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Research Article

Investigation and Evaluation of Corneal Parameters in Patients with Thyroid Ophthalmopathy

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Abstract

Objective: To evaluate corneal findings in patients with thyroid ophthalmopathy (TO) according to clinical activity score using corneal densitometry and corneal topography parameters.

Methods: This cross-sectional study was conducted in the department of Ophthalmology of Cukurova University between January 1, 2021, and June 31, 2022. The patients underwent a comprehensive ophthalmological examination, including best-corrected visual acuity, slit lamp biomicroscopy, intraocular pressure measurement with Goldmann applanation tonometry, fundoscopic examination, and hertel exophthalmometry. Clinical activity scores according to the European Group of Graves' Orbitopathy (EUGOGO) classification and retinal nerve fiber layer values were also recorded. Corneal densitometry and topography data recorded for 3 months were noted, and evaluated together according to the EUGOGO classification.

Results: Fifty eyes of 25 thyroid ophthalmopathy cases (15 female, 10 male) with a mean age of 52.6 ± 12.87 years were included in the study. For corneal densitometric measurements in the first month of evaluation, there were significant differences in 2-6 mm zone specifically in anterior and posterior layers ($p < 0,040$, $p < 0,010$), 6-10 mm zone specifically in anterior, center, posterior layers and total diameter ($p < 0,008$, $p < 0,002$, $p < 0,002$, $p < 0,003$). When it comes to corneal topography, changes were detected in Sim K values especially a decrease in K1 and Avg in patients with mild and severe TO ($p < 0,046$, $p < 0,010$) and in patients with mild and moderate TO ($p < 0,027$, $p < 0,017$). During the third month the retinal nerve fiber layer values were significantly thinner in patients with moderate-severe TO ($p < 0,029$).

Conclusion: Mechanical and inflammatory factors play a significant role in the ocular findings of TO, and can change corneal biomechanical properties. The present study showed differences in corneal topography and densitometry parameters among the patients with thyroid ophthalmopathy.

Keywords: Thyroid ophthalmopathy, corneal densitometry, corneal topography.

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INTRODUCTION

Graves' disease is an autoimmune disease associated with an imbalance in thyroid hormone levels. The most common cause of hyperthyroidism is Graves' disease. Graves' disease is typically seen in middle aged (40-60 years) period. Thyroid ophthalmopathy (TO), is the most common extrathyroidal manifestation of Graves' disease which is characterized by orbital inflammatory infiltration and activation of orbital fibroblasts resulting in their activation of orbital inflammation and tissue remodeling (1). TSH receptors are also found on orbital fibroblasts and this is the primary mechanism of ophthalmopathy. Previous studies showed that approximately 60% of the patients have mild symptoms like redness, proptosis, eyelid retraction, and lag exophthalmos (1,2). The others experience extraocular muscles involvement that causes diplopia, intraocular hypertension and as well as optic neuropathy due to optic nerve compression (2). Risk factors include smoking, high serum level of thyrotropin receptor antibodies, radioactive iodine (RAI) treatment, thyroid dysfunction and hypercholesterolemia. Eventhough, there are a variety of scoring systems used to classify TO, our study classified thyroid patients as mild, moderate and severe according to EUGOGO (European Group on Graves' Orbitopathy) classification (1-3). On the other hand, in order to minimize irreversible damages a stage-adapted anti-inflammatory therapy is of great importance. TO classification is based on clinical activity score (CAS). Treatment decisions are based on clinical activity, severity, and duration of Graves' orbitopathy (GO) (2,3). In this study, we aimed to evaluate the effects of systemic and thyroid ophthalmopathy findings via using optical coherence tomography (OCT), corneal densitometry, and corneal topography parameters according to clinical activity score in thyroid patients.

METHODS

This cross-sectional study was conducted in the Department Ophthalmology of Cukurova University between January 1, 2021, and June 31, 2022. This

study included 50 eyes of 25 thyroid patients who applied to the Oculoplasty unit of Cukurova University, Department of Ophthalmology. This study was approved by the Institutional Ethics Review Board of Cukurova University (03.06.2022-123/22), and informed consent was obtained from each patient, and all research adhered to the tenets of the Declaration of Helsinki. All patients fulfilled the TO comprehensive diagnostic criteria and were diagnosed by same ophthalmologists (BU, AAO). During the study period, 25 patients who met all diagnostic criteria and continued their full follow-up were included in the study.

