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ORIGINAL ARTICLE

Corneal biomechanical properties in thyroid eye disease

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Abstract The purpose of this study is to investigate the effect of thyroid eye disease (TED) on the measurement of corneal biomechanical properties and the relationship between these parameters and disease manifestations. A total of 54 eyes of 27 individuals with TED and 52 eyes of 30 healthy control participants were enrolled. Thyroid ophthalmopathy activity was defined using the VISA (vision, inflammation, strabismus, and appearance/exposure) classification for TED. The intraocular pressure (IOP) measurement with Goldmann applanation tonometer (GAT), axial length (AL), keratometry, and central corneal thickness (CCT) measurements were taken from each patient. Corneal biomechanical properties, including corneal hysteresis (CH) and corneal resistance factor (CRF) and noncontact IOP measurements, Goldmann-correlated IOP (IOP_g) and corneal-compensated IOP (IOP_{cc}) were measured with the Ocular Response Analyzer (ORA) using the standard technique. Parameters such as best corrected visual acuity, axial length, central corneal thickness, and corneal curvature were not statistically significant between the two groups ($p > 0.05$). IOP measured with GAT was higher in participants with TED ($p < 0.001$). The CH of TED patients was significantly lower than that of the control group. There was no significant difference in the corneal resistance factor between groups. However, IOP_g and IOP_{cc} were significantly higher in TED patients. CH and VISA grading of TED patients showed a negative correlation ($p = 0.007$). In conclusion, TED affects the corneal biomechanical properties by decreasing CH. IOP with GAT and IOPg is found to be increased in these patients. As the severity of TED increases, CH decreases in these patients.

Conflicts of interest: All authors declare no conflicts of interest.

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Introduction

Thyroid eye disease (TED) is an inflammatory and autoimmune expression of Graves' disease causing functional and cosmetic problems. The clinical manifestations of TED are periorbital edema, increase in orbital volume which may lead to increase in intraorbital pressure, conjunctival hyperemia and chemosis, proptosis, restrictive myopathy leading to strabismus and/or diplopia, eyelid retraction, exposure keratopathy, lagophthalmus, and compressive optic neuropathy [1,2].

The alterations in the ocular surface due to increased palpebral fissure width, increased blink rate, lagophthalmus, and lid lag in TED patients resulting in hyposecretory and evaporative mechanism, modify the tear film and leads to dry eye syndrome [3,4]. The increase in tear film osmolarity in patients with TED is also related to increased proptosis and palpebral fissure width [4—6]. Villani et al [3] demonstrated that the significant reduction in surface epithelial cell density is due to the damaged ocular surface, increase in the number of basal epithelial cells owing to a proliferative stimulus, and the increase in activated keratocytes and dendritic cells as a sign of inflammation with confocal microscopy in Graves' ophthalmopathy. They also showed that the number of nerves was reduced, and the tortuosity of the nerve fibers and the number of beadlike formations were increased.

The cornea is not purely elastic but rather viscoelastic, which means that the rate at which a load is applied changes the measured value for the Young modulus [7,8]. *In vivo* corneal biomechanical evaluation was first introduced by Luce [9] using the Ocular Response Analyzer (ORA; Reichert Ophthalmic Instruments, Depew, NY, USA). This instrument measures the corneal biomechanical properties as corneal hysteresis (CH) and corneal resistance factor (CRF), and determines the noncontact intraocular pressures (IOP) as Goldmann-correlated IOP (IOP_g) and corneal-compensated IOP (IOP_{cc}) [9—11]. The ORA evaluates corneal response to indentation by a rapid air pulse using an infrared light to measure applanation of the cornea. The air pulse results in an inward, and concave state of cornea. As the air pressure decreases, the cornea passes back through the applanation and moves outward. It provides two applanation measurements and pressures within 20 milliseconds: one when the cornea is flat on the way in (P1) and the other on the way out (P2) (Fig. 1) [12]. The difference between two pressures is CH, reflecting corneal viscoelasticity. CRF is calculated from the formula (P1 − *k*P2), where *k* is a constant. The constant *k* is determined from an empirical analysis of the relationship between both P1 and P2 and the central corneal thickness (CCT) to develop a parameter more strongly associated with CCT than CH [13]. CRF is thought to represent the overall resistance and the elastic properties of the cornea. IOP_g is the average of two pressure measurements, which is intended to correspond to the Goldmann applanation tonometer (GAT). IOP_{cc} is a pressure measurement that is said to be compensated for corneal properties, and uses information provided by CH measurement to obtain an IOP that is less affected by CCT and corneal curvature [8,9].

