Comparison of ocular response analyzer parameters in primary open angle glaucoma and exfoliative glaucoma patients

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Aim: We sought to identify differences in the following measures of the ocular response analyser (ORA) between primary open angle glaucoma (POAG) and exfoliative glaucoma (EXG) patients: Corneal hysteresis (CH), corneal resistance factor (CRF), corneal-compensated intraocular pressure (IOPcc) and Goldmann-correlated intraocular pressure (IOPg). We also sought to relate these ORA measures with central corneal thickness (CCT). Materials and Methods: This cross-sectional study was conducted on a total of 162 individuals (46 EXG patients, 66 POAG patients and 50 healthy subjects without any ocular and systemic disease). ORA measurements were performed, and a minimum of three readings were obtained from each test subject. Groups were compared according to their ORA parameters. Results: The mean CH levels of the EXG, POAG and healthy subjects were 7.6 ± 2.1, 9.1 ± 1.9 and 9.6 ± 1.7 mmHg, respectively. CH was significantly lower in the EXG patients compared to the other groups (P < 0.001). The mean CRF levels of the EXG, POAG and healthy subjects were 9.0 \pm 2.0, 10.1 ± 1.7 and 9.8 ± 1.8mmHg, respectively. CRF levels in the eyes of the EXG patients were significantly lower compared to those of either the POAG patients (P = 0.005) or the healthy subjects (P = 0.03), but there was no significant difference in CRF levels between the POAG patients and the healthy subjects (P = 0.59). There was a significant positive correlation between CH and CCT in the EXG patients and healthy subjects (P < 0.001), but this correlation was not present in the POAG patients (P = 0.70). Conclusions: In this study, CH and CRF were found to be significantly reduced in the eyes of EXG patients compared to both the POAG patients and healthy subjects. Reduced CH in EXG patients might result in decreased support of peripapillary scleral structure and increased damage to the optic nerve during IOP increase.

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Although the pathogenesis underlying glaucoma is not fully understood, it is clear that intraocular pressure (IOP) remains the most important modifiable risk factor. [1,2] However, new studies have shown that reduced central corneal thickness (CCT) is also a strong risk factor for glaucoma pathogenesis [3] and, importantly, that CCT appears to be positively correlated with IOP. [4] The effects of corneal rigidity and thickness on IOP measurements and glaucoma pathogenesis have been reported in recently published studies. [5,6] These studies demonstrated that corneal rigidity directly affects the accuracy of IOP measurements and, furthermore, that corneal biomechanical properties are likely related to glaucoma progression and may reflect optic nerve head resilience capacity against IOP increase. [7]

Corneal biomechanical properties likely influence the results of ocular measurements and may be relevant when diagnosing and managing ocular pathologies. The Ocular Response Analyzer (ORA) has recently been introduced to compensate for the corneal effects on IOP measurements by providing new measurements of corneal tissue properties.

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The ORA measures corneal hysteresis (CH), which is a measure of the viscous dampening properties of the cornea, and the corneal resistance factor (CRF), which is a measure of overall resistance of the cornea. ^[8] The ORA utilises a dynamic air puff and electro-optical system to detect inward and outward corneal bends while measuring pressure values at each point. The average of these two pressure values is the Goldmann-correlated IOP (IOPg). The corneal-compensated IOP (IOPcc) represents the IOP that is less influenced by corneal properties.

In this set of studies, we sought to identify differences in ORA measures (CH, CCT, IOPcc and IOPg) between POAG and EXG patients and to determine whether any of these parameters were directly related to one another.

