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ORIGINAL PAPER

Thicknesses of the retinal layers in patients with Graves' disease with or without orbitopathy

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Abstract

Purpose Graves' orbitopathy (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 (Group 1), 84 without GO (Group 2)] and eighteen volunteers (Group 3) were enrolled. The spectral-domain optical coherence tomography (SD-OCT) was used for ophthalmologic evaluation. Seven retinal layers including retinal nerve fibre 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 were 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 ($p=0.001$). 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 ($p=0.93$). RNLF, INL, OPL, ONL were similar in all three ($p>0.05$ for each).

Conclusion Ganglion cell layer and IPL were thinner in patients with GO than in healthy controls, while both were similar in patients without GO and healthy controls. RPE was thinner in all Graves patients than in healthy controls. Early detection of changes in retinal layers of GD may guide the physician to prevent significant vision problems.

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Introduction

Graves' disease (GD) is an autoimmune disorder that primarily affects the thyroid, with most patients showing hyperthyroidism. However, GD can also affect the eyes and skin. GD is characterized by the infiltration of thyroid antigen-specific T cells into tissues expressing thyroid-stimulating hormone receptor (TSH-R), including the thyroid, extraocular eye muscles, and retrobulbar fat tissues. Circulating TSH-R antibodies (TRAB) are thought to trigger inflammation and the activation of orbital fibroblasts leading to intraorbital swelling in the early active stage of the disease and subsequently to fibrosis in later stages [1, 2]. Orbital involvement is known as Graves' orbitopathy (GO) and is observed in about 25–50% of GD patients [3–5]. Like GD, GO is more common in women than in men [6].

Graves' orbitopathy is an inflammatory and proliferative process that may involve the ocular surface, orbital fat, extraocular muscles, and optic nerves [4, 7]. Most patients initially present with redness of the eyes or eyelids, swelling, or a feeling of fullness in upper eyelids and bags under the eyes [8]. The most common presenting sign is eyelid swelling followed by eyelid lagging. Early symptoms are a gritty sensation in the eyes, light sensitivity (photophobia), and excess tearing. Upper eyelid retraction occurs in most patients with disease progression. Exophthalmos (also known as proptosis) is seen frequently in these patients and is significantly correlated with lower lid retraction [9]. Altered colour perception, diplopia, and blurred vision may occur in severe cases. Decreased visual acuity, loss of colour vision, visual field defects, and blurred vision usually occur due to compression of the optic nerve [10]. The presence of these symptoms often refers to dysthyroid optic neuropathy (DON). Extraocular muscle involvement may result in an aberrant position of the globe or, in extreme cases, fixation of the globe. Limited eye muscle movement in specific directions of gaze causes diplopia [11].

Visual field, visual acuity, and colour sensation tests are used to evaluate visual functions in patients with GO and have some limitations. Optical coherence tomography (OCT) is an imaging technique developed to assess the retinal tissue thickness in vivo. As OCT imaging closely approximates the histological appearance of the retina, and it has been referred to as an in vivo optical biopsy [12]. High-resolution cross-sectional images of the retina are produced using the optical reflectivity of the tissue [13]. The different properties of the cell layers, which can be determined from the interference pattern, allow their discrimination. In spectral-domain OCT (SD-OCT), different colours in the reflected light provide depth information. It provides the opportunity to evaluate each layer of the retina separately [14]. As a result, single layers affected in specific diseases can be assessed separately, which provides more reliable predictions than total retinal thickness assessments for the pathophysiology of retinal diseases [15, 16]. The thicknesses of seven layers [i.e. the retinal nerve fibre layer (RNFL), ganglion cell layer (GCL), inner plexiform layer (IPL), inner nuclear layer (INL), outer plexiform layer (OPL), outer nuclear layer (ONL), and retinal pigment epithelium (RPE)] can be determined automatically [17, 18].

In this study, we examined the retinal layers by SD-OCT in patients with GD and healthy control subjects to investigate whether retinal thickness can be used to determine orbitopathy earlier in patients with GD. In this context, we measured the thickness of seven retinal layers in patients with GD with or without clinical signs of orbitopathy.

