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ORIGINAL ARTICLE

Evaluation of the optic disk and macular vessel density in inactive thyroid eye disease using optical coherence tomography angiography

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Abstract

Purpose: The purpose of the study was to evaluate the vascular density (VD) in the optic disk (OD) head and macula by optical coherence tomography angiography (OCT-A) in patients with inactive thyroid eye disease (TED), as well as the relationship between extraocular muscle (EOM) thickness and the VD of the retina and OD.

Methods: The study group and control group each consisted of 65 eyes of 65 participants. The foveal, parafoveal, and perifoveal VD were examined for both superficial capillary plexus and deep capillary plexus. In addition, choriocapillaris flow, foveal avascular zone (FAZ) areas, and the perimeter were calculated. The thicknesses of the peripapillary retinal nerve fiber layer (RNFL) and VD were recorded. EOM thickness was measured with magnetic resonance imaging.

Results: VD was significantly lower in all quadrants for the superficial foveal areas, as well as the deep and superficial parafoveal and perifoveal areas in the study group ($p<0.05$ for all). The study group had significantly lower choriocapillaris flow area (2.08±0.1; 2.12±0.10 p=0.049) and higher FAZ (0.29 (0.22–0.36); 0.26 (0.17–0.32) p=0.037) and perimeter (2.08±0.46; 1.92±0.35 p=0.03) values compared with the controls. VD was higher in the inferior half of the peripapillary region in the study group than the controls (p=0.045).

Conclusion: Macular VD measured using OCT-A was found to be significantly lower in TED patients compared to healthy controls. It is thought that noninvasive quantitative retinal perfusion analysis using OCT-A may be useful in the follow-up of TED, close monitoring of complications, and early treatment decision.

Keywords: Inactive thyroid eye disease; magnetic resonance imaging; optical coherence tomography angiography; vessel density.

Graves' disease (GD) is an autoimmune disorder caused by autoantibodies against thyroid-stimulating hormone receptors (TSH-R) and affected by genetic, environmental, and endogenous factors. These antibodies mimic thyroid-stimulating hormone (TSH), activate their TSH-R, and cause uncontrolled thyroid hormone production.[1] Al-

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though the pathogenesis of thyroid eye disease (TED) has not been fully elucidated, cytokines and immunological mechanisms are thought to be responsible for the pathogenesis. The pathological autoimmune reaction was found to be directed to cross-reactive autoantigens in the orbital tissues.[2] It is characterized by enlarged extraocular muscles (EOM) and increased volume of orbital fat and connective tissue due to the activation of fibroblasts by thyroid receptor autoantibodies.

The increased volume of muscles and adipose tissue leads to an increase in retrobulbar pressure.[3] Impairment occurs in the venous drainage and herniation of orbital fat tissue from the orbital septum, which causes proptosis, redness, and swelling in the eyelids, conjunctiva, and caruncle.[2] If the high orbital pressure does not decrease, direct compression on the optic nerve may result in optic neuropathy.[3]

Pathological changes in orbital tissue may cause alteration in orbital blood flow in patients with TED. Studies have measured ocular blood flow in TED using Heidelberg retinal flowmetry, oculodynamometry, ocular blood flow tomography, and color Doppler imaging (CDI) methods.[4]

With high-resolution, cross-sectional, and three-dimensional imaging, optical coherence tomography angiography (OCT-A) allows qualitative and quantitative evaluation of the retina and choroidal vessels.[5] It can also be used to assess the blood flow in the optic disk (OD) and the peripapillary nerve fiber layer. The purpose of our study is to evaluate macular and OD perfusion using OCT-A in patients with inactive TED and to determine if there is a relation between the EOM thicknesses and retinal blood flow.