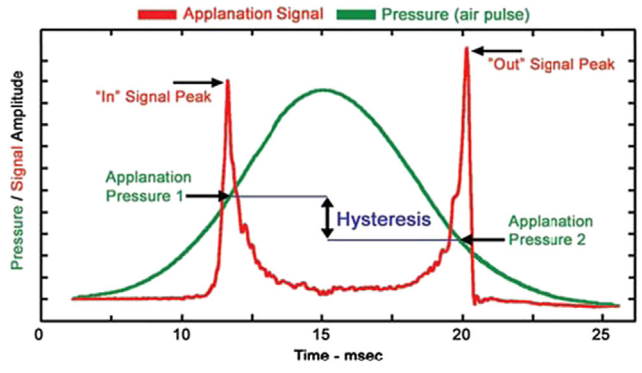

Figure 1. Corneal hysteresis is the difference between "inward" and "outward" applanation pressures.

In recent years, evidence suggests that the biomechanical properties of the cornea are altered in glaucomatous eyes [10,14—16], keratoconic corneas [17—19], myopic eyes [13,20,21], in eyes of individuals with diabetes mellitus [11,22] and systemic lupus erythematosus [23], in post-laser *in situ* keratomileusis eyes [24,25], and in eyes following penetrating keratoplasty [26]. The aim of this study was to investigate biomechanical parameters of the cornea measured with ORA in TED, and the relationship between these parameters and disease manifestations.

Methods

A total of 54 eyes of 27 patients who were admitted to the oculoplastic and reconstructive surgery department because of TED and 52 healthy eyes of 30 control individuals were enrolled in this observational comparative study in Beyoglu Eye Training and Research Hospital, Istanbul, Turkey between January 2011 and June 2011. Informed consent was obtained from all participants. The study followed the tenets of the Declaration of Helsinki and was approved by the local ethics committee.

Exclusion criteria consisted of glaucoma, diabetes, history of ocular surgery or trauma, use of any topical medication, contact lens wear, and high refractive error or corneal abnormalities such as keratoconus and corneal dystrophy, which may affect measurement.

Diagnosis of TED was based on the criteria of the European Group on Graves' Orbitopathy Consensus Statement [27,28]. Thyroid ophthalmopathy activity was defined by using the VISA classification for TED [29]. This classification system is based on four disease end points: vision, inflammation, strabismus, and appearance/exposure. Each section records subjective and measurable objective inputs and plans ancillary testing. The goal of the vision section is described as to rule out optic neuropathy. Details on vision loss and color change were asked from TED patients as subjective measurements. Best corrected visual acuity (BCVA; using Snellen chart), color vision (using Ishihara plates), pupil response, and the appearance of optic nerve head were used as objective tests for vision. Ancillary testing included Standard Automated Perimetry with the Humphrey Field Analyzer (Carl Zeiss Meditec, Dublin, CA, USA) using the 30-2 SITA Standard program as well as computed tomography or magnetic resonance imaging scans to confirm crowding of orbital apex and extraocular

muscle involvements and visual evoked potential. As a result of the vision section, we were able to record whether optic neuropathy is present or absent. The inflammatory score included orbital pain at rest or with gaze, chemosis, eyelid edema, conjunctival injection, and eyelid injection. For evaluating strabismus symptoms, we looked for corneal light reflex, using the Hirschberg principle, and made prism cover testing (measured in prism diopters) in different gaze directions. Eyelid retraction (measured in millimeters), proptosis (measured with the Hertel exophthalmometer), presentation of redundant skin, fat prolapse, and corneal staining were documented for appearance grading. Because none of the patients in the TED group had optic neuropathy and management of the disease is based on inflammatory score and evidence of progression [29], we used the VISA inflammatory score in grading patients. In addition, photographs of patients at nine cardinal gaze positions and with eyelids closed were taken with the same camera and by the same technician.

