

Evaluation of macular choroidal and microvascular network changes by activity scores and serum antibodies in thyroid eye patients and healthy subjects

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Abstract

• **AIM:** To investigate the choroidal thickness and the microvascular network changes around the macula in thyroid eye disease (TED) patients at different stages and the relationship of those changes with risk factors, serum antibodies and the severity of TED.

• **METHODS:** A total of 85 participants were enrolled. All participants underwent ophthalmology and endocrinology examinations. Subfoveal choroidal thickness (SFCT), superficial (s) and deep (d) foveal avascular zone (FAZ) area, mean (m) and central (c) superficial vascular density (SVD), deep vascular density (DVD) measurements of the enrolled cases were performed with Topcon swept source optical coherence tomography (OCT)/OCT angiography (OCTA) DRI OCT Triton. Multiple linear regression analysis was used to explore the associations between SFCT, FAZ area, SVD, DVD and the relevant factors of TED.

• **RESULTS:** Those with active TED patients had higher c-DVD and m-DVD levels ($P < 0.05$), however there is no statistically significant difference in SFCT between active and stable TED patients. Among the serum antibodies, it was observed that s-FAZ and d-FAZ increased, c-SVD and m-SVD decreased in patients with high thyroid stimulating hormone-receptor autoantibodies (TRAB) level, whereas SFCT thickened in patients with high levels of both TRAB and human thyroglobulin (hTG). There was no significant difference in SFCT, FAZ, SVD and DVD measurement at gender, between hyperthyroid and euthyroid patients and among those with or without thyroid papillary carcinoma.

• **CONCLUSION:** The results show that both disease activation and serum antibodies differentially affect both superficial and deep retinal vascular density. It has also been shown that high serum antibody levels affect choroidal thickness independent of clinical activity.

• **KEYWORDS:** thyroid eye disease; optic coherence tomography angiography; vascular density; choroidal thickness; foveal avascular zone area

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INTRODUCTION

Graves' disease is an organ specific autoimmune disease affecting the thyroid gland and orbit. Approximately 35%-47% of all patients with Graves' disease have orbital manifestations described as thyroid eye disease (TED)^[1]. Possible risk factors include female gender, smoking and circulating antibodies against thyroid-stimulating hormone (TSH)^[2-3]. The inflammatory response involves ocular surface, orbital soft tissue, mainly orbital fat and extraocular muscles. Common clinical manifestations of TED include conjunctival redness and chemosis, orbital soft tissue swelling, eyelid retraction, lag exophthalmos, extraocular muscle involvement, corneal involvement, intraocular hypertension and optic neuropathy^[4-5]. The effects of the disease are mild in the majority of patients but about 3%-8% of the TED patients have sight-threatening dysthyroid optic neuropathy (DON)^[6]. Orbital inflammation and mechanical compression in TED are known to affect the orbital vessels^[7-8]. Raised retrobulbar and episcleral venous pressure in TED patients may affect both retinal and choroidal vasculature. Besides, decreased orbital venous outflow detected using color doppler ultrasound may have a role in developing DON^[9]. However, color doppler ultrasound cannot adequately show the retinal microvascular network. Optical coherence tomography (OCT) is one of the biggest advancements in ophthalmic imaging. Built on that platform,

OCT angiography (OCTA) is a new functional method that detects the motion contrast in the bloodstream and visualizes the capillary artery of the retina and choroid without using dye with a level of detail which is far beyond the one obtained *via* older forms of imaging^[10]. In this study, we evaluated the choroidal thickness and the microvascular network changes around the macula in TED patients at different stages and the relationship of those changes with risk factors, serum antibodies and the severity of TED.

SUBJECTS AND METHODS

Ethical Approval The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of Akdeniz University Clinical Research Ethics Committee (protocol code KAEK 66 and date of approval 27.01.2021) for studies involving humans. Informed consent was obtained from all subjects involved in the study.

