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Graves ophthalmopathy a neglected comorbidity of graves' disease; a detailed investigation and management of sixty-eight patients in a tertiary healthcare center

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Abstract

Purpose To compare the measurements of macular thickness, intraocular pressure and RNFL and hormone parameters before and after antithyroid therapy in patients with Graves' Ophthalmopathy (GO).

Methods A prospective observational study conducted at a tertiary care center. Patients with GO were included and scored (Clinical Activity Score, CAS) according to EUGOGO guideline. The participants underwent extensive ophthalmological examinations including intraocular pressure measurements with Goldmann applanation tonometry and RNFL with macular thickness evaluations via optical coherence tomography (OCT). Baseline and follow-up (24 weeks) hormone parameters including free T3, free T4, Thyroid stimulating hormone (TSH), Thyroid receptor autoantibodies (TRAbs) and intraocular measurements (RNFL, macular thickness, intraocular pressure) were performed and compared in the current study.

Results Comparisons of baseline and follow-up biochemical parameters TSH, fT3, fT4, TRAbs, anti-TPO ($p < 0.001$). Although baseline score of CAS was mildly increased in all patients (0.5 ± 0.8 vs. 0.1 ± 0.4, $p < 0.001$) but it was significantly decreased after the antithyroid therapy. Mean intraocular pressure (14.9 ± 2.8 vs. 14.2 ± 1.9), RNFL (100.2 ± 9.05 vs. 99.9 ± 8.7) and macular thickness (274.7 ± 42.9 vs. 271.2 ± 43.3) were similar between baseline and after antithyroid therapy. And baseline RNFL measurements showed significant negative correlation with serum baseline TRAbs, antiTPO, fT3, fT4 ($p < 0.05$).

Conclusion Baseline serum fT3, fT4 and TRAbs in patients with Graves' Disease levels may be the prognostic factors in the evaluation of affecting intraocular structure, especially Retinal Nerve Fiber Layer, in patients with GO.

Significance

What is known? Thyroid eye disease (TED) is an auto-immune disorder characterized by inflammation and cellular infiltrate into the orbital tissues. This results in increase in orbital volume and consequently an increase in intraorbital pressure.

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What is new? RNFL thickness is significantly associated with disease activity parameters, including plasma fT3, fT4, TRAbs, and anti-TPO levels, despite a mild clinical activity score.

Keywords Graves' Disease, Thyroid Eye Disease, Thyrotoxicosis, Intraocular pressure, Retinal Fiber nerve layer, Macular Thickness

Introduction

Graves' Disease (GD) is an autoimmune condition which is related to increased thyroid hormone levels. Graves' Disease is the most common cause of hyperthyroidism, typically seen in patients between 40 and 60 years of age [1]. Clinical and biochemical features of GD are characterized specifically by ophthalmopathy (and/or dermopathy). Elevated thyroid hormone levels in GD arise because of stimulating thyroid stimulating hormone (TSH) Receptor Autoantibodies (TRAbs) which mimics the action of TSH [2, 3].

TSH receptors are also found in orbital fibroblasts where the binding of TRAbs results in proliferative response that contributes to the extrathyroidal signs seen in GD called as Graves' Orbitopathy (GO) [4, 5]. Classification of orbitopathy is based on clinical activity, severity and duration of GO. Clinical activity score (CAS) is frequently used as the best validated scoring system. CAS is composed of seven items where an activity is defined as score of 3 or greater for a patient with GD (Fig. 1). For accurate diagnosis, there have been several classifications which are called European Group of Graves' Orbitopathy'/ EUGOGO or VISA inflammatory system [6, 7]. And both recommend that control of thyroid hormone levels is crucial in all patients with GO.

Nearly 50% of patients with GD report symptoms of ophthalmopathy which are generally mild. If an accurate diagnosis could not be performed in time; more cases might have severe sight-threatening form of the disease due to corneal exposure or compressive optic neuropathy [8, 9]. Retinal nerve fiber layer (RNFL), the innermost layer of retina, consists of unmyelinated fibers generated from ganglion cells and thickness of RNFL could be used to evaluate the axon loss [10]. Optic nerve damage could be shown due to orbital mechanical compression by the extraocular muscles and soft tissue expansion. Sometimes it is difficult to evaluate the involvement of optic nerve in patients with GO [11]. Optic coherence tomography (OCT) is a valuable and noninvasive method to detect retinal diseases and optic disc pathologies. It has been commonly used to diagnose and monitor RNFL, central macular thickness [12, 13]. Previously mentioned measurements and those comparisons with thyroid function tests in patients with GO have been performed in limited studies and reported as prognostic value for these patients.

