Thicknesses of Retinal Layers in patients with Graves' Disease with or Without Orbitopathy

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Research Article

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Abstract

Purpose: Graves' ophthalmopathy (GO) is an inflammatory process that may involve the ocular surface, orbital fat, extraocular muscles, and optic nerves in patients with Graves' disease (GD). We aimed to compare thicknesses of retinal layers in patients with GD with and without GO.

Methods: One hundred seven patients with GD (23 with GO (Group1), 84 without GO (Group2)) and eighteen volunteers (Group3) were enrolled. The spectral-domain optical coherence tomography (SD-OCT) is used for ophthalmologic evaluation. Seven retinal layers including retinal nerve fiber layer (RNFL), ganglion cell layer (GCL), inner plexiform layer (IPL), inner nuclear layer (INL), outer plexiform layer (OPL), outer nuclear layer (ONL), retinal pigment epithelium (RPE) were assessed. The thicknesses of layers are compared in groups.

Results: The median GCL thickness values in groups 1,2, and 3 were 14 μm, 15 μm, and 17.5 μm, respectively ($p = 0.02$). The median IPL thickness was 20 μm in group 1, 21 μm in group 2, and 22 μm in group 3 ($p = 0.038$). The median RPE thickness values in groups 1,2, and 3 were 16 μm, 17 μm and 18.5 μm, respectively. The median GCL, IPL, RPE were different in the groups, while RNLF, INL, OPL, ONL were similar ($p>0.05$ for each).

Conclusion: The median GCL, IPL and RPE were thinner in patients with GO than healthy controls.

Introduction

Graves' disease (GD) is an autoimmune disease that may consist of hyperthyroidism, goitre, eye disease, and occasionally a dermopathy referred to as pretibial or localised myxedema. Hyperthyroidism is the most common feature of GD, affecting nearly all patients. GD is characterised by the infiltration of thyroid antigen-specific T cells into thyroid-stimulating hormone receptor (TSH-R)-expressing tissues. TSH-R can be found in the thyroid and the extraocular eye muscles, and retrobulbar fat tissues. It is thought that circulating TSH-R trigger inflammation and activation of orbital fibroblasts leading to intraorbital swelling in an early active stage and, subsequently, to fibrosis at a later stage [1, 2]. Orbital involvement is known as Graves' orbitopathy (GO) [3, 4]. GO is observed in about 25–50% of the patients with GD [5]. GO, like GD, is more common in women than men [6].

GO is an inflammatory and proliferative process that may involve the ocular surface, orbital fat, extraocular muscles, and optic nerves [4, 7]. The characteristic signs of GO are exophthalmos, tearing, periorbital oedema, conjunctival injection and oedema. Patients with GO may have a gritty or foreign object sensation in the eyes, retroorbital discomfort or pain. In most severe cases, alterations in colour perception, diplopia and blurring of vision may occur due to compression of the optic nerve [8]. Some studies demonstrated that optic disc dysfunction might occur before optic neuropathy and extraocular muscle swelling in patients with GO [9–11]. Diagnostic and follow-up tests that were previously used to

assess the visual function of the patients with GO, such as visual field test, visual acuity test and colour sensation test, have some limitations. Optical coherence tomography (OCT) is an alternative noninvasive imaging technique. High-resolution cross-sectional images of the retina are produced by using the optical reflectivity of the tissues [12]. The different properties of the cell layers, derived from the interference pattern, allow them to discriminate. OCT demonstrates high-resolution anatomic images of the retina and retinal pigment epithelium. In spectral-domain OCT (SD-OCT), different colours in the reflected light provide reaching depth information. It is possible to evaluate each layer of the retina separately [13]. As a result, single layers affected in specific diseases can be evaluated separately, which provides more reliable predictions than total retinal thickness assessments for clinical outcomes and pathophysiology of retinal diseases [14, 15]. The thickness of seven layers including retinal nerve fiber layer (RNFL), ganglion cell layer (GCL), inner plexiform layer (IPL), inner nuclear layer (INL), outer plexiform layer (OPL), outer nuclear layer (ONL), retinal pigment epithelium (RPE) were provided automatically [16, 17].

In this study, we have examined retinal layers by SD-OCT in patients with GD and healthy subjects. We hypothesised that the inflammatory process and resulted alterations of the orbital structure and periocular tissues in GD leads to the expectation of retinal alterations. In this context, we investigated changes in seven retinal layers in patients with GD with or without clinical signs of orbitopathy.

