Retinal Microvascular Changes in Euthyroid Graves' Disease without Ocular Involvement Using Optical Coherence Tomography Angiography

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ABSTRACT

Objective: This study was designed to evaluate macular perfusion in asymptomatic Graves' disease using optical coherence tomography angiography (OCTA).

Materials and Methods: Thirty-three patients with Graves' disease and 38 healthy individuals were included in the study. The superficial (VDs), deep (VDd) and choriocapillary (VDc) vascular densities of the subjects were examined. Foveal avascular zones in the superficial (FAZs) and deep layer (FAZd) with central macular thickness (CMT) and subfoveal choroidal thickness (SFCT) were evaluated.

Results: The mean age of Graves' disease patients was 34.18 ± 12.12 years, while the mean age of the healthy control group was 35.56 ± 13.7 years. Age and gender distribution between the patients and control groups did not show significant difference ($p < 0.05$). Central sector value of VDs was significantly found to be increased ($p = 0.035$). The mean FAZs and FAZd were significantly higher in Graves' disease cases ($p = 0.0001$; $p = 0.001$). No significant difference was observed in VDd, VDc and other sectors of the VDs ($p > 0.05$). While mean CMT was found to be significantly higher in the Graves' disease group than in the control group ($p = 0.001$), mean SFCT was found to be significantly lower ($p = 0.026$).

Conclusion: Alterations of retinal micro vascularity were observed in euthyroid Graves' disease patients. A significant change in FAZ areas and choroidal thickness shows that the retina may be affected in inactive asymptomatic Graves' disease.

Keywords: Graves' disease, macular vasculature, optical coherence tomography angiography, choroidal thickness

INTRODUCTION

Graves' disease is an autoimmune disease that primarily affects the thyroid gland and is the most common cause of hyperthyroidism in all age groups.[1] While there is a familial background, various environmental factors such as smoking and pregnancy can also trigger Graves' disease.[2] Abnormal levels of thyroid-stimulating antibodies (TSA) play a role in the pathophysiology of the disease. TSA binds to the thyroid-stimulating hormone receptor causing excessive thyroid hormone production. Elevated thyroid hormones can lead to systemic problems such as irritability, tachycardia, intestinal hypermobility, excessive weight loss, hot flashes, and difficulty in concentrating.[3] Graves' disease affects numerous organs and tissues, lead-

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ing to systemic problems. The most significant connective tissue problem resulting from the direct effects of TSA is thyroid-associated ophthalmopathy (TAO).[4]

Various studies have reported that thyroid hormone has similar effects to catecholamines on vascular structures by targeting the vascular endothelium.[5] It has also been demonstrated that TSA can affect vascular function by triggering endothelial damage.[6] Beyond the classical ophthalmologic manifestations, the ocular involvement of Graves' disease has increasingly been investigated using multimodal imaging techniques, as the disease may induce microvascular alterations in highly vascularized ocular tissues, particularly the choroid.[7]

Retinal and choroidal perfusion can be visualized noninvasively with swept-source optical coherence tomography angiography (OCTA). With this unique function, OCTA can provide guidance in numerous isolated eye diseases and systemic diseases. OCTA combines the intravascular movement of red blood cells with multiple B-scan images and provides information about microvascular structures such as the superficial and deep capillary plexus of the retina, the foveal avascular zone (FAZ), and the choriocapillaris.[8] Several studies have investigated retinal and choroidal perfusion and other morphological and functional changes in the eye in patients with thyroid orbitopathy or hyperthyroidism.[9-12] However, there are a few studies in the literature conducted with different OCTA devices in asymptomatic Graves' disease.[13-15] In the present study, we aimed to evaluate retinal and choroidal microvascular structures in asymptomatic patients with Graves' disease using OCTA.