We wanted to clarify some important questions with difficult answers.

For this reason, we aimed.

1) To evaluate the effect of thyroid hormone levels on retinal nerve layer and thickness of macula in patients with GD.
2) To determine whether there is a correlation between those parameters and severity of orbital disease,
3) To compare those patients' measurements before and after antithyroid treatment.

Materials and methods

We included patients between the ages of 18–70 aged who were referred to the Endocrinology Department in our university hospital. Patients with elevated free thyroxine (free T4) and/or free triiodothyronine (free T3) concentrations, a suppressed TSH, positive TRAbs and presence of diffuse goiter were diagnosed as GD. Written informed consent was obtained from all patients.

The exclusion criteria were as follows:

1) presence of thyroid nodules suspicious for malignancy,
2) injection of iodinated radiographic contrast media within the 4 weeks prior to radioiodine therapy, concurrent or previous amiodarone treatment,
3) previous history of lymphoma, idiopathic orbital inflammation, cellulitis, orbital tumors, glaucoma, uveitis, retinal and corneal disease,
4) history of ocular trauma or surgery, and patients using eye drops and contact lenses.
5) previous and concomitant treatment for hyperthyroidism by any means.
6) previous history of smoking.

All patients were evaluated in detail for the GD and baseline biochemical and hormonal parameters including hemogram, liver function tests, TSH (mIU/L), free T4 (fT4, ng/dL), free T3 (fT3, pg/mL), thyroid peroxidase autoantibody (Anti TPO, U/mL), TRAbs (U/L). Physical examination including pulse and blood pressure measurement was performed and recorded by the same clinician.

Eye examination

The patients underwent a comprehensive ophthalmological examination, including best-corrected visual acuity, slit lamp biomicroscopy, intraocular pressure measurement with Goldmann applanation tonometry,

1.	Spontan retrolbulber pain
2.	Pain of attempted upward or downward gaze
3.	Redness of eyelids
4.	Redness of conjunctiva
5.	Swelling of caruncle or plica
6.	Swelling of eyelids
7.	Swelling of conjunctiva (chemosis)

Fig. 1 Assessment of activity by the clinical activity score (CAS). CAS < 3 = inactive GO; CAS ≥ 3 = active GO

fundoscopic examination and hertel exophthalmometry. Central macular thickness which was taken from macula center and optic disc retinal nerve fiber layer which was taken from optic disc values were recorded and evaluated by optic coherence tomography (Heidelberg Spectralis OCT; Heidelberg Engineering Inc, Heidelberg, Germany) (Figs. 2 and 3). All ophthalmological examinations and tests performed on the patients were performed by a single ophthalmologist (B.U.) between 9:00 and 10:00 in the morning period. Clinical activity scores were evaluated according to the European Group of Graves' Orbitopathy (EUGOGO) classification [6]. The activity was graded on clinical activity score. Thyroid eye diseases were deemed to be active if the score was more than 3 on 7 at the first examination or 4 on 10 on the follow-up examinations of a patient. EUGOGO classification defines eye diseases as mild moderate and severe. Central macular thickness and optic disc RNFL values were recorded and evaluated by optic coherence tomography (Heidelberg Spectralis; Heidelberg Engineering Inc).

