The Effect of Thyroid Eye Disease on Corneal Biomechanical Properties

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Abstract

Objectives: The aim of this study was to identify corneal biomechanical parameters measured by ORA in patients with TED compared to the healthy group. The NOSPECS classification of patients is used to assess the relation between biomechanical changes and disease severity.

Methods: We included 22 TED patients, diagnosed with TED for more than five years, and 43 healthy participants. The NOSPECS classification was assessed as mild (grade 1-3) and severe (grade 4-6) disease. For each group, corneal hysteresis (CH), corneal resistance factor (CRF), central corneal thickness (CCT), Goldmann-correlated intraocular pressure (IOPg) and corneal compensated intraocular pressure (IOPcc) parameters were measured by ORA.

Results: The mean age was 38.8±11.6 years for the TED patients and 42.9±15.58 years for the control group. For TED patients and healthy volunteers, the mean levels of CRF, CH, and CCT were measured as follows: 10.43±2.04 vs 10.28±1.91 mmHg, p=0.67; 10.18±1.81 vs 10.21±1.68 mmHg, p=0.90; 550.31±35.73 vs 545.23±37.91 µm, p=0.47, respectively. These values were not significant between groups, but they were significantly higher in females compared to males in TED patients [CRF: 10.68 (IQR: 9.49-12.14) vs 8.96 (IQR: 8.04-9.92) mmHg, p=0.002, CH: 10.43 (IQR: 9.48-11.25) vs 8.58 (IQR: 7.90-9.95) mmHg, p=0.003 and CCT: 554.25 (IQR: 536.05-579.52) vs 527.40 (IQR: 492.25-545.90) µm, p=0.014]. CRF values were negatively correlated with NOSPECS score (r=-0.317, p=0.036) and significantly higher CRF was observed in mild patients compared to severe disease (11.43 (IQR: 10.14-12.87) vs 9.46 (IQR: 8.75-10.28) mmHg, p=0.008).

Conclusion: We found a significant gender effect on corneal biomechanical parameters of TED patients. CRF, CH and CCT values were significantly higher in females compared to males with TED. The clinical severity score of TED showed negative correlation with CRF. CRF value might be a useful parameter in follow-up of TED patients in clinical practice.

Keywords: Corneal biomechanical parameters, corneal resistance factor, NOSPECS classification, thyroid eye disease, ocular response analyzer

Introduction

Thyroid eye disease (TED) affects 25–50% of individuals with Graves’ disease (1). TED can appear at any time over the course of the disease but it is most common in people in their fifth and seventh decades (2). Autoimmune activation leads to retro-orbital inflammation, orbital fibroblast over-production of glycosaminoglycans, and adipose tissue hyperplasia in the etiology of TED (2-5). Clinical signs of TED emerge as a result of these pathophysiological alterations, as well as cytokine production and structural modifications (3). Clinical signs and symptoms of TED range from mild
ocular and extraocular discomfort to restrictive myopathy, severe proptosis, lid retraction, and exposure keratitis (6). One of the most important manifestations of TED is corneal changes as the disease progresses. The corneal involvement of TED has not been fully understood yet. Using confocal microscopy, corneal pachymetry, and fluorophotometry, previous investigations produced some data on corneal microstructural changes in TED (7-9). While it is suggested that hyperthyroidism or severity of TED had no effect on central corneal thickness, the average permeability value of the corneal epithelium in TED was significantly higher than the control. The nerve density was reduced, and the tortuosity of the nerve fibers was raised, compared to healthy controls, in the TED group’s corneal in vivo confocal microscopy parameters.

Conical structural alterations in TED patients studied from different perspectives with different examination methodologies and using various examination procedures. However, it needs to be further evaluated to establish the best of our knowledge. In our study, we investigated the effect of microstructural changes on corneal biomechanical properties of TED patients with an ocular response analyzer (ORA) (Reichert Ophthalmic Instruments, Buffalo, USA).

The ORA was introduced to measure corneal biomechanical properties using an air jet that generates pressure on the cornea and aims to provide information on corneal hysteresis (CH) and corneal resistance, which gives the value of CH, corneal resistance factor (CRF), central corneal thickness (CCT), and non-contact intraocular pressure measurement as well as Goldmann-correlated intraocular pressure (IOP) and corneal compensated intraocular pressure (IOPc) (5).

Several classification systems have been conceived to assess the clinical manifestations of TED. The vision, inflammation, strabismus, and appearance (VISA), the European Group of Graves’ Orbitopathy (EUGOGO), and NOSPECS classification are widely used grading systems to assess the activity and severity (10,11). NOSPECS classification is composed of no TED signs (N), only eyelid sign (O), soft-tissue involvement (S), proptosis (P), extraocular motility restriction (E), corneal involvement (C), and sight loss (S). It is one of the oldest and widely used classification systems which was introduced by Werner in 1969 (12). This classification grades exclusively the clinical severity of TED objectively and practically. On the other hand, the EUGOGO and VISA classification also evaluate disease activity in their scoring systems. Therefore, we obtained the NOSPECS classification in our study to evaluate only the clinical severity.

