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ORIGINAL ARTICLE

Comparison of corneal biomechanical properties in primary open angle glaucoma, normal-tension glaucoma, and ocular hypertension

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Abstract

Purpose: The aim of the study is to compare the biomechanical properties of the cornea and intraocular pressure (IOP) in primary open-angle glaucoma (POAG), normal-tension glaucoma (NTG), ocular hypertension (OHT), and normal eyes (N) measured by the ocular response analyzer (ORA).

Methods: This is a retrospective, cross-sectional, and comparative clinical trial. Corneal hysteresis (CH), corneal resistance factor (CRF), Goldmann IOP (IOPg), and corneal compensated IOP (IOPcc) were obtained using an ORA for all patients. IOP using Goldmann applanation tonometry (IOPGAT) and ultrasonic central corneal thickness (CCT) were also measured for each eye. Results were compared between groups.

Results: The mean CH in POAG, NTG, OHT, and normal control eyes was 9.2 ± 2.1 mmHg, 9.9 ± 1.6 mmHg, 10.1 ± 2.0 mmHg, and 10.93 ± 1.4 mmHg; CRF was 13 ± 2.3 mmHg, 10.7 ± 1.7 mmHg, 13.3 ± 1.9 mmHg, and 11.1 ± 1.7 mmHg; CCT was 567.9 ± 44.5 μ m, 553.9 ± 35.0 μ m, 576.7 ± 35.5 μ m, 558.9 ± 41.3 μ m, respectively. CH was significantly lower in the POAG group compared with the OHT and N group ($p < 0.05$). CRF was significantly lower in the NTG group compared with the POAG and OHT group ($p < 0.05$). There was a positive correlation between CCT and CH, CRF in all eyes. We found that IOPGAT, IOPcc, and IOPg were positively correlated with CCT and CRF, and negatively correlated with CH in all eyes.

Conclusion: In this study, CH was lower in the POAG and NTG groups. CRF was higher in the POAG and OHT groups. Further studies may help explain the relationship between the pathogenesis of glaucoma and corneal biomechanical properties.

Keywords: Corneal biomechanics; normal-tension glaucoma; ocular hypertension; primary open angle glaucoma.

Glaucoma is a chronic, progressive ocular disease that is characterized by optic disc damage and visual field loss. Intraocular pressure (IOP) is the main risk factor for glaucoma and it is the only factor that can be modified

for the treatment of glaucoma. Goldmann applanation tonometry (GAT) is regarded as the gold standard for estimating IOP. It is known that central corneal thickness (CCT) affects GAT measurement. Many studies showed



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that patients with ocular hypertension (OHT) have thicker CCT and patients with normal-tension glaucoma (NTG) have thinner CCT.^[1,2] Hence, knowing the CCT may allow an estimate for the true IOP.

Corneal biomechanical properties also influence the result of IOP like CCT. The ocular response analyzer (ORA) is the device capable of determining in vivo biomechanical corneal properties. The ORA measures corneal hysteresis (CH) and corneal resistance factor (CRF). CH is a measure of the viscoelasticity of the cornea and the CRF is a measure of the overall resistance of the cornea. However, the ORA measures Goldmann correlated IOP (IOPg) and corneal compensated IOP (IOPcc).^[3] The ORA uses a non-contact air puff method to detect IOP. The IOPcc is accepted less influenced by corneal biomechanical properties and CCT.^[4]

The aim of our study is to compare the ORA parameters (CH, CRF, IOPg, and IOPcc) and IOP using GAT (IOPGAT) in newly diagnosed primary open-angle glaucoma (POAG), NTG, OHT, and normal eyes (N).

Materials and Methods

This retrospective, cross-sectional, and comparative clinical trial was performed in the glaucoma department of Beyoglu Eye Training and Research Hospital. The study was conducted in accordance with the tenets of the Declaration of Helsinki. Ethics committee approval was obtained from Health Sciences University Turkey Beyoglu Eye Training and Research Hospital. Written informed consent was obtained from all participants. One hundred and sixty-eight newly diagnosed patients with POAG, NTG, OHT, and age-matched, healthy eyes were recruited. Measurements were taken in glaucoma patients before starting antiglaucomatous therapy.