After the biochemical evaluation and the eye examination, antithyroid drugs (methimazole or propylthiouracil) were given in proper doses to all patients and they were followed-up for 24 weeks. All parameters including demographic (age, gender) biochemical (fT3, fT4,

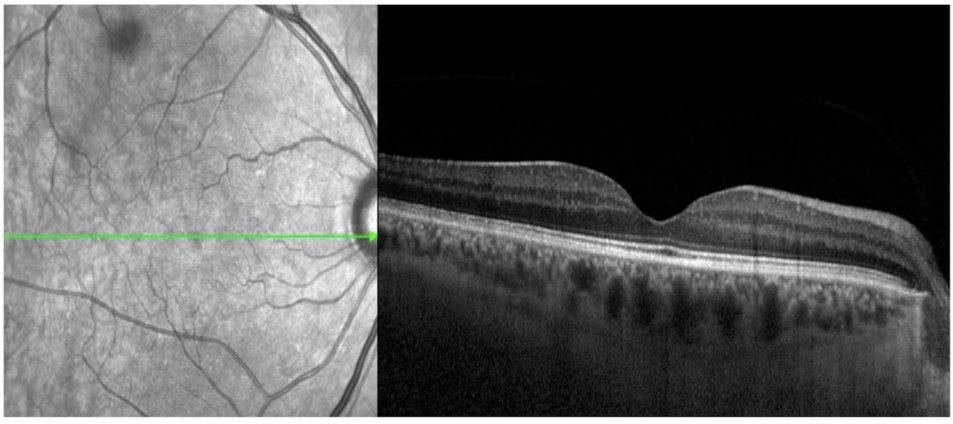

Fig. 2 Measurement of central macular thickness with optical coherence tomography using a section through the central macula

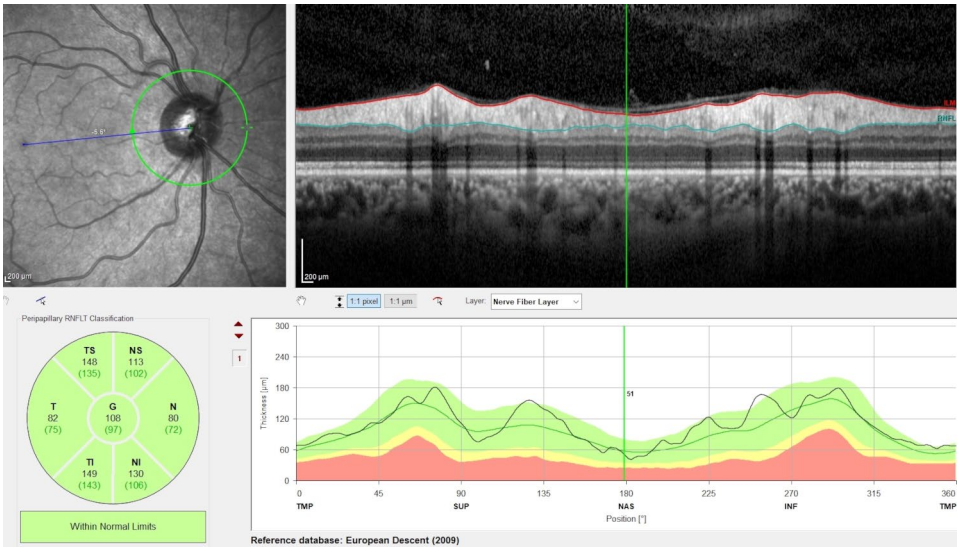

Fig. 3 Measurement of retinal nerve fiber layer average at the optic disc head by optical coherence tomography

Table 1 Comparison baseline and follow-up hormone parameters of all patients

N = 68	Baseline	Follow-up	*p*
TSH (0.38–5.33, mIU/L)	0.07 ± 1.2	3.4 ± 1.9	< 0.001
fT3 (2.3–4.2,pg/mL)	10.5 ± 7.4(3.2–32)	3.6 ± 1.35	< 0.001
fT4 (0.61–1.12,ng/dL)	2.7 ± 2.0 (0.6–11.9)	0.9 ± 0.4	< 0.001
TRAbs (1-1.5, U/L)	12.1 ± 14.3 (0.17-50)	2.3 ± 4.5	< 0.001
AntiTPO (U/mL)	208.7 ± 320.6 (0-1100)	NA	NA
ALT (U/L)	29.6 ± 16.6	21.6 ± 11.8	< 0.001
WBC (10^3/μL)	7229 ± 1977	7911 ± 2064	0.03
CAS (Score)	0.5 ± 0.8	0.1 ± 0.4	< 0.001

Data is demonstrated as mean standard deviation

CAS: Clinical Activity Score, TSH: Thyroid Stimulating Hormone, fT3: Free T3, fT4: Free T4 WBC: White Blood Cell counter