The patients underwent a comprehensive ophthalmological examination, including best-corrected visual acuity, slit lamp biomicroscopy, intraocular pressure measurement with Goldmann applanation tonometry, ultrasonic pachymetry, eyelid laxity evaluation, fundoscopic examination and hertel exophthalmometry. Clinical activity scores according to the European Group of Graves' Orbitopathy (EUGOGO) classification and retinal nerve fiber layer values were also recorded. Cases with lymphoma, idiopathic orbital inflammation, cellulitis, orbital tumors, glaucoma, uveitis, retinal and corneal disease, a history of ocular trauma or surgery, and patients using eye drops and contact lenses were excluded from the study. Corneal densitometry and topography (CSO, Italy) data recorded for 3 months were noted and evaluated together according to the EUGOGO classification. The densitometry measurements are expressed in gray scale unit and measurements range from 0 (no clouding, maximum transparency) to 100 (completely opaque cornea, no transparency) depending on the degree of light scatter from the cornea.

Statistical analysis

Statistical analysis of the data was conducted using the Statistical Packages for the Social Science (SPSS 20.0, IBM corp. IBM SPSS Statistics for Windows, Version 20.0.Armonk, NY). The variables were investigated using analytical methods (Kolmogorov-Smirnov/

Shapiro-Wilk's test) to determine whether or not they are normally distributed. Descriptive analyses were presented using means and standard deviations for normally distributed variables while medians and interquartile range for the non-normally distributed and ordinal variables. Student's t-test was used to find differences between independent groups, and Chi-square analysis was used for qualitative data comparison. A value of $p < 0.05$ was considered to be statistically significant.

RESULTS

Fifty eyes of 25 thyroid orbitopathy cases (15 female, 10 male) with a mean age of 52.6 ± 12.87 years were included in the study. For corneal densitometric measurements, the cornea was divided into four concentric radial zones (0-2mm, 2-6mm, 6-10mm, 10-12mm and total) and anterior, central, and posterior layers according to corneal thickness. In the first month of evaluation, there were significant differences in 2-6 mm zone specifically in anterior and posterior layers ($p < 0.040$, $p < 0.010$), 6-10 mm zone specifically in anterior, center, posterior layers and total diameter ($p < 0.008$, $p < 0.002$, $p < 0.002$, $p < 0.003$) and in overall corneal thickness specifically in anterior, center, posterior layers and total diameter ($p < 0.008$, $p < 0.004$, $p < 0.002$, $p < 0.007$) (Table 1). During the second month of evaluation, there were significant differences in posterior layers of 0-2mm and 2-6mm zones ($p < 0.045$, $p < 0.034$), and in the central layers of 2-6mm zone and overall corneal thickness ($p < 0.037$, $p < 0.041$) (Table 2). In the third month of evaluation only in the anterior layer of total corneal thickness a significant difference is seen ($p < 0.039$) (Table 3). When it comes to corneal topography, changes were detected in Sim K values especially a decrease in K1 and Avg in patients with mild and severe TO ($p < 0.046$, $p < 0.010$) and in patients with mild and moderate TO ($p < 0.027$, $p < 0.017$). Another decrease is also seen in K2 values specifically in patients with mild and severe disease ($p < 0.005$) during the first month of evaluation. Hertel exophthalmometry measurements when compared between groups (mild - moderate -

severe) significant differences were seen in the 1st month in mild and severe TO patients ($p < 0.041$) and 3rd month especially in patients with mild-moderate ($p < 0.025$) and mild-severe TO ($p < 0.020$). During the third month the retinal nerve fiber layer values were significantly thinner in patients with moderate-severe TO ($p < 0.029$).