Despite the fact that the previous studies also focused on corneal biomechanical changes in TED, there is relatively little information on the link between disease severity score and corneal biomechanics. The major goal of this study, from this perspective, was to investigate altered biomechanical properties of the cornea in patients with TED and to determine their relationship with clinical severity, as measured by the NOSPECS classification.

Methods
Twenty-two patients with TED and 43 age- and sex-matched healthy participants were included in this study. Patients who have been diagnosed with thyroid disease for more than 5 years by an endocrinologist and healthy volunteers were included in the study. For both patients and healthy control groups, we excluded high refractive error cases. Spherical equivalent between −3.00 D and +3.00 D was included in the study. Subjects with diabetes mellitus, glaucoma, cornea, or ocular surface disorders, contact lens usage, or history of ocular surgery were excluded from the study. The study followed the tenets of the Declaration of Helsinki and was approved by the local ethics committee. All the patients with TED were routinely followed by the endocrinology department and were under treatment for their thyroid disease. All subjects underwent complete detailed ophthalmologic examination including visual acuity, biomicroscopy, and fundoscopy.

All subjects underwent ORA in primary position (13) for the measurement of CH, CRF, CCT, IOP, and IOPc parameters. All ORA measurements were obtained using the same calibrated instrument by a single masked person. All ORA examinations were performed between 09.00 AM and 12.00 PM to reduce the effects of diurnal variation in corneal biomechanics. Testing was performed according to the equipment manual of ORA. Three measurements with a minimum waveform score of 6.0 were obtained for each subject.

The clinical severity of TED was assessed with the NOSPECS classification as shown in Table 1. Soft-tissue and extraocular muscle involvements were evaluated with an MRI or CT scan. Best-corrected visual acuity (Snellen chart), color vision (Ishihara plates), and optic disk evaluation with a

| Table 1. NOSPECS classification[12] |
|-----------------|------------------|
| Class | Clinical features |
| 0 | No signs and symptoms |
| 1 | Only signs, no symptoms |
| 2 | Soft-tissue involvement with signs and symptoms (i.e., tearing, conjunctival and eyelid edema, foreign body sensation) |
| 3 | Proptosis (rop mm) |
| 4 | Extraocular motility restriction |
| 5 | Corneal involvement |
| 6 | Sight loss (optic nerve involvement) |
fundus examination were done to evaluate optic nerve involvement. We grouped the patients according to their NOSPECS classification as mild (Grades 1–3) or severe (Grades 4–6) disease.

All the statistical analyses were performed using the software, SPSS version 26.0 (SPSS Inc., Chicago, USA). The parameters used in the study were expressed as means ± standard deviation and median (interquartile range [IQR]). The analysis was conducted with the normality test for continuous variables and the non-parametric test for the data that cannot meet normality criteria. Demographic features of the TED group and control were analyzed using a Student’s t-test for age and Yates’ continuity correction Chi-square test for sex. The Student’s t-test was used to determine the significance of the difference between the TED and control groups. P<0.05 was considered statistically significant with a 95% confidence interval (CI). Mann–Whitney U non-parametric test is applied to both the diseased and healthy control groups individually with gender grouping variables. The same method was used to run correlation analysis between IOP cc, CH, and CRF values in both the TED and healthy control groups. A post hoc power analysis is conducted for TED gender groups with the program G*Power.

**Results**

The mean age was 38.8±11.6 years for the TED patients and 42.9±15.58 years for the control group (p=0.095). There was no significant difference in sex and age between groups. The mean values of CRF, CH, CCT, IOP cc, and IOP gc were measured for the TED patients and control group as follows:

| Parameter                        | TED patients | Healthy controls | p    |
|----------------------------------|--------------|------------------|------|
| n                                | 22           | 43               |      |
| Female/male (n)                  | 17/5         | 26/17            | 0.085|
| Mean age±SD (year)               | 38.8±11.6    | 42.9±15.58       | 0.095|
| Corneal resistance factor (CRF) (mmHg) (mean±SD) | 10.43±2.04 | 10.28±1.91 | 0.67 |
| Corneal hysteresis (CH) (mmHg) (mean±SD) | 10.18±1.81 | 10.21±1.68 | 0.672|
| Central corneal thickness (CCT) (µm) (mean±SD) | 550.31±35.73 | 554.23±37.91 | 0.356|
| Goldmann-correlated intraocular pressure (IOP gc) (mmHg) (mean±SD) | 16.20±3.66 | 15.59±3.42 | 0.354|
| Corneal compensated intraocular pressure (IOP cc) (mmHg) (mean±SD) | 16.81±3.41 | 16.26±3.16 | 0.362|