Methods

This study was designed prospectively. Patients with GD older than 18 who had been followed in our clinic between April 2015 and May 2018 were selected. One hundred seven patients with GD (23 with GO, 84 without GO) and eighteen healthy controls were included. The control group was chosen from voluntary hospital staff. A previous history of chronic renal disease, hypertension, diabetes mellitus, chronic liver disease, glaucoma, keratitis, uveitis, ocular surgery, and intravitreal injection were exclusion criteria. Also, participants were questioned and examined about their refractive status, and for those with myopia, hypermetropia, or astigmatism, more than three diopters were excluded. Eyes with the best-corrected visual acuity worse than 20/30 were excluded. Forty-four (the two were excluded due to previous ocular surgery) eyes of 23 patients with GO, 168 eyes of 84 patients without GO and 36 eyes of 18 age- and sex-matched healthy subjects were compared.

All participants signed the informed consent form. An approval from the local ethics committee was obtained following the ethical standards of the Helsinki Declaration.

A single specialist performed a detailed ophthalmological examination, including best-corrected visual acuity, colour vision, biomicroscopic anterior segment examination, and OCT. Patients are questioned for symptoms and signs of GO. Disease activity is assessed using a seven-point clinical activity score (CAS), including painful feeling behind the globe, pain with eye movement, redness of the eyelids, redness of the conjunctiva, swelling of the eyelids, oedema of the conjunctiva and swollen caruncle. GO is considered active in patients with a CAS $\geq$3 [18]. The proptosis levels of all patients were measured with a Hertel exophthalmometer. The Spectralis OCT system (Heidelberg Engineering GmbH, Germany) was used for

retinal OCT imaging. Spectralis mapping software the Heidel berg Eye Explorer (6th version) assisted segmentation and measurement of the retinal layers from each OCT scan (Figure 1). The measurements can be made from the central, inner, and outer ring subfields defined by the ETDRS [17]. We used the measurements of the central subfield in this study (Figure 2).

The study population was divided into three groups. Patients with GD and GO enrolled in group 1, patients with GD and no clinical signs of GO enrolled in group 2, and healthy controls enrolled in group 3.

The name, sex, age, therapies received (medical therapy, surgery, radiation), total disease duration, and laboratory findings (serum thyroid-stimulating hormone (TSH), free triiodothyronine (fT3), free thyroxine (fT4), TSH-receptor antibody (TRAB), anti-thyroglobulin antibody (anti-TgAb), and anti-thyroid peroxidase antibody (anti-TPOAb)) at the time of ophthalmological examination were recorded for each Graves patient.

We investigated the correlations of retinal layers with TSH, fT3, fT4 levels, age, and disease duration in all patients with GD and CAS and Hertel value in patients only with GO.

Statistics

For categorical variables, differences were assessed by Chi-Squared and Fisher's exact tests, as appropriate. The distributions of the continuous variables were examined by Shapiro-Wilk's test. The comparisons between groups were performed using the Student t-test or the ANOVA test for parametric variables and the Mann Whitney U or Kruskal-Wallis test for non-parametric variables. All continuous and categorical variables were summarised as medians (min-max) and percentages (%). Spearman's correlation analyses were used to determine possible associations between variables. Statistical analysis was performed using IBM Statistical Package for Social Sciences for Windows v25.0. (IBM Corp., Armonk, NY). $P < 0.05$ was considered statistically significant.

Results

Twenty-three patients (15 females, 8 males) with GO (Group 1), 84 patients (60 females, 24 males) without GO (Group 2), and 18 (11 females, seven males) healthy subjects (Group 3) enrolled. The mean ages were 38.78 ± 10.8 years, 43 ± 12.9 years and 35.9±8.7 in group 1, group 2 and group 3, respectively. Age and sex distribution were similar in all three groups ($p>0.05$). The median TSH, fT4 and fT3 levels were similar in group 1 and group 2 ($p>0.05$ for each parameter, Table 1). Also, TRAB, anti-TPOAb, and anti-TgAb positivity were similar in group 1 and group 2, as shown in Table 1. The duration of the disease in group 1 and group 2 was similar (Median:19 months (0-90 months), 7 months (0-36 months), respectively $p=0.27$). The median RNFL values were 12 µm (10-16), 13 µm (8-20), 13 µm (9-17) in group 1,2, and 3, respectively ($p = 0.281$). The median GCL thickness values in group 1, 2, and 3 were 14 µm (9-25), 15 (8-54) µm, and 17.5 µm (11-34), respectively ($p = 0.02$). The median IPL thickness was 20 µm (15-30) in group 1, 21 µm (15-44) in group 2, and 22 µm (15-34) in group 3 ($p = 0.038$). The median thickness