Methods

Patients with GD who were older than 18 years and who followed up at our clinic between April 2015 and May 2018 were included in this prospective study. A total of 107 patients with GD (23 with GO, 84 without GO) and 18 healthy controls were enrolled in the study. The diagnosis of GO was made according to clinical signs of orbitopathy as defined in the NOSPECS classification system [no physical signs or symptoms (0), only signs (1), soft tissue involvement (2), proptosis (3), extraocular muscle signs (4), corneal involvement (5), and sight loss (6)] [19] and clinical activity score (CAS) [20].

A CAS ≥ 1 point or NOSPECS ≥ 1 point in patients with GD was taken to indicate GO. The control group was chosen from among volunteers from the hospital staff. The exclusion criteria were a previous history of chronic renal disease, hypertension, diabetes mellitus, chronic liver disease, glaucoma, keratitis, uveitis, ocular trauma or any surgery, systemic or topical corticosteroid use, and intravitreal injection. In addition, the refractive status of the subjects was examined, and those with myopia, hypermetropia, or astigmatism > 3 dioptres were excluded. Eyes with a best-corrected visual acuity worse than 20/30 were excluded. In total, 44 (2 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 controls were compared.

Written informed consent was obtained from all participants. The study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee (decision date: 21.01.2015; decision number: 2015-18; Ankara Ataturk Training and Research Hospital Clinical Research Ethics Committee).

A detailed ophthalmological examination, including colour vision, best-corrected visual acuity, slit-lamp examination, and OCT, was performed by a single specialist. Intraocular pressure (IOP) measurements were taken in the standard position using Goldmann applanation tonometry. Disease activity was assessed using a 7-point CAS: 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 a swollen caruncle. GO was considered active in patients with a CAS ≥ 3 [20]. The proptosis levels of all patients were measured with a Hertel exophthalmometer. A Spectralis OCT System (Heidelberg Engineering GmbH, Heidelberg, Germany) was used for retinal OCT imaging. Spectralis mapping software, Heidelberg Eye Explorer (6th version), assisted segmentation and measurement of the retinal layers from each OCT scan (Fig. 1). Central, inner or outer ring subfield measurements can be made as defined in the Early Treatment Diabetic Retinopathy Study [18]. Central subfield measurements were used in this study (Fig. 2).

The study population was divided into three groups: group 1, patients with GD and GO; group 2,

