

# Panic disorder causes an increase in choroid layer and a decrease in IPL, GCL, RNFL

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## Summary

**Background:** This study aimed to compare the retinal nerve fiber layer (RNFL), the inner plexiform layer (IPL), the ganglion cell layer (GCL), and the choroid thickness (CT) of patients diagnosed with panic disorder (PD) before and after four-weeks of the treatment and to compare the findings with the healthy subjects.

**Subjects and methods:** The PD group consisted of 32 subjects and the control group consisted of 64 subjects. All patients were managed by paroxetine plus alprazolam after PD diagnosis. The spectral-domain optical coherence tomography (SD-OCT) was applied twice to the PD group, before and after treatment, and once to the control group.

**Results:** Age ( $p=0.916$ ) and smoking status ( $p=0.850$ ) of PD (23 females, 9 males) and control (46 females, 18 males) groups were similar. Pre-treatment PD's RNFL sub-sectors, GCL, and IPL values were lower than the control group. Pre-treatment PD's CT value was higher than the control group. Four-weeks of PD treatment caused an increase in RNFL sub-sectors in the pre-treatment SD-OCT parameters of PD group, significantly in left mean and left TI. The sensitivity of mean CT ( $p<0.001$ ) related to the diagnosis of pre-treatment PD was 71.9 percent and the specificity was 93.8 percent (Nagelkerke  $R^2=0.636$ ). The area under the ROC curve of mean CT was 0.915 ( $p<0.001$ ; 95% CI [0.845-0.985]). The optimal cut-off value for mean CT was 321.75, and its sensitivity and specificity for the diagnosis of OUD were 68.8% and 98.4%, respectively.

**Conclusion:** This is the first study to examine the effect of PD treatment on SD-OCT parameters in patients diagnosed with PD. We suggest that acute exacerbation of PD is characterized by an increase in CT and a decrease in RNFL sub-sectors, GCL, and IPL. PD treatment causes an increase in RNFL sub-sectors.

**Keywords:** Choroid, inner plexiform layer, retinal nerve fiber layer, optical coherence tomography

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## INTRODUCTION

The fifth edition of diagnostic and statistical manual of mental disorder (DSM-5) criteria for panic disorder (PD) include experiencing recurrent panic attacks (PA), with one or more PAs followed by at least one month of fear of another PA or maladaptive behavior associated with the PAs (American Psychiatric Association, 2013). PD is a common psychiatric disorder that is characterized by structural and functional abnormalities and affects up to 5% of the population at some point in life (Roy-Byrne et al., 2006). Gorman's hypothesis and most studies have focused on the prefrontal cortex, amygdala, and hippocampus (Gorman et al., 1989; Gorman et al., 2000). In the following studies, different relationships were investigated and expressed that the PA arises from an altered fear network including the insula, the pre-frontal cortex, the cingulate, the thalamus, the amygdala and the projections of the amygdala into the brainstem, the septo-hippocampal system, and the hypothalamus (Gorman et al., 2000).

While some of the structural studies on the amygdala did not report alterations (Yoon et al., 2016), some reported a decrease (Massana et al., 2003). The amygdala has several connections with a region of the anterior cingulate cortex and orbitofrontal cortex (Devinsky et al., 1995), and recent structural neuroimaging studies have suggested that these regions and some cortical structures such as temporal and frontal lobes can play an important role in the pathophysiology of PD. The majority of studies reported a decrease in the volume of the cortex structures of PD patients (Asami et al., 2008), while some did not report any alterations. Studies investigating the concentration of grey matter report that some parts of the brain are affected and some parts are not. Massana et al. (2003) studied grey matter concentration in patients with PD and healthy control and found grey matter density of the left parahippocampal gyrus to be significantly lower in patients, without significant differences in other brain regions. Yoo et al. (2005) found decreased bilateral putaminal grey matter volume comparing PD and healthy

controls. Another study reported regional grey matter volume decrease in right caudate head and right parahippocampal gyrus in PD group (Lai, 2011).

