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Original Article

Association Between Optical Coherence Tomography Angiography Findings and Inner Retinal Thickness in Diabetic Patients

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Abstract

Objectives: To investigate the association between optical coherence tomography angiography (OCTA) findings and inner retinal thickness (IRT) in diabetic patients.

Materials and Methods: This retrospective study included 23 eyes of 23 diabetic patients with retinopathy (group 1), 30 eyes of 30 diabetic patients without retinopathy (group 2), and 27 eyes of 27 non-diabetic age-matched controls (group 3). Foveal avascular zone (FAZ) area (mm^2), average vessel density (%) in the parafoveal region, and average IRT in the parafoveal region (µm) were calculated using 6x6 mm OCTA images. Correlations between IRT and OCTA findings were analyzed.

Results: The mean FAZ area was 0.32±0.11 mm^2 in group 1, 0.29±0.08 mm^2 in group 2, and 0.22±0.09 mm^2 in group 3. There were statistically significant differences between groups 1 and 3 ($p<0.001$) and between groups 2 and 3 ($p=0.001$). Average IRT was 108.02±9.42 µm in group 1, 110.12±11.01 µm in group 2, and 114.41±5.21 µm in group 3, with statistically significant differences between groups 1 and 3 ($p=0.003$) and between groups 2 and 3 ($p=0.014$). In both group 1 and group 2, average IRT was correlated with FAZ area ($r=-0.320$ and -0.512, respectively).

Conclusion: The inner retina is significantly thinner in diabetic patients with and without retinopathy compared to controls. Quantitative OCTA findings and IRT are correlated in diabetic patients, suggesting that both structures are compromised in patients with diabetes with or without retinopathy. Microvascular changes in FAZ detected by OCTA might precede neurodegenerative changes.

Keywords: Diabetic retinopathy, optical coherence tomography angiography, inner retinal thickness

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Introduction

Diabetic retinopathy (DR) is considered to be a pathology of retinal microvascular complications caused by chronic hyperglycemia.[1] On the other hand, there is evidence suggesting that neurodegeneration of the retina is a critical component of DR and precedes the earlier clinical manifestations of DR.[2] This neurodegeneration is observed structurally as neural apoptosis, ganglion cell loss, and inner retinal thinning.[3] Studies have reported that increased proinflammatory mediators within the retina triggering ganglion cell apoptosis precede the occurrence of retinal microvascular abnormalities.[4,5]

Studies have demonstrated that the retinal nerve fiber layer (RNFL), ganglion cell layer (GCL), and inner plexiform layer (IPL) are thinner in diabetic individuals with and without DR, also suggesting that the death of neurons in the inner retinal layers occurs before microvascular structural damage.[6,7] Optical coherence tomography angiography (OCTA) provides both qualitative and quantitative information about the retinal microvascular structure.[8] OCTA can easily demonstrate subclinical vascular alterations before DR is clinically evident on fundus examination. Many studies using OCTA in diabetic patients have shown enlargement and disintegrity of the foveal avascular zone (FAZ) and reduced capillary density.[9,10,11,12] Kim et al.[13,14] evaluated the relation between inner retinal thickness (IRT) and vascular parameters detected by OCTA and confirmed the results with both cross-sectional and longitudinal studies. They demonstrated that quantitative OCTA parameters were correlated with GCL/IPL thinning in diabetic persons. To validate these findings and understand which part of the retina is compromised first in diabetes mellitus (DM), further studies should be conducted in diabetic patients without clinically evident DR or with early DR using OCTA and structural optical coherence tomography (OCT).

The purpose of the current study was to study quantitative microvascular changes using OCTA in the eyes of diabetic individuals with or without retinopathy from a single reference center and analyze the relationship between IRT and vascular structures to determine whether or not retinal neurodegeneration occurs together with impairments of the retinal microvasculature in diabetes.