Each participant underwent IOP measurement with GAT. Axial length (AL) and keratometry measurements were performed with IOL Master optical biometry (Zeiss Meditec AG, Jena, Germany). CCT was measured with ultrasonographic pachymetry (DGH-550, DGH Technology Inc., Exton, PA, USA).

Corneal biomechanical properties, including CH, CRF, IOP_g, and IOP_{cc}, were always measured by ORA using the standard technique [13,30,31]. All ORA measurements were obtained using the same calibrated instrument by the same masked technician. All patients underwent measurement while sitting and asked to fixate on a target light as the measurement was taken. A noncontact probe scanned the central corneal area and released an air puff. For each patient, three measurements were obtained; the reading with the best signal value was used in the statistical evaluation. CCT measurement was performed with an ultrasonic pachymeter by another experienced technician. Three replicate measurements were obtained, and the mean values of the measurements were accepted.

All statistical analyses were performed with SPSS for Windows version 16.0 (SPSS Inc., Chicago, IL, USA). The parameters of groups were compared using Student *t* test and one-way analysis of variance. The correlations between parameters were evaluated with the Pearson's correlation coefficient. A p value of < 0.05 was considered statistically significant.

We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during this research.

Results

The study included 54 eyes of 27 participants (24 female, 3 male) with TED as Group 1 and 52 healthy eyes of 30 control participants (17 female, 13 male) as Group 2 ($p = 0.001$). The mean $\pm$ SD age of patients was 46.3 $\pm$ 11.7 years (range 21–70 years) and 46.8 $\pm$ 11.6 years (range 20–69 years) for Group 1 and Group 2, respectively ($p > 0.05$). The mean duration of thyroid disease was 5.85 $\pm$ 4.76 years.

The parameters such as BCVA, AL, CCT, and corneal curvature were not statistically significant between groups ($p > 0.05$; Table 1). The IOP measured with GAT was higher in patients with TED ($p < 0.001$).

CH was significantly lower in Group 1 than in Group 2. There was no significant difference in CRF between the two groups. However, IOP_g and IOP_{cc} were significantly higher in Group 1 (Table 2). There was a positive correlation between GAT IOP readings and IOP_g and IOP_{cc} measured by ORA (Pearson correlation analyses, $p < 0.0001$).

When the patients with TED were classified according to VISA classification for TED activity, there was no significant difference in terms of ORA parameters between the subgroups. However, in correlation analysis, CH and VISA grading of TED patients showed a negative correlation although not at a significant level ($p = 0.007$; Fig. 2). However, there was a significant difference in CCT among grades 0 and 6 ($p = 0.019$) as well as in grades 4 and 6 ($p = 0.006$; one-way analysis of variance test). The distribution of the mean ORA parameters and CCT according to VISA classification is shown in Table 3.

To increase confidence of our study, in addition to the groups mentioned above, two groups were created including only one eye of the participants. We randomly enrolled only one eye of the patients with TED to the study group, which consisted of 27 eyes (24 female, 3 male), and compared it with our control group, which consisted of 26 eyes (17 female, 9 male). The age, BCVA, AL, CCT, and corneal curvature were not statistically significant between the two groups ($p > 0.05$). The IOP measured with GAT was significantly higher in the TED group ($p = 0.01$). CH was significantly lower; however, IOP_g and IOP_{cc} were significantly higher in the TED group ($p = 0.025$, $p = 0.007$, and $p = 0.01$, respectively). There was no statistically significant difference in CRF between the groups ($p = 0.86$). These results were correlated with the results of our previous groups included in this study.

Discussion

Tissue response and deformation when placed under stress is determined by biomechanical properties of the tissue. The measurement with ORA is a direct, noninvasive, and

Table 1 Comparison of clinical findings for patients with thyroid eye disease and healthy control participants.