The spectral-domain optical coherence tomography (SD-OCT) is another device that can be used to detect structural abnormalities in PD. The ganglion cell layer (GCL), inner plexiform layer (IPL), and retinal nerve fiber layer (RNFL), and choroid thickness (CT) are some parameters that can be measured using SD-OCT (Altun et al., 2020; Fujimoto, 2003; Kaštalan et al., 2022; Silić et al., 2020). The literature demonstrated that the retinal nerve fiber layers have the equivalent of non-myelinated white matter; the nuclear and the GCL have the equivalent of grey matter (Kim et al., 2017). According to our best knowledge, there is only one study examining SD-OCT parameters in PD. In the study conducted by Baykara et al. (2022), RNFL and GCL of patients with PD who are currently using an antidepressant were compared with the control group. Baykara et al. (2022) reported that there were no significant differences between the groups in terms of RNFL sub-sectors, GCL, and CT.

We designed a study to compare the IPL, GCL, RNFL, and CT parameters of drug-naïve PD patients before and after paroxetine plus alprazolam treatment with a healthy control group. Our hypothesis was that the SD-OCT parameters of patients with PD who did not receive any treatment would differ significantly compared to the control group.

## SUBJECTS AND METHODS

In this prospective study, drug-naïve female and male patients who admitted to the outpatient clinic of a district state hospital and met the diagnosis of PD according to DSM-5 (American Psychiatric Association, 2013) were included. The healthy control group consisted of hospital staff who applied to the ophthalmology clinic once a year for health screening and had no ophthalmological problems. Sociodemographic and clinical data were obtained from the hospital record system. While there was no additional psychiatric disorder according to the structured clinical interview for DSM-5 in the patient group, there was no any psychiatric disorder in the healthy control group. There was no diagnosis of ophthalmological disease in either group. Whether the patient and control groups had a systemic disease was confirmed through the *e-nabiz* national patient registry system. Sixty-five patients with psychotropic or other medical drug use and 19 controls were excluded from the study. All patients were managed by paroxetine plus alprazolam after PD diagnosis.

The Severity Measure for Panic Disorder—Adult (SMPD-A) (Balıkcı et al., 2017) was used to evaluate the severity of PD which is a 10-item measure that assesses the severity of symptoms of panic disorder in individuals age 18 and older. The measure was designed to be completed by an individual upon receiving a diagnosis of panic disorder (or clinically significant panic disorder symptoms) and thereafter, prior to follow-up visits with the clinician. Each item asks the individual receiving care to rate the severity of his or her panic disorder during the past 7 days.

IPL, GCL, CT, and RNFL sub-sectors (nasal (N), temporal (T), nasal inferior (NI), nasal superior (NS), temporal inferior (TI), temporal superior (TS), and global (mean)) were measured using the SD-OCT device (Spectralis™ OCT, Version 6.0, Heidelberg Engineering, Germany). Two independent researchers who had no prior knowledge of the patient or the control participants examined the SD-OCT measurements. All SD-OCT measurements have performed at 9.00 am-11.00 am. Local ethics committee approval was obtained.

Power analysis performed using the data from the study by Baykara et al. (2022) showed that at least 14 subjects should be included in each group.

SPSS 22.0 was used in statistical analyses. The diagnosis of PD and the effect of treatment were accepted as the independent variable, sociodemographic and clinical parameters as the dependent variable. Chi-square test was used to analyze the categorical data. Normal distribution suitability was assessed using the Kolmogorov-Smirnov test. Two variables with normally distributed distribution were compared using an independent samples t-test. Paired sample t-test was used to make comparisons between dependent variables. Pearson correlation analysis and Binary logistic regression analysis were used. Cohen's *d* and Glass's *delta* were calculated as the effect size. A value of less than 0.05 (*p* value) was considered statistically significant.

## RESULTS

Thirty-two PD patients (23 females, 9 males) and 64 healthy controls (46 females, 18 males) were included in the study. While the mean age was  $36.62 \pm 7.01$  years in the PD group ( $n=32$ ), it was  $36.34 \pm 14.14$  years in the control group. The groups were similar in terms of age ( $p=0.916$ ), family history of psychiatric disorder ( $p=0.134$ ) and smoking status ( $p=0.850$ ). There was a significant difference between PD and control groups in terms of marital status ( $p=0.022$ ) and educational status

**Table 1.** Comparison of Sociodemographic and Clinical Features of Patient and Control Groups

Variables		Patient (n=32)	Control (n=64)	p value
Marital Status	Married	30 (40.5%)	44 (59.5%)	0.022*
	Single	2 (10.5%)	17 (89.5%)	
	Widowed	0 (0.0%)	3 (100.0%)	
Education Status	Primary	3 (18.8%)	13 (81.3%)	<0.001**
	Secondary	22 (59.5%)	15 (40.5%)	
	High	4 (12.9%)	27 (87.1%)	
	University	3 (25.0%)	9 (75.0%)	
Family Psychiatric History	Yes	11 (45.8%)	13 (54.2%)	0.134
	No	21 (29.2%)	51 (70.8%)	
Smoking	Yes	6 (35.3%)	11 (64.7%)	0.850
	No	26 (32.9%)	53 (67.1%)	

\*p<0.05; \*\*p<0.001; Chi-square test was used for statistical analysis.