MATERIALS AND METHODS

Study population

This cross-sectional and comparative study was conducted at Selcuk University Faculty of Medicine, Department of Ophthalmology and Endocrinology. Our study was conducted with the approval of our hospital's ethics committee (Ethics Committee no: 2021/521) and in accordance with the Declaration of Helsinki. All participants were informed about the study, and written informed consent was obtained from all participants. Thirty-three eyes of 33 patients with TSA-positive asymptomatic and euthyroid Graves' disease who were being followed in Endocrinology and Metabolic Diseases Department and 38 eyes of 38 sex- and age-matched healthy individuals with no comorbid ophthalmologic or systemic conditions were included in the study. None of the included patients had a history of previous TAO episodes. Inactivity of the disease was evaluated using the NOSPECS score.[16] Patients with abnormal thyroid function tests, smokers, comorbid systemic diseases, high refractive vision correction (spherical equivalent higher than +3 or -3 diopter), an ophthalmological pathology (e.g., Glaucoma, retinal vascular diseases, uveitis and amblyopia) and a history of ocular surgery were excluded from the study.

Physical Examination, Image Acquisition and Processing

The best-corrected visual acuity (BCVA) of the patient and control groups was determined using the Snellen chart. Intraocular pressures measured by Goldmann applanation tonometry and a detailed anterior segment examination were performed using a biomicroscope. After complete pupil dilation with 0.5% Tropicamide, a detailed fundus examination was performed with a 90-diopter lens. Following full dilation with tropicamide, all participants rested in a sitting position for half an hour, and Swept-Source DRI Triton OCTA (Topcon Corp, Tokyo, Japan) images were obtained. A 6x6 mm area was scanned at the center of the fovea, and the scanned area was automatically segmented in en-face mode using OCTA software (IMAGEnet 6 V.1.14.8538) (Figure 1). Superficial capillary plexus density (VDs), deep capillary plexus density (VDd), and choriocapillary vascular complex density (VDc) were automatically obtained as numerical values from the OCTA images in five quadrants (central, superior, temporal, inferior, and nasal). Automatic segmentation of the retinal layers was performed on B-mode images. The superficial capillary plexus layer extends from 2.6 μm below the internal limiting membrane to 15.6 μm below the interface of the inner plexiform layer and the inner nuclear layer (IPL/INL). The deep capillary plexus layer extends from 15.6 μm below the IPL/INL to 70.2 μm below the IPL/INL. The choriocapillary vascular complex layer extends from Bruch's membrane to 10.4 μm below Bruch's membrane.[17] GNU Image Manipulation Program (GIMP) 2.8.14 was used to quantitatively analyze VDs, VDd, VDc, superficial foveal avascular zones (FAZs), and deep foveal avascular zones (FAZd). Each measurement was calculated as the percentage of vascularized tissue within the defined area. The subfoveal choroidal

