Continuing Medical Education:

Choroidal changes observed with enhanced depth imaging optical coherence tomography in patients with mild Graves orbitopathy

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Learning Objectives

Upon completion of this activity, participants will be able to:

1. Assess the pathophysiology of Graves orbitopathy.
2. Evaluate findings of the choroid among patients with Graves orbitopathy.
3. Analyze associations between changes in choroidal thickness and clinical variables among patients with Graves orbitopathy.

Authors/Editors disclosure information

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Choroidal changes observed with enhanced depth imaging optical coherence tomography in patients with mild Graves orbitopathy

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Abstract

Purpose To evaluate the choroidal thickness in patients with Graves orbitopathy (GO) using enhanced depth imaging-optical coherence tomography (EDI-OCT).

Methods Thirty-one patients with GO were evaluated prospectively. All subjects underwent ophthalmologic examination including best-corrected visual acuity, intraocular pressure measurement, biomicroscopic, and fundus examination. Choroidal thickness was measured at the central fovea. In addition, visual evoked potential measurement and visual field evaluation were performed.

Results The mean choroidal thickness was $377.8 \pm 7.4 \mu$ in the GO group, and $334 \pm 13.7 \mu$ in the control group. ($P=0.004$). There was a strong correlation between the choroidal thickness and the clinical activity scores (CAS) of the patients ($r=0.281$, $P=0.027$). Additionally, there was a correlation between the choroidal thickness and the visual-evoked potential (VEP) P100 latency measurements of the patients ($r=0.439$, $P=0.001$).

Conclusions The results of this study demonstrate that choroid is thicker in patients with GO. The choroidal thickness is also correlated with the CAS and VEP P100 latency measurements in these patients.

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Introduction

The choroid is the vascular layer of the eye and it provides oxygen and nourishment to the outer layers of the retina. Changes in the choroidal

circulation may be related to the pathogenesis of retina, retina pigment epithelium, choroid, and optic nerve. These disorders include hyperopia,¹ myopia,² central serous chorioretinopathy,³ polypoidal choroidal vasculopathy,⁴ age-related macular degeneration,⁵ inflammatory eye diseases,⁶ diabetes,⁷ glaucoma,⁸ and scleral buckling surgery.⁹ The enhanced depth imaging-optical coherence tomography (EDI-OCT) method of spectral domain optical coherence tomography (SD OCT) has enabled the quantitative measurement of choroidal thickness or volume, in addition to obtaining cross-sectional images of choroid.^{10,11}

Graves orbitopathy (GO), a disorder of autoimmune activity against orbital fibroblasts and adipocytes, is characterized by edema and inflammation of extraocular muscles and an increase in orbital connective tissue and fat. The immune basis of disease is suggested by perivascular and diffuse infiltration of CD4+ and CD8+ T cells, B cells, plasma cells, and macrophages.¹² Connective tissues are extensively remodeled with enlargement of the extraocular muscle, muscles, and orbital adipose tissues. The mass effect causes venous obstruction and congestion.

The aim of this study is to investigate whether the changes in the orbital tissues alter the choroidal circulation and subfoveal choroidal thickness in patients with GO. In addition, we aimed to evaluate whether the changes in choroidal thickness correlate with the visual-evoked potential (VEP) measurements and Visual Field examinations of the patients with GO.

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Materials and methods

Sixty-two eyes of 31 patients with a diagnosis of GO participated in this prospective study. All patients were euthyroid in both clinical and laboratory examinations. None of the patients were using systemic steroids. The patients were compared with 44 eyes of 22 control subjects who did not have any ophthalmologic or systemic pathology. The study received approval from the Kocaeli University, Faculty of Medicine Ethics Committee. An informed consent was obtained from the patients.

Ophthalmologic examination

All patients and control subjects received comprehensive ocular examination including best-corrected visual acuity, biomicroscopic examination, intraocular pressure (IOP) measurement, indirect ophthalmoscopy, Hertel measurements, and choroidal thickness measurements. The patients with GO additionally underwent visual field tests and VEP measurements.

Clinical activity scores (CAS) of the patients were also evaluated. Patients received one point from each of the symptoms including spontaneous eye pain, eye pain upon eye movement, eyelid swelling, eyelid erythema, conjunctival redness, chemosis, and swollen caruncle. When CAS was 3 points or over, it was defined as active GO.

