups are listed in Table 1. The mean age, AL, IOP, and sex distribution were not significantly different between the groups (p=0.528, p=0.633, p=0.543, and p=0.299, respectively). The clinical parameters of the study and control groups are summarized in Tables 2, 3, and 4.

**Table 1.** Patient demographics and characteristics

| | Group 1 | Group 2 | p |
|---|---|---|---|
| Sex, n | | | |
| Male | 25 (71) | 27 (77) | 0.299[a] |
| Female | 10 (29) | 8 (23) | |
| Age, years | 39.1±4.1 | 39.8±4.9 | 0.528[b] |
| IOP, mmHg | 14.7±1.8 | 14.9±1.7 | 0.543[b] |
| Axial length, mm | 23.3 (22.7–23.7) | 23.5 (22.5–23.7) | 0.63[b] |

IOP: Intraocular pressure. Values are expressed as n (%), mean±standard deviation or the median ($1^{st}/3^{rd}$ quartiles). [a]Chi-square test, independent sample test.

**Table 2.** Comparison of RNFL thicknesses between the study and control groups

| RNFL thickness, µm | Group 1 (n:35 eyes) | Group 2 (n:35 eyes) | p |
|---|---|---|---|
| Average RNFL | 109 (103–112) | 123 (117–126) | 0.000[b] |
| Superior RNFL | 126.8±10.8 | 139.4±10.4 | 0.000[a] |
| Inferior RNFL | 129.9±10.1 | 138.6±11.4 | 0.001[a] |
| Nasal RNFL | 79.1±6.7 | 84.1±6.0 | 0.002[a] |
| Temporal RNFL | 85 (81–87) | 88 (86–94) | 0.000[b] |

RNFL: retinal nerve fiber layer. Values are expressed as mean±standard deviation or median ($1^{st}/3^{rd}$ quartiles). [a] Mann-Whitney-U test, [b] Independent sample t-test.

**OCT parameters**

Table 2 compares RNFL thicknesses between the groups. The average, superior, inferior, nasal, and temporal RNFL thicknesses were significantly lower in schizophrenia patients than in controls (p<0.001, p<0.001, p=0.001, p=0.002, and p<0.001, respectively). The mean CMT and subfoveal and parafoveal CT were also compared (Table 3). There were no significant differences (subfoveal; p=0.676, 1.5 mm nasal; p=0.632, 3 mm nasal; p=1.000, 1.5 mm temporal; p=0.811 and 3 mm temporal; p=0.145). Likewise, the difference in the mean CMT was not statistically significant (p=0.678).

The BMO and LC measurements are listed in Table 4. LC thickness and LCD were not statistically significant between the groups (p=0.816 and p=0.161, respectively). However, the BMO measurement was lower in patients with schizophrenia than in controls, but not significantly so (p=0.143).

**Table 3.** Comparison of central macular and choroidal thicknesses between the groups

| | Group 1 (n:35 eyes) | Group 2 (n:35 eyes) | p |
|---|---|---|---|
| CMT, µm | 251.4±16.1 | 250.0±13.6 | 0.678[b] |
| Subfoveal CT, µm | 232.1±10.3 | 233.3±12.9 | 0.676[b] |
| Parafoveal CT, µm | | | |
| 1.5 mm nasal | 205 (201–213) | 209 (202–218) | 0.632[a] |
| 3 mm nasal | 188 (178–193) | 189 (183–196) | 1.000[a] |
| 1.5 mm temporal | 210 (190–216) | 209 (195–216) | 0.811[a] |
| 3 mm temporal | 190 (180–195) | 188 (179–190) | 0.145[a] |

**CMT:** central macular thickness, **CT:** choroidal thickness. Values are expressed as mean±standard deviation or median (1st/3rd quartiles). [a] Mann-Whitney-U test, [b]Independent sample t-test.

**Table 4.** BMO, LCT, and LCD of the schizophrenia and control groups

| LC measurements, µm | Group 1 (n:35 eyes) | Group 2 (n:35 eyes) | p |
|---|---|---|---|
| BMO | 1470 (1,378–1,590) | 1530 (1,420–1,634) | 0.143[a] |
| LC thickness | 329.5±59.7 | 332.5±46.1 | 0.816[b] |
| LCD | 353.7±78.1 | 380.5±80.4 | 0.161[b] |

**LC:** lamina cribrosa, **BMO:** Bruch's membrane opening, **LCD:** lamina cribrosa depth. Values are expressed as mean±standard deviation or median (1st/3rd quartiles). [a]Mann- Whitney-U test, bindependent sample t-test.

## DISCUSSION

Schizophrenia is a complex mental disorder with early abnormalities of the visual system (15). Our study identified posterior ocular structural changes in schizophrenia patients, as assessed using OCT. We found RNFL thinning, consistent with recent comparably sized studies, which denotes ganglion cell loss (7). These findings are in line with previous neuroimaging studies that have reported gray matter atrophy in schizophrenia patients (16, 17). The neural retina, which develops from the neuroectoderm, is an important component of the CNS, and schizophrenia is a progressive neurodegenerative disorder (4). Hence, this degeneration may spread to the retina via the optic nerve or other periocular structures.