DISCUSSION

TO is an autoimmune disease affecting the thyroid gland and eye (4). Mechanical and inflammatory factors play a significant role in the ocular findings of TO and can change ocular, corneal biomechanical and densitometric properties (5). Reduced tear production and rubbing of eyes, common in Graves' disease, is a known precipitant of keratoconus (KC). Our study showed some differences in corneal biomechanical properties among the patients with TO disease. By using Pentacam all the patients were evaluated and the results of this analysis demonstrate the haziness score at three layers of corneal depth: the anterior layer, comprising 120 μm of anterior cornea; the posterior layer, comprising 60 μm of the extreme posterior cornea; and the central layer, located between the anterior and posterior layers. A total densitometry score is also reported that represents the volume between the epithelium and endothelium. Eventhough there are not enough studies related with the effects of TO on corneal densitometry, we found out that there were significant differences in anterior and posterior layers of 2-6 mm zone ($p < 0.040$, $p < 0.010$), all layers of 6-10 mm zone ($p < 0.008$, $p < 0.002$, $p < 0.002$, $p < 0.003$) and in all layers of overall corneal thickness ($p < 0.008$, $p < 0.004$, $p < 0.002$, $p < 0.007$). During the second month of evaluation, there were significant differences in posterior layers of 0-2mm and 2-6mm zones ($p < 0.045$, $p < 0.034$), and in the central layers of 2-6mm zone and overall corneal thickness ($p < 0.037$, $p < 0.041$). In the last month of evaluation only in the anterior layer of total corneal thickness a significant difference is seen ($p < 0.03$). We can say that every stage of TO has effect on corneal densitometry and the most affected one is the anterior layer which is

supposed to lead to the thinning of epithelial layer. Previous studies have analyzed mostly corneal densitometries of keratoconus, primary congenital glaucoma and outcomes after keratoplastic surgeries. Lopes et al.⁵ found out a higher densitometry in all layers of the central cornea ($p < 0.001$). The difference was marked in all layers of 0-2mm and 2-6mm zones and these values were detected in different stages of KC (5). Monitoring the cornea in patients with TO using Pentacam may help to show the presence of subclinical inflammation and regulate the follow-up and treatment protocols. For this reason larger sample sizes and prospective design studies are needed to reach more conclusive results.

It is known that increased expression of inflammatory mediators in tears of GO patients suggests that the lacrimal glands could be a target for immune responses and this may play role in the pathogenesis of tear film and ocular surface stability (6). The pathophysiologic alterations of active TO could result in an increase in orbital soft tissue volume, which pushes the globe anteriorly, leading to raised retrobulbar pressure and progression of proptosis (7). In our study, Hertel exophthalmometry measurements increased during the severity of TO and significant differences were seen in the 1st month in mild and severe TO patients ($p < 0.041$) and 3rd month especially in patients with mild-moderate ($p < 0.025$) and mild-severe TO ($p < 0.020$). Same results were found in the study of Tran et al.⁸, where at initial presentations 41% of their patients demonstrated asymmetric proptosis (8). Upon reaching the stable phase, asymmetric proptosis persisted in only 22% of patients. A decline in the rate asymmetric proptosis was greatest within the first 3 months of the active phase (8). During the third month the retinal nerve fiber layer values were significantly thinner in patients with moderate-severe TO ($p < 0.029$). Luo et al.⁹, no statistically significant differences were found between the mild thyroid-associated ophthalmopathy group and the control group in nerve fiber layers of patients (9). In the moderate-to-severe thyroid-associated ophthalmopathy group, temporal and

nasal peripapillary nerve fiber layer thicknesses were lower compared to the control group ($p = 0.041$, $p = 0.012$). The thinning of RNFL might be a strong suggestion for closer vision follow-up and earlier decompression surgery.

Almost 50% of patients with TO symptoms are mild (10). If the diagnosis couldn't be performed at the active phase, some cases might have severe sight-threatening form of disease (11-13). TO is disfiguring and disabling autoimmune condition (14,15). Thyroid ophthalmopathy has been commonly seen in female patients who are 30-50 years old period (12-15). Consistent with the literature, the majority of patients in our study were female and their average age was approximately 50 years. Therefore, when evaluating TO patients, it is important to first examine demographic data.

Limitations of the study

There were several limitations to present study that including relatively few parameters. The main limitation is the retrospective nature of the study, followed by a relatively small number of patients. The difference in the sample size between the groups is another limitation. Despite the inherent limitations, there is a paucity of data about corneal findings of thyroid ophthalmopathy in the literature, and this study is important because it is one of the rare studies about thyroid ophthalmopathy from Southern Türkiye.

CONCLUSION

Thyroid ophthalmopathy is the most common extrathyroidal manifestation of Graves' disease. Mechanical and inflammatory factors play a significant role in the ocular findings of TO and can change ocular, corneal biomechanical and densitometric properties. The present study showed differences in corneal biomechanical properties among the patients with TO disease.