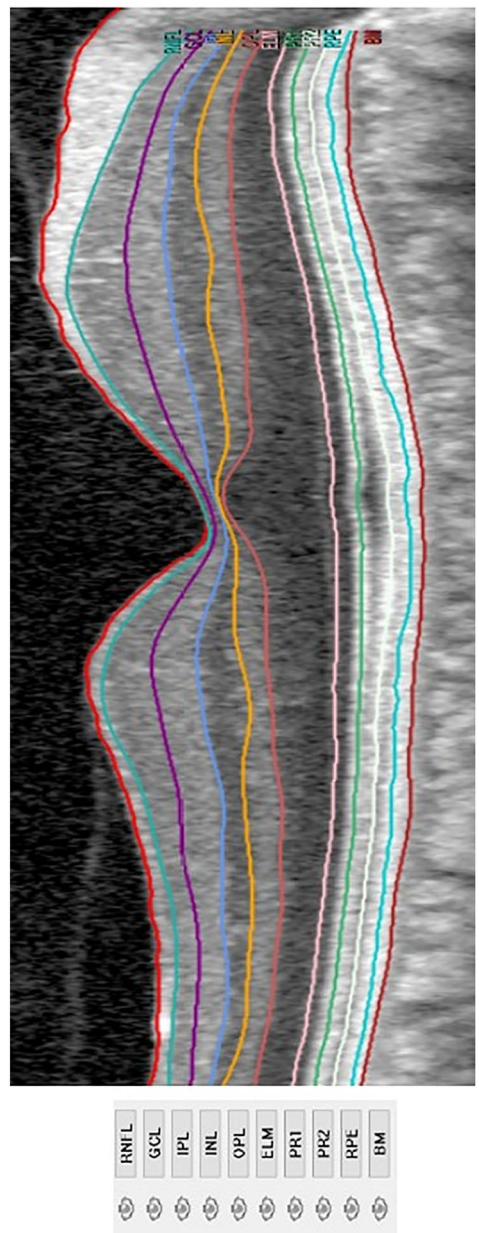

Fig. 1 A segmented view of the retinal layers

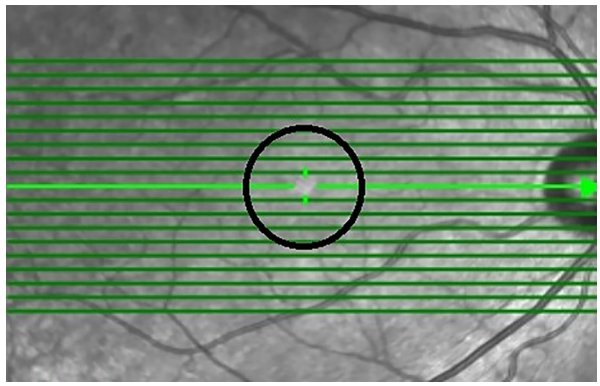

Fig. 2 The area within the circle is the central area

patients with GD without GO; and group 3, healthy controls.

The name, sex, age, therapies received [medical therapy, surgery, radioiodine (RAI)], total disease duration, and laboratory findings at the time of ophthalmological examination [i.e. serum TSH, free triiodothyronine (fT3), free thyroxine (fT4), TRAB, anti-thyroglobulin antibodies (anti-TgAb), and anti-thyroid peroxidase antibodies (anti-TPOAb)] were recorded for each patient.

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

Statistical analysis

For categorical variables, differences were assessed by Chi-square and Fisher's exact tests, as appropriate. The Shapiro–Wilk test was used to examine the distributions of continuous variables. Comparisons between groups were made using Student's *t* test or an analysis of variance for parametric variables and the Mann–Whitney *U* or Kruskal–Wallis test for nonparametric variables. All continuous and categorical variables were summarized as the median (min–max) and percentage (%). Spearman's correlation analyses were used to determine possible associations between variables. Statistical analyses were performed using IBM SPSS for Windows v25.0 (IBM Corp., Armonk, NY, USA). In all analyses, $p < 0.05$ was taken to indicate statistical significance.

Results

In total, 23 patients (15 women, 8 men) with GO (group 1), 84 patients (60 women, 24 men) without GO (group 2), and 18 (11 women, 7 men) healthy subjects (group 3) were enrolled in this study. The mean ages in groups 1, 2, and 3 were 38.78 ± 10.8 years, 43 ± 12.9 years, and 35.9 ± 8.7, respectively. The age and sex distribution was similar in all three groups ($p > 0.05$). The median TSH, fT4, and fT3 levels were similar in groups 1 and 2 ($p > 0.05$ for each parameter, Table 1). In addition, TRAB, anti-TPOAb, and anti-TgAb positivity were similar in groups 1 and 2 (Table 1). The duration of disease was similar in groups 1 and 2 [median: 19 months (0–90 months) and 7 months (0–36 months), respectively, $p = 0.27$]. Patients in groups 1 and 2 were treated with similar therapies for thyrotoxicosis. The rates of treatment with medical, surgical, and RAI therapy were 26.7%, 46.7%, and 26.7%, respectively, in group 1 and 36.4%, 27.3%, and 36.4%, respectively, in group 2 ($p = 0.68$). The median IOPs were 15.7 mmHg (9.7–20.5), 15.3 mmHg (8–22.7), and 14.5 mmHg (9–23) in groups 1, 2, and 3, respectively ($P = 0.159$). The median RNFL values were 12 µm (10–16), 13 µm (8–20), and 13 µm (9–17) in groups 1, 2, and 3, respectively ($p = 0.281$). The median GCL thicknesses were 14 µm (9–25), 15 µm (8–54), and 17.5 µm (11–34) in groups 1, 2, and 3, respectively ($p = 0.02$). The median IPL thicknesses were 20 µm (15–30), 21 µm (15–44), and 22 µm (15–34) in groups 1, 2, and 3, respectively ($p = 0.038$). The median thicknesses of the retinal layers are shown in Table 2. The RNFL, INL, OPL, and ONL were similar in all three groups ($p > 0.05$ for each). The GCL

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

Layers (μm)	Group 1 (n = 44 eyes) Median (min–max)	Group 2 (n = 168 eyes) Median (min–max)	Group 3 (n = 36 eyes) Median (min–max)	p*	p^a	p^b	p^c
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

