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ORIGINAL ARTICLE

Optical coherence tomography angiography evaluation of retinochoroidal and optic disc microvascular morphology in thyroid ophthalmopathy

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Abstract

Purpose: The purpose of the study was to investigate detailed optic disc, choroid, and retinal microvascular morphological changes in active Thyroid ophthalmopathy (TO) patients due to thyroid disease using Optical Coherence Tomography Angiography (OCTA).

Methods: Forty-six (34 females and 12 males) active TO patients and 41 (28 females and 13 males) healthy participants were included in the study. All patients underwent clinical examinations and ophthalmologic evaluations at first and last visits for visual acuity measurement, eyelid opening measurement, Clinical Activity Score (CAS) assessment (TO patients with CAS ≥3 were recorded, indicating active TO), exophthalmometry, cornea, and fundus examination, and those with initial intraocular pressure range of 14–21 mm Hg were included in the study. The overall degree of TO was assessed using the NOSPECS Score. The diagnosis of TO was made by a specialist according to the Bartley and Gorman Criteria.

Results: The mean retinal nerve fiber layer (RNFL) thickness was significantly different between the groups ($p<0.001$), with active TO patients having a thinner RNFL thickness than the control group ($p<0.001$). When temporal and inferior RNFL thicknesses were compared ($p=0.01$, $p=0.01$), different results were obtained when compared to the control group, but there were no significant differences in upper and nasal RNFL thicknesses ($p=0.604$, $p=0.513$). Choroidal thickness (CT) measurements were significantly higher in the macular region in TO patients than in healthy individuals ($p<0.05$). The mean FAZ area in the TO group was found to be 0.303±0.104 mm^2 at a significantly larger level compared to the control group (0.260±0.100) ($p=0.037$).

Conclusion: Significant differences were detected in the RNFL, CT, FAZ area, superficial and deep retinal vessels, and RPC in TO patients. The data obtained showed that the OCTA device is an important guide for diagnosis, treatment and follow-up in the early stages of TO.

Keywords: Foveal avascular zone; microvascular morphology; optical coherence tomography angiography; retina; thyroid ophthalmopathy; vessel density.

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Thyroid ophthalmopathy (TO) is a systemic autoimmune disorder that primarily affects the orbit, resulting in impaired vision and facial appearance, and, ultimately, a lower quality of life. Despite involving individuals of all ages, elderly men are disproportionately affected.[1] This disorder is typically bilateral and asymmetric. It is distinguished by excessively swollen extraocular muscles in orbital tissues, leading to orbital compression due to interstitial tissue edema, and orbital fat hyperplasia.[2] Clinical manifestations include periorbital tissue, conjunctival erythema, edema, upper eyelid retraction, proptosis, diplopia, or a pressure feeling behind the eyes.[3] Although the exact cause of TO is unknown, autoimmune inflammatory infiltration has been implicated. This disorder generally manifests in two stages: An active stage with rapid progression and an inactive stage with symptoms that stabilize.[4] Essentially, 3–5% of inactive TO patients become active, resulting in proptosis, lid retraction, dysfunctional eye motility, and even optic nerve compression, causing vision loss.[5]

Various imaging modalities have been used to examine retinochoroidal and ocular hemodynamic changes secondary to TO-induced compression.[3] Color Doppler flow imaging evaluates orbital vessel blood flow rate non-invasively; however, during the procedure, the color Doppler flow meter is adversely affected by subjective external factors such as pressure applied to the eyeball, ocular movement, sampling volume, and angle. Hence, alternative methods of measuring ocular hemodynamic changes have become necessary. One technique is magnetic resonance imaging (MRI). T2 levels can be determined by scanning extraocular muscles or using fat suppression technology, both of which have been developed to monitor changes in ocular blood flow in TO patients.[3] These techniques, on the other hand, have not widely been accepted as they are time-consuming and invasive. Besides, color Doppler flow imaging and MRI both appear insufficient for accurately analyzing retinochoroidal microcirculation in TO patients.