All of the participants underwent a comprehensive ophthalmologic examination that included corrected distance visual acuity through the Snellen chart, biomicroscopy, gonioscopy, and a dilated fundus examination using the 90-diopter lens. The CCT was measured using an ultrasound pachymeter (Pachette DGH 500; DGH Technology, Inc, Philadelphia, PA) over an undilated pupil and three measurements were taken and the average value recorded. The thickness of the retinal nerve fiber layer was measured with the Stratus optical coherence tomography (OCT) 3000. Visual field testing was performed using automated perimetry (30-2 Humphrey Visual Field Analyzer 750i; Humphrey Instruments, Dublin, California).

The GAT was used following the ORA to measure IOP. There

was at least 15 min interval between measurement of IOP by GAT and ORA. The IOP was measured with the patient seated by GAT after instillation of topical proxymetacaine 0.5% and fluorescein. Non-contact IOP and corneal biomechanical parameters were measured by an experienced clinician using the ORA Software 3.01 (Reichert, Inc., Buffalo, NY) while the patient was sitting comfortably in a chair. Three replicate measurements with ORA were acquired for each eye. Poor-quality waveforms were deleted and a new measurement was taken and the mean values of each parameter were used for statistical analysis. The clinician was masked in terms of groups.

Our ocular exclusion criteria were myopia or hyperopia (greater than +3 or -3 diopters), astigmatism (>2 diopters), contact lenses use, any topical and systemic steroid use, any systemic metabolic disease, any history of ocular disease, previous intraocular surgery or laser therapy, and any corneal abnormality affecting IOP measurements. However, ocular disease that could mimic glaucomatous visual field loss particularly congenital or acquired optic nerve diseases were excluded from the study.

The IOP values measured by GAT were taken into account when the groups were identified. IOP adjustments were made according to CCT.^[1]

Inclusion Criteria for the POAG Group

The following criteria were included in the study:

- IOP measured with GAT more than 22.0 mmHg with no anti-glaucomatous drugs
- Glaucomatous nerve head damage and optic nerve excavation associated with visual field defects by automated perimetry examinations, nerve fiber layer defects through OCT
- Open angle on gonioscopy.

Inclusion Criteria for the NTG Group

The following criteria were included in the study:

- IOP measured with GAT <21.0 mmHg with no anti glaucomatous drugs
- Glaucomatous nerve head damage, nerve fiber layer defects via OCT
- Optic nerve excavation associated with visual field defects and no neurological disease or fundus lesions associated with these defects
- Open angle on gonioscopy.

Inclusion Criteria for the OHT Group

The following criteria were included in the study:

- IOP measured with GAT more than 21.0 mmHg on two consecutive visits
- Absence of optic nerve head damage and visual field defects.

Inclusion Criteria for the Control Group

The following criteria were included in the study:

- Untreated GAT-IOP lower than 21.0 mmHg, healthy discs and no ocular pathologies
- No OCT or visual defects.

Statistical Analysis

Statistical analyses were performed with SPSS version 16.0 for Windows (SPSS, Chicago, IL, USA). Independent samples t-test, analyses of variance (ANOVAs), and Pearson correlation test were used for statistical analyses of the results. $P < 0.05$ was considered to be statistically significant.

Results

Sixty-three eyes of 40 patients (14 female/26 male) with POAG, 66 eyes of 39 patients (14 female/25 male) with NTG, 80 eyes of 45 patients (26 female/19 male) with OHT, and 85 eyes of 44 (26 female/18 male) normal controls were included in this study. Mean age of patients was 56.5 ± 9.9 years (36–80 years) in POAG group, 57.7 ± 9.7 years (30–74 years) in NTG group, 56.1 ± 9.9 years (31–76 years) in OHT group, and 54.2 ± 7.1 years (35–68 years) in normal group. No significant difference was observed between age between the groups ($p = 0.37$). The IOPGAT, IOPg, and IOPcc values in the groups are shown in Table 1.