Exclusion criteria were suggestion of inflammatory orbital disease except GO, previous orbital radiotherapy, high myopia (greater than -6 diopters), high IOP (>21 mm Hg), and ocular diseases that effect choroidal thickness (glaucoma, uveitis, retinal and choroidal diseases).

OCT examination

Choroidal thickness was measured using EDI-OCT imaging using spectral domain OCT (Spectralis; Heidelberg Engineering, Heidelberg, Germany). To obtain an EDI-OCT image, the instrument was brought increasingly closer to the eye until we obtained an inverted image. Choroidal thickness, defined as the distance from the inferior margin of the retinal pigment epithelium to the choroid/sclera border was measured at central fovea. After the EDI image is obtained, two blinded clinicians measured the choroidal thickness manually by using calipers. Mean of the two measurements of each patient were taken into consideration. Choroidal thickness was measured at the central fovea (Figure 1).

VEP examination

VEP is defined as variation of bioelectrical potentials in the visual cortex evoked by visual stimuli and evaluates

Figure 1 Choroidal thickness measurement of a patient with GO from EDI-OCT image.

the transmission of neuronal impulses that originate from the retinal photoreceptors passing through visual pathways to the occipital cortex. VEP is obtained by averaging the responses from occipital scalp electrodes generated by 100 or more sequential stimuli. The VEP is generated using a black-white checkered-board pattern on a television monitor. Patients sat one meter away from the monitor. The patients' gaze was fixed on a point at the center of the television monitor monocularly. The bioelectric signal was filtered (bandpass 0.5–200 Hz). Two hundred responses were averaged for every trial (Neuropack Nihon Kohden, MEB-5504 K, Tokyo, Japan). The analysis time was 250 msec. Sweep length was 300 msec (30 msec/div) and stimulus rate was 1 Hz. Peak latencies of the P100 component were measured.

Statistical analysis

All statistical analyses were performed using software IBM SPSS Statistics 19.0 version (SPSS, Inc., Chicago, IL, USA). The results were reported as mean values $\pm$ SD. Choroidal measurements of the GO and control eyes were compared by using independent samples *t* test. The significance of correlations between the choroidal thickness, VEP, mean deviation (MD) of visual field and CAS were determined by Pearson's correlation coefficient test. A $P < 0.05$ was considered statistically significant.

Results

Mean age of the GO group and controls were 44.13 ± 2.2 and 45.3 ± 3.1 , respectively ($P = 0.747$). Twenty-four patients were female and 8 patients were male in the GO group. There was no statistical difference in gender between the groups ($P > 0.05$). Eleven patients demonstrated the CAS evaluated as 0, six patients as 1, five patients as 2, five patients as 3, and four patients as 4.

There was no patient with CAS of 5,6 or 7. None of the patients had decrease in visual acuity related with the GO. The IOP of the patients were within the normal limits. The clinical characteristics of the patients were summarized in Table 1.

The mean choroidal thickness was $377.8 \pm 7.4 \mu$ in the GO group, and $334 \pm 13.7 \mu$ in the control group ($P=0.004$). We correlated the CAS of the patients with their choroidal thickness. We observed that choroid was thicker in patients with higher CAS. The correlation between these two parameters were statistically significantly different ($r=0.281$, $P=0.027$; Figure 2).

We correlated the VEP measurements of the patients with their choroidal thickness. We found that choroid was thicker in patients with elongated VEPp100 measurements ($r=0.439$, $P=0.001$; Figure 3).

We also evaluated the correlation between choroidal thickness and MD in visual field examination. The choroid thickness increased as the MD decreased. However, this correlation did not reach to the statistical significance ($r=-0.273$, $P=0.061$).

Table 1 Clinical and demographic characteristics of the patients are summarized

Characteristic	n	Mean $\pm$ SD
Gender		
Male	8	
Female	23	
Mean age		44.13 ± 2.2 (20–75)
Clinic activity score:		
0	11	
1	6	
2	5	
3	5	
4	3	
5	0	
6	0	
7	0	
Visual acuity ^a :		
1.0	27	
0.9	1	
0.7	1	
0.5	1	
0.4	1	
Dyschromatopsia	0	
Relative afferent pupillary defect	0	
Optic disc edema	0	
Intraocular pressure		15.68 ± 1.75 mm Hg
T3 ^b		2.83 ± 0.84
T4 ^b		1.16 ± 0.36
TSH ^b		1.81 ± 3.44

^aOnly four patients had visual acuity <1.0 . However, none of them was related with GO. ^bThe patients were euthyroid.

