ORIGINAL ARTICLE

MANAGEMENT OF PATIENTS WITH THYROID-ASSOCIATED OPHTHALMOPATHY: ROLE OF SPECTRAL DOMAIN OPTICAL COHERENCE TOMOGRAPHY

Tiroid İlişkili Oftalmopatili Hastaların Yönetimi: Spektral Alan Optik Koherens Tomografinin Rolü

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ABSTRACT

Objective: To demonstrate the changes in optic nerve head (ONH), retinal nerve fiber layer (RNFL) and macula in patients with thyroid-associated ophthalmopathy (TAO) by spectral domain optical coherence tomography (SD-OCT).

Material and Methods: We included forty-one eyes of 41 patients with a diagnosis of TAO and forty-eight eyes of 48 age- and sex-matched healthy subjects (control group) from June 2016 to July 2018. The ONH parameters, RNFL and macular thicknesses in the nine macular quadrants were measured with SD-OCT. Proptosis level was determined by Hertel exophthalmometer. Clinical activity score (CAS) according to the European Group of Graves' Orbitopathy (EUGOGO) guidelines was determined in all patients. Student t-test was used to compare study and control groups. A p value less than 0.05 was considered as statistically significant.

Results: Superior, inferior, and average RNFL thicknesses were significantly lower in the TAO group compared to the control group ($p < 0.05$). Optic disc area was significantly larger in the TAO group. Outer quadrant macular thicknesses and average macular thicknesses were significantly lower in the TAO group ($p < 0.05$). CAS had a weak correlation with RNFL thickness and average macular thickness.

Conclusion: Alterations in RNFL thicknesses and macular thicknesses can be detected before the development of ocular symptoms in patients with TAO. Patients can be diagnosed at an early stage prior to the development of functional damage. However, the low number of studies investigating this subject and the conflicting findings of existing studies necessitate further studies.

Keywords: *Thyroid-Associated Ophthalmopathy; Optical Coherence Tomography; Macula; RNFL*

ÖZET

Amaç: Tiroit ilişkili oftalmopatili (TİO) hastalarda optik sinir başı (OSB), retina sinir lifi tabakası (RSLT) ve maküladaki değişiklikleri spektral alan optik koherens tomografi (SD-OKT) ile göstermek.

Gereç ve Yöntemler: Haziran 2016 ile Temmuz 2018 tarihleri arasında TİO tanılı 41 hastanın 41 gözü ve 48 yaş ve cinsiyet uyumlu sağlıklı bireyin (kontrol grubu) 48 gözü dahil edildi. OSB parametreleri, RSLT ve dokuz maküla kadrandaki maküla kalınlıkları SD-OKT ile ölçüldü. Piroptoz seviyesi Hertel ekzoftalmometre ile belirlendi. Tüm hastalarda European Group of Graves' Orbitopathy (EUGOGO) kılavuzlarına göre klinik aktivite skoru (CAS) belirlendi. Çalışma ve kontrol gruplarını karşılaştırmak için Student t testi kullanıldı. 0,05'ten küçük p değeri istatistiksel olarak anlamlı kabul edildi.

Bulgular: Üst, alt ve ortalama RSLT kalınlıkları, kontrol grubuna kıyasla TİO grubunda anlamlı olarak daha düşüktü ($p <0,05$). Optik disk alanı TİO grubunda anlamlı olarak daha büyüktü. Dış kadran maküla kalınlıkları ve ortalama maküla kalınlığı TİO grubunda anlamlı olarak daha düşüktü ($p <0,05$). CAS, RSLT kalınlığı ve ortalama maküla kalınlığı ile zayıf bir korelasyona sahipti.

Sonuç: TİO'lu hastalarda RSLT kalınlıklarında ve maküla kalınlıklarındaki değişiklikler oküler semptomlar gelişmeden tespit edilebilmektedir. Hastalara fonksiyonel hasar gelişmeden erken bir aşamada teşhis konulabilir. Ancak bu konuda yapılan çalışma sayısının az olması ve mevcut çalışmaların çelişkili bulguları daha fazla çalışmayı gerekli kılmaktadır.