Eighty-five TED patients admitted to the Akdeniz University hospital between 2021 and 2022 were registered in the study. Healthy controls were recruited during the same study period from among subjects who received annual eye examinations. Patients with retinal disease like diabetic macular edema or age-related macular degeneration and uveitis or glaucoma as well as systemic diseases like hypertension and diabetic retinopathy were excluded from this study.

Lid width, proptosis (in millimeters), best corrected visual acuity (BCVA), slit-lamp biomicroscopy, intraocular pressure (IOP), ophthalmoscopy examinations and OCTA images were recorded. The demographic data including age, sex, duration of hyperthyroidism, smoking status, therapy history (¹³¹I, thyroidectomy or medicine), any systemic disease was reported. Laboratory tests were conducted including free triiodothyronine (FT3), free thyroxine (FT4), TSH, autoantibodies [thyroid stimulating hormone-receptor autoantibodies (TRAB), anti-thyroid peroxidase (TPO) and human thyroglobulin autoantibodies (hTG)]. The clinical activity scoring (CAS)^[5] and European Group on Graves' Orbitopathy Classification (EUGOGO)^[11] was used to estimate TED activity.

Subfoveal choroidal thickness (SFCT), foveal avascular zone (FAZ) area and macular vascular density measurements of the enrolled cases were performed with Topcon swept source OCT/OCTA DRI OCT Triton (Topcon Co. Japan). Fovea-centered 6×6 mm² OCTA images of the patients had better quality and higher reproducibility than 3×3 mm² images. 6×6 mm² OCTA images were preferred to ensure adequate quality imaging and reproducibility. The scanning area centered on the fovea was 6×6 mm² with a signal strength index of >40 for each eye was selected. Any image with a double vessel pattern or motion artifacts of more than three lines was excluded. The superficial and deep retinal capillary plexuses were detected and separated automatically by the instrument.

Subfoveal Choroidal Thickness Measurements The vertical distance from the hyperreflective line corresponding to the retinal pigment epithelium (RPE) in the subfoveal area to the hyporeflexive line of the choroido-scleral interface was measured manually using the OCT images by three different ophthalmologists. The average of the measured values was taken and compared with the values of the other patients and healthy controls group. All ophthalmologists were experts on OCT and also they were unaware of each other.

Foveal Avascular Zone Measurements The FAZ boundaries in the superficial retina and deep retinal layer were marked on the images by two different ophthalmologists and the field was automatically measured by the device. The average of the measured values was taken and compared with those of the other patients and healthy controls group.

Macular Vascular Density Measurements By selecting the "density map" measurement on the OCTA device, the capillary plexus of the superficial retinal layer and the deep retinal layer was measured automatically by the device. Superficial capillary plexus was segmented from 3 μm below the internal limiting membrane to 15 μm below the inner plexiform layer. Deep capillary plexus was segmented from 15 μm below the inner plexiform layer to 70 μm below the inner plexiform layer. These dimensions were placed on the macula with ETDRS Grid scale including 1 mm diameter of the central area and 3 mm diameter of the paracentral area. It was divided into separate quadrants as superior, temporal, inferior and nasal and the vascular densities of these quadrants were recorded separately.

Statistical Analysis The SAS version 9.4 was used to perform statistical analysis. While evaluating the study data, descriptive statistics including the means and standard deviations were obtained. The Kolmogorov-Smirnov test was conducted to check the normality distribution of the variables. Since the data was found to have non-normal distribution, the independent Mann-Whitney *U* test and Kruskal Wallis *H* test were used for the comparative analysis. A *P* value of <0.05 was considered statistically significant.

RESULTS

One hundred fifty-six eyes of 78 participants were analyzed after excluding 14 eyes of 85 participants because of poor segmentation and/or quality of images. Totally 78.2% of 78 TED patients were female and 48.6% were smokers. While 41 patients had hyperthyroidism, 37 patients had euthyroidism. TRAB, TPO and hTG antibody were measured in all patients. TRAB, TPO and hTG antibody were present in 53 patients (69.7%), 40 patients (60.6%) and in 32 patients (45%), respectively. Other patients had normal levels.