Table 2 Comparison of the hormone parameters between two gender

	All patients	Female (*n* = 45)	Male (*n* = 23)	*p*
Age (year)	45.4 ± 13.7	47.4 ± 14.5	46.5 ± 13.7	0.341
TSH (0.38–5.33, mIU/L)	0.27 ± 1.3	0.08 ± 0.36	0.43 ± 1.81	0.255
fT3 (2.3–4.2, pg/mL)	10.60 ± 7.44	10.3 ± 6.06	11.3 ± 9.17	0.302
fT4 (0.61–1.12,ng/mL)	2.79 ± 2.06	2.82 ± 1.32	3.06 ± 2.26	0.512
TRAbs (1-1.5, U/L)	12.15 ± 14.34	14.3 ± 14.72	10.56 ± 14.2	0.629
CAS (Score)	0.58 ± 0.89	0.47 ± 0.72	0.77 ± 1.1	0.416

Data is demonstrated as mean standard deviation

CAS: Clinical Activity Score, TSH: Thyroid Stimulating Hormone, fT3: Free T3, fT4: Free T4

TSH, TRAbs, hemogram, Alanine Transaminase), dosage of antithyroid treatment and eye examination were recorded at the beginning and during the follow-up period.

Statistical analysis

For the right and the left eye, to examine the correlation between TSH, TRAbs, FT3 and FT4 measurements and the treatment difference (before-after), Pearson correlation was used if the assumptions were met, and Spearman correlation was used if the assumptions were not met.

Considering the correlation between both eyes, Generalized Linear Mixed Model (GLMM) was used to compare pre- and post-treatment IOP, RNFL, Macular thickness and CAS measurements.

Categorical variables were expressed as numbers and percentages, whereas continuous variables were summarized as mean and standard deviation and as median and minimum-maximum where appropriate.

All analyses were performed using IBM SPSS Statistics Version 20.0 statistical software package. The statistical level of significance for all tests was 0.05. SPSS reference: IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0 Armonk, NY: IBM Corp.

Results

Baseline biochemical parameters

We enrolled 68 patients (female to male, 66.2% vs. 33.8%) with mean age of 45.4 ± 13.7 years. Mean duration of GO all patients was 11 ± 3 months (min-max 6–15 months). Mean baseline and follow-up hormonal and biochemical parameters including TSH, fT3, fT4, TRAbs, anti-TPO, ALT and score of CAS of all patients were demonstrated in Table 1. Mean TSH ($p = 0.255$), fT3 ($p = 0.302$), fT4 ($p = 0.512$) and TRAbs ($p = 0.629$) values between two genders were similar (Table 2).

Baseline measures of intraocular structure and correlation with serum thyroid function tests

Mean intraocular pressure (mmHg), macular thickness (μm) and RNFL (μm) was 14.79 ± 2.57, 270.30 ± 42.07 and 101.11 ± 9.38, respectively. Mean CAS of all patients was evaluated as 0.5 ± 0.8 (range 0–3). There was no difference between the two genders in terms of all hormone parameters (Tables 1, 2 and 3). RNFL measurements showed significant negative correlation with serum baseline TRAbs, antiTPO, fT3, fT4 ($p < 0.05$) (Table 4; Fig. 4).

Intraocular pressure ($p = -0.034$) and macular thickness ($p = -0.046$) of all patients were negatively correlated with serum baseline TSH levels but there was no relation with other hormone parameters (Table 4).

When comparing the gender differences, we also did not see a significant difference between the genders and measurements of RNFL, central macular thickness and intraocular pressure. Detailed results are indicated in Tables 3 and 4.

Table 3 Comparison between before and after treatment of OCT parameters

	Before treatment		After treatment		
	Male	Female	Male	Female	
	Mean ± sd	Mean ± sd	Mean ± sd	Mean ± sd	*p*
IOP (mmHg)	15.11 ± 2.46	14.69 ± 2.79	14.41 ± 2.28	14.92 ± 2.58	0.890
RNFL (μm)	102.36 ± 8.85	101.54 ± 9.93	101.27 ± 7.93	99.86 ± 9.92	0.374
MT (μm)	272.91 ± 41.25	269.14 ± 43.29	271.30 ± 39.15	269.36 ± 43.65	0.614