RNFL thickness and macular parameters in schizophrenia patients have previously been studied. Ascaso et al. reported that the average and nasal quadrant RNFLs were significantly thinner in schizophrenia patients than in controls (18). However, they did not find any significant difference in the other quadrants or macular parameters (thickness and volume). In a similar study, Cabezon et al. reported significantly lower average and superior RNFL thicknesses, but not macular thicknesses, in patients with schizophrenia (19). Ascaso et al. assessed OCT measurements of schizophrenia patients during recent illness episodes and non-recent illness episodes, and compared them with healthy controls (20). They found that schizophrenia patients in non-recent illness episodes had significantly thinner maculae and RNFLs and lower macular volume in overall measurements as well as in nasal and superior quadrants. In a similar manner, Lee et al. reported that RNFLs and maculae were significantly thinner in chronic schizophrenia patients, but not in acute patients, compared to controls (21). By contrast, Chu et al. reported no differences in RNFL thickness or macular volume between schizophrenia patients and normal controls (22). However, they reported a moderate relationship between the reduction of macular volume and positive symptom severity. Our findings confirm the results of previous studies. We found a significant reduction of average and all-quadrant RNFL thicknesses in schizophrenia patients compared to normal subjects.

Similar to previous studies, differences in the CMT were not statistically significant between the groups. These findings suggest that there is detectable loss of optic nerve axons in the retinas of schizophrenia patients. The thinning of RNFLs may be important in demonstrating the frequently reported reductions in brain volume in schizophrenia patients.

We also specifically evaluated CT in patients with schizophrenia. In previous studies, dilated retinal veins in color fundus images were detected in schizophrenia patients; moreover, the numbers of veins correlated with the severity of psychotic symptoms (23). Thinning of the RNFL and macula have previously been reported in different studies (20, 24). However, the choroid has not been evaluated in schizophrenia patients, although it is a major vascular supply to the outer retina. To the best of our knowledge, our study is the first to assess the choroid in patients with schizophrenia. Only one previous pilot study was designed similarly to our study (25). However, their study included only six patients with psychosis with either schizophrenia or bipolar disorders. They reported that the mean CT was reduced in psychosis patients, but not significantly so. In our study, the thicknesses of the subfoveal and parafoveal choroids were similar between patients with schizophrenia and normal controls. Macular thinning, which might be a consequence of a neurodegenerative process, has been observed in the inner layers of the retina (20). However, there is no evidence that the outer layers of the retina and choroid are thinner in schizophrenia patients.

The thinning of the LC increases mechanical damage to RGC axons (26). However, it is not clearly understood whether a thin LC can be found naturally in some eyes, or if LC thins are due to the process of degeneration that occurs during aging or neurodegeneration associated with ailments such as glaucoma or other neurodegenerative diseases (27). To the best of our knowledge, this is the first study to reveal a relationship between schizophrenia and the characteristics of the LC. The neurodegenerative process has been supported by progressive gray matter volume loss seen in schizophrenia patients (28). LC morphology has previously been studied in some neurodegenerative diseases (27, 29). Eraslan et al. reported that LC thickness is significantly reduced in Parkinson's disease patients compared to healthy controls (30). However, Lee et al. did not find any significant differences in LC thickness between such groups (27). In our study, there were no differences in LC thickness and LCD between groups. This indicates that optic nerve damage in patients with schizophrenia is not caused by a structural defect in the LC. However, more neuroimaging studies are required to better understand the relationships between brain atrophy and LC characteristics in schizophrenia patients.

We tried to minimize the sources of error in this study, although we acknowledge some limitations. The duration of illness was recorded according to the description of the patient at the first examination. We considered the time elapsed since the onset of the first symptoms as the duration of illness. However, this may not reflect the real duration, depending on the history of each patient. Furthermore, many patients were receiving psychotropic drugs during the data collection, so we cannot exclude the effects of these medications on our results.

In sum, RNFL thicknesses in all quadrants were significantly lower in schizophrenia patients than in controls. However, we did not find any statistically significant difference in the CMT, parafoveal and subfoveal CT, LC thickness, or LCD between the groups. Although OCT can be used to image neuronal loss by evaluating the RNFL, further studies comparing OCT results and neuroimaging findings of the brain are necessary to fully understand the ocular effects of schizophrenia.

Acknowledgments:
Funding: No author has a financial or proprietary interest in any material or method mentioned.
Conflict of Interest: The authors declare that they have no conflict of interest.
Informed Consent: Informed consent was obtained from all individual participants included in the study.
Ethical approval: All procedures performed in studies involving human participants were in
accordance with the ethical standards of the

institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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