Pairwise comparisons were calculated for statistically significant differences. Significant values have been adjusted by the Bonferroni correction for multiple tests. Values in bold indicate that the difference is significant

GO Graves' ophthalmopathy; *RNFL* retinal nerve fibre 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

*Comparison of Group 1, Group 2, and Group 3

[a]Group 1 compared to Group 3

[b]Group 2 compared to Group 3

was thinner in group 1 than in group 3 ($p=0.02$), but similar in groups 2 and 3 ($p=0.06$). The IPL was thinner in group 1 than in group 3 ($p=0.035$), but similar in groups 2 and 3 ($p=0.13$). The RPE was thinner in groups 1 and 2 than in group 3 ($p=0.009$, $p=0.001$, respectively), but similar in groups 1 and 2 ($p=0.93$). Only two (8.6%) of the patients had a CAS score of 4, with all others showing CAS scores < 3. The median Hertel value was 20 mm (17–24) in group 1 and 18 mm (16–22) in group 2 ($p=0.001$). There was no statistically significant relation between retinal layer thickness and CAS ($p>0.05$) (Table 3). The ONL and RPE thicknesses were significantly correlated with the Hertel value ($p=0.001$, $r=0.56$; $p=0.006$, $r=-0.44$, respectively) (Table 3).

Discussion

This study was performed to compare the thicknesses of retinal layers between GD patients with GO, GD patients without GO, and healthy controls. The GCL and IPL were thinner in patients with GO than healthy controls, while both were similar in patients without GO and healthy controls. The RPE was thinner in all GD patients than in healthy controls. The

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**

Values in bold indicate that the difference is significant

RNFL retinal nerve fibre 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

RNFL, INL, OPL, and ONL were similar in all three groups.

In this study, the IOP measured in the standard position was similar in all three groups. An elevated IOP in upgaze is a common finding in patients with GO (65–100%), which is explained by a tight inferior rectus muscle that blocks the episcleral aqueous outflow and orbital congestion [21–26]. Some patients with GO show elevated pressures and are therefore identified and treated as patients with ocular hypertension. In a retrospective study of 482 patients with GO, one of the most extensive studies published to date, 23 patients (4.8%) had an elevated IOP as measured in primary gaze [27]. Four patients (0.8%) were shown to have primary open-angle glaucoma (POAG) [27]. This prevalence of POAG in GO patients corresponds to the prevalence of 1.1% in the present study [28]. Thus, although IOP is elevated on upgaze in most GO patients, it does not lead to glaucomatous injury more often than in the normal population. This difference is probably caused by the fact that normally when using an applanation tonometer, the eyes are in mild upgaze, giving rise to a slight elevation in IOP in patients with GO. Therefore, it is important to check the position of the eyes when measuring the IOP in patients with GO. Increased IOP may result from slight elevation of the eyes during applanation tonometry. A higher IOP is usually associated with more rapid RNFL thickness loss [28, 29]. The similarity of IOP in the groups with GD detected in our study eliminated RNFL thickness as a confounding factor.

Casini et al. [30] reported that the RNFL was similar in GD patients with GO, patients with GD with no signs of orbitopathy, and healthy controls ($p > 0.05$). Sayin et al. [31] compared the RNFL between patients with GO and healthy controls. The inferior RNFL was slightly thinner in the patients with GO than controls ($p = 0.043$), while the superior, temporal, and nasal RNFL were similar in GO patients and healthy controls ($p > 0.05$). In addition, Forte et al. [32] found no significant reduction in RNFL thickness between patients with GO and ocular hypertension and healthy controls. A recent study by Kurt et al. [33] showed that the RNFL was thinner than in healthy controls only in the superior zone in patients with GO ($p = 0.039$). Similar values were noted in the temporal, nasal, and inferior areas. Meirovitch et al. [34] demonstrated significant thickening of the RNFL in patients with GO compared to controls, unlike other studies. They suggested that this may have been due to the effect of inflammation instead of the dominant compression effect or a combination of these effects. Our study and most previous studies support the conclusion that the RNFL is not markedly affected by GD or GO.