There is significantly difference all pressure values in all groups using ANOVA method ($p < 0.001$). However, the difference was statistically significant in all groups except POAG and OHT groups using an unpaired t-test.

Table 1. Measured IOP values in the groups

	IOPGAT Mean \pm SD (mmHg) (min-max)	IOPg Mean \pm SD (mmHg) (min-max)	IOPcc Mean \pm SD (mmHg) (min-max)
POAG	27.0 \pm 5.3 (22–47)	27.3 \pm 7.1 (10–46)	27.3 \pm 7.3 (11–47)
NTG	17.0 \pm 2.8 (10–21)	17.8 \pm 4.6 (8–32)	18.5 \pm 4.6 (7–32)
OHT	25.5 \pm 3.2 (22–37)	26.06 \pm 4.8 (15–42)	25.3 \pm 5.2 (13–43)
N	15.5 \pm 3.3 (9–21)	16.4 \pm 4.0 (8–27)	16.2 \pm 3.8 (8–27)

POAG: Primary open angle glaucoma; NTG: Normal tension glaucoma; OHT: Ocular hypertension; N: Normal; SD: Standard deviation; IOP: Intraocular pressure; IOPGAT: IOP using Goldmann applanation tonometry; IOPg: Goldmann correlated IOP; IOPcc: Corneal compensated IOP.

Table 2. CH, CRF, and CCT values in the groups

	CH Mean \pm SD (mmHg) (min-max)	CRF Mean \pm SD (mmHg) (min-max)	CCT Mean \pm SD (μ m) (min-max)
POAG	9.2 \pm 2.1 (4–14)	13.0 \pm 2.3 (8–19)	567.5 \pm 44.5 (479–676)
NTG	9.9 \pm 1.6 (6–14)	10.7 \pm 1.7 (8–15)	553.9 \pm 35.0 (472–620)
OHT	10.1 \pm 2.0 (6–15)	13.3 \pm 1.9 (9–18)	576.7 \pm 35.5 (490–663)
N	10.9 \pm 1.4 (7–15)	11.1 \pm 1.7 (7–16)	558.9 \pm 41.3 (449–668)

POAG: Primary open angle glaucoma; NTG: Normal tension glaucoma; OHT: Ocular hypertension; N: Normal; CCT: Central corneal thickness; CH: Corneal hysteresis; CRF: Corneal resistance factor.

IOPcc was significantly higher compared with IOPGAT and IOPg ($p = 0.007$, $p = 0.005$). The IOPg was significantly higher compared with IOPcc in the OHT group ($p = 0.006$). IOPcc and IOPg were significantly higher compared with IOPGAT