Table 1. Corneal densitometry parameters of 1st month.

1.month					
		Mild GO	Moderate GO	Severe GO	P
0-2mm	ANTERIOR	21,00	24,36	28,34	>0,05
	SANTRAL	16,02	16,50	18,13	>0,05
	POSTERIOR	13,10	12,96	14,13	>0,05
	TOTAL	16,70	17,94	20,19	>0,05
2-6mm	ANTERIOR	20,13	22,37	29,10	0,040
	SANTRAL	14,76	14,95	19,23	>0,05
	POSTERIOR	12,32	11,94	14,99	0,010
	TOTAL	15,75	16,42	21,11	>0,05
6-10mm	ANTERIOR	26,61	24,21	41,88	0,008
	SANTRAL	21,38	17,99	32,51	0,002
	POSTERIOR	17,96	14,79	24,05	0,002
	TOTAL	21,99	19,00	32,81	0,003
TOTAL	ANTERIOR	24,43	25,26	36,21	0,008
	SANTRAL	19,01	17,74	25,69	0,004
	POSTERIOR	15,98	14,22	19,63	0,002
	TOTAL	19,86	19,08	27,16	0,007

Table 2. Corneal densitometry parameters of 2nd month.

2.months					
		Mild GO	Moderate GO	Severe GO	P
0-2mm	ANTERIOR	21,72	23,66	28,69	>0,05
	SANTRAL	16,11	16,26	18,03	>0,05
	POSTERIOR	13,13	12,76	14,10	0,045
	TOTAL	16,98	17,53	20,28	>0,05
2-6mm	ANTERIOR	20,87	22,11	23,38	>0,05
	SANTRAL	14,85	14,97	18,85	0,037
	POSTERIOR	12,31	12,04	14,63	0,034
	TOTAL	16,04	16,41	20,63	>0,05
6-10mm	ANTERIOR	26,61	24,21	41,88	>0,05
	SANTRAL	21,38	17,99	32,51	>0,05
	POSTERIOR	17,96	14,79	24,05	>0,05
	TOTAL	21,99	19,00	32,81	>0,05
TOTAL	ANTERIOR	24,43	25,26	36,21	>0,05
	SANTRAL	19,01	17,74	25,69	0,041
	POSTERIOR	15,98	14,22	19,63	>0,05
	TOTAL	19,86	19,08	27,16	>0,05

Table 3. Corneal densitometry parameters of 3rd month.

3. month		Mild GO	Moderate GO	Severe GO	P
0-2mm	ANTERIOR	21,25	21,77	23,34	>0,05
	SANTRAL	15,91	16,37	17,00	>0,05
	POSTERIOR	13,05	13,20	13,92	>0,05
	TOTAL	16,73	17,10	18,10	>0,05
2-6mm	ANTERIOR	20,21	20,34	23,91	>0,05
	SANTRAL	14,78	15,03	17,21	>0,05
	POSTERIOR	12,31	12,37	13,82	>0,05
	TOTAL	15,77	15,92	18,31	>0,05
6-10mm	ANTERIOR	27,00	24,21	34,73	>0,05
	SANTRAL	21,81	19,46	27,94	>0,05
	POSTERIOR	18,07	16,47	21,60	>0,05
	TOTAL	22,24	20,03	28,09	>0,05
TOTAL	ANTERIOR	24,78	23,30	30,36	0,030
	SANTRAL	18,98	18,08	22,84	>0,05
	POSTERIOR	15,94	15,03	18,01	>0,05
	TOTAL	19,91	18,80	23,74	>0,05

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Peer-Review

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Conflict of Interest

The authors declare that they have no conflict of interests regarding content of this article..

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Ethical Declaration

This study was approved by the Institutional Ethics Review Board of Cukurova University (03.06.2022-123/22), informed consent was obtained from each patient, and Helsinki Declaration rules were followed to conduct this study.

Authorship Contributions

Concept: BU, AAÖ, Design: BU, AAÖ, Supervising: BU, AAÖ, Financing and equipment: BU, AAÖ, Data collection and entry: BU, AAÖ, Analysis and interpretation: BU, AAÖ, Literature search: BU, AAÖ, Writing: BU, AAÖ, Critical review: BU, AAÖ,

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