of the retinal layers was reported in Table 2. The median GCL, IPL, RPE were different in the groups, while RNLF, INL, OPL, ONL were similar (p>0.05 for each). GCL in group 1 was thinner than in group 3 (p=0.02), while similar in groups 2 and 3 (p=0.06). IPL in group 1 was thinner than in group 3 (p=0.035), while similar in groups 2 and 3 (p=0.13). RPE in groups 1 and 2 was thinner than in group 3 (p=0.009, p=0.001, respectively), while it was similar in groups 1 and 2 (p=0.93). Only 2 (11.1%) of the patients had a CAS score of 4; others had a CAS score <3. The median Hertel value was 20 mm, ranging from 17 mm to 24 mm in group 1, while 18 mm (16-22) in group 2. The difference was significant (p=0.001). There was no statistically significant relationship between retinal layer thickness and CAS (p>0.05) (Table 3). ONL and RPE of retinal layers were significantly correlated with Hertel value (p=0.001, r=0.56; p=0.006, r=-0.44, respectively) (Table 3).

Table 1
Comparison of thyroid hormone levels and thyroid antibodies in patients with and without GO

	Group 1 (n=23)	Group 2 (n=84)	P
TSH mU/L (median)	0.029 (0.005–5.07)	0.062 (0.005-37.84)	0.527
fT4 ng/dl (median)	1.25 (0.359-5.83)	1.41 (0.162-7.77)	0.130
fT3 ng/dl (median)	3.67 (2.29-12.030)	3.6 (0.96-27.610)	0.656
TRAB positivity %	83.3	70.4	0.38
Anti-TPOAb positivity %	61.1	75	0.25
Anti-TgAb positivity %	38.9	59	0.19
Group 1= Patients with GO; Group 2= Patients without GO			
TSH= Thyroid-stimulating hormone; fT3= free triiodothyronine; fT4= free thyroxine, TRAB= TSH-receptor antibody; Anti-TgAb=Anti-thyroglobulin antibody; Anti-TPOAb= Anti-thyroid peroxidase antibody			

Table 2
Comparison of Retinal layer thickness in Group 1, Group 2 and Group 3

	Group 1 (n=44 eyes)	Group 2 (n=168 eyes)	Group 3 (n=36 eyes)	P*	P^a	P^b	P^c
Layers (µm)	**Median (min-max)**	**Median (min-max)**	**Median (min-max)**				
RNFL	12 (10-16)	13 (8-20)	13 (9-17)	0.281			
GCL	14 (9-25)	15 (8-54)	17.5 (11-34)	**0.02**	**0.035**	0.13	0.72
IPL	20 (15-30)	21 (15-44)	22 (15-34)	**0.038**	**0.02**	0.06	0.84
INL	18 (11-31)	18 (8-53)	19 (10-29)	0.277			
OPL	24 (16-34)	24 (12-46)	23 (15-35)	0.814			
ONL	91 (80-111)	90 (41-110)	87.5 (59-100)	0.4			
RPE	16 (14-22)	17 (11-22)	18.5 (15-23)	**0.001**	**0.009**	**0.001**	0.93
Group 1= Patients with GO; Group 2= Patients without GO; Group 3=Healthy controls							
*Comparison of Group 1, Group 2 and Group 3							
[a] Group 1 compared to Group 3							
[b] Group 2 compared to Group 3							
[c] Group 1 compared to Group 2							
Pairwise comparisons were calculated for statistically significant differences. Significant values have been adjusted by the Bonferroni correction for multiple tests.							
GO=Graves' ophtalmopathy; RNFL= retinal nerve fiber layer; GCL= ganglion cell layer; IPL= inner plexiform layer; INL= inner nuclear layer; OPL= outer plexiform layer; ONL= outer nuclear layer; RPE= retinal pigment epithelium							

Table 3. Correlations of CAS and Hertel value with the thickness of retinal layers in patients with GO

	RNFL		GCL		IPL		INL		OPL		ONL		RPE	
	r	p	r	p	r	p	r	p	r	p	r	p	r	p
CAS score	-0.09	0.81	-0.007	0.98	0.18	0.67	-0.15	0.71	0.014	0.97	-0.20	0.62	0.16	0.69
Hertel value	-0.24	0.14	-0.12	0.46	-0.18	0.26	-0.02	0.89	-0.07	0.64	0.56	**0.001**	-0.44	**0.006**

RNFL= retinal nerve fiber layer; GCL= ganglion cell layer; IPL= inner plexiform layer; INL= inner nuclear layer; OPL= outer plexiform layer;

ONL= outer nuclear layer; RPE= retinal pigment epithelium; CAS=Clinical activity score.