Discussion

OCT is a non-invasive method that is used for quantitative assessment of retinal morphology, and it offers valuable data about the prognosis of the patients. A relatively new technique, EDI-OCT uses light with a longer wavelength, which is more effective for choroidal scanning and provides valuable data about choroidal morphology. Recently, many SD OCT instruments have been used the EDI method for the choroidal thickness measurements in various diseases.^{3,13,14} Changes in the choroidal thickness might be related to the pathogenesis of retinal, retina pigment epithelium, and optic nerve diseases. These studies reported increased choroidal thickness in patients

Figure 2 The choroidal thicknesses of the patients with GO were correlated with their clinical activity scores. There was a correlation between these two parameters and this correlation was statistically significant ($r=0.281$, $P=0.027$).

Figure 3 The choroidal thicknesses of the patients with GO were correlated with their VEP measurements. The choroid was significantly thicker in patients with longer VEPp100 latency ($r=0.439$, $P=0.001$).

with posterior uveitis including Vogt-Koyanagi Harada disease, multiple evanescent white dot syndrome and Behçet's disease.^{15–17} In this study we found that subfoveal choroidal thickness of eyes with GO was significantly higher than normal eyes.

Patients with GO commonly have evidence of both extra-ocular muscle and orbital adipose tissue involvement. The hallmark of GO is swelling of the extraocular muscles in association with an increase in orbital connective tissue and fat volume to a variable extent. The expanded orbital tissues causes increase in intra-orbital pressure. As a result, the venous outflow from the orbit is impeded.¹⁸ Elevated episcleral venous pressure value has been demonstrated in GO, and raised retrobulbar pressure above normal venous pressure has been reported as a possible cause of reduced orbital venous drainage.^{19,20} Konuk *et al*²¹ found that the superior ophthalmic vein blood flow velocity was significantly lower in severe GO cases compared with moderate and mild ones. The increase in venous pressure may lead to an elevation with IOP in some patients with GO.²² In addition, it has been shown that orbital decompression reduces the IOP and superior ophthalmic vein velocity significantly.²³ None of our patients had severe GO, and the mean IOP was within the normal limits. However, the mean choroidal thickness was elevated. We think that choroidal thickness might be affected from the venous obstruction and congestion in patients with GO. The elevation of the choroidal thickness might be an early sign of venous congestion that occurs before the elevation of IOP.

Another mechanism that might alter the thickness of choroid might be the direct compression of the globe. Choroidal folds might occur with extraocular process that induces sufficient compressive stress within the choroid.²⁴ Jorge *et al*²⁵ reported that choroidal folds might resolve and visual acuity might increase after orbital decompression for GO despite persistent enlargement of extraocular muscles. They claim that tension on the choriocapillaris could be generated by direct pressure on the sclera by enlarged eye muscles.²⁵ Odrobina *et al*⁹ found that subfoveal choroidal thickness of eyes after scleral buckling surgery using an encircling band, in long-term observation, was significantly thicker. They claim that scleral buckling reduces blood flow and increases hemostasis in choroidal circulation. This may cause an elevation in choroidal pressure and may increase the subfoveal choroidal thickness.⁹

The compression of the optic nerve by an orbital apex crowding often results with the optic neuropathy in patients with GO. This condition occurs in ~5% of the patients with GO.²⁶ It might be asymptomatic with good vision, but it might also manifest with decreased visual acuity, reduced color vision, visual field defects, or

afferent pupillary defects. If these symptoms and signs are not present, the patient might be unaware of visual loss until advanced clinical changes have occurred. VEP might help us gaining objective information about the optic nerve dysfunction in GO.^{27–29} Weis *et al*³⁰ evaluated the relationship between the orbital bony geometry and the volume of the intraorbital structures in predicting optic neuropathy in GO. They found that medial rectus muscle size was a predictor of compressive optic neuropathy.³⁰ As compression on the optic nerve is also related with the stasis in the choroid, we hypothesize that increase in extra-ocular volume might also be related with the increase in choroidal thickness. In our study, none of the patients had the clinical signs of optic neuropathy. However, we found that choroid was thicker in patients with longer VEP latency. We believe that choroidal thickness measurements might be used to discriminate the early changes in optic nerve in patients with GO. Further investigations are needed to understand the relationship between these two parameters.