Materials and Methods

This prospective cross-sectional study included a total of 130 eyes, which comprised 65 right eyes of 65 patients with inactive TED and 65 right eyes of 65 healthy individuals. Since there were no similar studies before, a pilot study was conducted with seven individuals in each group to perform power analysis. In this study, the effect size was tried to be estimated by calculating descriptive statistics only for the whole image superficial capillary plexus (SCP) vascular density (VD) variable. As a result of the power analysis based on the descriptive statistics obtained from the pilot data, with 80% power and 5% Type 1 error conditions, it was aimed to study with 28 individuals, at least 14 in each group, to obtain a statistically significant difference of 4.9 units in the whole image SCP VD mean between the groups. The study was terminated when 65 individuals in each groups were reached. As a result of the post hoc power analysis made on the last data collected, the power of the study was calculated as 99%. Power analysis was done with G*Power 3.1.9.7 for Windows package program.

All patients in the TED group were followed up with a diagnosis of TED in the oculoplasty clinic between September 2019 and March 2021. The diagnosis of TED was based on medical history, symptoms, radiographic imaging, and laboratory results (TSH, thyroid peroxidase antibody, and TSH-R antibody levels). Age, gender, smoking history, treatments for thyroid disease, and surgical history of all patients were recorded. Best-corrected visual acuity (BCVA), biomicroscopic anterior segment, and fundus examinations were performed on all patients. BCVA was determined according to a Snellen chart and converted to the Logarithm of the Minimum Angle of Resolution. All ophthalmologic examination were performed by same physician.

Intraocular pressure (IOP, mmHg) and central corneal thickness (μm) were measured with a TRK-2P system (Topcon, Tokyo, Japan) and proptosis was measured using a Hertel exophthalmometer. The axial length was measured using optical biometry (AL-Scan, Nidek Co, Ltd., Gamagori, Japan) and color vision was tested using Ishihara color plates. The activity of TED patients was determined with the clinical activity score (CAS), for which the following was assigned one point each: spontaneous orbital pain, gaze-evoked orbital pain, eyelid swelling, eyelid erythema, conjunctival redness, chemosis, and caruncle edema findings. Mild to moderately severe patients in the inactive period with CAS ≤2/7 were included in the study. Patients were excluded from the study with a spherical equivalent of 6 diopters and above, diabetic retinopathy or other choroidal/retinal disorders, cataract, glaucoma, thyroidectomy within 3 months or received RAI treatment, ocular surgery, oculoplastic surgery within 6 months, and OCT-A image quality of <7.

This study was carried out in accordance with the principles of the Declaration of Helsinki and approval was obtained from the Local Ethics Committee (decision number 14.01.2020–2636). Informed consent was obtained from all participants.

OCT-A Measurement

With OCT-A, 6 × 6-mm macula imaging and 4.5 × 4.5-mm OD imaging were performed (AngioVue Avanti RTVue-XR, OptoVue, Fremont, CA). In the central macula, the superficial foveal avascular zone (FAZ) area, perimeter (peripheral length) of FAZ boundaries, SCP, and deep capillary plexus (DCP) vessel densities were examined. In the macula, SCP was measured between three microns below the inner lim-

iting membrane and 15 microns below the inner plexiform layer. DCP was measured by the device to cover an area of 15 microns to 70 microns below the inner plexiform layer. Using the algorithm in the software of the device, VD (%) in SCP and DCP was measured in the area (fovea, parafovea, and perifovea) divided by 1-mm, 3-mm, and 6-mm-diameter circles with FAZ in their center.

VD was defined as the percentage of perfused vascular area relative to the entire region selected in the " en face: view. Foveal, parafoveal, and perifoveal VD values in eyes with TED were compared with those of the control group. The entire OD area, intra-disk area, and peripapillary area VD were evaluated and compared with those the control group. After determining the OD limits using, the AngioVue disk mode, the inner limiting membrane, and the layer extending up to 150 µm below the membrane were analyzed for vessel density within the disk. For the measurement of superficial peripapillary capillary density, the radial peripapillary capillary segment extending from the inner limiting membrane to the retinal nerve fiber layer (RNFL) was analyzed. RNFL and central macular thickness (CMT) were measured automatically by the device. All patients had signal strength index ≥7.