Data is demonstrated as mean standard deviation

IOP: Intraocular Pressure, RNFL: Retinal Nerve Fiber Layer, MT: Macular Thickness

Table 4 Correlation between OCT parameters and baseline hormone parameters and autoantibodies of all patients'

Before Treatment		IOP (mmHg)	RNFL (μm)	MT (μm)
TRAbs (U/L)	r	0.037	-0.216*	0.136
	p	0.725	0.036	0.190
AntiTPO (U/mL)	r	-0.017	-0.255*	0.144
	p	0.857	0.007	0.133
TSH (mIU/L)	r	-0.046	0.054	-0.39
	p	0.034	0.573	0.046
FT3 (pg/mL)	r	0.153	-0.290*	0.060
	p	0.132	0.004	0.556
FT4 (ng/dL)	r	0.125	-0.268*	0.093
	p	0.195	0.005	0.335

*$p < 0.005$

Data is demonstrated as mean standard deviation

IOP: Intraocular Pressure, RFNL: Retinal Nerve Fiber Layer, MT: Macular Thickness

Biochemical parameters after antithyroid therapy

During the 24 weeks, the patients were under the antithyroid therapy and all hormone parameters (TSH, fT3, fT4), TRAbs levels were decreased significantly (detailed results are shown in Table 1). In addition, CAS was significantly decreased after the treatment (0.1 ± 0.4, $p < 0.001$). (Table 1)

Measures of intraocular structure after antithyroid therapy and correlation with serum thyroid function tests

Intraocular pressure (14.9 ± 2.8 vs. 14.2 ± 1.9), RNFL (100.2 ± 9.05 vs. 99.9 ± 8.7) and macular thickness (274.7 ± 42.9 vs. 271.2 ± 43.3) were decreased after the antithyroid therapy but not significant statistically (Table 3).

Discussion

Our study showed that measurements of RNFL were significantly related with diseases activity parameters including plasma fT3 and fT4, TRAbs and antiTPO levels in patients with mild GO. Baseline intraocular pressure, macular thickness and RNFL measurements were decreased after the antithyroid therapy but not