Materials and Methods

This retrospective study was performed in the Ankara University Faculty of Medicine, Department of Ophthalmology from October 2016 to November 2018. All procedures performed in the study were in accordance with the ethical standards of the institutional committee and with the Declaration of Helsinki.

We evaluated 30 eyes of 30 patients among the diabetic patients without DR who presented to our hospital for routine ophthalmic examination or were referred for DR screening. In addition, 23 eyes of 23 patients with DR findings were selected from patients who were regularly followed in our retina clinic with the diagnosis of DR. The control group consisted of 27 age-matched healthy subjects. Only the right eye of each subject was included. The exclusion criteria were as follows: other retinal diseases, previous diagnosis of glaucoma, uveitis, previous retinal therapy (laser photocoagulation, intravitreal injection or vitreoretinal surgery), and previous ocular surgery. In addition, we did not include those with diabetic macular edema as they may affect the measurement of FAZ and vessel density (VD) in OCTA images. Individuals with spherical equivalent greater than ±2 D were also excluded from the study.

Demographic data were obtained from the patients' clinical records. DR was diagnosed based on ophthalmoscopic examination findings and graded as mild, moderate, and severe nonproliferative DR.[15]

Optovue RTVue XR Avanti SD-OCT software (version 2014.2.0.93; Optovue Inc., Fremont, California, USA) was used to acquire the OCTA images. Automatic segmentation of the retinal layers was applied.

In the quantitative analysis using AngioVue OCTA software, the following parameters were evaluated: FAZ area (mm^2), average VD (%) in the parafoveal region, average IRT in the parafoveal region, and central IRT.

The AngioVue software provides automated FAZ boundary detection and calculation of FAZ area (Figure 1). The ring-shaped area between 1- and 3-mm diameter centered on the fovea was defined as the parafoveal region. The percentage area occupied by vessels in the segmented area was defined as VD. In the parafoveal region, VD was determined for each quadrant using the ETDRS grid and automatically calculated for superficial capillary plexus (SCP) and deep capillary plexus (DCP) (Figures 2 and 3).

The parafoveal IRT was also measured by OCTA from the internal limiting membrane to the outer boundary of the inner nuclear layer in all subjects. We calculated the parafoveal IRT in the superior, temporal, inferior, and nasal sectors of the ETDRS grid. Average IRT was automatically averaged within each quadrant sector.

Statistical Analysis

The evaluated parameters were compared statistically among all groups. The analysis of the data was done in the IBM SPSS version 11.5 (IBM Corp., Armonk, NY, USA) program. Descriptive statistics were shown as mean ± standard deviation for variables with normal distribution. For comparisons among three groups, the significance of the difference was investigated using one-way analysis of variance (ANOVA) or Kruskal-Wallis test. In case of a significant difference, binary comparisons were made to evaluate which group(s) the difference originated from. Statistical significance was set at a value of $p<0.05$.

Results

We retrospectively reviewed 23 eyes of 23 patients with DR (group 1), 30 eyes of 30 diabetic patients without DR (group 2), and 27 eyes of 27 healthy individuals (group 3). Mean age was similar between the three groups (group 1: 53.12±10.61, group 2: 52.62±14.42, group 3: 47.81±12.01 years; p=0.062). There were 10 women (43.5%) and 13 men (56.5%) in group