EOM Thicknesses

Orbital magnetic resonance imaging (MRI) was performed using a 1.5-Tesla MRI device (Siemens Magnetom Solo, Germany). For all TED patients, transverse, coronal, and sagittal section MRI were obtained in with the patient in a supine position. For each muscle, measurements were made at its widest point in the midsection. The sum of the four EOM thicknesses was calculated.

Statistical Analysis

Statistical analyses were performed with the statistical software Number Cruncher Statistical System (NCSS 2007; Utah, USA). In the evaluation of the data, besides descriptive statistics (mean, standard deviation), the distribution of variables was examined with the Shapiro–Wilk normality test, and then, an independent t-test was used to compare paired groups of normally distributed variables. A Mann–Whitney U-test was used to compare paired-groups of non-normally distributed variables and a Chi-square test was used to compare qualitative data. The correlation test was used to determine the relationships between variables. The results were evaluated using a significance level of $p<0.05$.

Results

This study included 65 right eyes from 65 individuals with TED and 65 right eyes of 65 healthy controls. There was no difference between the two groups in terms of mean age and gender distribution. The general demographic characteristics of the patients are shown in Table 1.

VA of the study group was higher than the control group (p=0.023, p=0.0001). While IOP was significantly higher in the study group than in the control group (p=0.0001), there was no significant difference between pachymetry values and AL (p=0.916, p=0.340). Hertel measurements were higher in the study group (p=0.0001) (Table 2). All patients had normal color vision.

Comparison of macular thickness in both groups showed that CMT was lower in the TED group than the control group (p=0.041). SCP foveal, parafoveal, and perifoveal region VD values were lower in the study group than the control group ($p<0.05$). Parafoveal region SCP VD values were lower in all four quadrants than in the control group ($p<0.05$; Table 3).

The comparison of DCP values between the two groups showed that VD was lower in the parafovea and perifovea regions in the study group ($p<0.05$), but there was no difference in the foveal region (p=0.061; Table 3). The mean FAZ and perimetry values of the study group were higher than those of the control group. The choriocapillaris flow area was lower in the TED group (p=0.049; Table 4).

There was no difference between the TED and control groups in VD of the OD; whole image, inside-disk, and

Table 1. The basic characteristics of the study and control population

	Control (n=65)	Study (n=65)	p-value
Age	41.65±12.85	41.54±10.74	0.959
Gender			
Male	22 (33.85)	16 (24.62)	0.247[+]
Female	43 (66.15)	49 (75.38)	

[+]Chi-square test.

Table 2. Intraocular pressure, pachymetry, visual acuities, axial length, and hertel exophthalmometer measurements in the study and control groups

	Control (n=65)	Study (n=65)	p-value
IOP	15.91±3.03	18.08±3.41	0.0001[*]
Pachymetry	557.62±23.58	558.06±24.45	0.916[*]
VA (logMAR)	0 (0-0)	0 (0-0.001)	0.023[‡]
AL	23.43±0.89	23.28±0.97	0.340[*]
Hertel exophthalmometer	16.77±1.77	21.2±2.78	0.0001[*]

[*]Independent samples t-test; [‡]Mann–Whitney U-test; [+]Chi-square test.

Table 3. Central macular thickness and superficial/deep capillary plexus vascular densities in the study and control groups