Anahtar Kelimeler: *Tiroit İlişkili Oftalmopati; Optik Koherens Tomografi, Maküla; RSLT*

INTRODUCTION

Graves' disease, which is the most common cause of hyperthyroidism, is an autoimmune disease characterized by hyperthyroidism, diffuse goiter, ophthalmopathy, and in rare cases, dermopathy (1). Thyroid-associated ophthalmopathy (TAO) is the most common extrathyroidal manifestation of Graves' disease. In addition to elevated free thyroid hormone levels and suppressed thyroid stimulating hormone (TSH) levels, serum antithyroglobulin (anti-TG) antibody, antithyroid peroxidase (anti-TPO) antibody, and TSH receptor antibody levels may increase in Graves' disease. Antibodies against TSH receptors play an important role in the pathogenesis of Graves' disease. TSH receptors are found not only in the thyroid tissue but also in the extraocular eye muscles and retrobulbar fat tissues. It is thought that circulating anti-TG antibodies trigger inflammation and activation of orbital fibroblasts leading to intraorbital swelling at an early active stage and, subsequently, to fibrosis at a later stage (2). TAO is accompanied by inflammatory cellular infiltration with lymphocytes, plasma cells, macrophages, and mast cells of interstitial tissues, orbital fat, and lacrimal glands are associated with accumulation of glycosaminoglycans and retention of fluid. This increases the volume of orbital contents and eventually, the intraorbital pressure is elevated (3). TAO is usually bilateral and often asymmetrical (4).

Thyroid autoantibodies and immune system genes can be helpful to predict the development of ophthalmopathy and to determine its severity after onset. Eckstein et al. showed that the positivity rates for anti-TPO antibody and anti-TG antibody were 90% and 50%, respectively, in the presence of ophthalmopathy (5).

Blum Meirovitch et al. TAO patients exhibited retinal nerve fiber layer (RNFL) thickening and inner macula thinning compared to healthy subjects. Mean RNFL thickness was correlated with the severity of the orbital disease (6).

The aim of this study was to examine the macular structural changes in patients with TAO. Furthermore, by comparing the optic nerve head (ONH) and the structural changes of RNFL with a healthy control group, we want to contribute to this topic, which has been investigated only by a few studies in the literature.

MATERIAL AND METHODS

The study was approved by the Clinical Research Ethics Board of the Eskisehir Osmangazi University Ethics Board (25403353-050.99-E.110601). A retrospective review of all patients with a diagnosis of TAO was performed at Eskisehir Yunus Emre State Hospital from June 2016 to July 2018. Our study was conducted according to the Declaration of Helsinki. A written informed consent was taken from all subjects. Forty-one eyes of 41 patients (TAO-study group) and forty-eight eyes of 48 age-and sex-matched subjects (control group) were included in the study. The clinically worse eye of each case was included for the study purpose. If both eyes are affected similarly, a simple random selection was done to decide upon the eye to be investigated. One eye was randomly selected in control subjects.

All subjects were previously examined by an endocrinologist. Patients were included if they met the following criteria: (1) diagnosis of TAO in the last 12 months, (2) euthyroid after treatment with antithyroid drugs, and (3) first episode of TAO.

The control group was chosen among healthy volunteers who did not have any eye pathology, who had a 20/20 vision, normal color vision, and who were age and sex-matched with the study group.

In both groups, those who had significant sight impairment, high myopia (<−5 D), high hyperopia (>+3 D) or spherical equivalent, axial length < 22 mm and >26 mm; intraocular pressure > 18 mmHg, cup/disc ratio > 0.5 optic disc anomaly, vitreoretinal interface disease, vascular and degenerative retinal diseases, cornea or lens opacity, ocular surgery history, glaucoma, neurological diseases that can affect the visual field, history of trauma, amblyopia, diplopia, keratitis, and history of diuretics, topical or systemic steroid use were not included in the study.

The proptosis levels of all subjects were measured with Hertel exophthalmometer. In the TAO group, ophthalmic involvement was evaluated according to the European Group of Graves' Orbitopathy (EUGOGO) 2016 classification. The activity of TAO was shown with the clinical activity score (CAS). According to the EUGOGO guidelines, patients were divided into non-active GO (CAS < 3) and active GO (CAS ≥3) groups (7).

