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Original Article

The Impact of Graves' Ophthalmopathy On Anterior and Posterior Ocular Structures: Ocular Imaging Based Study

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ABSTRACT

Objective: The aim of our study was to evaluate the anterior and posterior ocular parameters in patients with Graves' ophthalmopathy (GO) compared to control.

Methods: Sixty-eight patients with GO and 40 healthy controls were included in the study. The patients with GO were divided into two groups according to their clinical activity score (CAS). Patients with ≥3/7 CAS points were entitled as active GO and CAS points less than 3/7 were entitled as inactive GO. Spherical refractive error (SRE), astigmatic refractive error (ARE), central corneal thickness, intraocular pressure, and axial length (AL) were recorded. The subfoveal choroidal thickness (SFCT) and global and sectorial peripapillary retinal nerve fiber layer thickness (pRNFLT) were measured by spectral domain- optical coherence tomography.

Results: The patients with active GO had significantly higher myopic SRE and ARE compared to patients with inactive GO and healthy controls (p=0.040 and 0.030, respectively). The mean AL was statistically significant taller in both GO groups than control (p=0.048) but there were no significant differences in AL between the patients with active GO and inactive GO. Patients with active GO and inactive GO had significantly higher SFCT than controls (p≤0.001). Furthermore, patients with active GO had significantly thinner global pRNFLT, superior pRNFLT, inferior pRNFLT, and temporal pRNFLT than patients with inactive GO and active GO. The patients with inactive GO had only thinner inferior pRNFLT compared to healthy controls.

Conclusion: The patients with GO had significant alterations in refractive status, SFCT, and pRNFLT, especially patients with active GO. These parameters might be potential adjuncts in the evaluation of GO patients and preventing ocular serious complications.

INTRODUCTION

Graves' disease (GD) is an autoimmune disorder that mostly affects women and can be presented with any thyroid hormone level, such as hyperthyroidism, hypothyroidism, and euthyroid. Graves' ophthalmopathy (GO) is the most common extra-thyroidal manifestation of the GD.[1] GO can be clinically seen in approximately 25–50% of patients with GD.[2] Also a study reported that, subclinical GO in orbital imaging systems was detected in nearly 70% of patients with GD.[3] Severe GO is not a frequent manifestation but may lead to sight-threatening complications including intense pain, corneal ulcerations, increased intraocular pressure (IOP), or compressive optic neuritis.[1]

The immunologic mechanism of GO is perivascular and diffuse infiltration of CD4+ and CD8+ T cells, B cells, plasma cells, and macrophages to adipose and fibrose tissue of orbit. This autoimmune activity leads to enlargement of the extraocular muscle and orbital adipose tissues. The extensive remodeling of ocular tissues may cause venous obstruction and congestion by mass effect.[4]

The choroidal network is the most vascular part of the eye and responsible for blood supply to outer segment of the retina. After the widely use of spectral domain optic coherence tomography (SD-OCT) technologies, the importance of choroidal thickness in the diagnosis and follow-up of many diseases has increased.[5] Furthermore, SD-OCT has enabled the quantitative measurement of

choroid and retinal layers thicknesses or volume, in addition to obtaining cross-sectional images of choroid-retinal structures.

It is known that the GO can affect to various ocular structures.[3] In this study, we aimed to evaluate refractive errors, subfoveal choroidal thickness (SFCT), and peripapillary retinal nerve fiber layer thickness (pRNFLT), according to patients' GO severity and to compare with the healthy controls.

MATERIALS AND METHODS

This cross-sectional study was conducted in accordance with the tenets of the Declaration of Helsinki and written consents were obtained from all patients and controls. The study protocol was reviewed and approved by the institutional local ethics committee before the participants' enrollment (no: 514/188/7, date: 27.10.2020).