	Control (n=65)	Study (n=65)	p-value
CMT	252.09±18..9	245.89±15.05	0.041*
Whole Image SCP VD	50.56±3.07	48.80±4.09	0.006
Superior Hemi SCP VD	50.46±2.97	48.78±4.21	0.01
Inferior Hemi SCP VD	50.64±3.29	48.76±4.09	0.004
Fovea SCP VD	22.35±6.86	19.70±7.43	0.037
Parafovea SCP VD	52.77±4.55	50.64±5.02	0.012
Temporal SCP VD	52.92±3.07	50.91±5.25	0.009
Superior SCP VD	53.80±3.49	51.46±4.88	0.002
Nasal SCP VD	52.24±3.55	49.50±5.58	0.001
Inferior SCP VD	53.83±3.64	50.61±5.63	0.0001
Perifovea SCP VD	51.28±3.32	49.42±3.81	0.004
	Control (n=65)	**Study (n=65)**	**p*-value**
Whole Image DCP VD	53.56±5.23	49.45±6.32	0.0001
Superior Hemi DCP VD	53.90±5.27	50.07±6.23	0.0001
Inferior Hemi DCP VD	53.47±5.45	48.86±6.65	0.0001
Fovea DCP VD	38.73±7.94	36.10±7.92	0.061
Parafovea DCP VD	56.87±3.75	54.72±4.41	0.003
Temporal DCP VD	57.61±3.30	55.55±4.58	0.004
Superior DCP VD	56.29±4.15	54.46±4.53	0.017
Nasal DCP VD	57.92±3.54	55.32±4.43	0.0001
Inferior DCP VD	56.00±4.45	53.50±5.75	0.006
Perifovea DCP VD	55.32±5.65	50.41±6.94	0.0001

*Independent samples t-test. SCP: Superficial capillary plexus, VD: Vascular density; CMT: Central macular thickness; DCP: Deep capillary plexus.

Table 4. FAZ, perimetry, and choriocapillaris flow area in the study and control groups

	Control (n=65)	Study (n=65)	p-value
FAZ	0.26 (0.17-0.32)	0.29 (0.22-0.36)	0.037‡
Perimeter	1.92±0.35	2.08±0.46	0.03*
Choriocapillaris flow area	2.12±0.10	2.08±0.13	0.049

*Independent samples t-test; ‡Mann–Whitney U-test. FAZ: Foveal avascular zone.

peripapillary area except for the inferior part of the peripapillary area (Table 5). There was no significant difference in RNFL values between the groups ($p<0.05$; Table 6).

There was no correlation between the total EOM and VD of the whole image, inside-disk, and peripapillary area ($p=0.171$, $p=0.173$; Table 7). No correlation was detected between the total EOM and SCP/DCP VD of the macula, FAZ, and choriocapillaris flow area (Table 7). There was no statistically significant correlation between muscle thicknesses and SCP/DCP VD in the parafoveal quadrants, where the muscle is close.

Table 5. Optic disk and peripapillary vascular densities in the study and control groups

	Control (n=65)	Study (n=65)	p*-value
Whole Image VD	50.11±2.29	49.61±2.02	0.194
Inside Disk VD	50.50±4.84	49.08±4.37	0.08
Peripapillary VD	52.10±2.49	52.48±2.18	0.351
Superior VD	52.23±2.58	52.28±2.56	0.900
Inferior VD	51.79±2.92	52.73±2.35	0.045
Nasal-Superior VD	49.24±4.40	49.10±2.89	0.834
Nasal-Inferior VD	47.76±4.23	48.45±3.35	0.299
Inferior-Nasal VD	51.15±4.22	52.36±3.72	0.084
Inferior-Temporal VD	57.09±7.17	58.91±3.69	0.071
Temporal-Inferior VD	52.34±4.80	52.84±4.29	0.531
Temporal-Superior VD	55.67±3.44	55.80±2.91	0.813
Superior-Temporal VD	55.49±3.42	55.36±4.25	0.840
Superior-Nasal VD	49.27±4.17	50.31±4.18	0.157

*Independent samples t-test. SCP: Superficial capillary plexus, VD: Vascular density.

Table 6. Peripapillary RNFL thickness in the patient and control groups

	Control (n=65)	Study (n=65)	p*-value
Peripapillary RNFL	109.28±12.11	111.51±9.42	0.243
Superior RNLF	109.28±11.75	110.28±9.26	0.591
Inferior RNFL	109.34±13.69	113.05±11.17	0.093
Nasal-Superior RNFL	110.46±20.43	107.23±14.37	0.299
Nasal-Inferior RNFL	90.46±18.69	91.92±16.36	0.636
Inferior-Nasal RNFL	136.03±25.74	141.18±23.60	0.236
Inferior-Temporal RNFL	141.94±18.78	147.40±18.52	0.097
Temporal-Inferior RNFL	69.25±11.20	71.22±10.72	0.308
Temporal-Superior RNFL	73.08±10.17	76.63±10.52	0.052
Superior-Temporal RNFL	124.12±17.84	129.42±17.64	0.091
Superior-Nasal RNFL	131.34±19.99	130.66±22.76	0.857

*Independent samples t-test. RNFL: Retinal nerve fiber layer.