Mean	Patients with TED ($n = 54$)	Healthy control participants ($n = 52$)	p
Age (y)	46.3 $\pm$ 11.7	46.8 $\pm$ 11.6	0.81
BCVA (Snellen)	0.963	0.967	0.83
Axial length (mm)	23.03	23.31	0.44
CCT (μm)	550.87	550.77	0.99
Keratometry (diopter)	43.89	44.28	0.99
IOP-GAT (mmHg)	16.61	13.84	<0.001*

*Statistically significant.
BCVA = best corrected visual acuity; CCT = central corneal thickness; IOP-GAT = intraocular pressure measured by Goldmann applanation tonometry; TED = thyroid eye disease.

Table 2 Comparison of ORA parameters of the two groups.

ORA parameters	Patients with TED (n = 54)	Control participants (n = 52)	p
Corneal hysteresis	10.01	10.77	0.009*
Corneal resistance factor	10.85	10.75	0.76
Goldmann-correlated IOP	17.93	15.56	0.002*
Corneal-compensated IOP	18.5	15.62	<0.001*

IOP = intraocular pressure; ORA = Ocular Response Analyzer; TED = thyroid eye disease.

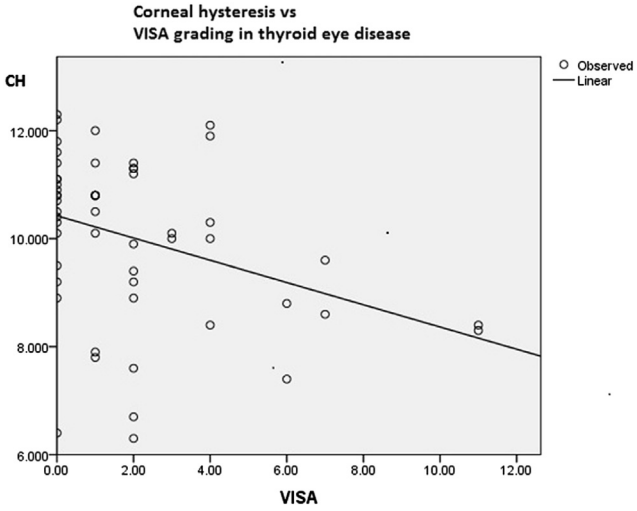

Figure 2. Correlation between corneal hysteresis (CH) and VISA classification.

in vivo method that helps us to study and understand ocular biomechanics. Beside the structural and functional effects of TED on corneal properties, we wanted to evaluate the effect of TED on corneal biomechanical properties measured via ORA and the relationship between these parameters and TED manifestations.

In this study, we found that the CH of TED patients was significantly lower than that of the healthy control group (Table 2). CH is a measurement of corneal viscoelasticity. Elasticity is the continuum mechanics of bodies that deform reversibly under stress and is directly proportional to the force applied [30]. Viscosity is the tendency of liquids to resist flow so that after deformation by stress, they do not regain their original shape [17]. While recovering to the original shape, the relaxation path is found to be different from the deformation path, which is called hysteresis [17]. CH is the dynamic response of the cornea reflecting the capacity of the corneal tissue to absorb and dissipate energy [9]. Low values of CH are often described to indicate a "soft" or "floppy" cornea [32] and less corneal viscous dampening. The dampening effects of the cornea decrease in diseases such as keratoconus [17–19], glaucoma [10,14–16], Fuchs' dystrophy [9], myopic eyes [13,20,21], in eyes with diabetes mellitus [11,22] and systemic lupus erythematosus [23], in post-laser *in situ* keratomileusis [24,25] eyes, and in eyes following penetrating keratoplasty [26]. Lower CH, described as a decrease in the dampening effects of the cornea, may be explained by an alteration in the corneal structure and functional problems resulting especially in dry eye in TED. In other words, the corneas of patients with TED may have similar alterations in the corneal microstructure known to occur in these corneal diseases. However, the CRF of TED patients was not significantly different from that of control participants (Table 2). CRF is thought to be a correction factor that reduces the effect of CCT on IOP measurements [9] and is a parameter more strongly associated with CCT than CH [13]. Because CCT measurements showed no statistical differences in Group 1 and Group 2, CRF may not differ between groups. This means that the elastic property of the cornea that appears to be an indicator of the overall "resistance" of the cornea does not change in TED. This study is a preliminary report, and further research is needed to elucidate this matter. We also enrolled only one eye of the study patients and the control group and compared all parameters. We found similar results with our previous groups included in this study.