Materials and Methods

Experimental group selection

This observational cross-sectional study was conducted on a total of 162 individuals (46 EXG patients, 66 POAG patients and 50 healthy subjects without any ocular or systemic disease). The experimental groups were recruited among patients who had been diagnosed with POAG or EXG and had received two or more regular follow-up visits at the Glaucoma Unit of the Ulucanlar Eye Research and Training Hospital. The control group was composed of healthy subjects without any systemic or ocular diseases. The intraocular pressures, optic disc measurements and retinal nerve fiber layer thicknesses of all subjects in the control group were within normal limits. Patients

with any corneal pathologies, systemic diseases (diabetes mellitus, hypertension, autoimmune diseases, etc.), significant refractive errors, ocular hypertension, dense cataracts that made examination of the optic disc impossible or histories of previous ocular surgery, laser intervention or ocular trauma were not included in the study. All EXG patients met the following criteria: Open drainage angles upon gonioscopy, glaucomatous optic disc changes (with no secondary cause), and clinical occurrence of biomicroscopically detectable exfoliation material at the pupillary border or on the anterior capsule after pupillary dilatation with 1.0% tropicamide. The inclusion criteria for the POAG patients were open drainage angles on gonioscopy, glaucomatous visual field defects and no secondary cause of glaucomatous optic disc changes. All glaucomatous patients had typical glaucomatous visual field defects that were confirmed with white-on-white automated 24- to 2 or 30 to 2 Humphrey visual field tests. The patients of all groups were above the age of 18 and had best-corrected visual acuities of 20/40 or better. All procedures conformed to the tenets of the Declaration of Helsinki. An ethical committee approved the study, and informed consent was obtained from each individual prior to the initiation of the study. All participants underwent a complete ocular examination. Thorough medical and topical drug histories were obtained to ensure that each individual met all of the inclusion criteria of the study. Uncorrected and best-corrected visual acuities were determined with Snellen charts, and experienced ophthalmology specialists performed all slit-lamp biomicroscopic, gonioscopic, goldmann applanation tonometry and fundus examinations.

ORA measurements

CH and CRF were measured using an Ocular Response Analyser (ORA; Reichert Ophthalmic Instruments, Depew, NY). ORA measurements were performed prior to any contact procedures and/or pupillary dilatation to eliminate the possible side effects of these procedures on the corneal biomechanical properties. A minimum of three and a maximum of four readings were obtained consecutively in each eye. Unreliable atypical signals (waveform scores below 4.0) were excluded and highest quality readings according to waveform scores were selected for analyses. After applying one drop of topical 0.5% proparacaine HCl (Alcaine; Alcon Laboratories, UK), CCT was measured using the ORA-attached handheld ultrasonic pachymeter.

Statistical analyses

Statistical analyses were performed with SPSS version 15.0 for Windows (SPSS Inc. Chicago. IL). Data was presented as the

mean values \pm the SDs, and P = 0.05 was considered statistically significant. Independent samples t test, Mann-Whitney U test, Tukey's HSD tests, analyses of variance (ANOVAs) and Pearson/Spearman's correlation tests were used for statistical analyses of the results.

Results

A total of 162 eyes of 162 patients (1 eye per patient) were included in the study. The demographic data and baseline ocular characteristics of the participants were summarized in Table 1. The mean age of the EXG patients was significantly greater than that of the control and POAG patients (P < 0.001). Moreover, the mean age of POAG patients was also significantly greater than that of the control subjects (P = 0.002). The mean IOP-GATs of the EXG and POAG patients were significantly higher than that of the control patients (P = 0.04 and P = 0.005, respectively), but the IOP-GATs were not different between the EXG and POAG groups (P = 0.83). The mean CCT level of the POAG patients was higher than that of the other groups, but the only significant difference was between the POAG and EXG patients (P = 0.04).