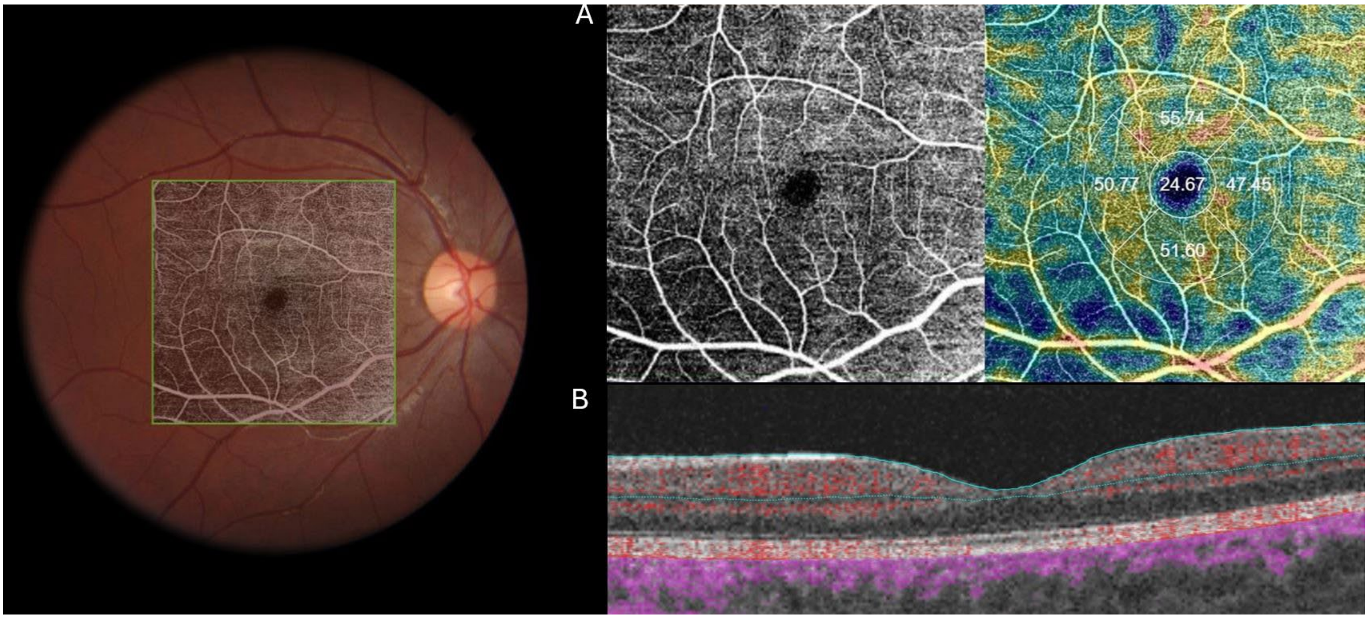

Figure 1: *Illustrative OCTA analysis of a 6 × 6 mm area in the superficial vascular complex, with the grid centered on the macula. The image shows the density map with the grid divided into five areas – central, nasal, inferior, temporal and superior – with the percentages of vessel density (A). The image at the bottom shows a B scan with the blue lines limiting the analyzed zone (B).*

thickness and central macular thickness (SFCT and CMT, respectively) analysis were performed for all subjects of the eyes in 9 regions of the macula. Macula sections were determined objectively with radii of 0.5 mm (center 1 mm), 0.5 to 1.5 mm (inner ring), and 1.5 to 3.0 mm (outer ring). CMT and SFCT values were achieved using an ETDRS grid overlay comprising the inner rings. All measurements were performed by the same experienced ophthalmologist (S. E.) at the same time interval of the day (i.e., 9–10 a.m.) to minimize any influence of the normal diurnal variations. Those with poor OCTA image quality (if Image Quality Index (IQI) were under 70, motion artifact, segmentation artifact, or focal signal loss) were excluded from the study. Afterall, the parameters were compared between the Graves' disease group and control group.

Statistical Analysis

SPSS Statistics (v. 26.0; IBM, Chicago, IL, USA) was utilized for statistical analysis. In descriptive analyses, frequency data are presented using number (n) and percentage (%), and numerical data are presented using the mean ± standard deviation (SD). The normality of each variable was measured using the Kolmogorov–Smirnov test. Comparisons of categorical data were performed using the Chi-square test. The distribution of normally distributed numerical data in two independent groups was assessed using the Independent Samples T-test, and the distribution of non-normally distributed numerical data was compared using the Mann-Whitney U test. Results were evaluated at a 95% confidence level, and significance was deemed at a $p < 0.05$ level.

RESULTS

The mean age of Graves' disease patients was 34.18 ± 12.12 years, while the mean age of the healthy control group was 35.56 ± 13.7 years. There was no significant difference in age and gender distribution between the patients and control groups ($p < 0.05$). According to the Snellen chart, BCVA was 6/6 among all participants. No significant difference was observed in intraocular pressure measurements. The subjects' OCTA parameters are demonstrated in Table 1.

The mean CMT was significantly higher in the Graves' disease group than in the control group ($p = 0.001$). The mean SFCT was 238.18 ± 65.04 in the Graves' disease group and 283.67 ± 89.33 in the control group; and found significantly lower in the Graves' disease group ($p = 0.026$).