Discussion

In this study, we compared the thickness of retinal layers of patients with GD with GO, without GO and healthy controls. GCL, IPL, RPE of patients with GO were thinner than the layers of healthy controls, while RNLF, INL, OPL, ONL were similar in groups.

Casini and colleagues evaluated RNLF in patients with GO, patients with GD with no sign of orbitopathy and healthy controls. RNLF was similar in the three groups ($p>0.05$). Sayin and colleagues compared RNFL in GO and healthy controls [19]. The inferior RNFL was slightly thinner in the patients with GO than controls ($p=0.043$). At the same time, superior, temporal and nasal RNFL were similar in GO and healthy controls ($p>0.05$). Also, Forte and colleagues [20] found no significant reduction in RNFL thickness between patients with GO and ocular hypertension and healthy controls. A recent study by Kurt and colleagues showed that RNLF was thinner only in the superior zone of the patients with GO when compared with healthy controls ($p = 0.039$). Similar values were noted in the temporal, nasal, and inferior areas [21]. Meirovitch et al. demonstrated significant thickening of the RNFL in patients with GO compared to controls, unlike the other studies [22].

Casini et al. found a significant decline in mean central GCL thickness in patients with GO compared with healthy controls [23]. Wang et al. compared RNFL and GCC (including the RNFL, ganglion cell layer and inner plexiform layer) between patients with active GO, Dysthyroid optic neuropathy (DON) and healthy controls [24]. In active GO and DON, the blood supply to the superficial layer of the macular area is reduced; the smaller the blood vessel density, the thinner the RNFL and GCC. Romano and colleagues found the average of GCC was significantly lower ($P=0.0005$) in the patients with GO with optic nerve compression than in healthy controls. The average RNFL thickness was not different in patients with GO and healthy controls. Kurt and colleagues did not observe any statistically significant difference in the ganglion cell layer between the patients with GO and healthy controls [21]. There are only a few studies that evaluate GCL separately from other layers in patients with GO. INL is evaluated within the GCC complex in only some studies, as shown above. To the best of our knowledge, this study is the first study that evaluates IPL alone apart from the GCC complex.

RPE has formed a monolayer of cells located between the retinal photoreceptors and the fenestrated choriocapillaris. RPE is essential for the maintenance and survival of the overlying photoreceptor cells and for organising the integrity of the choroidal capillaries. RPE was thinner in patients with GD (with and without GO) than in controls in our study. INL, OPL, and ONL were similar in three groups. No previous studies analysed the change in INL, OPL, ONL, and RPE patients with GD.

Our results showed no relationship between CAS and retinal layers in patients with GO. Also, there was no correlation between Hertel value and retinal layers, except ONL and RPE. Mugdha and colleagues found no correlation between CAS and RNFL [25]. Casini et al. demonstrated no significant relationship between CAS, retinal thickness, GCL and Hertel value [23]. There was no correlation between the severity of the orbital disease and the RNFL thickness in the study by Meirovitch et al. [22]. ONL and RPE of the patients with GD are only evaluated in our study; further studies are needed to interpret this relationship.

In our study, TRAB, Anti-TPOAb, and Anti-TgAb positivity are not different in patients with and without GO. Lee and colleagues investigated the relationship between ophthalmopathy and TRAB, Anti-TPOAb, and Anti-TgAb in pediatric patients with GD [26]. Similar antibody positivity was detected in patients with and without GO. The role of Anti-TPO Ab in autoimmune thyroid disease remains controversial. Wright-Pascoe et al. demonstrated that both TPO Ab and Tg Ab were correlated with the incidence of adulthood GO [27]. In contrast, Khoo et al. demonstrated that TPO Ab negativity was associated with an increased risk of GO in adults [28]. These studies assessed adult, adolescent and pediatric patients, in contrast to our study, which was limited to adult patients with GD.

This study has limitations. We have a relatively small number of cases because of our exclusion criteria and the limited GO range. However, our results reached a level of significance.

In summary, patients with GO have thinner GCL, IPL, and RPE than healthy controls, even without changes in visual acuity. We hope that evaluation of OCT images may yield early signs of optic neuropathy to allow for early treatment. Further investigations are needed to validate our findings and use these early findings in more timely treatment to prevent significant vision problems.

Declarations

Compliance with Ethical Standards

Funding

No funds, grants, or other support was received.