Patients were divided into two groups according to CAS, while 54 patients (69.2%) had CAS 0-3 and 24 patients (30.7%)

Table 1 All TED patients measurements

Items, n=156	Min	Max	Mean±SD
SFCT (μm)	118	575	318.88±75.7
s-FAZ (mm ²)	109	629	348.56±102.88
d-FAZ (mm ²)	37.4	619	247.02±99.85
c-SVD (%)	9.12	124	21.96±8.96
m-SVD (%)	36.1	51.6	41±2.46
c-DVD (%)	8.8	54.4	21.2±9.95
m-DVD (%)	30.4	51.7	41.95±2.43

TED: Thyroid eye disease; SFCT: Subfoveal choroidal thickness; s-FAZ: Superficial foveal avascular zone area; d-FAZ: Deep foveal avascular zone area; c-SVD: Central superficial vascular density; m-SVD: Mean superficial vascular density; c-DVD: Central deep vascular density; m-DVD: Mean deep vascular density.

Table 2 Comparison of the TED patients and healthy subjects measurements

Variables	Healthy (n=80)	TED (n=156)	P ^a
Superficial density			
FAZ (mm ²)	353.07±119.6	348.56±102.88	0.967
Central	21.33±3.36	21.96±8.96	0.048
Mean	40.75±2.94	41±2.46	0.401
Deep density			
FAZ (mm ²)	262.31±52.96	247.02±99.85	0.023
Central	21.41±5.27	21.2±9.95	0.005
Mean	41.85±2.21	41.95±2.43	0.870
SFCT (μm)	250.74±56.92	318.88±75.7	<0.001

^aMann-Whitney U test. FAZ: Foveal avascular zone area; SFCT: Subfoveal choroidal thickness.

had CAS 4-7. According to the EUGOGO classification, 22 patients (28.5%) were in the mild group, 45 patients (58.4%) were in the moderate to severe group and 10 patients (12.9%) were in the sight-threatening group. Fifteen patients (19.4%) had thyroid papillary carcinoma.

Measurement results of all 78 TED patients and 40 healthy subjects from OCT and OCTA images including SFCT, mean superficial FAZ (s-FAZ) area, mean deep FAZ (d-FAZ), mean central superficial vascular density (c-SVD), mean superficial vascular density (m-SVD), mean central deep vascular density (c-DVD), mean deep vascular density (m-DVD) are shown in Tables 1 and 2.

There was no significant difference in SFCT, FAZ, SVD and DVD measurements and gender, between hyperthyroid and euthyroid patients and among those with or without thyroid papillary carcinoma. In smokers group, there was a significant difference in SFCT as SFCT was thicker in the smokers group than in non-smokers group ($P=0.008$; Table 3).

As for OCT and OCTA measurements according to serum antibody levels, patients with high TRAB levels had increased SFCT ($P=0.01$), s-FAZ ($P=0.02$) and d-FAZ ($P=0.01$),

decreased c-SVD ($P=0.04$) and m-SVD ($P=0.03$) but no difference was observed in c-DVD ($P=0.58$) and m-DVD ($P=0.11$) measurements. In patients with high TPO levels, only m-SVD ($P=0.04$) decreased but no difference was observed in other parameters. In patients with high hTG levels, SFCT ($P=0.005$) increased but no statistically significant difference was observed in FAZ area and vascular density measurements (Table 4).

According to the severity of the disease, those with a CAS score from 4 to 7 had higher c-DVD and m-DVD levels ($P=0.02$, $P=0.03$). There was no statistically significant difference in other parameters. When we evaluated the patients according to the EUGOGO classification, no statistically significant difference was found between the 3 groups in any parameters (Table 5).