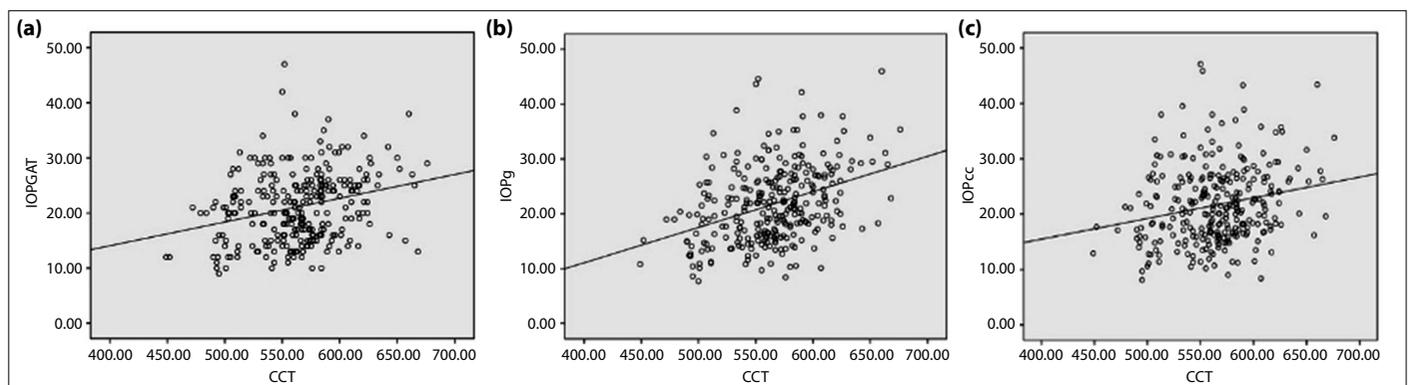


Fig. 1. (a) CCT- IOPGAT correlation. (b) CCT-IOPg correlation. (c) CCT-IOPcc correlation. IOPGAT: IOP using Goldmann applanation tonometry; CCT: Central corneal thickness; IOPg: Goldmann correlated IOP; IOPcc: Corneal compensated IOP.

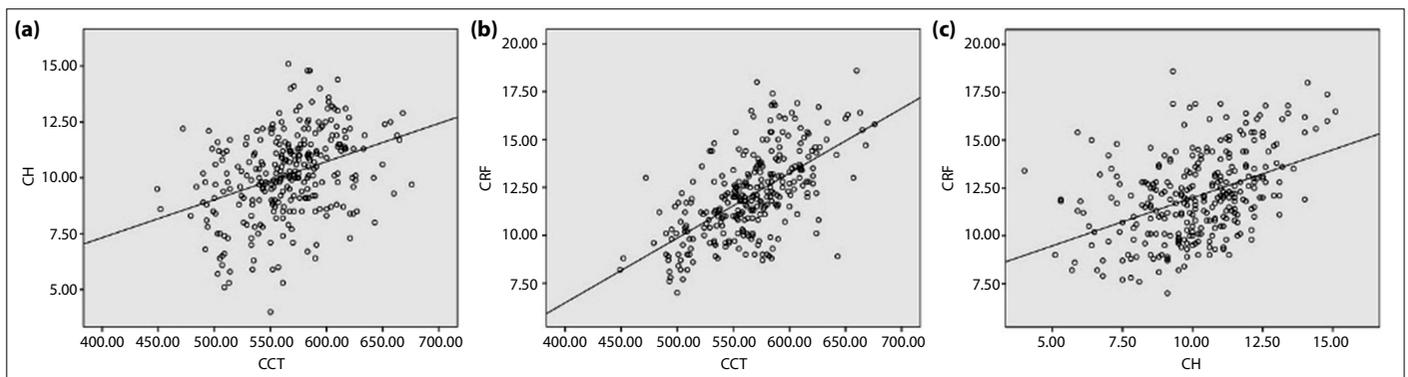


Fig. 2. (a) CCT-CH correlation. (b) CCT-CRF correlation. (c) CH-CRF correlation. CH: Corneal hysteresis; CCT: Central corneal thickness; CRF: Corneal resistance factor.