**Table 2.** Comparison of RNFL, GCL, IPL, and CT Values Between Pre-Treatment PD and Control Groups

Variables	PD Before Treatment (n=32) (Mean±SD)	Control (n=64) (Mean±SD)	p value	Cohen's d	Glass's delta
Right NS	109.59±16.96	114.00±19.58	0.281	0.24	0.26
Right N	75.84±10.69	82.57±15.39	0.029*	0.50	0.62
Right NI	114.46±25.99	127.64±27.45	0.026*	0.49	0.50
Right TI	156.25±24.37	153.71±16.45	0.549	0.12	0.10
Right T	73.71±9.13	75.03±8.12	0.476	0.15	0.14
Right TS	147.56±20.55	145.76±14.46	0.621	0.10	0.08
Right Mean	103.15±9.72	107.06±8.13	0.041*	0.43	0.40
Right Choroid	379.02±92.55	245.73±29.41	<0.001**	1.94	1.44
Right GCL	1.13±0.08	1.20±0.04	<0.001**	1.10	0.87
Right IPL	0.91±0.06	0.96±0.04	<0.001**	0.98	0.83
Left NS	121.75±17.56	126.14±20.00	0.294	0.23	0.25
Left N	68.21±8.66	77.81±13.88	0.001*	0.82	1.10
Left NI	115.93±25.37	124.39±26.37	0.137	0.32	0.33
Left TI	147.96±19.46	153.40±18.82	0.190	0.28	0.27
Left T	72.56±9.02	73.07±8.96	0.792	0.05	0.05
Left TS	147.65±16.18	146.78±14.64	0.791	0.05	0.05
Left Mean	102.06±9.58	107.50±9.71	0.011*	0.56	0.56
Left Choroid	360.09±92.77	243.54±34.18	<0.001**	1.66	1.25
Left GCL	1.12±0.08	1.20±0.04	<0.001**	1.26	1.00
Left IPL	0.92±0.06	0.96±0.04	0.003*	0.78	0.66

\*p<0.05, \*\*p<0.001; Independent-samples t-test was used; **Abbreviations:** PD: Panic Disorder; RNFL: Retinal Nerve Fiber Layer; GCL: Ganglion Cell Layer; IPL: Inner Plexiform Layer; CT: Choroidal Thickness; SD: Standard Deviation; NS: Naso-Superior; NI: Naso-Inferior; N: Nasal; TS: Temporo-Superior; TI: Temporo-Inferior; T: Temporal

( $p < 0.001$ ). In the PD group, 13 (40.62%) patients had a past psychiatric admission. There was no history of psychiatric hospitalization and psychotropic drug use in the PD group. Sociodemographic and clinical data were shown in Table 1.

The SD-OCT parameters of the drug-naive PD and the healthy control groups were compared. Significant differences were detected between the groups in terms of sub-sectors of RNFL, choroidal layer, GCL and IPL for both eyes. RNFL sub-sectors, GCL and IPL values of PD group were lower than the control group. The CT value was found to be higher in PD group than in the control group (Table 2).

The comparison of SD-OCT parameters before and after paroxetine plus alprazolam use in the PD group was shown in Table 3.

The comparison of SD-OCT parameters of PD group after treatment and the control group was shown in Table 4.

When the effect of age was controlled in the PD group before treatment, a correlation was found between SMPD-A and mean CT ( $r = 0.786$ ,  $p < 0.001$ ), mean GCL ( $r = -0.642$ ,  $p < 0.001$ ), and mean IPL ( $r = -0.523$ ,  $p = 0.001$ ) (Table 5).