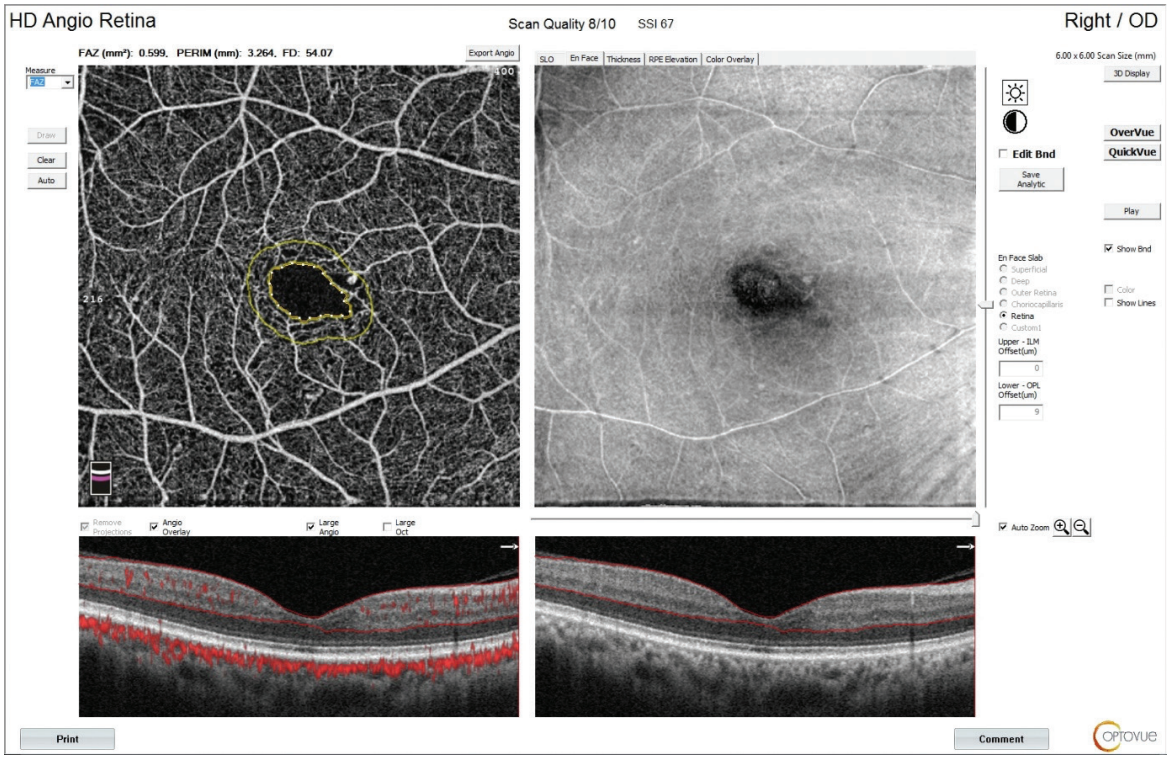
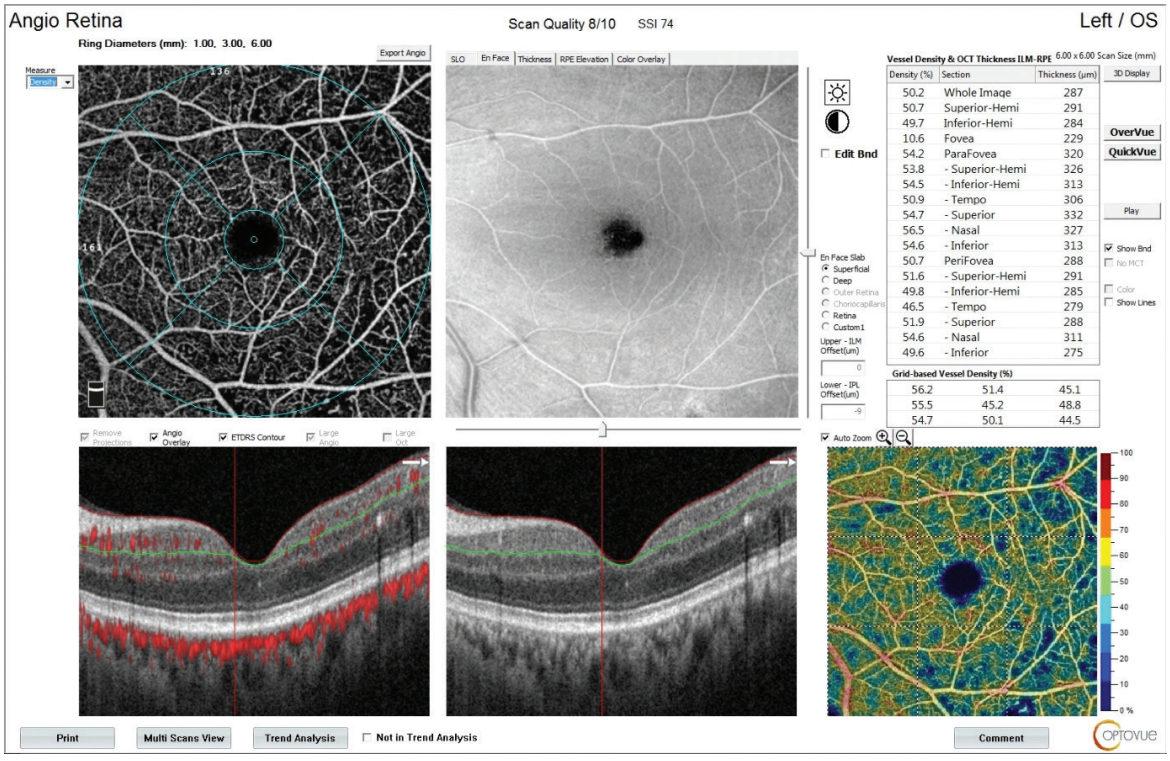