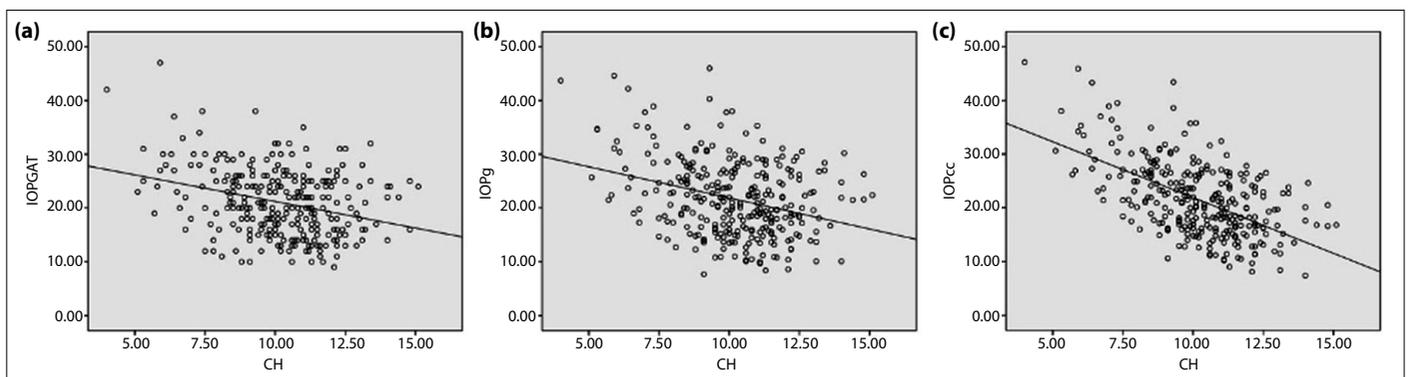


Fig. 3. (a) CH-IOPGAT correlation. (b) CH-IOPg correlation. (c) CH-IOPcc correlation. IOPGAT: IOP using Goldmann applanation tonometry; CH: Corneal hysteresis; IOPg: Goldmann correlated IOP; IOPcc: Corneal compensated IOP.

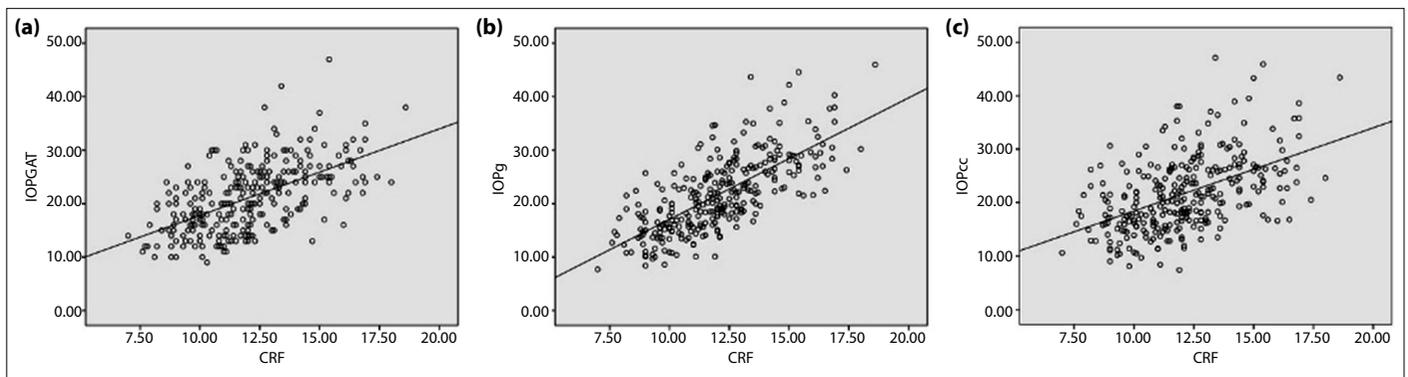


Fig. 4. (a) CRF-IOPGAT correlation. (b) CRF-IOPg correlation. (c) CRF-IOPcc correlation. IOPGAT: IOP using Goldmann applanation tonometry; CRF: Corneal resistance factor; IOPg: Goldmann correlated IOP; IOPcc: Corneal compensated IOP.

($p=0.039$, $p=0.012$).

Poor positive correlation was observed between CCT and IOPGAT, IOPg, and IOPcc ($r=0.27$, $r=0.37$, $r=0.21$, respectively, $p<0.001$ for all) (Fig. 1). There was no significant correlation between CCT and IOPcc -(IOPGAT) ($r=-0.065$, $p=0.443$).