Table 1. *Comparison of mean values of OCTA parameters between Graves' disease patients and healthy controls*

	Graves' Disease Group				Control Group				P	
	Mean / Sd			Median	Mean / Sd			Median		
FAZs	284.98	±	82.16	270.4	203.73	±	92.21	193.35	**0.0001**	t
FAZd	392.85	±	154.61	318.51	271.9	±	98.12	273.86	**0.001**	m
VDs Central	27.98	±	5.82	28.04	26.29	±	8.2	24.45	**0.035**	m
VDs Superior	49.04	±	3.22	48.36	50.24	±	4.23	50.11	0.189	t
VDs Temporal	46.74	±	5.09	46.28	46.78	±	3.59	46.98	0.969	t
VDs Inferior	49.68	±	5.17	48.13	48.71	±	5.99	47.62	0.576	m
VDs Nasal	45.51	±	5.65	43.88	46.07	±	3.7	46.38	0.624	t
VDd Central	26.36	±	6.03	26.47	25.75	±	9.37	23.49	0.075	m
VDd Superior	51.74	±	3.74	52.36	52.34	±	4.71	52	0.558	t
VDd Temporal	48.2	±	2.57	48.23	49.16	±	4.59	50.62	0.289	t
VDd Inferior	51.89	±	5.33	50.32	49.02	±	9.65	49.55	0.271	m
VDd Nasal	49	±	5.4	48.3	48.81	±	4.36	49.43	0.874	t
VDc Central	54.03	±	5.08	51.67	52.1	±	10.23	54.96	0.087	m
VDc Superior	54.02	±	2.2	53.99	54.03	±	54.81	54.81	0.281	m
VDc Temporal	53.17	±	5.68	52.23	53.37	±	4.24	53.69	0.163	m
VDc Inferior	56.68	±	4.73	55.19	54.08	±	5.68	55.2	0.133	m
VDc Nasal	54.49	±	3.88	54.2	52.57	±	4.5	54.11	0.355	m
CMT	203.72	±	23.32	201	188.18	±	15.99	185	**0.001**	m
SFCT	238.18	±	65.04	224	283.67	±	89.33	275	**0.026**	m

[m]Mann-Whitney u test / [t]Independent sample t test / Sd: standart deviation;
FAZs:superficial foveal avascular zone; FAZd: deep foveal avascular zone; VDs: superficial vascular density;
VDd: deep vascular density; VDc: choriocapillaris vascular density;CMT: central macular thickness;
SFCT: subfoveal choroidal thickness.

FAZs was 284.98 ± 82.16 in the Graves' disease group and 203.73 ± 92.21 in the control group; and was significantly higher in the Graves' disease group (p = 0.0001). Also, FAZd was significantly higher in the Graves' disease group (p = 0.001).

The mean value of VDs central sector was significantly higher in the Graves' disease group compared to the control group (p = 0.035). Other sectors of the VDs did not show any significant difference (p > 0.05). Additionally, no significant difference was detected in all sectors of VDd (p>0.05). Differences in VDc between the two groups were not statistically significant (p>0.05).

DISCUSSION

This study aimed to evaluate retinal and choroidal microcirculation and structural changes using OCTA in individuals with Graves' disease who were clinically asymptomatic. Our findings suggest that vascular and structural changes may occur in patients with TSA positive Graves' disease, despite the absence of clinical activity and orbitopathy. Particularly, the significant increase in FAZ areas indicates that Graves' disease patients may have subclinical changes in retinal vascularity, even if asymptomatic.

The systemic effects of Graves' disease occur through two main mechanisms. The first is the effect of high levels of thyroid hormones released as a result of overactivity of the thyroid gland, and the second is the effect of TSA binding to various receptors in the connective tissue and acting as a receptor.[18] TSA binds to fibroblasts in the periorbital and retroorbital tissues, causing abnormal growth, inflammation, and edema in these tissues. This mechanism, which also affects the extraocular muscles, can lead to advanced stage ocular involvement such as proptosis, optic nerve compression, limited eye movements, periorbital edema, diplopia, eyelid retraction, and chemosis.[4] The most common extrathyroidal manifestations of Graves' disease are related with eyes. Therefore, there are many studies on ocular involvement in Graves' disease.[19]

In our study, CMT was found to be significantly higher in the Graves' disease group compared to the healthy group. In a study comparing patients with TAO and healthy individuals, CMT was found to be significantly higher in the TAO group compared to the controls.[20] These findings were thought to be related to increased retinal inflammation and perfusion. In an animal model of retinal degeneration, increased local thyroid hormone receptor activity in the retina was observed to correlate with retinal degeneration.[21] This finding suggests that, even in the absence of systemic clinical activity, thyroid hormone-related activities at the tissue level may have negative effects on the retina. The direct effect of TSA on retinal cells is the subject of future studies.