*Table 2. Demographic features and corneal parameters of participants*

Demographic features of the TED group and control were analyzed using a Student’s t-test for age and Yates continuity correction Chi-square test for sex. The Student’s t-test was used to determine the difference of corneal parameters between groups. Data expressed as means ± standard deviation (SD) and p<0.05 considered statistically significant.
increased with the increased severity of disease, whereas CH, CCT, IOP\textsubscript{cc}, and IOP\textsubscript{g} did not. The correlation analysis of CH, CCT, IOP\textsubscript{cc}, and IOP\textsubscript{g} with NOSPECS score resulted as follows: CH (r=−0.202, p=0.190), CCT (r=−0.096, p=0.545), IOP\textsubscript{cc} (r=−0.177, p=0.249), and IOP\textsubscript{g} (r=−0.279, p=0.067). A significantly higher CRF was calculated in mild compared to severe disease: 11.43 (IQR: 10.14–12.87) versus 9.46 (IQR: 8.75–10.28) mmHg, p=0.038. A post hoc power analysis showed for female and male TED patients, based on means, the effect size (d) of CRF as 1.03 with a power (1-\nicefrac{\beta}{\alpha}) of 0.80. Thyroid orbitopathy is more prevalent among females whereas it is known to have a worse disease course among males (2,26). In our study, female-to-male ratio was around 6.14:1 (24). The demographics of our TED patients are distributed in favor of female gender compared to male as given above. Since the natural demographics of the disease also show female dominance, we did not consider this disparity as a limitation, but our biggest limitation is its low sample size. Through Cohen’s G\textsuperscript{Power} analysis system, we justified that our sample size is enough to meet widely accepted power (1-\nicefrac{\beta}{\alpha}) of 0.80 (25). Thyroid orbitopathy is more prevalent among females whereas it is known to have a worse disease course among males (2,26). In our study, in Graves’ patient group, significantly lower CRF and CH values were found in females compared to males as given above. Since some studies have found that people with Graves’ disease have higher IOP values than the general population, implying that higher IOP values are more common among Graves’ patients (19-21). Although there was no statistical difference in mean or median values between the sick and healthy groups, there was statistically significant gender influence in some biomechanical measures of the TED group.

In comparison to the control group, we found that IOP\textsubscript{cc} and IOP\textsubscript{g} in Graves’ patients are not substantially different. Some studies have found that people with Graves’ disease did not link ORA findings to NOSPECS clinical severity grading. In that aspect, there is a need to investigate the relation between ORA measurements and this clinical severity.

Table 3. Comparison of corneal parameters between female and male TED patients

| Parameter                                      | Female patients            | Male patients             | P     |
|-----------------------------------------------|----------------------------|----------------------------|-------|
| Corneal resistance factor (CRF) (mmHg) (median (IQR)) | 10.68 (IQR: 9.49–12.14) | 8.96 (IQR: 8.04–9.92)      | 0.002 |
| Corneal hysteresis (CH) (mmHg) (mean±SD)      | 10.43 (IQR: 9.48–11.25) versus | 8.58 (IQR: 7.90–9.95)      | 0.003 |
| Central corneal thickness (CCT) (µm) (median (IQR)) | 554.25 (IQR: 536.05–579.52) | 527.40 (IQR: 492.25–545.90) | 0.014 |
| Goldmann–correlated intraocular pressure (IOP\textsubscript{g}) (mmHg) (median (IQR)) | 15.44 (IQR: 13.81–19.84) | 15.13 (IQR: 13.54–16.23) | 0.118 |
| Corneal compensated intraocular pressure (IOP\textsubscript{cc}) (mmHg) (median (IQR)) | 15.73 (IQR: 14.40–20.07) | 17.23 (IQR: 15.07–19.02) | 0.685 |

Difference in corneal parameters between genders was analyzed by Mann–Whitney U (MWU). Data expressed in median (IQR) and P<0.05 considered statistically significant.

In our study, we found a relationship between CRF values of biomechanical corneal parameters and the clinical severity of TED. Despite the fact that no significant differences in any of the biomechanical measures existed between the TED and control groups, CRF values declined as disease severity increased, according to the NOSPECS classification.

Corneal alterations are one of the most critical, but poorly understood, symptoms of TED. ORA, an in vivo system that uses standard air-puff tonometry to induce stress on the cornea and records the level of corneal deformation to evaluate ocular biomechanics, can be used to measure changes in biomechanical corneal properties in these individuals (5,14).