GO is an inflammatory and autoimmune disorder of the orbit. The immune basis of the disease is composed by a perivascular and diffuse infiltration of CD4+ and CD8+ T cells, B cells, plasma cells, and macrophages.³¹ Orbital fibroblasts are thought to have crucial role in the pathogenesis by their ability to produce hydrophilic glycosaminoglycans that result in retention of fluid and edematous swelling of orbital tissues. The immune activity of ophthalmopathy is neither synonymous nor coincident with clinical severity of the disease.³² Several methods have been proposed to evaluate disease activity; none has yet become generally accepted for routine use in clinical practice. The CAS has been shown to be a useful method, in spite of sensitivity and inter-observer variation weakness. Mourits *et al*³³ found good correlation between initial and post immune-suppressive treatment CAS. In another study, Tortora *et al*³⁴ evaluated correlation between the orbital MRI imaging and CAS. They found a statistical correlation between CAS and both STIR and contrast enhanced T1-weighted sequences.³⁴ In our study, we found that choroid was thicker in patients with higher CAS. However, our patients' CAS scores were distributed between 0 and 4. We believe that comparison of choroidal thickness of the patients with higher CAS might give a better idea in relationship between CAS and choroidal thickness. Absence of patients with higher CAS might be considered as a weakness in our study.

In conclusion, we found that patients with GO have higher choroidal thickness than the healthy controls, and we observed that choroid was thicker in patients with higher CAS. In addition, VEP measurements of the patients were correlated with the choroidal thickness of the patients. Choroidal thickness measurement might be a beneficial test for evaluating GO, and discriminating optic

neuropathy. The patients in our study did not have severe GO and they did not have high CAS. We believe that further investigations with a larger and variable group of patients would show more disease-specific results.

Summary

What was known before

- Thyroid orbitopathy is a disease of the orbit that causes inflammation and fibrosis.
- The changes in the orbita might result with the compression of the optic nerve.
- However, there is no information about the changes inside the globe related with this compression.

What this study adds

- Evaluation of the choroid with EDI OCT showed that Graves orbitopathy causes choroidal thickening.
- This might be related with the direct compression of the orbit or venous stasis.
- In addition, choroidal thickening is correlated with the clinical activity scores and VEP p100 latency of the patients.
- We believe that EDI OCT measurements might provide a better evaluation of the patients with Graves orbitopathy.

Conflict of interest

The authors declare no conflict of interest.

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1. You are seeing a 44-year-old woman sent to your office for visual disturbance and a history of Graves orbitopathy. What should you consider regarding the pathophysiology of this condition?
 - A The principal pathologic mechanism is autoimmune activity against myocytes
 - B Graves orbitopathy is characterized by a decrease in orbital connective tissue and fat
 - C The inflammatory reaction of Graves orbitopathy involves T cells, B cells, and macrophages
 - D In Graves orbitopathy, there is severe atrophy in extraocular muscles
2. Which of the following statements regarding the clinical findings of patients with Graves orbitopathy vs control participants in the current study is **most** accurate?
 - A Choroidal thickness was increased, and it correlated positively with clinical activity scores (CAS)
 - B Choroidal thickness was increased, but it was unrelated to CAS
 - C Choroidal thickness was similar in comparing patients with vs those without Graves orbitopathy
 - D Choroidal thickness was decreased by approximately half among patients vs control participants
3. What other examination findings were associated with Graves orbitopathy in the current study?
 - A Choroidal thickness was positively related to elongated visual evoked potential P100 (VEPp100) measurements
 - B Choroidal thickness was not significantly related to VEPp100 measurements
 - C Choroidal thickness was most strongly associated with the mean deviation in visual field examination
 - D Most patients with Graves orbitopathy had evidence of optic neuropathy

Activity evaluation

1. The activity supported the learning objectives.

Strongly disagree				Strongly agree
1	2	3	4	5

2. The material was organized clearly for learning to occur.

Strongly disagree				Strongly agree
1	2	3	4	5

3. The content learned from this activity will impact my practice.

Strongly disagree				Strongly agree
1	2	3	4	5

4. The activity was presented objectively and free of commercial bias.

Strongly disagree				Strongly agree
1	2	3	4	5