Figure 1. Foveal avascular zone area measurement using 6x6 mm optical coherence tomography angiography scan



Density (%)	Section	Thickness (µm)
50.2	Whole Image	287
50.7	Superior-Hemi	291
49.7	Inferior-Hemi	284
10.6	Fovea	229
54.2	ParaFovea	320
53.8	- Superior-Hemi	326
54.5	- Inferior-Hemi	313
50.9	- Tempo	306
54.7	- Superior	332
56.5	- Nasal	327
54.6	- Inferior	313
50.7	PeriFovea	288
51.6	- Superior-Hemi	291
49.8	- Inferior-Hemi	285
46.5	- Tempo	279
51.9	- Superior	288
54.6	- Nasal	311
49.6	- Inferior	275

56.2	51.4	45.1
55.5	45.2	48.8
54.7	50.1	44.5

Figure 2. Parafoveal average vessel density measurement in the superficial capillary plexus using 6x6 mm optical coherence tomography angiography scan

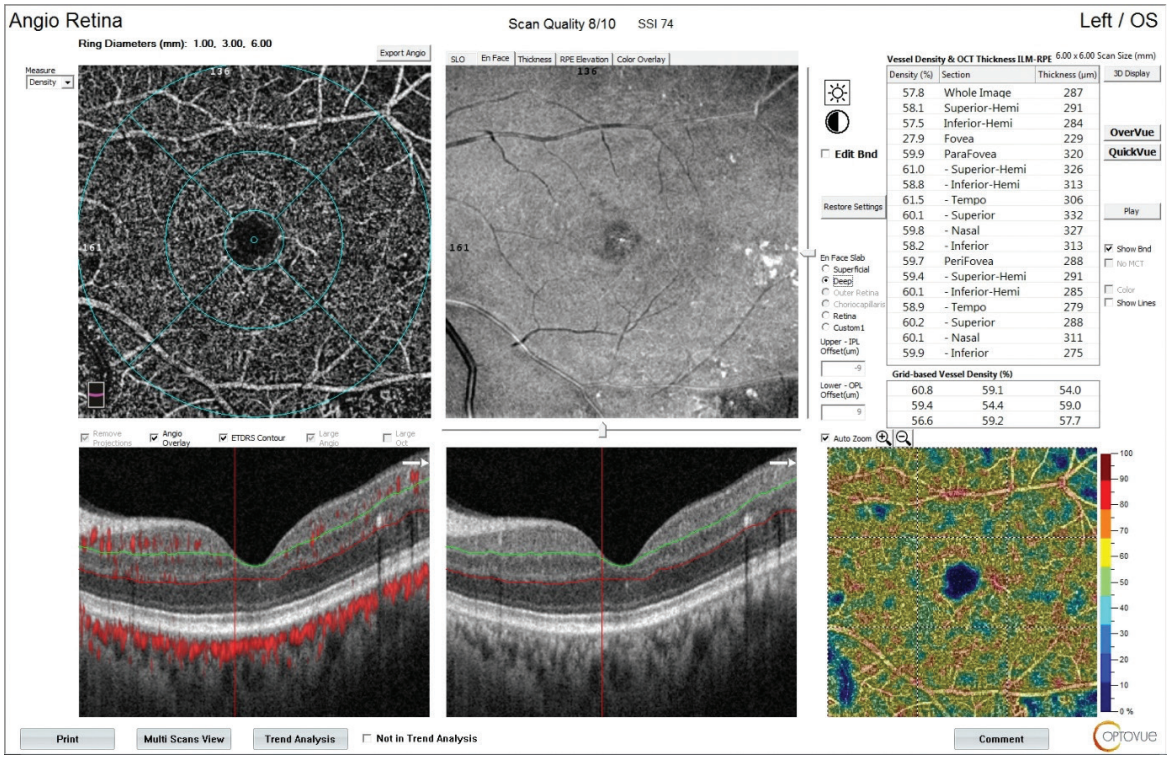


Figure 3. Parafoveal average vessel density measurement in the deep capillary plexus using 6x6 mm optical coherence tomography angiography scan

1; 16 women (53.3%) and 14 men (46.7%) in group 2, and 13 women (48.1%) and 14 men (51.9%) in group 3. There was no significant difference among the three groups in terms of gender (p=0.077).

In group 1, 3 patients had type 1 and 20 had type 2 DM, while in group 2, 4 patients had type 1 and 26 had type 2 DM. The distribution of DM type was similar in both groups (p=1.000). The mean duration of DM was 13.51±4.4 years in group 1 and 12.5±13.3 years in group 2 (p=0.053). Mean glycated hemoglobin (HbA1c) level was 9.6±1.5% (81.4±16.4 mmol/mol) in group 1, 8.4±1.8% (68.3±19.6 mmol/mol) in group 2, and 4.2±0.3% (22.4±3.3 mmol/mol) in group 3. There was a significant difference in HbA1c between groups 1 and 2 (p=0.005), groups 1 and 3 (p=0.001), and groups 2 and 3 (p=0.001).