The CH, CRF, and CCT values in the groups are shown in Table 2. There is significant difference all values between all of groups using ANOVA method ($p<0.001$). There was a positive correlation between CH, CRF, and CCT in all the groups. The correlation between CRF and CCT was significantly stronger

than CH and CCT ($r=0.61$, $r=0.35$, respectively, $p<0.001$ for all). The CH showed a positive moderate correlation with CRF ($p<0.001$, $r=0.43$) (Fig. 2). There was a significantly negative correlation between CH and IOPGAT, IOPg, and IOPcc in all the groups ($r=-0.30$, $r=-0.31$, $r=-0.56$, respectively, $p<0.001$ for all) (Fig. 3). The CRF showed strong positive correlation with IOPg and moderate correlation with IOPGAT and IOPcc ($r=0.71$, $r=0.57$, $r=0.49$, respectively, $p<0.001$ for all) (Fig. 4).

No significant correlation was observed between age and CCT, CRF whereas poor negative correlation was observed

between age and CH ($p=0.007$, $r=-0.20$). However, there was no significant correlation between age and IOPGAT, IOPg whereas there was poor positive correlation between age and IOPcc ($p=0.025$, $r=0.17$).

Discussion

The effects of the corneal parameters, especially CCT on the IOP measurement and risk of glaucoma have been investigated and currently, CCT is accepted as an important parameter for the diagnosis and follow-up of glaucoma. The OHT study found that thin cornea was a risk factor for the development of POAG.^[5] Latest studies have shown that, besides CCT, corneal biomechanics also play an important role in the diagnosis and treatment of glaucoma, especially in obtaining reliable IOP measurements.

Shah et al.^[6] have studied the relationship between CCT, CH, and CRF in normal subjects and found that there was a significant relationship between CRF and CH, with a strong correlation coefficient. However, the relationships between CH-CCT and CCT-CRF were significant, the correlation coefficients were moderate. The study demonstrated that CH and CRF increased with the increase of CCT. Similar to the literature, a positive correlation was observed between CH and CCT and CRF in our study. The correlation between CRF and CCT was found to be stronger than the correlation between CH and CCT. However, a moderate correlation was found between CH and CRF. In the study by Mangouritsas et al.,^[7] the relationship between CCT and CH was found to be stronger in non-glaucomatous eyes compared to glaucomatous eyes. They emphasized that it should be clarified whether the differences in corneal viscoelastic properties between POAG and non-glaucomatous eyes are primary or secondary to chronic raised IOP or to anti-glaucomatous treatment. The authors stated that if it is primary etiology, CH may be a biometric parameter for determining glaucomatous damage, just as the low CCT values are known to be a risk factor for glaucoma.

Ang et al.^[8] have found a statistically significant difference between POAG and NTG by means of CH values but did not find a statistically significant difference by means of CRF and CCT. They suggested that the alterations to the CH and CRF may not be structural risk factors for glaucoma but may occur as a result of chronic IOP elevation. The authors postulated that in POAG, chronic raised IOP may cause ocular hardness and rigidity, which in turn might cause an increase in CRF and a decrease in CH in the long term.

However, Grise-Dulac et al.^[9] have spotted statistically significantly lower CH and CRF values in the NTG group

compared to the control group. Thus, they proposed that glaucoma itself may be held responsible for the biomechanical changes in the corneas of the patients with NTG. The authors stated that the optic disc of eye with lower CH value is likely to be more sensitive to increases in IOP. They suggested that CH is a parameter which reflects the biomechanics properties of not just the cornea but the whole eye tissue. Similar to the previous studies, they have found that the CH values are lower in the POAG group compared to the control group. However, the CRF value was found to be higher compared to the NTG group. Many researchers state that the pathogenesis of POAG and NTG are different and that the pressure tolerable by the optic nerve in patients with NTG may be lower compared to patients with POAG.^[9] It was emphasized that under the same IOP, corneal resistance may be lower in NTG compared to POAG. When the OHT and NTG groups were compared, the IOPcc was found significantly lower in the NTG group. Although the CH values were similar between the two groups, the CRF values were significantly higher in the OHT group. It was hypothesized that high CRF values may be related to an absence of glaucomatous optic disc appearance.