Table 3 Distribution of the mean ocular response analyzer parameters and central corneal thickness according to VISA classification.

VISA grading	Number of patients	Corneal hysteresis	Corneal resistance factor	Corneal-compensated IOP	Goldmann-correlated IOP	Central corneal thickness (μm)
0	20	10.55	11.48	18.5	18.6	560.3
1	10	10.29	10.51	16.6	16.1	542.8
2	11	9.38	10.43	19.1	17.9	541.2
3	2	10.05	11	19.0	18.4	539.5
4	5	10.54	11.32	17.9	18.0	587.0
6	2	8.10	8.15	17.6	14.5	457.5
7	2	9.10	11.2	23.0	21.9	564.0
11	2	8.35	9.65	21.1	18.9	551.0
p		0.39	0.286	0.584	0.452	0.772

IOP = intraocular pressure.

As documented by several studies, GAT measurements can be affected by several ocular properties such as CCT, AL, and corneal curvature [14,33,34]. It has been found that the difference in thickness ranged from 9% to 52% greater for peripheral cornea in addition to describing the relationship between IOP and CCT [34]. Konuk et al [35] also investigated CCT alterations in Graves' disease and Graves' ophthalmopathy cases according to the disease severity and hormonal status of the patients and healthy control participants. They found that the CCT values of patients with Graves' disease and patients with Graves' ophthalmopathy with hyperthyroid and euthyroid hormonal status showed no statistical difference among themselves and versus control participants. In our study, CCT was not statistically significantly different between Group 1 or Group 2. ORA may provide additional factors over CCT to help with the assessment of the accuracy of IOP measurement [13].

Corneal curvature is another variable that can affect GAT measurements [33]. More force must be applied against a steep than a flat cornea, increasing the indicated value of the IOP. In this study, it is found that ocular biometric measurements such as AL and corneal curvature were also not significantly different between groups.

There was a statistically significant difference in the ratio of female and male cases between our control and study groups, but sex bias had no effect on the results of ORA parameters. In the study of Shah et al [18], no correlation was found between hysteresis in males and females. Wells et al [36] investigated the corneal biomechanical properties in glaucoma patients and reported a strong sex bias toward male patients in the glaucoma study group, which had a tangible influence on the results. In the study of Ortiz et al [24], no difference in biomechanical properties was observed between men and women, suggesting that it is not necessary to sex-match the patients.

An increase in IOP in upward gaze is regarded as a restrictive ocular motility disorder owing to the compression of globe [37]. All measurements including GAT and ORA were taken in the primary position of gaze in all patients. Although we eliminated the variables affecting the IOP measurements between groups, we found that GAT IOP measurements, IOP_{cc}, and IOP_g were higher in TED patients. Compression of globe due to extraocular muscle involvement with or without restrictive myopathy and biomechanical properties changing with corneal microstructure and functional problems may have an impact on IOP measurement.

Dolman and Rootman [29] pointed out that research studies can be facilitated by using VISA classification, which helps direct the appropriate management of patients with TED in a logical sequence. We used this classification and searched whether corneal biomechanical properties change according to disease severity. In our study, it is found that none of the ORA parameters significantly correlated with VISA grading. However, there was a negative correlation between CH and VISA grading. Although our study may be accepted as a preliminary report, it may be indicated that corneal biomechanical properties do not change with the disease severity.

In conclusion, TED affects corneal biomechanical properties by decreasing CH, indicating that the structural, functional, and biomechanical properties of the cornea may be different in eyes with TED than in control eyes. IOP measurement with GAT, IOP_{cc}, and IOP_g is found to be increased in these patients. Although there was no statistically significant difference between ORA parameters in subgroups according to VISA classification, there was a negative correlation between CH, and so with corneal viscoelasticity and disease severity. This study is the first report to investigate the corneal biomechanics in TED. Further studies with larger numbers of participants are necessary to establish the relevance and usefulness of biomechanical measurements in TED.

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