Optical coherence tomography (OCT) is a non-invasive imaging technique used to extensively visualize retinochoroidal microstructural configuration. In TO patients, OCT revealed decreased retinal nerve fiber layer (RNFL) and macular thicknesses,[6] as well as increased choroidal thickness (CT).[7] OCT angiography (OCTA) is a novel imaging technique that employs cutting-edge technology to visualize the retinochoroidal microvascular system non-invasively and without the use of exogenous dyes.[8,9] It is possible to create retinochoroidal 3D microcirculation vascular maps using this technologically advanced method, which allows for simultaneous visualization of the inner and outer retinal (OR) microcirculation. It has recently been widely used in the diagnosis and monitoring of various ophthalmic pathologies, including glaucoma, diabetic retinopathy, central serous chorioretinopathy, senile macular degeneration, and so on.[10] Nonetheless, very few OCTA-based reports on the retinochoroidal microvascular system in TO patients have been published.

The purpose of our study was, therefore, to examine microvascular morphological changes in the retinochoroidal layer, as well as optic disc using OCTA in patients with active TO, and compare the results to healthy controls.

Materials and Methods

Study Design and Participants

This single-center cross-sectional study was conducted between March 2021 and March 2022 at Afyonkarahisar Health Sciences University's Department of Ophthalmology. It was approved by the University Clinical Research Ethics Committee and was carried out in accordance with the principles of the Helsinki Declaration. The method and purpose of the study were thoroughly explained to all participants, and each patient provided informed consent. Participants were divided into two groups: patients with active TO in Group 1 and healthy controls in Group 2.

Initially, all participants were clinically and ophthalmologically assessed for visual acuity, eyelid aperture status, exophthalmometry, cornea, as well as Clinical Activity Score (CAS) (CAS≥3 denoting active TO). The CAS is a 10-item scale that is based on four of the five well-known classic signs of inflammation (pain, redness, swelling, and dysfunction). One point is awarded for each item present. Each item weighs the same. The CAS is the sum of these points (range 0–10). Participants with intraocular pressures (IOP) ranging from 14 to 21 mmHg were included in the study. The NOSPECS Score was used to assess the overall level of TO. A senior specialist diagnosed TO using the Bartley and Gorman Criteria.

Participants, who smoked on a regular basis, had non-TO-related ocular diseases, systemic vascular disease (diabetes, systemic hypertension, etc.), a history of depression therapy, were pregnant or lactating, had hypersensitivity or intolerance to topical anesthetics or mydriatics, or had ocular surgery within the previous 6 months were excluded from the study.

Ocular Assessment

All participants underwent thorough ophthalmic examinations by a single senior ophthalmologist, which included

best-corrected visual acuity and Goldman applanation tonometry IOP measurements, as well as slit-lamp biomicroscopy of the anterior and posterior segments before and after artificial mydriasis. The ocular and orbital structures were evaluated using a B-scan USG. The Lenstar LS900 (Haag-Streit AG, Switzerland) was used to measure the central corneal thickness (CCT) and axial length (AL). The same physician who was skilled in Hertel Exophthalmometry also measured proptosis.

OCTA Acquisition

The Optovue AngioVueTM was used to perform OCTA measurements. An optic disc was quantified in a 4.5×4.5 mm^2 area with Angio Analytics 2.0. The wavelength was 840 nm, the scanning frequency was 70.000 Hz, and the lateral and axial direction discrimination distances were 15 m and 5 m, respectively. The scanning depth was 2–3 mm, the A-scan number was 304×304, and the B-scan was repeated twice in the same spot. Motion correction technique and DualTrac were used throughout the process. To scan a 4.5×4.5 mm area surrounding the optic nerve, the HD Angio Disc 4.5 mm mode was used.

OCTA angiograms of the four layers were recorded as superficial capillary plexus density, deep capillary plexus density, OR, and choriocapillaris (CC). The macula was imaged by using a 6x6 mm scanning model. Tracking technology was applied to reduce the effect of motion artifacts. Only high-quality images that had a signal strength >8 were included for analysis. The parameters to evaluate the superficial and deep retinal vessels (from the inner boundary membrane layer to the inner plexus layer), including the foveal avascular zone (FAZ), and vascular density (VD) were calculated by using the manufacturer's angiometric software. VD was defined as the linear length of the vessels divided by the select area. Perfusion density was calculated by dividing the area of vessel distribution by the select area. Despite the fact that both eyes were suitable for the study, only the right eye was used in the final data analysis. Peripapillary RNFL and VD were measured twice for each position. Optical disc 200×200 mode was used to obtain the RNFL results. CT was taken in the upper, lower, nasal, and temporal zones at 500, 1000, 1500, and 2000 m from the fovea. A single senior ophthalmologist performed all of the measurements.