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The assessment with OCT was done by an ophthalmologist by using an spectral domain optical coherence tomography (SD-OCT) (Heidelberg Engineering, Heidelberg, Germany) without the need for pupil dilatation. ONH, RNFL and macula analysis were performed in all subjects. Rim area (mm^2), disc area (mm^2), average cup/disc (C/D) ratio, vertical C/D ratio, cup volume (mm^3) data were recorded during ONH analysis. The average RNFL thickness and the thickness of four quadrants (superior, inferior, nasal, and temporal) were established in microns. In total, nine macular quadrants (micron) involving the foveal region according to the Early Treatment Diabetic Treatment Study (ETDRS) template were measured and average macular thickness (micron) were recorded during macula analysis.

Statistical analysis was performed using SPSS v22.0 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). Descriptive statistics are presented with frequency, percentage, mean, and standard deviation. X^2 (Chi-square) test was used to analyze the gender and eye distribution in two groups. Student t-test was used to compare study and control groups in terms of the optic nerve, retinal thickness, and nerve fiber layers. Correlation analysis was performed to investigate the relationship between average thickness, CAS and Hertel score. A correlation analysis was performed to observe the relationship between compared parameters, and the level of significance was set at 0.05 with a 95% confidence interval. A p value less than 0.05 was considered as statistically significant (α=0.05).

RESULTS

We diagnosed forty-one eyes of 41 patients (TAO-study group) and forty-eight eyes of 48 age- and sex-matched subjects (control group) at Eskisehir Yunus Emre State Hospital from June 2016 to July 2018.

The average age of the subjects was similar in the TAO and control groups (p=0.67). There was no significant difference between the groups in terms of central corneal thickness (p=0.41), refraction measurement(p=0.38), and intraocular pressure (p=0.20). In conclusion, TAO and control groups were similar in terms of general characteristics (p>0.05)

On the other hand, Hertel measurement was, as expected, significantly higher in the TAO group compared to the control group (p=0.01, p<0.05) (Table1).

Rim area (p=0.14), average C/D ratio(p=0.18), vertical C/D ratio(p=0.16) and cup volume (p=0.18) values were similar in the TAO and control groups (p>0.05). On the other hand, disc area was significantly larger in the TAO group (p=0.03, p<0.05) (Table 2).

In the comparison of RNFL thicknesses between the TAO group and the control group, we found that the average RNFL (p=0.02), superior RNFL (p=0.02) and inferior RNFL (p=0.01) thickness measurements were

Table 1. Investigation of General Characteristics of the TAO and Control Groups

General features	Group	n	Mean	SD	p
Age(year)	Control	48	41.66	12.14	0.67
	TAO	41	40.51	12.61	
Central Corneal Thickness(mm)	Control	48	0.548	36.32	0.41
	TAO	41	0.555	36.20	
Refraction(D)	Control	48	-0.03	1.13	0.38
	TAO	41	-0.26	1.33	
Intraocular Pressure (mmHg)	Control	48	15.79	2.28	0.20
	TAO	41	15.73	2.40	
Hertel Measurement(mm)	Control	48	15.24	0.82	**0.01***
	TAO	41	18.98	1.37	

*p <0.05 a statistically significant difference
TAO: Thyroid-Associated Ophthalmopathy

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Table 2. Investigation of optic nerve parameters in Patients with TAO

Optic Nerve Parameters	Group	n	Mean	SD	p
Rim Area(mm^2)	Control	48	1.39	0.28	0.14
	TAO	41	1.34	0.32	
Disc Area(mm^2)	Control	48	1.66	0.33	**0.03***
	TAO	41	1.91	0.39	
Average C/D ratio	Control	48	0.51	0.16	0.18
	TAO	41	0.58	0.18	
Vertical C/D ratio	Control	48	0.54	0.16	0.16
	TAO	41	0.56	0.17	
Cup Volume(mm^3)	Control	48	0.25	0.15	0.18
	TAO	41	0.26	0.28	

*p <0.05 a statistically significant difference
TAO: Thyroid-Associated Ophthalmopathy

significantly lower in the TAO group (p<0.05). There was no statistically significant difference between the groups in terms of temporal RNFL and nasal RNFL measurements (p=0.37, p=0.74, respectively p>0.05) (Table 3).