Seventy-eight patients with GO who were followed up our ophthalmology clinic, were in included the study. All participants were euthyroid in both clinical and laboratory assessments. Patients were divided into two groups according to their clinical activity score (CAS).[6] Patients with CAS ≥3/7 were classified as active GO, and those with CAS ≤2/7 were classified as inactive GO. Age and gender matched 40 healthy controls were included in the study from the outpatient facility of the department. Exclusion criteria were listed as: Inflammatory orbital disease except GO, history of orbital radiotherapy, history of hormone therapy within 6 months, patients with greater than − 6 or +3 diopters, and ocular disorders that effect RNFLT and SFCT (glaucoma, uveitis, optic neuritis, retinal vascular diseases, and choroidal diseases, etc.).

All participants were undergone detailed ophthalmic examination including spherical refractive error (SRE) and astigmatic refractive error (ARE) measurements with autorefractometry, best corrected visual acuity assessment with Snellen chart, IOP measurement with Goldman applanation tonometry, anterior segment examination with slit-lamp biomicroscopy, and dilated fundus examination. The proptosis was measured by the same examiner with Hertel exophthalmometry. The clinically worse eye of each patients with GO was selected for the study purpose. If both the eyes behaved similarly, a simple random selection was done to decide on the inclusive eye. The inclusive eye from the controls was randomly selected. The axial length (AL) was measured with the IOL Master 500 (Carl Zeiss Meditec Inc., Jena, Germany).

The SFCT and the pRNFLT were measured by SD-OCT (Nikon RS-3000, Japan). All SD-OCT measurements were done by the same technician. All SFCT data, determined as the axial distance from the RPE to the outer choroid/sclera interface, were assessed by the same ophthalmologist (HSK) using enhanced-depth imaging scans. The pRNFL thickness was measured by SD-OCT with a 3.46 mm in diameter scan circle centered on the optic disc. This provided the pRNFL thickness values for four quadrants (N – Nasal, T – Temporal, S – Superior, and I – Inferior) and global mean values (360°).

Statistical analysis

All statistical analyses were performed using software IBM SPSS Statistics 21.0 version (SPSS, Inc., Chicago, IL, USA). Chi-square tests were used to analyze the categorical variables. The normality of the data was confirmed using the Kolmogorov–Smirnov test. Continuous variables were expressed as mean value±standard deviation. An independent Student's t-test and ANOVA were used to compare variables among groups. P<0.05 was considered statistically significant. The sample size was calculated using G Power 3.1.9.

RESULTS

Overall, 33 eyes of patients with active GO, 35 eyes of patients with inactive GO were included in the study and their data were compared with those of 40 age-matched healthy eyes of 40 controls. The mean age of the active GO group, inactive GO group, and controls was 38.12±8.81 years, 37.43±9.54 years, and 36.60±7.66 years, respectively (p=0.027). Females were the majority in all groups and there was no statistical difference in gender distribution among the study groups (p=0.36). Proptosis was presented more prominently in patients with active GO (19.67 mm) compared to that presented in patients with inactive GO and controls (17.21 mm and 15.02 mm, respectively; p<0.001).

In comparison of SRE and ARE, there were statistically significant difference among three groups (p=0.040 and p=0.030, respectively). The patients with active GO had significantly higher myopic SRE and ARE compared to patients with inactive GO and healthy controls. The mean AL was statistically significant taller in both GO groups than control (p=0.048) but there were no significant differences in AL between the patients with active GO and inactive GO. There were no significant differences in IOP and central corneal thickness among the three groups (p=0.51 and 0.058, respectively). Table 1 shows the clinical data of the three groups.

The mean SFCT was 358.40±41.44 μm in patients with active GO, 334.11±59.22 μm in patients with inactive GO, and 305.21±65.50 μm in controls. There was a statistically significant difference in SFCT among the three groups (p<0.001). Both groups with GO had significantly thinner SFCT than healthy controls. Furthermore, patients with active GO had significantly thinner SFCT than patients with inactive GO.