DISCUSSION

TED is an autoimmune disease, but its pathogenesis is not still clearly understood. As we emphasized above, orbital inflammation and mechanical compression observed in TED are known to affect orbital vessels. Increased retrobulbar and episcleral venous pressure may affect both the retinal and choroidal vasculature. In our current study where we used OCT and OCTA, we compared the changes in choroidal thickness, FAZ area and retinal microvascular density in patients with TED according to clinical severity and serum antibody levels. We found that especially DVD increased in patients with high CAS score, and SVD decreased especially in patients with high serum antibodies such as TRAB and TPO. Moreover, patients with high TRAB were found to have increased SFCT and enlargement in the FAZ area. We suggest that these related factors may perhaps help us to better understand the pathogenesis of the disease.

Vascular Density Previous studies focused on the intra-orbital blood flow in TED^[8-9], whereas little attention has been paid to intraocular hemodynamic changes such as FAZ area and retinal vascular density. In a study with color Doppler ultrasonography, Alp^[8] argued that orbital blood flow velocity was altered in patients with TED and increased blood flow velocity in arteries might be secondary to orbital inflammation. Konuk *et al*^[9] also showed that superior ophthalmic vein blood flow velocity decreased significantly in patients with DON. Wu *et al*^[12] reported that the retinal microvascular density was significantly reduced in TED patients compared to healthy controls. Zeng *et al*^[13] reported that the macular microvascular density decreased significantly in the TED patients with chorioretinal folds compared to the TED patients with no chorioretinal folds. Ceylanoglu *et al*^[14] reported that no significant difference was observed in macular microvascular structure among pediatric TED patients compared to the healthy controls. In our study, demographic characteristics and

Table 3 Comparative measurements with sex, thyroid hormone, thyroid papillary carcinoma and smokers

Items	Sex			Thyroid hormone			Thyroid papillary carcinoma			Smokers		
	M	F	P	Dysthyroid	Euthyroid	P	Yes	No	P	Yes	No	P
n (%)	17 (21.7)	61 (78.2)		41 (52.5)	37 (47.4)		15 (19.2)	63 (80.7)		38 (48.7)	40 (51.2)	
SFCT (µm)	293.7	293.1	0.99	311.3	321.5	0.44	314.1	316.7	0.67	336.5	293.3	0.008
s-FAZ (mm ²)	351.7	352.3	0.68	351.7	354.1	0.88	379	347.4	0.27	336.4	364.0	0.38
d-FAZ (mm ²)	328.5	300.5	0.48	247.8	256.3	0.96	247.7	252.9	0.99	240.9	257.2	0.23
c-SVD (%)	22.1	21.4	0.44	21.9	24.8	0.83	22.2	21.0	0.33	21.8	24.9	0.53
m-SVD (%)	40.8	40.5	0.40	40.6	40.9	0.95	40.89	40.75	0.56	40.6	40.9	0.50
c-DVD (%)	22.3	19.4	0.28	21.0	20.7	0.92	25.2	23.9	0.23	20.6	21.3	0.78
m-DVD (%)	41.9	42.1	0.73	41.6	42.3	0.28	41.66	42.07	0.72	42.1	42.0	0.90

M: Male; F: Female; SFCT: Subfoveal choroidal thickness; s-FAZ: Superficial foveal avascular zone area; d-FAZ: Deep foveal avascular zone area; c-SVD: Central superficial vascular density; m-SVD: Mean superficial vascular density; c-DVD: Central deep vascular density; m-DVD: Mean deep vascular density.