Statistical Analysis

The SPSS Statistics 23 (SPSS Inc., Chicago, IL, USA) was used to analyze the data. Numbers, percentages, mean values, standard deviation, median, and Interquartile Range were used as descriptive statistical methods in the data evaluation. The Kolmogorov–Smirnov test was used to test whether the data showed normal distribution. Relationships between variables were evaluated with the Independent Sample T-Test and Mann–Whitney U Test. Results were evaluated at a 95% Confidence Interval and 5% significance level ($p<0.05$).

Results

Demographics

A total of 87 eyes from 87 patients were studied, including 46 active TO patients (Group 1: 34 females and 12 males) and 41 healthy controls (Group 2: 28 females and 13 males). No significant differences were detected between Groups 1 and 2 in terms of age, gender distribution, imaging quality, AL, and CCT ($p=0.428$, $p=0.225$, $p=0.595$, $p=0.117$, $p=0.528$, respectively). Group 1 was associated with significant proptosis (23±4 vs. 15±2) for Groups 1 and 2, respectively, $p<0.001$) (Table 1). In comparison to Group 2, Group 1 had higher IOP ($p<0.001$).

The mean RNFL thickness was found to be significantly different between Groups 1 and 2 ($p<0.001$), with the former having significantly decreased RNFL thickness. When compared in terms of temporal and inferior RNFL thicknesses ($p=0.01$, $p=0.01$), different results were obtained

Table 1. Demographic and ophthalmic examination data of the participants

	Thyroid ophthalmopathy	Control group	p-value
Age	45.4±12.4	42.1±11.7	0.428
Gender (F/M)	34/12	28/13	0.225
Proptosis (mm)	22±4	15±2	<0.001
Intraocular pressure (mm/hg)	21.07±2.04	15.4±2.8	<0.001
Axial length	24.02±1.02	24.10±1.01	0.121
Central corneal thickness	541±25	539±27	0.554

Table 2. RNFL results obtained with OCT in groups

RNFL thickness	Thyroid ophthalmopathy	Control group	p-value
Superior	116±15	122±16	0.604
Temporal	72±10	83±13	0.01
Inferior	117±11	132±15	0.01
Nasal	63±7	67±9	0.513
Average	89±8	102±9	<0.001

RNFL: Retinal nerve fiber layer; OCT: Optical coherence tomography.

Table 3. Vascular density values obtained by OCTA in TO and control groups

	Thyroid ophthalmopathy	Control group	p-value
Capture quality	9±2	9±1	0.595
Faz Area	0.303±0.104	0.26±0.10	0.037
Vascular density (Superficial)			
Whole Image	52.45±5.6	51.60±4.5	0.294
Fovea	20.924±7.648	19.010±6.725	0.0120
Parafovea	56.450±5.000	54.500±4.300	0.0123
Perifovea	53.941±3.607	51.361±3.693	0.0214
Vascular density (Deep)			
Whole Image	55.800±9.900	55.550±7.600	0.205
Fovea	36.289±8.956	36.105±6.374	0.120
Parafovea	59.800±8.700	57.300±6.000	0.033
Perifovea	58.600±11.200	56.300±8.000	0.024
Flow (Outer Retina)			
Select Area	28.264±0.070	28.248 ±0.071	0.303
Flow Area	8.362±2.967	8.431±2.693	0.661
Flow (Choriocapillaris)			
Select Area C	28.237±0.073	28.251±0.104	0.136
Flow Area C	19.908±1.32	19.891±1.282	0.986
Radial peripapillary Capillary density (RPC)			
Whole Image	49.198±2.008	49.646±2.092	0.224
Superior	51.256±5.15	51.686±5.09	0.122
Temporal	53.080±2.50	54.840±4.00	0.048
Inferior	51.52±4.76	53.49±8.64	0.035
Nasal	49.000±4.000	49.310±5.000	0.231
Inside Disk	51.015±5.636	52.559±3.352	0.120

RNFL: Retinal nerve fiber layer; OCT: Optical coherence tomography.

from Group 2, but there were non-significant differences in upper and nasal RNFL thicknesses (p=0.548, p=0.487). Group 1 had significantly higher macular CT than Group 2 (p<0.05) (Table 2).