In the analysis of macular thicknesses measured at different macular areas according to ETDRS template in the TAO group and the control group, we found that average macular thickness (p=0.01) and all outer quadrant measurements (superior, temporal, inferior, nasal) (p=0.01, p=0.01, p=0.01, p=0.01) were statistically significantly thinner in the TAO group (p<0.05). Although the macular thickness of inferior inner quadrant was also significantly lower in the TAO group (p=0.03, p<0.05), other inner quadrant measurements were similar between the groups (p>0.05) (Table 4).

A representative comparison of OCT scans of the eyes with TAO patients and of the eyes in the control group is shown in Fig. 1 and Fig 2. thinning is observed in the TAO patient macula (Fig. 1).

We detected that the CAS score had a weak negative correlation with average RNFL thickness in patients with TAO (r=-0.26, p=0.01). Hertel measurements had a moderate negative correlation with average RNFL thickness (r=-0.46, p=0.01). CAS score had a weak negative correlation with the average macular thickness in patients with TAO (r=-0.35, p=0.01). Hertel measurements had a moderate negative correlation with average macular thickness (r=-0.51, p=0.01).

DISCUSSION

TAO is a progressive and organ-specific autoimmune disease with significant impact on quality of life. However, ophthalmopathy is mild in most patients and in non-progressive stages (1).

Prior to the study, we were expecting to see alterations in ONH parameters similar to glaucoma. However, disc area was the only variable among ONH parameters that showed a significant difference among groups. Other ONH parameters were not significantly different between the groups. In fact, it is known that elevated intraocular pressure and extraocular muscle hypertrophy in patients with TAO causes compressive optic neuropathy (8).

Optic nerve function is evaluated clinically in terms of color vision, contrast sensitivity, visual acuity, pupillary reaction, and visual field evaluation. However, irreversible structural damage occurs earlier than functional impairment, which is well known and repeatedly emphasized in glaucoma patients through RNFL thickness evaluation by OCT (9-12). In our study, we detected a significant reduction in superior, inferior, and average RNFL thicknesses in patients with TAO. In macular thickness evaluations, all the outer quadrants, inferior inner quadrant and average macular thickness were significantly lower in patients with TAO (p<0.05).

We think that the thinning of the posterior pole is caused by compressive optic neuropathy. As known, compressive optic neuropathy is characterized by an increase in resistance to orthograde axonal transport,

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Table 3. Investigation of Retinal Nerve Fiber Layer Measurements in Patients with TAO

Nerve Fiber Layer	Group	n	Mean	SD	p
Average RNFL thickness(µm)	Control	48	94.66	10.80	**0.02***
	TAO	41	87.23	13.79	
Superior quadrant(µm)	Control	48	119.06	20.06	**0.02***
	TAO	41	110.05	20.29	
Temporal quadrant(µm)	Control	48	64.87	9.31	0.37
	TAO	41	62.49	10.77	
Inferior quadrant(µm)	Control	48	124.36	16.12	**0.01***
	TAO	41	110.44	20.54	
Nasal quadrant(µm)	Control	48	70.55	9.30	0.74
	TAO	41	70.13	10.27	

*p <0.05 a statistically significant difference
TAO: Thyroid-Associated Ophthalmopathy, RNFL: Retinal Nerve Fiber Layer

Table 4. Macular Thickness Measurements in patients with TAO

Retinal Thickness Map	Group	n	Mean	SD	p
Fovea(µm)	Control	48	250.91	18.95	0.30
	TAO	41	246.22	23.37	
Superior inner quadrant(µm)	Control	48	327.17	16.78	0.31
	TAO	41	322.37	18.59	
Superior outer quadrant(µm)	Control	48	282.34	13.83	**0.01***
	TAO	41	267.73	16.33	
Temporal inner quadrant(µm)	Control	48	314.89	15.31	0.13
	TAO	41	309.39	16.67	
Temporal outer quadrant(µm)	Control	48	267.28	13.84	**0.01***
	TAO	41	253.46	13.54	
Inferior inner quadrant(µm)	Control	48	323.94	15.25	**0.03***
	TAO	41	308.71	12.50	
Inferior outer quadrant(µm)	Control	48	271.66	15.27	**0.01***
	TAO	41	259.15	15.90	
Nasal inner quadrant(µm)	Control	48	325.49	14.88	0.06
	TAO	41	319.95	17.51	
Nasal outer quadrant(µm)	Control	48	300.06	15.12	**0.01***
	TAO	41	286.41	15.62	
Average macular thickness(µm)	Control	48	283.34	12.90	**0.01***
	TAO	41	268.83	13.40	