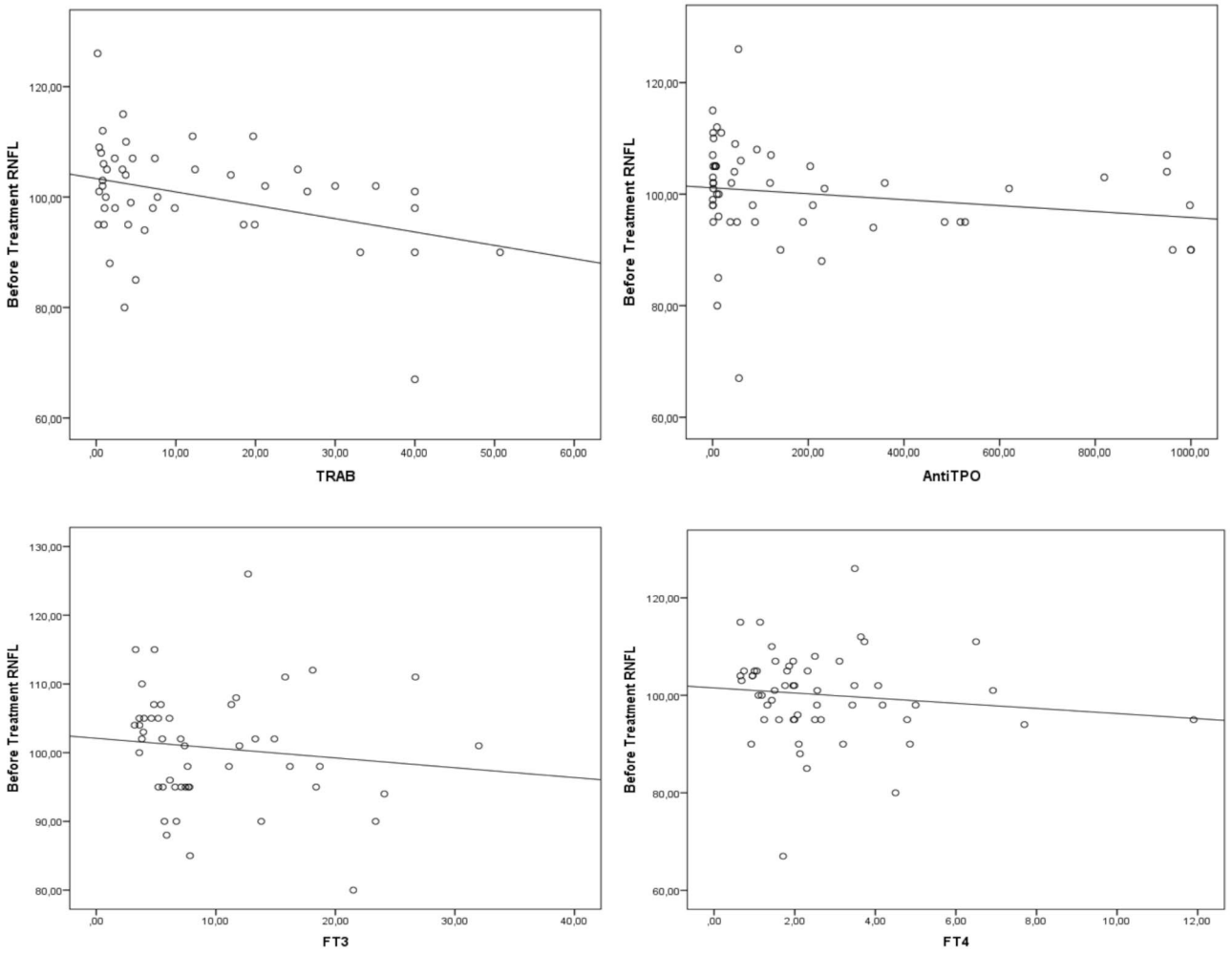

Fig. 4 Comparison between the measurements of RFNL and TRAbs, anti TPO, fT3 and fT4 values for right eye of the patients with GO

significant statistically. This result could be related to the baseline mild orbitopathy of all patients. And this study showed fT3, fT4 and TRAbs levels may affect the intraocular structure especially optic nerve, harmfully. By providing those objective measures of retinal damage, early and effective antithyroid therapy is necessary for all patients with GO.

GO is an uncommon, disfiguring and disabling autoimmune condition and more than 90% of cases occur in patients presenting with hyperthyroidism due to GD [14]. Thyroid eye diseases and Graves' hyperthyroidism have been commonly seen in female patients who are 30–50 years old. In addition, some studies [15, 16] reported severity of the disease tends to be worse in men and in patients over the 50 years old. Our study showed that mean age values were similar. Although mean serum fT3, fT4 values and CAS were more increased in male patients than the female patients but we did not find any significance between the two genders. This may be related with the small sample size of our study.

Graves orbitopathy is related to the involvement of the orbital fibroblast as a result of the autoimmune processes that collectively induce proliferation excess adipogenesis and overproduction of the extracellular matrix [17, 18]. Extracellular matrix including glycosaminoglycans is able to absorb up to 1000 times its weight in water. This results in an increase in the orbital volume and therefore an increase in intraorbital pressure [19]. This is evaluated clinically as the disease activity by using clinical activity score. In general, optic nerve involvement is expected in patients with severe thyroid eye disease [20]. Tehrani et al. [21] showed that macular and peripapillary vessel density were significantly lower in patients with active GO compared to nonactive noncompressive which reported CAS as equal to or less than 3. They also reported mean intraocular pressure for active GO and nonactive noncompressive GO were similar (18.7 ± 5.4 vs. 16.4 ± 3.3). In their cohort, TRAbs was present in 90% of patients and anti-thyroid peroxidase was positive in 12.7% patients. Dave et al. [22] showed that peripapillary and macular vascularity indexes were lower in patients with active GO. They also presented that RNFL thickness was increased in active GO versus the inactive eyes and healthy controls. Sayın et al. [23] demonstrated that intraocular pressure (14.3 ± 2.7 vs. 12.9 ± 1.9, $p < 0.001$) was higher in patients with GO (NOSPECS score; 2.4 ± 0.9) than the healthy controls. But they did not show any significant difference of RNFL (98.3 ± 29.4 vs. 101.7 ± 30.7) among the patients with GO and healthy controls. In the above mentioned study, the authors studied intraocular pressure and macular thickness measurement in patients with GO but majority of them did not report baseline and follow-up hormone levels or autoantibodies between the patient groups. Otherwise we know that well-studied risk factors for GO are as smoking, autoantibodies (TRAbs), age and sex and degree of hyperthyroidism. In our study baseline and follow-up measurements of patients were minimally decreased between pre and after antithyroid therapy. All patients achieved euthyroid status and within this situation intraocular pressure and macular thickness were decreased but not significant statistically. We suggested this result may be related with the initial mild GO and relatively short follow up period. But we found a significant correlation between serum fT3, fT4, TRAbs, anti TPO levels and RNFL measurements. And before the ATDs intraocular pressure and macular thickness were negatively correlated with TSH levels. we found serum TSH levels were a significant factor that affected macular thickness and intraocular pressure. We also suggested that this can be related with maintaining long term TSH suppression even normalized fT3, fT4 levels.