The FAZ area was 0.32±0.11 mm^2 in group 1, 0.29±0.08 mm^2 in group 2, and 0.22±0.09 mm^2 in group 3. The difference was significant between groups 1 and 3 (p<0.001) and groups 2 and 3 (p=0.001).

Average VD in the SCP in the parafoveal region was 49.42±4.81% in group 1, 51.12±3.61% in group 2, and 52.93±2.24% in group 3. There were statistically significant differences between groups 1 and 2 (p=0.001) and between groups 1 and 3 (p<0.001). Average VD in the DCP in the parafoveal region was 50.62±3.91% in group 1, 52.29±4.22% in group 2, and 54.23±2.43% in group 3. There were significant differences between groups 1 and 2 (p=0.002), groups 1 and 3 (p<0.001) and groups 2 and 3 (p=0.023).

Average IRT was 108.02±9.42 µm in group 1, 110.12±11.01 µm in group 2, and 114.41±5.21 µm in group 3. Central IRT was 55.84±6.91 µm in group 1, 58.13±12.22 µm in group 2, and 62.21±8.12 µm in group 3. Compared to group 3, both average and central IRT were significantly decreased in group 1 (p=0.003, p=0.001) and group 2 (p=0.014, p=0.014). Comparisons of demographic data and OCTA findings are shown in Table 1.

There was a moderate negative correlation between DM duration and IRT (r=-0.450, p<0.001). When the relationship between FAZ area and average IRT was analyzed, negative correlations were detected in both group 1 and group 2 (r=-0.320 and -0.512, respectively). Similarly, central IRT and FAZ area showed a negative correlation in both group 1 and group 2 (r=-0.620 and -0.531, respectively).