Table 4 Comparative measurements with serum antibodies

Items	TRAB			TPO			hTG		
	Low	High	P	Low	High	P	Low	High	P
n (%)	25 (32)	53 (67.9)		38 (48.7)	40 (51.2)		46 (58.9)	32 (41.0)	
SFCT (µm)	292.4	326.8	0.01	303.7	327.8	0.06	299.0	343.1	0.005
s-FAZ (mm ²)	321.0	362.0	0.02	374.4	345.1	0.49	363.3	350.0	0.37
d-FAZ (mm ²)	219.1	259.4	0.01	262.2	256.1	0.70	253.9	258.2	0.50
c-SVD (%)	24.3	21.4	0.04	24.0	23.5	0.34	24.7	21.4	0.55
m-SVD (%)	41.9	40.1	0.03	41.4	40.2	0.04	40.9	40.5	0.25
c-DVD (%)	24.5	20.6	0.58	23.1	19.9	0.70	20.5	20.9	0.59
m-DVD (%)	42.3	41.8	0.11	42.1	42.1	0.88	42.1	42.0	0.68

TRAB: Thyrotropin-receptor antibody; TPO: Thyroid peroxidase; hTG: Human thyroglobulin; SFCT: Subfoveal choroidal thickness; s-FAZ: Superficial foveal avascular zone area; d-FAZ: Deep foveal avascular zone area; c-SVD: Central superficial vascular density; m-SVD: Mean superficial vascular density; c-DVD: Central deep vascular density; m-DVD: Mean deep vascular density.

Table 5 Comparative measurements with activity scores

Items	CAS			EUGOGO			
	0-3	4-7	P	1	2	3	P
n (%)	108 (69.2)	48 (30.7)		46 (29.4)	90 (57.6)	20 (12.8)	
SFCT (µm)	286.3	321.9	0.055	307.6	318.2	319.4	0.39
s-FAZ (mm ²)	353.9	344.9	0.75	363.2	346.3	363.2	0.69
d-FAZ (mm ²)	323.4	245.4	0.051	273.9	237.2	275.9	0.57
c-SVD (%)	21.2	23.5	0.051	22.9	23.9	23.4	0.41
m-SVD (%)	40.4	41.2	0.21	40.5	40.8	41.1	0.81
c-DVD (%)	19.4	23.3	0.02	19.6	20.3	20.5	0.14
m-DVD (%)	41.8	42.9	0.03	41.6	42	42.6	0.63

CAS: Clinical Activity Scores; EUGOGO: European Group on Graves' Orbitopathy Classification; SFCT: Subfoveal choroidal thickness; s-FAZ: Superficial foveal avascular zone area; d-FAZ: Deep foveal avascular zone area; c-SVD: Central superficial vascular density; m-SVD: Mean superficial vascular density; c-DVD: Central deep vascular density; m-DVD: Mean deep vascular density.

OCTA parameters of the TED patients were compared with those of 40 healthy subjects. No significant difference was observed between their demographic characteristics. In the healthy subjects, c-SVD was measured as 21.33%±3.36% in OCTA parameters. It was considered to be reduced statistically significantly in the healthy group compared to the TED group (P=0.048). When the DVD of the healthy group and

TED group was compared, c-DVD (P=0.005) values were found to be statistically reduced in the TED group. We tried to determine the association of retinal microvascular changes with serum antibody and clinical activity score. We found that especially SVD decreased in patients with high TRAB and high TPO levels, whereas DVD increased in patients with high CAS scores. Such increase in DVD might be due to the

fact that orbital inflammation was higher in patients with a high CAS score, and that inflammation caused an increase especially in DVD. There is some evidence that TRAB can increase inflammation through oxidative stress-induced apoptosis but its role in the pathogenesis of TED is still unclear. TRAB reflects the amount of antibodies depositing in the microvascular system. We think that the accumulation of these antibodies in the vascular system may impair circulation and reduce SVD in particular.

Foveal Avascular Zone Area The FAZ area known as the most sensitive part of the retina is an area that does not contain capillaries in the fovea. It is known that the FAZ area expands in ischemic diseases such as diabetic retinopathy^[15]. Yu *et al*^[16] argued that the FAZ area expanded in active TED patients. In our study, both the superficial and deep FAZ areas were observed to have expanded with decreased SVD only in TED patients with high TRAB. Furthermore, the d-FAZ area was also statistically significantly higher in TED patients compared to the healthy group ($P=0.023$). However, many factors such as age, gender, axial length can affect the size of the FAZ area^[17].