In post hoc analyses, the mean global pRNFLT of the patients with active GO (99.94±8.71 μm) was significantly thinner than those of patients with inactive GO (104.92±6.48 μm) and control (107.29±8.97 μm) (p<0.001), while there were no statistically significant differences in global RNFLT between patients with inactive GO and controls (p>0.05). The patients with active GO had significantly lower pRN-

Table 1. The comparison of anterior segment evaluations among the study groups

	Patients with active GO (n=33)	Patients with inactive GO (n=35)	Controls (n=40)	p-value
SRE (D)	–2.04±1.84[a,b]	–0.27±1.32	–0.20±0.93	0.040
ARE (D)	–0.21±0.8[3a,b]	–0.07±0.81	0.21±0.54	0.030
BCVA (decimal)	0.98±0.81	0.99±0.40	1.00±00	0.121
CCT (μm)	524,44±36.9	519.91±25.9	526.80±26.2	0.058
IOP (mm Hg)	17.01±3.6	16.62±2.3	15.84±2.6	0.51
AL (mm)	23.13±0.7[b]	23.02±0.6[c]	22.65±0.7	0.048
CAS point	4.29±0.80	0.97±0.78	N/A	<0.001

Data are presented as mean±standard deviation. AL: Axial length; ARE: Astigmatic refractive error; BCVA: Best corrected visual acuity; CCT: Central corneal thickness; IOP: Intraocular pressure; SRE: Spherical refractive error. Post hoc analysis (Tukey): [a]Denotes statistical difference between active GO and inactive GO, [b]Denotes statistical difference between active GO and control, [c]Denotes statistical difference between inactive GO and control.

Table 2. The comparison of the SFCT and pRNFLT among the study groups

	Patients with active GO (n=33)	Patients with inactive GO (n=35)	Controls (n=40)	p-value
SCFT (μm)	358.40±41.44[a,b]	334.11±59.22[c]	305.21±65.50	<0.001
Global pRNFLT (μm)	99.94±8.71[a,b]	104.92±6.48	107.29±8.97	<0.001
S-pRNFLT (μm)	121.34±10.45[a,b]	126.47±9.65	127.03±10.19	0.011
I-pRNFLT (μm)	118.24±12.23[a,b]	123.37±9.93[c]	129.34±11.71	<0.001
N-pRNFLT (μm)	79.94±11.02[a,b]	86.17±5.63	87.62±6.21	0.008
T-pRNFLT (μm)	80.00±9.78[b]	83.41±7.00	85.24±5.32	0.006

Data are presented as mean±standard deviation. GO: Graves' ophthalmopathy; I: Inferior; N: Nasal; S: Superior; T: Temporal; pRNFLT: Peripapillary retinal nerve fiber layer thickness; SFCT: Subfoveal choroidal thickness. Post hoc analysis (Tukey): [a]Denotes statistical difference between active GO and inactive GO, [b]Denotes statistical difference between active GO and control, [c]Denotes statistical difference between inactive GO and control.

FLT in all quadrants than healthy control and lower superior, inferior, and nasal pRNFLT than patients with inactive GO. In comparison of quadrants of pRNFLT between patients with inactive GO and control, the statistically significant difference was observed only in inferior pRNFLT. Table 2 shows the comparison of the SFCT and pRNFLT among the study groups.