*p <0.05 a statistically significant difference
TAO: Thyroid-Associated Ophthalmopathy

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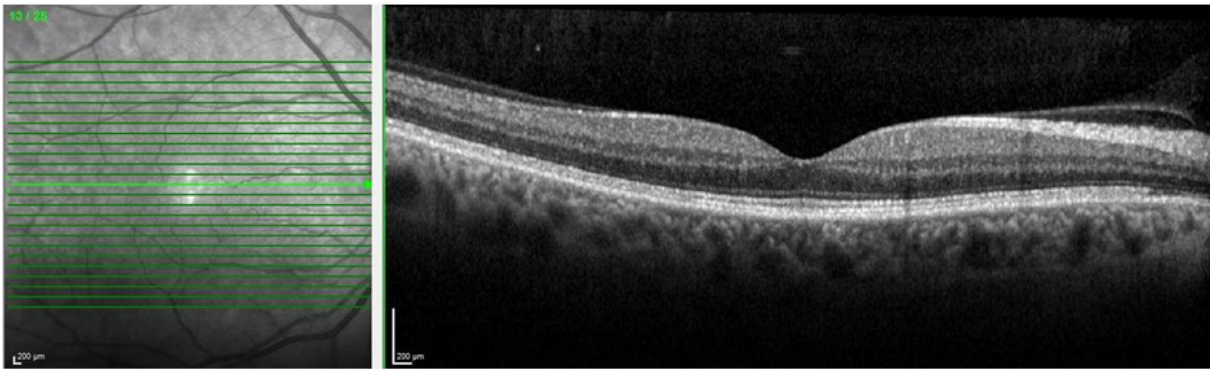

Figure 1. The illustration of macular OCT scans of a PD patients.

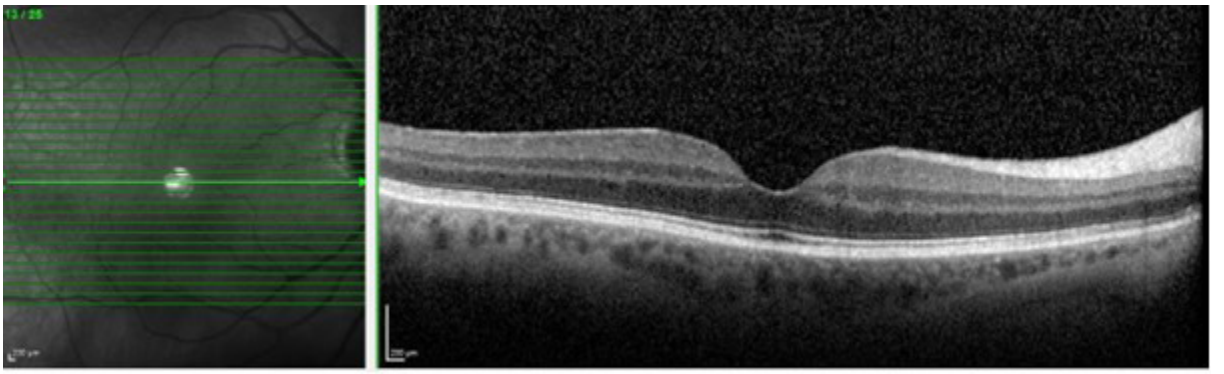

Figure 2. The illustration of macular OCT scans of an eye in the control group.

leading to axonal injury (13). This injury is reversible in the initial period, whereas a severe involvement causes changes in the RNFL in the form of thinning, which can be objectively documented on OCT evaluation of the RNFL and macula (9, 14, 15).

Studies on TAO have reported conflicting findings. Sayın et al. found similar results to our study (16). TAO group had thinner inferior RNFL thickness and macular thicknesses (superior, inferior, temporal, and nasal) and higher disc area and the C/D ratio when compared to the control group. Mugdha er al. reported a significantly lower average RNFL thickness compared to the normal group. They detected a correlation between CAS and RNFL, but they evaluated neither ONH nor macular thickness (9). Wei et al. measured the average RNFL thickness in patients with TAO and reported a significant thinning in patients with TAO. In addition, they also showed that enlargement of extraocular muscles can be an early sign of optic neuropathy (17).