OCTA Analysis

The mean FAZ area in Group 1 was 0.323±0.115 mm^2, which was significantly larger than group 2 (0.260±0.100 mm^2) (p=0.028). In addition, Group 1 had significantly increased superficial VD (fovea, parafovea, and perifovea) than Group 2 (p=0.011, p=0.0112, p=0.0208, respectively). VDs in the OR and CC selection areas were compared and significant differences were found between the patient and control groups (p=0.032, p=041, respectively). Deep VD increased significantly in the parafoveal (p=0.026) and perifoveal (p=0.019) areas in Group 1 compared to Group 2; however, there was no significant difference in the foveal area (p=0.086).

Table 4. The 10 items of the clinical activity score (CAS)[33]

Pain	1	Painful, oppressive feeling on or behind the globe, during the last 4 weeks
	2	Pain on attempted up, side or down gaze, during the last 4 weeks
Redness	3	Redness of the eyelid(s)
	4	Diffuse redness of the conjunctiva, covering at least one quadrant
Swelling	5	Swelling of the eyelid(s)
	6	Chemosis
	7	Swollen caruncle
	8	Increase of proptosis of ≥2 mm during a period of 1–3 months
Impaired function	9	Decrease of eye movements in any direction ≥58 during a period of 1–3 months
	10	Decrease of visual acuity of ≥1 line(s) on the Snellen chart (using a pinhole) during a period of 1–3 months

For each item present, 1 point is given. The sum of these points is the CAS, e.g. a CAS of 7 means that seven items were present, regardless of which items.
In this study average of CAS was 7 points in TO patients.

The inferior (p=0.029) and temporal (p=0.038) areas of Group 1 had significantly higher radial peripapillary capillary density. The superior (p=0.110) and nasal (p=0.198) radial peripapillary capillary density, on the other hand, did not differ significantly between Groups 1 and 2 (Table 3).

The mean clinical activity score (CAS) in Group 1 was 7 points (Table 4).

Discussion

Active TO pathophysiological changes may result in increased retro-orbital soft-tissue volume, anterior displacement of the eyeball, elevation of retrobulbar and episcleral venous pressure, or disruption of the choroidal vascular bed supply. Changes in orbital blood flow have previously been studied in TO patients. Moreover, Graves' ophthalmopathy clinical manifestations have been linked to decreased ophthalmic vein flow velocity, compression, and orbital venous occlusion.[11,12]

In our study, we used the NOSPECS Classification to categorize the severity of TO patients, with Stage III and higher patients deemed eligible. Increased retinal microvascular density may result from systemic and ocular hypertension caused by hyperthyroidism in TO patients, as well as several factors related to orbital inflammation caused by the

disease's autoimmune nature.[13] Further, cardiovascular hemodynamic changes may occur in hyperthyroidism as a result of systemic vascular resistance.[4] Therefore, increased cardiac output increases orbital blood flow.[13] Furthermore, orbital inflammation may increase the volume of retrobulbar connective tissue and extraocular muscle.[14] Changes in orbital arterial blood flow velocity may cause extraocular muscle growth in Graves' ophthalmopathy patients by associating orbital vascular dynamics with muscle activities.[15]

We observed decreased RNFL thickness in TO patients in our study, which could be due to significantly higher ocular hypertension. Participants with normal IOP ranges of 14–21 mmHg were included; however, decreased RNFL thickness were observed due to high IOP fluctuations, especially during the active phase of the disease. Temporal and inferior RNFL quadrants were the most affected. Although the superficial macular VD remained intact in TO patients, RNFL had significantly decreased thickness, implying that the losses in peripapillary RNFL in TO patients may not be due to retinal microcirculation alone. Compression-induced IOP elevation is common in TO patients, and it could be the cause of RNFL defects.[16,17] Extraocular muscle enlargement and increased orbital soft-tissue volume may result in direct compression of the optic nerve, leading to dysthyroid optic neuropathy.

Moreover, we found that TO patients had significantly higher CT, particularly in the macular zone, when compared to healthy controls. This finding is consistent with the findings of Caliskan et al.,[18] who reported that subfoveal CT in TO patients was significantly higher than in healthy controls, even after adjusting for age, AL, and IOP. Similarly,Yu et al.[19] reported increased CT in different zones of the macular zone in TO patients. Increased CT could be due to venous obstruction and congestion caused by decreased orbital venous drainage due to increased retrobulbar pressure.[20]