Investigating retinal and choroidal perfusion is important both for examining the effects of systemic diseases on the eye and for identifying the characteristics of systemic disease.[22, 23] Numerous studies in the literature evaluate the effects of autoimmune diseases on choroidal thickness.[24] In our study, SFCT was found to be significantly lower in the Graves' disease group. This finding may be related to impaired choroidal perfusion in TSA-positive patients despite inactive state. On the other hand, an article investigating choroidal thickness in patients with euthyroid Graves' ophthalmopathy reported that SFCT thickness was higher in the patient group, and that this finding was interpreted as being related to venous congestion and increased orbital inflammation.[25] There are studies reporting that choroidal thickness increases due to increased inflammation in the active phases of systemic diseases and decreases due to impaired vascular perfusion in chronic or recurrent conditions.[18] When evaluated together with our study and the literature, the findings suggest that perfusion impairment may predominate in asymptomatic Graves' disease, leading to choroidal thinning. In active disease, choroidal thickness may increase due to the predominant inflammatory process.

FAZs and FAZd measurements were found to be significantly increased in the Graves' group. FAZ enlargement is an indirect indicator of retinal perfusion impairment.[26] In a study comparing active TAO, inactive TAO, and healthy patients; FAZ area was found to be significantly higher in the active group compared to the other two groups, while there was no significant difference between inactive TAO and healthy patients.[27] Another study, similar to our results, reported a significantly increased FAZ area in inactive TAO patients compared to the healthy group.[11] Our findings suggest that retinal microvascular alteration may be observed in clinically inactive Graves' disease patients. The increase in FAZ areas and the decrease in choroidal thickness suggested that there may be a silent ischemic process in the asymptomatic stage of Graves' disease.

In the Graves' disease group, a significant increase was detected only in central sector of VDs, while no significant difference was observed in the other sectors. One study reported a significantly decreased VDs in active TAO patients compared to the healthy group.[13] A decrease in VDs has been associated with vascular perfusion impairment in various systemic diseases.[28, 29] We found no significant difference between the groups in VDd and VDc. However, there are studies that have reported decreased VDd and VDc in patients with active TAO.[12] In a meta-analysis evaluating studies conducted in patients with inactive Graves' orbitopathy, it was reported that macular VD and the FAZ area did not show a statistically significant difference between patients with inactive Graves' orbitopathy and healthy controls, and that macular microvascular changes are more likely to occur during the active phase of the disease.[30] Similarly, in our study, since the study group consisted of clinically inactive and euthyroid Graves' disease patients, no significant differences were detected in vascular plexus parameters. Nevertheless, this meta-analysis also reported that variability in VD measurements may exist due to the inclusion of different OCTA devices.[30] There are limited studies in literature targeting inactive Graves' disease patients using OCTA.[13-15]

The present study has some limitations. The sample size was relatively small and did not consist of different demographic groups. Because of the lack of a prospective design, we could not examine the changes in retinal vascular parameters in the active stages of the disease. It would be useful to conduct comprehensive studies that can reveal which OCTA parameters change in the silent phase who develop TAO in the future.

CONCLUSION

Our study demonstrated that retinal and choroidal microvascular structures can be changed in clinically inactive and euthyroid Graves' disease patients. Ocular involvement has been demonstrated even in inactive Graves' disease patients, with increased FAZ and decreased choroidal thickness. Further longitudinal studies may reveal whether these assessments could be useful in evaluating the risk of progression to active disease and in monitoring vascular changes using OCTA.

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