In most studies, the GCL was specified as part of the retinal ganglion cell complex (GCC including the RNFL, GCL, and inner plexiform layer). There have been few studies like ours that examined it separately. Casini et al. [30] reported a significant decline in mean central GCL thickness in patients with GO compared with healthy controls. GD patients without GO and healthy controls had similar mean central GCL thicknesses. These GCL results are similar to those of the present study. Kurt et al. [33] did not observe any significant difference in the GCL between patients with GO and healthy controls. Wang et al. [35] compared the RNFL and GCC between patients with active GO, DON, and healthy controls. Both the RNFL and GCC were thinner in patients with active GO and DON. Romano et al. [36] reported that the average GCC was significantly lower in patients with GO with optic nerve compression than in healthy controls ($p = 0.0005$). The average RNFL thickness was not different between patients with GO with optic

nerve compression and healthy controls in the present study. This difference may have been due to the thinness of the GCL, IPL, or both. The IPL within the GCC has been evaluated in only some studies, as discussed above. The present study is the first to evaluate the IPL separately from the GCC. The alterations in IPL and GCL detected in our study seem to represent early changes of GO.

The RPE is formed by a monolayer of cells located between the retinal photoreceptors and the fenestrated choriocapillaris. The RPE is essential for the maintenance and survival of the overlying photoreceptor cells and for organizing the integrity of the choroidal capillaries. The RPE was thinner in patients with GD (with and without GO) than in controls in our study. Dysfunction of the RPE causes diseases related to vision, including age-related macular degeneration (AMD) [37]. AMD is a degenerative disorder of unknown aetiology with increasing prevalence and is one of the most common causes of blindness in developed countries, especially in the elderly [38]. Recent studies suggested that thyroid dysfunction is a modifiable risk factor for AMD [39, 40]. The population-based Rotterdam study showed that serum-free thyroxine levels were positively associated with the development of AMD [39]. The observation that the RPE was thinner in patients with and without GO than in the control group suggests that it is not related to the compression effect seen in ophthalmopathy. It may be caused by high thyroid hormone levels as in AMD and inflammation involved in the pathogenesis of GD. Additional studies are needed to gain further insight into these issues.

Age and sex-related changes in intra-retinal layers have been reported [41–43]. In a study by Ooto et al., retinal layer thicknesses showed significant variations by sex and age [43]. Chua et al. observed thicker retinal layers in men than in women among Asians [44]. In this study, the sex and age distributions were similar in all groups. In addition, the duration of disease and the therapies for thyrotoxicosis were similar in groups 1 and 2. Therefore, the effects of these confounding factors on the results can be ignored.

Our results show no relationship between CAS and retinal layers in patients with GO. In addition, there were no correlations between the Hertel value and retinal layers, except the ONL and RPE. Mugdha et al. [45] found no correlation between CAS and RNFL. Casini et al. [30] demonstrated no significant relations between CAS, retinal thickness, GCL, and Hertel value. The ONL and RPE of GD patients were only evaluated in our study, and a correlation between Hertel values was detected. Further study is needed to interpret this relationship.

In our study, TRAB, anti-TPOAb, and anti-TgAb positivity were not different between GD patients with and without GO. Lee et al. [46] investigated the relations between ophthalmopathy and TRAB, anti-TPOAb, and anti-TgAb in paediatric patients with GD. Similar antibody positivity was detected in patients with and without GO. Wright-Pascoe et al. [47] demonstrated that both anti-TPOAb and anti-TgAb were correlated with the incidence of adulthood GO. In contrast, Khoo et al. [48] reported that anti-TPOAb negativity was associated with an increased risk of GO in adults. These studies assessed adult, adolescent, and paediatric patients, in contrast to the present study, which was limited to adult patients with GD. However, the results did not appear to differ significantly according to age group.

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

In summary, patients with GO have a thinner GCL and IPL, and patients with GD have a thinner RPE than healthy controls, even without changes in visual acuity. Evaluation of OCT images may yield early signs of optic neuropathy to allow for early treatment. Further investigation is needed to validate our findings and use these early findings to allow more timely treatment and thus prevent significant visual impairment in these patients.

Author contributions All authors contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by Berna Evranos Ogmen, Nagihan Ugurlu, Muhammed Cuneyt Bilginer, Sefika Burcak Polat, Birgul Genc. The first draft of the manuscript was written by Berna Evranos Ogmen, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Declarations

Conflict of interest All authors declares that they have 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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