Discussion

The study has shown that patients with inactive TED had lower VD in all quadrants of the SCP foveal region and the SCP and DCP parafoveal and perifoveal regions than the controls. Furthermore, these patients had lower CC flow areas but higher FAZ and perimeter values. Except for one quadrant in the peripapillary area, there was no difference between RNFL values in all quadrants.

It has been shown that increased systemic blood pressure, IOP, and orbital inflammation may affect ocular perfusion in cases of hyperthyroidism.[6] In patients with GD, peak systolic and end-diastolic velocities and the maximum and minimum velocities of the ophthalmic artery and central retinal artery (CRA) were measured using CDI and their association with IOP and EOM growth were evaluated. Kurioka et al.[7] measured the blood flow and resistance index of

Table 7. The relationship between muscle thickness and optic disk, peripapillary vascular density, FAZ, SCP/DCP vascular densities, and choriocapillaris flow area

		Total EOM Thickness
Whole Image OD	R	0.171
	p	0.173
Inside Disk	R	0.097
	p	0.443
Peripapillary	R	0.120
	p	0.339
FAZ	R	0.069
	p	0.585
Whole Image SCP VD	R	0.070
	p	0.577
Fovea SCP VD	R	–0.085
	p	0.501
Parafovea SCP VD	R	0.011
	p	0.932
Perifovea SCP VD	R	0.083
	p	0.509
Whole Image DCP VD	R	0.018
	p	0.890
Fovea DCP VD	R	0.002
	p	0.989
Parafovea DCP VD	R	–0.020
	p	0.873
Perifovea DCP VD	R	–0.080
	p	0.526
Choriocapillaris Flow Area	R	–0.170
	p	0.175

Pearson correlation analysis, SCP: Superficial capillary plexus; VD: Vascular density; EOM: Extraocular muscle; OD: Optic disk; DCP: Deep capillary plexus.

CRA with a pulse-Doppler method and mentioned the possible effects of hyperthyroidism seen in GD and inflammation in EOM on altered retinal hemodynamics. We did not include patients in the active stage in our study, as there may be changes in orbital blood flow during the inflammatory stage.[6]

In recent years, studies have been carried out with OCT-A in both active and inactive TED. Some studies have shown a reduction in retinal perfusion with OCT-A.[8–10] Our study also found that both SCP and DCP VD values were lower in inactive TED than healthy controls. However, there are also opposite findings in the literature. Yu et al.[11] detected high VD in inactive TED compared to active TED and healthy subjects, but there was no difference in VD in active TED than healthy subjects. Akpolat et al.[12] also showed that temporal and nasal parafoveal VD was higher in the inactive TED group. The reason for these different results in the literature in individuals with inactive TED may be that the criteria considered when grouping patients according to activity do not provide sufficient information about the severity of the disease or the use of different technologies in measuring devices. In addition, TED is a systemic disease that can affect the whole body, so less attention is given to euthyroidism in patients or changes in drug doses may affect the results. Similar studies do not mention whether patients were in a euthyroid state at the time of OCT-A imaging.

In our study, we found a decrease in macular thickness, which is in line with various studies in the literature. We attributed this to a decrease in blood flow secondary to mechanical compression of the vessels perfusing the retina due to orbital inflammation.[13,14] Recent studies also reported that the enlargement of the FAZ area supports the findings of capillary nonperfusion.[15] In our study, the FAZ area was found to be wider than in the control group and similar results have been reported in the literature. Yu et al.[11] found the FAZ area to be wider in active TED.