Conflict of interest

Berna Evranos Ogmen declares that she has no conflict of interest. Nagihan Ugurlu declares that she has no conflict of interest. Muhammet Cuneyt Bilginer declares that he has no conflict of interest. Sefika Burcak Polat declares that she has no conflict of interest. Birgul Genc declares that she has no conflict of interest. Reyhan Ersoy declares that she has no conflict of interest. Bekir Cakir declares that he has no conflict of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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Figures

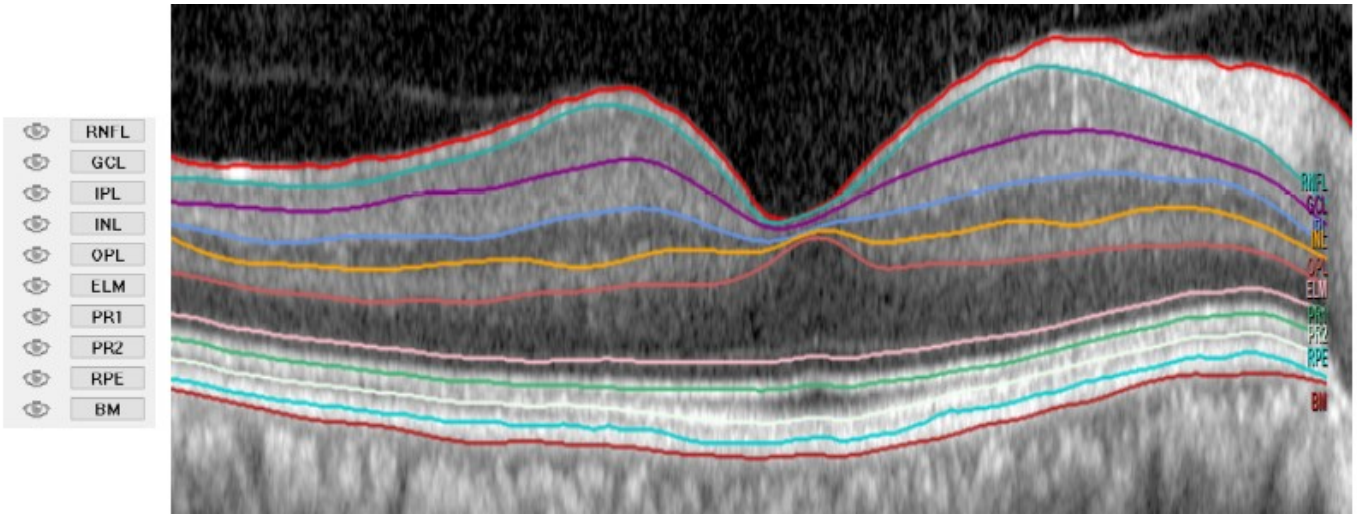

Figure 1

A segmented view of the retinal layers

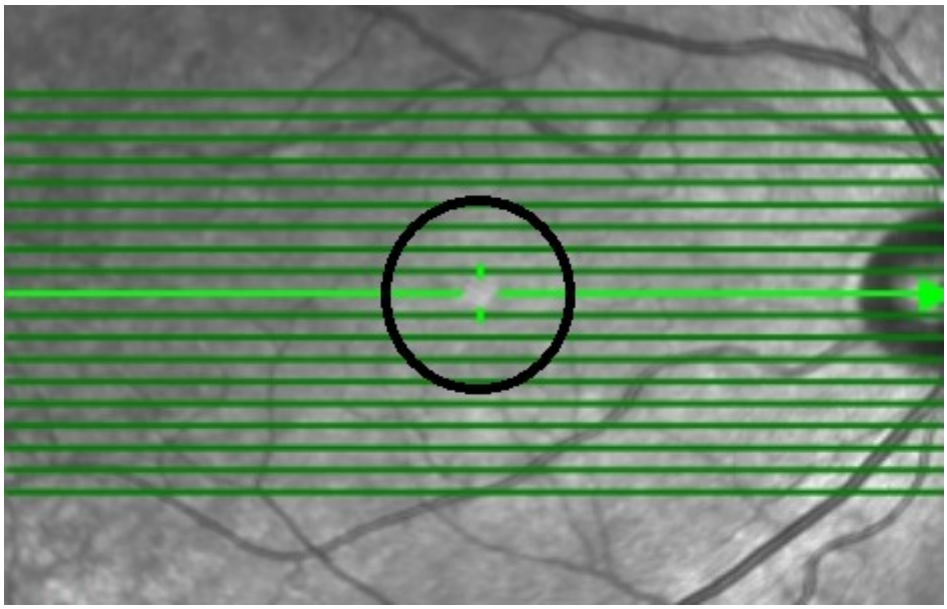

Figure 2

The area within the circle is the central area.