In the study by Kaushik et al.,^[10] CH was found to be significantly lower in the POAG and NTG groups compared to the control group, whereas there was no significant difference between the OHT group and the control group. They postulated that the corneal viscous structure may be protecting the eye from the harmful oscillations of the IOP. The absence of glaucomatous damage despite high IOP was considered to be a result of high CH values in patients with OHT.

Sullivan-Mee et al.^[11] suggested that CRF is an independent distinguishing factor in the OHT and POAG groups and that CRF showed the average resistance against deformation. They postulated that more effort was spent for appplanation in corneas with higher CRF compared to corneas with low CRF, which, in turn, leads to higher levels of IOPGAT and IOPg in corneas with high CRF. They emphasized that higher IOP levels in OHT may harden the cornea and that CRF increased in their study as IOP increased. The CH values were found to be different for patients with and without glaucoma. CH is thought to affect the energy absorption of the cornea and buffer the fluctuations in the IOP. Thus, high-CH eyes are thought to have higher buffering capacity for long and short-term IOP increments compared to low-CH eyes. Conversely, if the cornea may not absorb the IOP increments adequately in low-CH eyes, IOP stress is increased in the lamina cribrosa and the peripapillary region. The authors suggest that the low energy absorption capacity of the cornea may be a risk factor for

the development of glaucomatous optic neuropathy. The CH and CCT are correlated; therefore, thick-CCT eyes have higher CH and higher IOP absorption abilities. In the OHT Study, the reduced risk of glaucoma in thick corneas was associated with the greater energy absorption capacity of the corneas of these eyes. In addition, they indicated that CH may be a parameter that predicts glaucoma development and progression.

To reduce age-related corneal variations in our study, we formed our groups so that there was no statistically significant difference between the groups in terms of mean age. We also included patients who did not receive any medical treatment, considering that in experimental studies prostaglandin analogs were demonstrated to harden the cornea by modifying the extracellular matrix.^[12] The lowest mean CCT in our study was found in the NTG group and the highest mean CCT was found in the OHT group. There was a significant positive correlation between CCT and CH and CRF. In accordance with the previous studies, we found significantly lower CH values in the POAG and NTG groups compared with the control group. The lowest CH values were found in the POAG group and the highest CH values were found in the OHT and control groups. Regarding these findings, we consider that the absence of glaucomatous damage despite high IOP in OHT may be related to high CH values.

In our study, there was a negative correlation between the IOP values (IOPGAT, IOPg and IOPcc) and CH. Although we may explain the low CH in the POAG group with this result, the high CH values in the OHT group despite high IOP values are in stark contrast. We believe that instead of a simple inverse relationship, there exists a complex relationship between CH and IOP that has yet to be explained. We found the highest CRF values in the POAG and OHT groups, and the lowest CRF values in the NTG and control groups. Regarding the positive correlation we found between CRF and IOP, we consider that the corneal hardening caused by high IOP leads to an increase in the CRF values in the POAG and OHT groups. In addition, when compared to POAG under the same IOP levels, low CRF values in the NTG group may be responsible for glaucomatous changes at the optic nerve head. Similarly, high CRF values in the OHT group, along with CH, may be related to the absence of changes in the optic nerve.

Lam et al.^[13] compared the ORA and GAT measurements and found that there was no statistically significant difference between IOPGAT, IOPg and IOPcc measurements. However, the differences between IOPg-IOPGAT and IOPcc-IOPGAT were found higher in patients with high IOPGAT

levels. The authors advised the physicians to be cautious during diagnosis in patients with suspected glaucoma because the ORA parameters may be high during measurement. The IOPGAT and IOPg were found to be related to CCT, while no relation was found between IOPcc and CCT. Because IOPcc was independent of CCT, the difference between IOPcc-IOPGAT was found to be negatively correlated with CCT. When CCT was around 580 μm , the difference was shown to approach zero, and for every 100 μm increase in CCT, the difference between IOPGAT-IOPcc increased by an average of 1.3 mmHg. In healthy young people, the IOPg and IOPcc measurements were similar to IOPGAT.