We used OCTA in our study, a technique that is not associated with unfavorable conditions such as allergies and is an efficient, high-quality, and as well as reliable method for imaging fundus microvascular system.[21,22] When comparing TO patients to healthy controls, we revealed significantly increased superficial VD (fovea, parafovea, and perifovea) in the former. Deep VD increased significantly in the parafoveal and perifoveal areas than health controls. Moreover, significant differences were found in OR or CC flow areas in TO patients compared to healthy controls. Consistent findings have been reported, including increased retinal microvascular density in active TO patients,[23] as well as increased VDs in temporal and nasal parafoveal regions of the superficial and deep capillary plexus.[24] Unlike earlier research, Tehrani et al.[25] reported that both active and inactive TO patients had significantly decreased nasal parafoveal superficial VD. Again, Mihailovic et al.[26] revealed reduced VD in superficial OCTA of inactive TO patients. It appears natural that our findings were higher than the health controls because the entire patient group in our study consisted of NOSPECS classifications greater than Stage III and active TO patients.

Our study found that TO patients had increased radial peripapillary capillary density in the inferior and temporal areas. Regardless, there were no differences in superior and nasal radial peripapillary capillary density. In contrast to our findings, Mihailovic et al.[26] reported that patients with Graves' ophthalmopathy had lower radial peripapillary capillary density.

Anatomically, FAZ is the most sensitive part of the retina, with no capillaries in the central macula.[27,28] We revealed significantly enlarged FAZ in TO patients. The interruption of blood supply to the fovea due to high IOP fluctuations during the active period of chronic TO patients, the development of circulatory problems in the patient as the disease progresses, and, most importantly, the fact that this is directly proportional to the duration of the active period of the disease, could explain the significantly enlarged of FAZ in these patients. We included chronic TO patients, so, expectedly, the findings were consistent with the literature. We are aware that FAZ measurements vary across studies, and past research has reported that age, gender, spherical equivalent, and AL all influence the size of the FAZ.[29,30] FAZ area had a positive relationship with IOP and a negative relationship with AL. A positive relationship was also revealed between FAZ and foveal VD. There were no relationships found between the flow area and any of the other areas investigated.

Matter of fact, changes in orbital blood flow may be related to retinochoroidal microvascular morphological alterations. Prior research using Doppler imaging of the orbital vessels found that the resistance index in the ophthalmic artery decreased in TO patients while the systolic heart rate increased, increasing blood flow in the ophthalmic artery in TO patients. Compared to healthy controls, resistance index has been reported to increase in the central retinal artery while there were no differences in velocity or resistance index in the superior ophthalmic vein.[31] The increased VD could be explained by increased blood flow in

the ocular microvasculature. It could be argued that while the rate and resistance index increase in the central retinal artery, the resistance index decreases in the superior ophthalmic vein, causing circulatory disorder in the ocular vascular system.

The superior ophthalmic vein has been observed with reverse flows, which could cause severe stasis and is usually accompanied by extraocular muscle enlargement. In addition, this vein is thought to be important in the inflammatory stage of TO: recent research has shown that high intraorbital pressure causes a decrease in blood flow in this vein during active TO. The main cause of high intraorbital pressure is autoimmune inflammation in orbital tissues, which includes interstitial tissues, orbital fat, and extraocular muscles. It has also been reported that after orbital decompression, superior ophthalmic vein flow increases after reverse flow disappears.[32] Consequently, changes in fundus blood flow in active TO, as well as changes in RNFL thickness, CT, FAZ, and perfusion density, could be caused by vascular physiological changes and high intraorbital pressure secondary to autoimmune inflammation on the ocular microvasculature and orbital tissues.

Our study has some limitations. There was no follow-up data for TO patients due to the cross-sectional design of the study. Hemodynamic changes in the morphology of superficial retinal vessels may limit our understanding of pathogenesis. Unlike past studies, however, deep retinal VDs were also investigated, and the software allowed for both superficial and deep VD analysis. Another limitation was the insufficient number of participants to separate the comparison by disease stage. Furthermore, the analyses were limited to TO patients; dysthyroid patients were not included in the absence of TO. Regardless of the potential impact on study results interpretation, TO patients were found to be associated with changes in retinochoroidal microvascular morphology.

Conclusion

TO patients had significant changes in RNFL thickness, CT, FAZ area, superficial and deep retinal VDs, and radial peripapillary capillary density. Identifying these parameters may be useful not only for diagnosis but also for monitoring TO patients, particularly from the standpoint of ocular microvascular morphology.

Ethics Committee Approval: This study was approved by Afyonkarahisar Health Sciences University Faculty of Medicine Ethics Committee (date: 03.12.2021; number: 2021/13).

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