DISCUSSION

In this study, we assessed the anterior and posterior ocular segment alterations in patients with active and inactive GO. In GO pathogenesis, there is an enlargement of retrobulbar tissue and elongation of four rectus muscles. This condition may push the eyeball forward and cause the rectus muscles to pull the eyeball more strongly posterior. Moreover, the direction of the final vector on the eyeball results in a compressive force parallel to the visual axis, increasing the amplitude of the vector. This process may induce alteration of ocular AL and the refractive error. Mombaerts et al.[7] reported that GO was related to greater with the-rule corneal astigmatism and suggested that this was due to fibrosis of the soft tissue in the superolateral orbital region. Our findings suggested that, patients with active GO had higher myopic SRE and ARE and both patients with GO groups had higher AL compared to healthy controls. The previous studies revealed that patients with GO have more myopic refractive errors and it is related with exophthalmos levels.[8,9] Furthermore, Kim et al.[10] evaluated the ARE changes after orbital decompression surgery in patients with severe GO and they revealed that patients with orbital decompression had higher ARE than patients with GO without orbital decompression surgery. Another study reported that patients with GO who underwent orbital decompression showed myopic refractive change through increase in AL and they added possible refractive changes should be considered in cases of GO complaining of decreased visual acuity after orbital decompression.[11]

The previous studies have reported that ocular blood flow was increased in patients with GO. Various techniques including Doppler imaging, ocular blood flow tonography, and oculo-dynamometry can ensure more reliable ocular blood flow measurements.[12,13] More than 70% of the ocular blood flow goes to the choroidal network.[14] The choroidal thickness might be affected in several systemic diseases.[5] SD-OCT can provide non-invasive and quick evaluation of choroidal thickness. Özkan et al.[15] reported that patients with GO had thicker SFCT than healthy controls in their study, which included patients with a 3 or more CAS points. Yu et al.[16] evaluated the choroidal thickness in five sectorial region not only in subfoveal area and they revealed that choroidal thickness was higher in all region in patients with GO than controls. In our study, we found that patients with GO whether active or inactive

had significantly higher SFCT than healthy controls. Furthermore, patients with active GO had significantly thicker SFCT than patients with inactive GO. These results suggested that SFCT increased in patients with GO according to their GO activity and increase in SFCT might be an indicator for retrobulbar vascular congestion.

Compressive optic neuropathy is one of the most serious complication of TO. The functional tests, such as color vision, contrast sensitivity, and visual field test, can be used for determining the for optic nerve damage, especially irreversible damages. The pRNFLT measurements with SD-OCT provide valuable information for determination the viable retinal ganglion cell in the axonal mass and generally use for diagnosis of glaucoma and optic nerve diseases.[17] The SD-OCT analyses are very useful in diagnosis of the patients with pre-perimetric glaucoma who have not any damage in visual field tests. In our study, patients with active GO had thinning in all pRNFLT quadrants compared to controls while patients with inactive GO had thinning in only inferior quadrants. Furthermore, patients with active GO had thinner global and quadrants pRNFLT than patients inactive GO except nasal pRNFLT. Similarly, Mugdha et al.[18] found that patients with GO (who have >3 CAS points) had thinner global pRNFLT and thinner pRNFLT quadrants than controls and they found a significant thinning only in inferior pRNFLT during the 6 months follow-up. Yu et al. evaluated the patients with active and inactive GO using by optic coherence tomography angiography which is a newer technology, and they found that patients with active GO had thinner global pRNFLT, inferior, and temporal pRNFLT than patients inactive GO and controls. Therefore, early detection of thinning of pRNFLT might be useful for prevent irreversible optic nerve damage.

In this study, we divided patients with GO according to their CAS points. However, there are different disease severity classification systems for grading GO.[19] In our study, patients with active GO, with high CAS points, had significantly higher SFCT and lower pRNFLT. Cagiltay et al.[20] evaluated the choroidal thickness in patients with GO and they used the VISA (vision, inflammation, strabismus, and appearance) inflammatory score system and they reported that the mean choroidal thickness was positively correlated with VISA score. Özkan et al.[15] reported that SFCT was thicker in patients with higher CAS. On the other hand, Mugdha et al.[18] did not found a relationship CAS points and pRNFLT. However, their patients' mean CAS scores were 1.95 and the distribution of CAS points were very limited. We believe that comparison of SD-OCT parameters of the patients with higher CAS might give a better idea in relationship between CAS and SD-OCT parameters.