In addition, our findings showed that in both group 1 and group 2, there was a positive correlation between average VD in the SCP and average IRT in all four quadrants (r=0.192 and 0.364, respectively). The relationship between the average VD in the SCP and central IRT was not significant (p>0.05).

When the relationship between average VD in the DCP and average IRT in the four quadrants was analyzed, it was seen that average IRT was weakly but significantly correlated with

Table 1. Comparisons of demographic data and optical coherence tomography angiography findings				
	Group 1 (DR+) n=23	**Group 2 (DR-) n=30**	**Control group n=27**	**p value**
Mean age (years)	53.12±10.61	52.62±14.42	47.81±12.01	0.062
Male/female (n)	13/10	14/16	14/13	0.077
FAZ area (mm^2)	0.32±0.11	0.29±0.08	0.22±0.09	0.001*
Average VD in SCP (%)	49.43±4.81	51.12±3.61	52.93±2.24	0.001*
Average VD in DCP (%)	50.62±3.91	52.29±4.22	54.23±2.43	0.001*
Average IRT (µm)	108.02±9.42	110.12±11.01	114.41±5.21	0.005*
Central IRT (µm)	55.84±6.91	58.13±12.22	62.21±8.12	0.001*
FAZ: Foveal avascular zone, VD: Vessel density, SCP: Superficial capillary plexus, DCP: Deep capillary plexus, IRT: Inner retinal thickness, *Statistically significant				

average VD in the DCP in both group 1 (r=0.025, p=0.034) and group 2 (r=0.214, p=0.032). Central IRT was not significantly correlated with average VD in the DCP (p>0.05).

There was no significant relationship between IRT values and FAZ or VD in the control group. Comparisons of quantitative OCTA parameters with average and central IRT are shown in Table 2.

Discussion

Studies in diabetic individuals with OCT have shown that the RNFL, GCL, and IPL are thinner in eyes with DR.[6,7] Even in the absence of DR findings in diabetic patients, it has been reported that the thickness of the inner neuroretinal layers is reduced.[16] Progressive inner retina loss was reported as a risk factor for DR progression.[17] This also suggests that neuronal death in the inner retina occurs before damage to the microvascular structures. Actually, some studies showed that reduced blood flow in the choroid and retina in diabetic patients causes chronic ischemia in the retina pigment epithelium and neural retina.[18,19] The underlying mechanisms behind retinal neurodegeneration are not yet fully understood. The oxygen demand of the inner retina is provided by the retinal circulation. Therefore, it is relatively hypoxic in comparison with the outer retina, which makes the inner retinal structures even more vulnerable to metabolic stress.[3] Chronic hyperglycemia and advanced glycosylation end products may also contribute to the apoptosis of neuroglial cells.[20]

OCTA is a non-invasive imaging method that provides three-dimensional, detailed images of blood flow using the intrinsic motion contrast of erythrocytes.[21] With this imaging technique, quantitative assessment of microvascular changes can reveal subclinical changes that may be important in the prevention of visual impairment. In diabetic persons, enlargement and fragmentation of the vascular arcades of the FAZ have been reported, as well as reduced perifoveal VD.[22,23,24,25,26] In these studies, it was shown that even though there were no signs of DR, changes in FAZ and VD could be detected with OCTA. In our study, diabetic eyes had significantly lower VD and larger FAZ area than controls, in accordance with previously reports in the literature. In addition, we determined that FAZ changes and capillary non-perfused areas were more common in diabetic individuals without DR findings than in the healthy group.