Despite our findings that ORA measurements were not statistically different between the TED and healthy groups, such significance in terms of CH was identified by Karabulut et al., Moghimi et al., and Kuebler et al. for Graves’ disease, and by Kirgiz et al. for Hashimoto’s thyroiditis (15-18). Kuebler et al. also discovered that CRF differed significantly between the TED and healthy groups (18). In comparison to our analysis, these studies feature an older patient population and a lower female-to-male ratio in the control group. We can explain why our results differ from those of earlier studies when it relates to demographic diversity. Two of those studies included Hashimoto’s thyroiditis patients in their patient groups, which could indicate differences in pathophysiological pathways, leading to different outcomes than our study. These earlier research, on the other hand, did not link ORA findings to NOSPECS clinical severity grading. In that aspect, there is a need to investigate the relation between ORA measurements and this clinical severity.

In further analysis, we found that CRF, CH, and CCT values were significantly higher (p<0.015) in females compared to males in the TED group, while there is no gender difference within the control group. The studies of Ortiz et al. and Shah et al. were consistent with our control group findings, showing no difference in biomechanical properties observed between men and women in the healthy group, however, gender role on corneal biomechanics in TED has not been fully identified in the literature (22,23). In our study, female-to-male ratio of TED calculated 3.4:1 while in previous incidence studies, female-to-male ratio was around 6.14:1 (24). The demographics of our TED patients are distributed in favor of female gender compared to male as given above. Since the natural demographics of the disease also show female dominance, we did not consider this disparity as a limitation, but our biggest limitation is its low sample size. Through Cohen’s G\textsuperscript{Power} analysis system, we justified that our sample size is enough to meet widely accepted power (1-\nicefrac{\beta}{\alpha}) of 0.80 (25). Thyroid orbitopathy is more prevalent among females whereas it is known to have a worse disease course among males (2,26). In our study, in Graves’ patient group, significantly lower CRF and CH values were found in...
the male population compared to females. Those parameters can be a predictive parameter for bad prognostic expectations in the male patient population. However, preclinical data from Schlüter et al. revealed in the mouse model that gender is not solely a predisposing factor for the development or progression of TED (27). Altogether, the TED is affected not only by gender but sex-related factors as an explanation for significant severity in men.

The ORA measures CH parameter accurately which represents cornea’s ability to take in and free energy comes from the ejected high-speed airflow (5). The previous studies showed significantly lower CH values in patients diagnosed with glaucoma compared to control and describe it as predict glaucoma progression risk (28,29). In our study, the TED group showed mean IOP in normal range, which might be an explanation for our conclusion of insignificant CH values between the diseased population compared to the control group. Pniakowska et al. revealed decreasing CH and increasing IOPcc of Graves’ patients and explicated IOPcc as a marker of the early subclinical stages of glaucoma in patients with TED (30). Similarly, we observed a significant negative correlation between CH and IOPcc of patients which supports this hypothesis. In addition, it is suggested that corneal biomechanical properties appear to be compromised with varying degrees of myopia and axial length (AL). AL is an important indicator of the development of myopia and a major factor, leading to visual impairment. In literature not only increasing level of myopia (31-33) but also AL (34,35) is associated with lower CH. It is known that that AL is the largest determinant of myopia and a great number of reports have shown a negative relationship between AL and myopia (36,37). In our study, only emmetropic or mild myopic patients and controls were selected but AL of eyes was not measured. Due to its strong correlation with refractive error, not measuring AL was not considered as a limitation in our study.

In our study, we found a significant association between CRF value and clinical severity, when we grouped patients as mild (Classes 1–3) and severe (Classes 4–6) disease based on their NOSPECS score. CRF was calculated significantly higher in patients with moderate disease than in patients with severe disease, and CRF value decreased with increasing TED disease severity score in correlation analysis. This considerable difference could indicate that as the disease advances, the cornea’s viscoelastic response declines. This finding may be used in the clinical practice as a follow-up parameter of TED patients. There was not any previous study that investigated the association between corneal biomechanical properties and NOSPECS classification in TED patients. However, Karabulut et al. used another grading system called VISA to classify TED patients based on VISA/exposure (15). Karabulut et al. showed no significant difference between CRF value and VISA, but they showed a negative correlation (P = 0.007) between CH value and VISA of TED patients (15). On the other hand, we showed a negative correlation between CRF value and NOSPECS classification. This discrepancy may be caused because of different TED severity classification rather than NOSPECS used in Karabulut’s study.

We acknowledge that there are some limitations in this study. More subjects would only improve the significance. Adding another classification system would have allowed for a great comparison and remove the objectivity of using only one classification system. Further studies may be needed to support our findings to prove it as a reliable parameter in the follow-up of TED patients.

Conclusion

We showed that TED progression affects the biomechanical properties of the cornea by decreasing CRF. This parameter indicates that the viscoelastic response of the cornea decreases while disease progresses. Based on our findings, CRF might be a useful parameter in the follow-up of TED patients in clinical practice.

Disclosures

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