There are various results in the literature regarding the relation between choroidal thickness (CT) and TED. Çalışkan et al.[16] emphasized that CT in active TED patients was significantly higher than in those with inactive TED or healthy individuals. Yu et al.[11] also reported that increased CT in TED patients at different locations in the macular area. Our study also found that study group had low blood flow in the choriocapillaris. We attributed this change to the fact that our study examined patients in the inactive period, while other studies examined patients in the active period.

Although the diagnosis of TED is primarily made clinically based on laboratory tests indicative of thyroid dysfunction and autoimmunity, imaging studies, such as computed tomography, MRI, ultrasound, and CDI play an important role both in the diagnosis and follow-up after clinical or surgical treatment of the disease. Imaging may also be useful to distinguish the inflammatory early stage from the inactive stage of the disease. When CON due to orbital apex crowding is suspected, MRI is the imaging modality of choice.[17] MRI is better at showing soft-tissue involvement and is used for detailed imaging of the optic nerve and extraocular muscles.[18] Evaluation of muscle thickening and OD blood flow with OCT-A can provide information for the development of the early optic neuropathy. In a study on individuals with TED with and without CON, Zhang et al.[19] reported a decrease in macular and peripapillary micro VD in CON cases and suggested that peripapillary VD could be in a diagnostic method that gives positive results in differentiating eyes with CON from eyes without CON. Except for the lower half of the peripapillary area, our study found no

significant difference in VD in the OD entire area, intra-disk area, peripapillary area, and peripapillary upper half.

OCT is an useful device in the evaluation and management of OD and retinal diseases.[20] By monitoring the RNFL thicknesses obtained with OCT imaging, we can monitor CON due to orbital congestion and the effect of stretching on the optic nerve due to proptosis. Various studies reporting a decrease in RNFL values secondary to high IOP in active TEDs,[11,13] but some studies have found an increase in RNFL and attributed it to inflammatory axonal swelling.[21] In our study, no statistically significant difference in the RNFL values was detected between the groups ($p<0.05$).

Our study revealed that the macular vessel density decreased, the FAZ area expanded, and the choriocapillaris flow decreased in inactive TED. The most important reasons for this may be the inflammatory changes in the microvascular system that feed the inner layers of the retina, as well as changes in the choroidal circulation that feed the deep layers. We found that VD values increased in only one quadrant in the peripapillary area, and RNFL did not change. This may be secondary to decreased optic nerve pressure due to the disease being in the inactive period and decreased orbital inflammation.

Our study has several limitations, such as the lack of an active patient group and the small sample size. Further studies can be conducted with a large population and compare active and inactive TED according to the disease stage. Since our study was a cross-sectional study, only inactive period findings of patients who underwent OCT-A imaging were obtained and the effect of disease progression on vessel density could not be evaluated. In patients who show signs of activation in long-term follow-up, it can be investigated whether imaging with OCT-A will indicate a finding that is a precursor to activation. Fat predominant orbital involvement in young TED patients may have affected the correlation result between EOM and VD. Furthermore, OCT-A technology can evaluate only a limited area of the retinal posterior pole.

Early diagnosis, close monitoring of complications, and prompt treatment are very important in TED. The advantage of this study is that both examining the VD of the OD and macula and evaluating the RNFL thickness, focusing on inactive patients. Our study demonstrated macular ischemia in inactive TED patients. Since our patients are in the young population and easily adapt to OCT-A scan, the quality of image was obtained at least seven and above, artifact was observed at a minimum level. This increases the reliability of the OCT-A results.

Conclusion

OCT-A is a noninvasive technique that demonstrates retinal macular and peripapillary microvascular changes. It can be a useful tool in the early diagnosis of macular ischemia and the optic neuropathy that may develop. The clinical significance of our study is its contribution to the prevention of possible visual complications with early diagnosis of OCT-A in patients with TED. Our study also showed that patients with inactive TED should be evaluated not only for orbital inflammation but also for possible retinal flow changes.

Ethics Committee Approval: This study was approved by Sisli Hamidiye Etfal Training and Researvh Hospital (SUAM) Clinical Research Ethics Committee (date: 14.01.2020; number: 2636).

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