Gungor et al.^[14] compared IOP measurements with the noncontact tonometer that uses the same formula as the ORA, and GAT in healthy eyes and to assess the effect of CCT. The IOPcc and IOPg were significantly higher than IOPGAT measurements. Furthermore, IOPcc was significantly higher than IOPg. They found that both IOPg and IOPGAT were significantly associated with CCT but IOPcc was not statistically significant. They claimed that IOPcc is not affected by the corneal factors and IOPcc may be an evaluation factor in glaucoma examination.

Likewise, Medeiros and Weinreb did not find a relationship between IOPcc and CCT in single and multivariate analysis. There was no statistically significant difference between IOPGAT and IOPcc but it was shown that the difference between them was affected by CCT. They found that IOPGAT was higher in thick corneas than IOPcc; however, it tended to be less in thin corneas. There was no relationship between IOP level and IOPcc-IOPGAT difference. In multivariate analysis, IOPGAT was found to be correlated with CRF, but no correlation existed between IOPcc and CRF. They suggested that CRF showed the total effect of CCT, tissue material properties and corneal curvature. They indicated that IOPcc was not affected by CRF. Copt et al.^[1] have classified 31% of NTG patients as POAG and 56% of OHT as normal, when they corrected the IOP readings according to CCT. Medeiros and Weinreb claimed that misclassifications may be minimized by taking IOPcc into account, because IOPcc is not affected by corneal tissue properties.^[4]

Morita et al.^[15] have compared the IOP measurements with dynamic contour tonometer and ORA in patients with NTG, and IOPcc was found significantly higher than all other parameters in the NTG group. They stated that IOPcc may be a valuable measurement method in this patient group because it is not affected by CCT and corneal tissue properties. In most studies, the results of the IOPGAT, IOPg and IOPcc measurements are either similar, or IOPcc is shown to

be slightly higher than IOPGAT. In our study, the IOPcc results were found to be higher than IOPGAT in all groups except the OHT group. However, the difference between IOPcc-IOPGAT was statistically significant only in the NTG and the control groups. We found a weak positive correlation between the CCT and the IOPGAT, IOPg, and IOPcc. The strongest correlation we found was between CCT-IOPg and the weakest correlation we found was between CCT-IOPcc. These findings are in line with the previous studies, and we can say that IOPcc is less affected by CCT compared to other measurement results. However, in our study, we could not find a statistically significant relationship between CCT and IOPcc-IOPGAT difference. In the NTG group, IOPcc was found to be significantly higher than other measurement methods. We consider that IOPcc may be a valuable diagnostic and follow-up method in this group because it is less affected by CCT and corneal biomechanical properties.

The major limitation of our study is that it is a retrospective and nonrandomized design. We include both eyes of some patients in the study and this may lead to being a high correlation probability between the measurements taken from the right and left eyes of the same patient.

Conclusion

We compared the corneal biomechanical properties of POAG, OHT, NTG, and healthy eyes using ORA in this study. CH was found lower in the POAG and NTG groups compared to OHT and healthy eyes. In contrast, the highest CRF values were found in patients with POAG and OHT. A significant negative relationship was found between IOPGAT, IOPg, IOPcc, and CH. On the other hand, a significant positive relationship was found between CCT and CH and CRF. Further studies with more number of patients will help distinguish the relationship between the etiopathogenesis of glaucoma and the biomechanical properties of the cornea.

Ethics Committee Approval: This study was approved by Beyoglu Eye Training and Research Hospital Ethics Committee (date: 27.02.2018; number: 13).

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept: D.T.S., C.A.; Design: D.T.S., C.A., B.S., B.B.; Supervision: B.S., B.B.; Data Collection and/or Processing: D.T.S., C.A., B.S.; Literature Search: B.B.; Writing: D.T.S., C.A., B.B.; Critical Reviews: D.T.S., C.A., B.S., B.B.

Conflict of Interest: None declared.

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