We suggest that the lack of significant thinning of RNFL in nasal and temporal quadrants in our study can be due to the lower density of RNFL in these quadrants.

While some studies reported increased intraocular pressure in patients with TOA others found no significant difference (18-19). Authors who found an increase in intraocular pressure suggested that the thinning of the macula is related to glaucoma. Macular thinning is known in patients with glaucoma (12). In our study, intraocular pressure was higher in patients with TAO, it did not reach statistical significance ($p>0.05$).

In contrast to our findings, some studies have demonstrated increased RNFL thickness in patients with TAO compared to normal subjects. These findings

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are quite surprising. Meirovitch et al. found significant thickening of RNFL in all quadrants but the reduction of macular thickness, especially in the inner quadrant (20). It is proposed that this RNFL thickening, which is independent of intraocular pressure, is due to compressive optic neuropathy. The effects of compressive optic neuropathy on RNFL are known (21-22). Inflammation-induced thickening over optic disc can contribute to this process.

We think that the reduction of average macular thickness and thinning especially in outer quadrants in our study are possibly the result of the effect of mechanical compression at orbital and glob level on retina and choroid. However, we have observed that there are not enough studies in the literature investigating the effect of mechanical compression on retina and choroid. Another possible reason for the thinning may be the decrease in blood flow in the retina and choroid. There are studies in the literature supporting this assumption (23).

In our study, the choroidal thickness of patients with TAO was not taken into consideration. This is a limitation of our study. However, the choroidal thickness is evaluated manually, and the results are often based on subjective data. There are a few studies on this subject. Recently, Bruscolini et al. found a significant increase in subfoveal thickness in choroids of patients with Graves' disease. They also attributed this condition to the congestion in ophthalmic veins. In their study, they found a significant correlation between CAS and proptosis and choroidal thickness (24). Similarly, Ozkan et al. found a significant increase in choroidal thickness. They found a strong correlation between CAS and choroidal thickness and a correlation between choroidal thickness and VEP P100 (25). In a similar study, Caliskan et al. found an increase in subfoveal choroidal thickness in patients with active Graves' ophthalmopathy. This increase in choroidal thickness was correlated with CAS, young age and low intraocular pressure (26).

As a hypothesis, this increases in choroidal thickness together with the increase in the volume of the extraocular muscle and orbital fat tissue in TOA might contribute to the thinning of the retinal thickness. Because the increase in the volume of extraocular muscles has been recently demonstrated with enhanced-depth imaging spectral-domain anterior segment optical coherence tomography (27). The reduction in orbital venous drainage due to increased episcleral venous pressure and increased retrobulbar pressure is also known (28, 29). Together with elevated intraocular pressure, this may be another cause of morphological changes in the macula in patients with TOA.

When the literature is reviewed, there are some studies conducted with OCT angiography. Del Noce et al. found TAO disease may be associated with changes in deep capillary plexus-peripapillary vascular blood flow indices and choriocapillaris-peripapillary vascular blood flow indices; also, they claim choriocapillaris-peripapillary vascular blood flow indices seems to correlate with disease activity (30). Yuet al. found that TAO patients had significant variations in RNFL thickness, choroidal thickness, foveal avascular zone area and superficial retinal vessels. These parameters may appear to be potential adjuncts in the evaluation of TAO patients (31).

The current EUGOGO guidelines for the management of Graves' orbitopathy are based on clinical activity and clinical severity of the disease, which are determined by a set of pre-defined criteria (6). In our study, average RNFL thickness and average macular thickness showed a weak correlation with CAS. However, a stronger correlation was detected with Hertel measurements.

CONCLUSION

Alterations in RNFL thicknesses and macular thicknesses according to ETDRS template can be detected before the development of ocular symptoms in patients with TAO. OCT is a convenient non-invasive tool for the evaluation and follow-up of macular structural changes. Patients can be diagnosed at an early stage prior to the development of functional damages. However, the low number of studies investigating this subject in the literature and the conflicting findings of existing studies necessitate further studies. The retrospective nature of our study and the small sample size limit our study.

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