Choroidal Thickness The choroid is the dense vascular network layer between the sclera and the retina that provides blood flow and nutrition to the RPE and outer retinal layers. Current literature suggests that it decreases in women, myopia, advanced age, cardiovascular diseases such as chronic hypertension, coronary artery disease, carotid artery stenosis^[18], and the choroid of patients thickens in active phases of inflammatory diseases such as lupus, Behçet's disease, systemic sclerosis and familial Mediterranean fever^[19]. Çalışkan *et al*^[20] were the first ones to describe the changes in choroidal thickness in eyes with TED. They reported that the mean SFCT increased in eyes with active TED compared to the healthy control group. In our study, choroidal thickness was statistically higher in the healthy group compared to the TED group ($P<0.001$). Gul *et al*^[21] compared choroidal thicknesses in active and stable TED patients and they found that SFCT was significantly higher in patients with TED at the active phase than in those at the stable phase of the disease. However, in our study including a larger patient group, we did not find a statistically significant difference in SFCT between active and stable TED patients by dividing the patients into groups according to CAS and EUGOGO severity classification. We think that increased blood flow velocity in the arteries during the active TED disease possibly caused primarily an increase in DVD. But it did not affect the SFCT. SFCT increased only in patients with high TRAB and hTG levels, who might perhaps have more severe inflammation. Additionally, it was observed that the SFCT was statistically thicker in active smokers group. It is still controversial, though. El-Shazly *et al*^[22] found that

SFCT was significantly lower in active smokers compared to passive smokers. On the other hand, Ulaş *et al*^[23] argued that SFCT significantly increased from baseline at 0 and 5min after smoking and then decreased until reaching baseline at 1h after smoking.

There were some limitations in our current study. This is a cross-sectional study and prevents us from associating vascular changes with disease progression. We only analyzed the hemodynamic changes in an area of approximately 6 mm diameter in the foveal region but did not analyze larger areas around the macula and optic disc. Perhaps more valuable information could be obtained in those regions. Moreover, dysthyroid patients in the absence of TED were not enrolled, which might also limit the interpretation of the results to some extent.

In conclusion, we used OCT and OCTA imaging to compare the macular choroidal and microvascular network changes in TED patients with different activity scores and the effect of serum antibodies. The results showed that both disease activation and serum antibodies had a different effect on both superficial and deep retinal vascular densities. High serum antibody levels were also demonstrated to affect choroidal thickness independent of disease activity. We believe that the ocular vascular network clearly plays an important role in the pathogenesis because of the hemodynamic changes that occur in eyes with TED.

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REFERENCES

- 1 Lim SL, Lim AKE, Mumtaz M, Hussein E, Wan Bebakar WM, Khir AS. Prevalence, risk factors, and clinical features of thyroid-associated ophthalmopathy in multiethnic Malaysian patients with Graves' disease. *Thyroid* 2008;18(12):1297-1301.
- 2 Weetman AP. Graves' disease. *N Engl J Med* 2000;343(17):1236-1248.
- 3 Prummel MF. Smoking and risk of Graves' disease. *JAMA* 1993;269(4):479.
- 4 Sun R, Zhou HF, Fan XQ. Ocular surface changes in Graves' ophthalmopathy. *Int J Ophthalmol* 2021;14(4):616-621.
- 5 Mourits MP, Prummel MF, Wiersinga WM, Koornneef L. Clinical activity score as a guide in the management of patients with Graves' ophthalmopathy. *Clin Endocrinol* 1997;47(1):9-14.