According to the binary logistic regression analysis, the sensitivity of mean CT ( $p < 0.001$ ) related to the diagnosis of pre-treatment PD was 71.9 percent and the specificity was 93.8 percent ( $\text{Exp}(B) = 0.968$  [95%CI for  $\text{Exp}(B) = 0.955-0.982$ ], Constant  $p < 0.001$ ; -2 Log likelihood = 63.409; Cox & Snell  $R^2 = 0.458$ ; Nagelkerke  $R^2 = 0.636$ ) (Table 6).

Receiver operating characteristic (ROC) curve analysis performed on the basis of 96 cases (32 pre-treatment patients and 64 healthy controls). The area under the ROC curve of mean CT was 0.915 ( $p < 0.001$ ; 95% CI [0.845-0.985]). The optimal cut-off value for mean CT was 321.75, and its sensitivity and specificity for the diagnosis of OUD were 68.8% and 98.4%, respectively.

**Table 3.** Comparison of SD-OCT Parameters Before and After Treatment in the PD Group (n=22)

Variables	Before PD Treatment (Mean±SD)	After PD Treatment (Mean±SD)	p value
Right NS	111.40±18.60	114.63±19.77	0.083
Right N	76.22±8.12	77.68±7.71	0.185
Right NI	113.27±21.72	115.31±23.73	0.481
Right TI	153.31±22.76	152.95±20.86	0.858
Right T	73.68±10.29	74.40±11.30	0.656
Right TS	147.95±21.87	146.09±16.73	0.517
Right Mean	103.18±9.13	104.27±8.96	0.069
Right CT	377.51±92.60	377.93±95.00	0.956
Right GCL	1.14±0.08	1.14±0.08	0.761
Right IPL	0.92±0.06	0.92±0.06	0.329
Left NS	123.18±19.93	123.18±19.43	>0.999
Left N	69.40±8.31	70.45±9.31	0.492
Left NI	115.36±23.66	115.27±22.64	0.972
Left TI	146.13±18.55	152.90±19.59	0.014*
Left T	73.22±10.00	73.31±9.54	0.934
Left TS	146.50±15.54	145.68±15.14	0.643
Left Mean	102.04±8.53	103.54±10.32	0.009*
Left CT	353.75±94.07	350.68±92.42	0.711
Left GCL	1.13±0.08	1.13±0.08	0.925
Left IPL	0.92±0.06	0.92±0.06	0.055

\* $p < 0.05$ , \*\* $p < 0.001$ ; Paired sample t-test was used; **Note:** Four-weeks from baseline to second application; **Abbreviations:** SD-OCT: Spectral-Domain Optical Coherence Tomography; PD: Panic Disorder; SD: Standard Deviation; NS: Nasal Superior; NI: Nasal Inferior; N: Nasal; TS: Temporal Superior; TI: Temporal Inferior; T: Temporal; GCL: Ganglion Cell Layer; IPL: Inner Plexiform Layer; CT: Choroidal Thickness

**Table 4.** Comparison of SD-OCT Parameters of PD Group After Treatment and Control Group

Variables	PD After Treatment (n=22) (Mean±SD)	Control (n=64) (Mean±SD)	p value	Cohen's d	Glass's delta
Right NS	114.63±19.77	114.00±19.58	0.896	0.03	0.03
Right N	77.68±7.71	82.57±15.39	0.157	0.40	0.63
Right NI	115.31±23.73	127.64±27.45	0.064	0.48	0.51
Right TI	152.95±20.86	153.71±16.45	0.861	0.04	0.04
Right T	74.40±11.30	75.03±8.12	0.781	0.05	0.05
Right TS	146.09±16.73	145.76±14.46	0.931	0.02	0.02
Right Mean	104.27±8.96	107.06±8.13	0.180	0.39	0.55
Right CT	377.93±95.00	245.73±29.41	<0.001**	1.87	1.39
Right GCL	1.14±0.08	1.20±0.04	<0.001**	0.94	0.75
Right IPL	0.92±0.06	0.96±0.04	0.004*	0.78	0.66
Left NS	123.18±19.43	126.14±20.00	0.548	0.15	0.15
Left N	70.45±9.31	77.81±13.88	0.023*	0.62	0.79
Left NI	115.27±22.64	124.39±26.37	0.152	0.39	0.61
Left TI	152.90±19.59	153.40±18.82	0.916	0.03	0.02
Left T	73.31±9.54	73.07±8.96	0.915	0.03	0.03
Left TS	145.68±15.14	146.78±14.64	0.764	0.05	0.05
Left Mean	103.54±10.32	107.50±9.71	0.109	0.42	0.55
Left CT	350.68±92.42	243.54±34.18	<0.001**	1.53	1.15
Left GCL	1.13±0.08	1.20±0.04	<0.001**	1.10	0.87
Left IPL	0.91±0.06	0.96±0.04	0.001*	0.98	0.83