Our study has some limitations. This study was a single center study with relatively small sample size. A manual method was used to measure SFCT; instead using an automated software program could be more reliable. Furthermore, only SD-OCT was performed, and optic disc perfusion was not evaluated. The use of ultrasound and/or optical coherence tomography angiography may be more reasonable for showing perfusion in future studies.

CONCLUSION

The patients with GO had significantly higher SFCT compared to healthy controls and patients with active GO had significantly thinner pRNFLT than patients with inactive GO and controls but only the inferior pRNFLT were significantly lower in patients with inactive GO. Screening by SD-OCT might be beneficial for preventing optic neuropathy and choroid-retinal diseases in patients with GO.

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Ethics Committee Approval

Approved by the local ethics committee (no: 514/188/7, date: 27.10.2020).

Peer-review

Internally peer-reviewed.

Authorship Contributions

Concept: H.S.S.K., M.O.; Design: H.S.S.K.; Supervision: A.A., E.E.Ş.; Materials: E.E.Ş., M.O.; Data: H.S.S.K.; Analysis: H.S.S.K., A.P.; Literature search: A.P.; Writing: H.S.S.K.; Critical revision: A.A., E.E.Ş.

Conflict of Interest

None declared.

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Graves' Oftalmopatisinin Oküler Ön ve Arka Segment Yapılarına Etkileri: Oküler Görüntüleme Temelli Çalışma

Amaç: Çalışmamızın amacı Graves oftalmopatili (GO) hastalarda ön ve arka segment oküler parametreleri değerlendirmek ve sağlıklı kontrol grubuyla karşılaştırmak.

Gereç ve Yöntem: Çalışmaya 68 GO hastası ve 40 sağlıklı kontrol grubu dahil edildi. GO hastaları klinik aktivite skorlarına (KAD) göre iki gruba ayrıldı. KAD puanı ≥3/7 olan hastalar aktif GO, 3/7'den az KAD puanları inaktif GO olarak adlandırıldı. Sferik kırılma kusuru (SKK), astigmatik kırılma kusuru (AKK), merkezi kornea kalınlığı, göz içi basıncı ve aksiyel uzunluk (AU) kaydedildi. Subfoveal koroidal kalınlık (SFKT) ve global ve sektörel peripapiller retina sinir lifi tabakası kalınlığı (pRSLTK) spektral alan-optik koherens tomografi ile ölçüldü.

Bulgular: Aktif GO hastaları, inaktif GO hastaları ve sağlıklı kontrollere kıyasla anlamlı derecede daha yüksek miyopik SKK ve AKK'ye sahipti (sırasıyla, p=0.040 ve 0.030). Ortalama AU değeri her iki GO grubunda kontrole göre istatistiksel olarak anlamlı derecede daha uzundu (p=0.048) ancak aktif GO ve inaktif GO olan hastalar arasında AU açısından anlamlı fark yoktu. Aktif GO ve inaktif GO olan hastalar, kontrollere göre anlamlı derecede daha yüksek SFKK'ye sahipti (p=<0.001). Ayrıca, aktif GO'lu hastalar, inaktif GO ve aktif GO hastalarına göre önemli ölçüde daha ince global pRSLTK, superio pRSLTK, inferior pRSLTK ve temporal pRSLTK'ye sahipti. İnaktif GO hastalarında sağlıklı kontrollere kıyasla sadece daha ince inferiyor pRSLTK vardı.

Sonuç: GO hastalarında, özellikle aktif GO olan hastalarda refraktif durumda, SFKK ve pRSLKT'de önemli değişiklikler saptandı. Bu parametreler GO hastalarının değerlendirilmesinde ve ciddi oküler komplikasyonların önlenmesinde potansiyel yardımcılar olabilir.

Anahtar Sözcükler: Graves' oftalmopati; retinal sinir lifi kalınlığı; spectral alan optic koherans tomografi; subfoveal koroidal kalınlık.