- 6 Neigel JM, Rootman J, Belkin RI, Nugent RA, Drance SM, Beattie CW, Spinelli JA. Dysthyroid optic neuropathy. The crowded orbital apex syndrome. *Ophthalmology* 1988;95(11):1515-1521.
- 7 Goel R, Shah S, Sundar G, Arora R, Gupta S, Khullar T. Orbital and ocular perfusion in thyroid eye disease. *Surv Ophthalmol* 2023;68(3):481-506.
- 8 Alp MN. Colour Doppler imaging of the orbital vasculature in Graves' disease with computed tomographic correlation. *Br J Ophthalmol* 2000;84(9):1027-1030.
- 9 Konuk O, Onaran Z, Ozhan Oktar S, Yucel C, Unal M. Intraocular pressure and superior ophthalmic vein blood flow velocity in Graves' orbitopathy: relation with the clinical features. *Graefes Arch Clin Exp Ophthalmol* 2009;247(11):1555-1559.
- 10 Spaide RF, Fujimoto JG, Waheed NK, Sadda SR, Staurengi G. Optical coherence tomography angiography. *Prog Retin Eye Res* 2018;64:1-55.
- 11 Bartalena L, Kahaly GJ, Baldeschi L, et al. The 2021 European Group on Graves' orbitopathy (EUGOGO) clinical practice guidelines for the medical management of Graves' orbitopathy. *Eur J Endocrinol* 2021;185(4):G43-G67.
- 12 Wu YF, Tu YH, Bao LL, Wu CM, Zheng JW, Wang JH, Lu F, Shen MX, Chen Q. Reduced retinal microvascular density related to activity status and serum antibodies in patients with Graves' ophthalmopathy. *Curr Eye Res* 2020;45(5):576-584.
- 13 Zeng P, Wang J, Tian P, Peng YY, Liang JQ, Wang M, Zhou SY. Macular and peripapillary optical coherence tomography angiography metrics in thyroid-associated ophthalmopathy with chorioretinal folds. *Photodiagn Photodyn Ther* 2023;42:103146.
- 14 Ceylanoglu KS, Sen EM, Karamert SS, Erdeve SS, Cetinkaya S. Optical coherence tomography angiography findings in pediatric patients with Graves ophthalmopathy. *Int Ophthalmol* 2023; 43(10):3609-3614.
- 15 Abdelshafy M, Abdelshafy A. Correlations between optical coherence tomography angiography parameters and the visual acuity in patients with diabetic retinopathy. *Clin Ophthalmol* 2020;14:1107-1115.
- 16 Yu LC, Jiao Q, Cheng Y, Zhu YJ, Lin ZJ, Shen X. Evaluation of retinal and choroidal variations in thyroid-associated ophthalmopathy using optical coherence tomography angiography. *BMC Ophthalmol* 2020;20(1):421.
- 17 Zhou YF, Zhou MW, Gao M, Liu HY, Sun XD. Factors affecting the foveal avascular zone area in healthy eyes among young Chinese adults. *BioMed Res Int* 2020;2020:1-8.
- 18 Yeung SC, You YY, Howe KL, Yan P. Choroidal thickness in patients with cardiovascular disease: a review. *Surv Ophthalmol* 2020;65(4):473-486.
- 19 Steiner M, del Mar Esteban-Ortega M, Muñoz-Fernández S. Choroidal and retinal thickness in systemic autoimmune and inflammatory diseases: a review. *Surv Ophthalmol* 2019;64(6):757-769.
- 20 Çalışkan S, Acar M, Gürdal C. Choroidal thickness in patients with Graves' ophthalmopathy. *Curr Eye Res* 2017;42(3):484-490.
- 21 Gul A, Basural E, Ozturk HE. Comparison of choroidal thickness in patients with active and stable thyroid eye disease. *Arq Bras Oftalmol* 2019;82(2):124-128.
- 22 El-Shazly AAE, Farweez YAT, Elzankalony YA, Elewa LS, Farweez BAT. Effect of smoking on macular function and structure in active smokers versus passive smokers. *Retina* 2018;38(5):1031-1040.
- 23 Ulaş F, Çelik F, Doğan Ü, Çelebi S. Effect of smoking on choroidal thickness in healthy smokers. *Curr Eye Res* 2014;39(5):504-511.