\*p<0.05, \*\*p<0.001; Independent-samples t-test was used; **Abbreviations:** SD-OCT: Spectral-Domain Optical Coherence Tomography; PD: Panic Disorder; SD: Standard Deviation; NS: Nasal Superior; NI: Nasal Inferior; N: Nasal; TS: Temporal Superior; TI: Temporal Inferior; T: Temporal; GCL: Ganglion Cell Layer; IPL: Inner Plexiform Layer; CT: Choroidal Thickness

**Table 5.** Correlation Analysis of SMPD-A and Various SD-OCT Parameters

Variable (r, p)	Mean CT	Mean GCL	Mean IPL
SMPD-A	r=0.786, p<0.001**	r=-0.642, p<0.001**	r=-0.523, p=0.001*

\*p<0.05, \*\*p<0.001; Pearson correlation analysis was used; **Abbreviations:** SMPD-A: The Severity Measure for Panic Disorder—Adult; SD-OCT: Spectral-Domain Optical Coherence Tomography; GCL: Ganglion Cell Layer; IPL: Inner Plexiform Layer; CT: Choroidal Thickness

**Table 6.** Regression Analysis of Mean CT's Predictive Feature for Pretreatment PD

Variable	Sensitivity (%)	Specificity (%)	Exp(B)	95%CI for Exp (B)	Constant p
Mean CT	71.9	93.8	0.968	0.955-0.982	<0.001**

\*p<0.001; Binary logistic regression analysis was used (-2 Log likelihood = 63.409; Cox & Snell R<sup>2</sup>= 0.458; Nagelkerke R<sup>2</sup>=0.636). **Abbreviations:** CT: Choroidal Thickness; PD: Panic Disorder

## DISCUSSION

This study is the first to investigate the effect of four weeks of PD treatment on SD-OCT parameters. The similarity of the groups in terms of age, gender, and smoking status facilitated the interpretation of the findings. RNFL sub-sectors, GCL, and IPL values of pre-treatment PD group were lower than the control group. CT value of pre-treatment PD group was higher than the control group. Four-weeks of PD treatment caused an increase in RNFL sub-sectors in the pre-treatment SD-OCT parameters of PD group, significantly in left mean and left TI.

There is only one study in the literature examining SD-OCT parameters in PD. Our study also examined IPL, unlike Baykara et al. (2022)'s study, by including more patient and control participants. In our study, the limitations of Baykara et al. (2022)'s study –age, smoking status were not similar between the groups, the patients were currently using antidepressant medication, the duration of antidepressant use was not known, and it was a cross-sectional study– were eliminated. Baykara et al. (2022) found no significant difference between the groups in terms of RNFL, GCL, and CT. The dissimilarity of the findings of the two studies is thought to be due to methodological differences. In particular, the age difference between the groups and the fact that the patients were using antidepressants were the main confounding factors in Baykara et al. (2022)'s study. It is likely that psychiatric symptoms of PD patients currently receiving treatment will have improved to a certain extent. It is also possible that the SD-OCT parameters of patients with a certain degree of well-being in terms of PD were found to be similar to those of healthy controls, and that no correlation was found between the severity of PD and SD-OCT parameters.

Somas of the ganglion cells form GCL, dendrites of ganglion cells form IPL, and their axons form RNFL. So our findings imply degeneration in axons, somas and dendrites of the neurons in the retina. The reductions in RNFL sub-sectors, which is an unmyelinated white matter tissue (Kim et al., 2017), are in line with the findings of the studies in the literature. Until now, a few imaging studies of white matter have been conducted in patients with PD. Konishi et al. (2014) conducted to evaluate differences in regional white matter volume between patients with PD and healthy control subjects using a voxel-based morphometry study. In this study, correlation analyses were performed between the regional white matter volumes and patients' scores on the PD severity scale. They have reported that patients with PD demonstrated significant volumetric reductions in widespread white matter regions and there was a significant negative relationship between right orbitofrontal gyrus white matter volume and the severity of patients' clinical