Prior studies have demonstrated that the RNFL, GCL, and IPL are thinner in diabetic eyes. Rodrigues et al.[27] stated that diabetic persons without signs of DR had reduced RNFL thickness, suggesting that neurodegeneration occurs before retinal microvascular alterations. Scarinci et al.[28] recently reported a significant thinning of the GCL in persons with DM and no DR. Srinivasan et al.[29] reported that IRT is significantly reduced in eyes with DR compared to the control group. Vujosevic and Midena[30] documented decreased RNFL thickness in patients with no DR and with nonproliferative DR. In the current study, we observed significant thinning of the inner retina in the parafoveal region in eyes with DR in comparison with controls. Also, average and central IRT were lower in diabetic individuals without DR compared to healthy subjects. The difference was significant for the central inner retina. These findings are in agreement with previous reports that observed reduced thickness in the parafovea in individuals with DR in comparison to healthy subjects.[30] However, we have to keep in mind that all of the studies we mentioned were done before the OCTA era and classified patients as having diabetes with retinopathy and without retinopathy based on fundus examination.

It is not yet clear whether neural alterations in the inner retina precede, follow, or occur in parallel with early retinal microvascular changes. With the advance of structural OCT and detailed analysis of the retinal layers, some authors have claimed that unlike conventional knowledge, neuronal structures are affected first in diabetic patients.[27,31] But as we mentioned above, studies with OCTA have shown that vascular structures are already influenced by diabetes even if there are no signs of DR on fundus examination. Kim et al.[13] reported that in diabetic eyes, early alterations in foveal microvascular structures related to GCL/IPL thickness could be detected using OCTA, and the decrease in FAZ circularity and parafoveal VD were highly correlated with decreased GCL/IPL thickness.

Table 2. Correlation analysis between quantitative optical coherence tomography angiography parameters and inner retinal thickness values

	Group 1						Group 2						Group 3					
	FAZ area		Vessel density				FAZ area		Vessel density				FAZ area		Vessel density			
			SCP		DCP				SCP		DCP				SCP		DCP	
	r	p	r	p	r	p	r	p	r	p	r	p	r	p	r	p	r	p
Average IRT	-0.320	0.001*	0.192	0.020*	0.025	0.034*	-0.512	0.001*	0.364	0.018*	0.214	0.032*	-0.046	0.668	0.241	0.352	0.168	0.564
Central IRT	-0.620	0.001*	0.104	0.416	0.020	0.820	-0.531	0.001*	0.234	0.346	0.210	0.742	-0.092	0.692	0.086	0.468	0.082	0.524

OCTA: Optical coherence tomography angiography, IRT: Inner retinal thickness, FAZ: Foveal avascular zone, SCP: Superficial capillary plexus, DCP: Deep capillary plexus, *: Statistically significant p value

Similar to these results from Kim et al.,[13] we found that the microcirculatory changes observed with OCTA were correlated with IRT. Moreover, decreased parafoveal VD and higher FAZ area were strongly associated with IRT thinning.

Study Limitations

Possible limitations of our study are the limited number of eyes included and its retrospective nature. In addition, patients with significant artifacts on OCTA imaging were excluded from our study.

Conclusion

In conclusion, one can claim that the retinal microvasculature is affected by diabetes even if DR findings are not observed on fundus examination. OCTA can easily reveal early-stage changes. Retinal neurodegeneration might progress with impairments of the retinal microvascular structures detectable by OCTA. However, further studies are necessary to understand whether neuroretinal degeneration or microvascular damage occurs first and to determine the link between them.

Ethics

Ethics Committee Approval: This retrospective study was performed in the Ankara University Faculty of Medicine, Department of Ophthalmology from October 2016 to November 2018.

Informed Consent: All procedures performed in the study were in accordance with the ethical standards of the institutional committee and with the Declaration of Helsinki.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: E.T., S.D., F.B., E.Ö., Design: E.T., S.D., F.B., E.Ö., Data Collection or Processing: E.T., S.D., F.B., E.Ö., Analysis or Interpretation: E.T., S.D., F.B., E.Ö., Literature Search: E.T., S.D., F.B., E.Ö., Writing: E.T., S.D., F.B., E.Ö.

Conflict of Interest: No conflict of interest was declared by the authors.

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