Optic nerve pathology in thyroid ophthalmopathy is compressive neuropathy. Some studies [24–27] reported RNFL thickness was decreased in patients with GO versus the inactive eyes and healthy controls. The reduction in the RNFL may be hypothesized to be due to hypoxia and resultant ischemia caused by edema in the orbital soft tissue. And they concluded that long-term hypoxia and ischemia has been related with the presence of the atrophy in RNFL. But some of the other studies [28–30] reported the opposite argument related with RNFL thickness. They suggested that an increase in RNFL thickness may be related with initial edema caused by optic nerve compression. Studies presented different results and a challenge issue. This may be related with many confounding factors for RNFL measurements including age, ethnicity and especially duration of the diseases and time of the measurement. To find more accurate results of these measurements, they should be evaluated in the same patient population during the treatment or matched with patients with similar age and clinical activity score or health controls. During the follow-up time, we evaluated the same patients with GO before and after antithyroid therapy. Probably, initial mild GO (lower CAS) we did not observe wide range of changes in thickness of RNFL or macular thickness. But we found a negative correlation between initial fT4, fT3 and TRAbs titer and RNFL thickness. Although patients with GO had similar measurements of RNFL; initial fT3, fT4 have been independent risk factors that influence the thickness of RNFL.

It has been known that TSH receptor antibodies are a major risk factor for the occurrence of GO. TSH receptor activation enhances the differentiation of orbital preadipocytes into adipocytes, favoring the expansion of orbital adipose tissue [31–33]. A multicenter prospective study [34] from 2018 proposed a predictive value of developing GO with baseline ocular inflammation, smoking, duration of thyroid disfunction and especially the TRAbs titer

as the four key risk factors. Even though patients received euthyroid status during the follow-up, ophthalmopathy could progress in patients with high titer of TRAbs. We found a significant negative correlation between serum TRAbs and before-after RNFL thickness. This may be related with long-term positivity of TRAbs titers.

There were several limitations in our study. This was an observational prospective study with a small sample size. Long-term follow-up studies need to evaluate the changes in the intraocular structure. In addition, all measurements including intraocular pressure, RNFL and macular thickness of patients could be compared with the age and sex of healthy controls.

The strength of our study is that we detailed evaluated intraocular structure before and after antithyroid therapy. All patients had lower CAS at baseline namely nonactive GO, but we found serum TRAbs, fT3 and fT4 had a significant factor for the RNFL. Up to date there have not been any studies which showed the correlation between macular thickness, RNFL and serum fT3, FT4 and TRAbs titers in patients with GO.

In conclusion, serum baseline fT3, fT4 and TSH levels were independent and important parameters for the retinal nerve thickness in patients even with non-active orbitopathy. We suggest that these results could reflect early retinal effects by the thyroid hormone and autoantibody levels should be evaluated in all patients with GO.

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Author contributions
GA, BU, MS; wrote the main manuscript. BU, AO, FO; collection of data. HB; biostatistical analyses. GA, RSS; editing.

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Data availability
The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest
In our study there is no conflict of interests.

Ethical approval
Ethical approval document was obtained from Cukurova University ethical committe.

Informed consent
We obtained informed consent of all patients.

Consent to Publish
Not applicable.

Clinical trial number
Not applicable.

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