symptoms, as assessed with the PD severity scale (Konishi et al., 2014). A diffusion tensor imaging study demonstrated that patients with PD have decreased fractional anisotropy in the white matter tracts of left superior longitudinal fasciculus, right inferior fronto-occipital fasciculus, and left body of the corpus callosum (Lai & Wu, 2013a). Although the number of studies conducted in this area is not at the desired level, the findings of these studies show us that PD causes regional differences in the white matter of the brain. The effect of treatment on the structural changes in the brains of PD patients has not been studied sufficiently yet. Lai and Wu (2012) found increased fractional anisotropy in some regions of right uncinate fasciculus and left fronto-occipital fasciculus after remission in PD group. They suggested that subtle changes of white matter micro-structural integrity after remission might represent neural correlates of treatment effects for first-episode, medication-naive and very late-onset PD (Lai & Wu, 2012). The current study reveals that four-weeks of psychotropic treatment provides an increase in RNFL values of PD patients and this increase is significant in the left TI and left mean sub-sectors of RNFL.

The nuclear and the GCL have the equivalent of grey matter and the studies reporting that grey matter is affected in PD are at a considerable level (Del Casale et al., 2013). A limited number of studies have also investigated the effect of treatment on the change in the brain grey matter of PD patients. There is some preliminary evidence pointing to the possibility that structural brain parameters, such as hippocampus grey matter volume, might also represent potential predictors of treatment response. Lai and Wu (2013b) investigated the changes in the grey matter volume of first-episode, remitted drug-naive patients under six-weeks of escitalopram treatment for PD and reported that the remitted patients indicated increased grey matter volume in the left superior frontal gyrus after escitalopram therapy. Unlike this limited number of studies in the literature, the present study did not find a significant change in the post-treatment GCL and IPL values of the PD group. This situation was thought to be related to the fact that the four-week treatment period was not sufficient to produce a volumetric change in the grey matter structures.

Another important finding of this study is alterations in CT in PD patients. Choroid tissue is affected by any inflammatory or autoimmune conditions affecting blood flow (Fujimoto, 2003). Research in some autoimmune diseases with retinal involvement also demonstrated that choroid thickness increases during acute attack periods due to increased inflammation but then decreases with progressing disease (Coskun et al., 2013). We detected a significant increase in CT in PD patients who did not have any systemic disease that can disturb the vascular structure of affect blood flow when compared with. This

increase in CT may be due to the inflammatory process accompanying PD. However, this increase in CT did not change with the four-week paroxetine plus alprazolam treatment. The effects of paroxetine and other selective serotonin reuptake inhibitors on brain volumes have not yet been clarified (Vermetten et al., 2003; Szeszko et al., 2004). In other words, it is difficult to interpret the effect of paroxetine and alprazolam administered to patients in this study on current findings. It would be more appropriate to talk about this as a limitation. Longer use of antidepressants and being in remission may normalize the CT level. Baykara et al. (2022)'s finding that CT was similar between the groups may also be due to this situation.

After four-weeks of treatment, while SD-OCT was applied, patients had paroxetine plus alprazolam in their body. The effect of these medications on SD-OCT values was not excluded. Deep chamber, thick lens and axial length parameters are considered to be able to influence the measurements made and their absence is considered as a limitation. It may be helpful to report diet habits of patients. In addition, possible undiagnosed medical conditions are another limitation. Further studies are needed to clarify the limitations.

## CONCLUSION

In conclusion, this is the first study to show the SD-OCT findings of patients diagnosed with PD before and after paroxetine plus alprazolam treatment. We have

suggested that there was a significant difference between the patient and the control groups in terms of SD-OCT parameters. In the patient group, there was an increase in choroidal thickness and a decrease in RNFL, GCL, IPL volumes. Four-weeks of PD treatment caused an increase in RNFL sub-sectors in the pre-treatment SD-OCT parameters of PD group, significantly in left mean and left TI.

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**Author contributions:** Aysun Kalenderoglu: Concept, design, supervision, materials, analysis and/or interpretation, critical reviews. Asli Egeli: Resource, materials, data collection and/or processing, writing. Mehmet Hamdi Örum: Resource, materials, data collection and/or processing, literature search, writing. Ayşe Sevgi Karadağ: Concept, design, supervision, analysis and/or interpretation.

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