Intergroup comparisons of the ORA measurements revealed numerous differences, which were illustrated in Table 2. The mean CH levels of the EXG, healthy and POAG patients were 7.6 ± 2.1 mmHg, 9.1 ± 1.9 mmHg and 9.6 ± 1.7 mmHg, respectively. CH was markedly lower in the EXG patients compared to the other groups (P < 0.001). The CH levels of the POAG patients were also lower than those of the healthy subjects, but this result did not reach significance (P = 0.46). The mean CRF levels of the EXG, POAG and healthy subjects were 9.0 ± 2.0 mmHg, 10.1 ± 1.7 mmHg and 9.8 ± 1.8 mmHg, respectively. The mean CRF levels were also markedly lower in the EXG patients than POAG and healthy subjects (P = 0.03 and P = 0.005, respectively). But there was no significant difference between the POAG patients and the healthy controls (P = 0.59). The box-and-whisker plots in [Figs. 1 and 2] illustrate the comparisons of CH and CRF (median and interquartile ranges are shown) between the EXG patients, POAG patients and healthy subjects. The mean IOPcc levels of the EXG, POAG and healthy subjects were 21.8 ± 7.8 mmHg, 19.6 ± 5.1 mmHg and 17.2 ± 3.6 mmHg, respectively. The mean IOPg levels of the EXG, POAG and healthy subjects were 18.8 ± 7.5 mmHg, 18.1 ± 4.7 mmHg and 15.8 ± 3.6 mmHg, respectively. The differences in both IOPcc and IOP, between groups were statistically significant (P < 0.05), with the exceptions of the differences between the EXG and POAG patients (P = 0.14 and P = 0.99 for IOPcc and IOP_o, respectively). The relationships between the ORA parameters were also analysed within each

Table 1: Demographic data and baseline ocular characteristics of the participants

	EXG	POAG	Control	P ¹	P ²	P ³	
Gender (n-%)							
Male	25 (54.3%)	22 (33.3%)	18 (36%)				
Female	21 (45.7%)	44 (66.7%)	32 (64%)				
Age (year)	68.6±8.5	58.9±10.7	51.2±11.6	<0.001	0.002	< 0.001	
IOP (GAT) ^a (mmHg)	16.5±4.1	16.4±4.2	14.0±3.2	0.04	0.005	0.83	
CCT⁵(µm)	535.7±43.0	550.4±36.3	537.3±38.5	0.23	0.52	0.04	

a: Intraocular pressure with Goldmann applanation tonometry, b: Central corneal thickness, P1: Significance between control and exfoliative glaucoma group,

P2: Significance between control and primary open angle glaucoma group, P3: Significance between primary open angle glaucoma and exfoliative glaucoma group

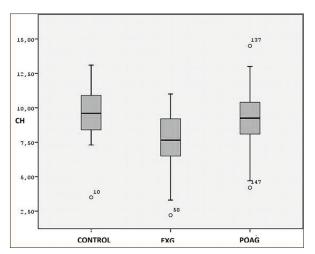


Figure 1: Box-and-whisker plots of the corneal hysteresis (CH) in the control group and experimental groups. The middle line in each box indicates the median. The bars indicate the range of the results. The height of the box indicates the upper and lower quartiles. The circles indicate the participants with outlier values that exceeded 1.5 times the first or the third interquartile range

Table 2: Intergroup comparisons of ORA parameters

(mmHg)	EXG	POAG	Control	P ¹	\mathbf{P}^2	P ³
IOPcc*	21.8±7.8	19.6±5.1	17.2±3.6	0.001	0.01	0.14
IOPg**	18.8±7.5	18.1±4.7	15.8±3.6	0.04	0.02	0.99
CH***	7.6±2.1	9.1±1.9	9.6±1.7	< 0.001	0.46	< 0.001
CRF****	9.0 ± 2.0	10.1±1.7	9.8±1.8	0.03	0.59	0.005

^{*}Cornea-compensated intraocular pressure, **Goldmann-correlated intraocular pressure, ***Corneal hysteresis, ****Corneal resistance factor,

group. There were positive correlations between CH and CCT levels in the EXG patients and healthy controls (P < 0.001), but no correlation was found in the eyes of the POAG patients (P = 0.70). There were also positive correlations between CRF and CCT of the EXG patients (P = 0.008) and the healthy controls (P < 0.001); however no correlations were found in the POAG patients (P = 0.08). There were negative correlations between the CH and IOPcc (P < 0.001) and positive correlations between the CRF and IOPg in all groups (P < 0.001). CH and IOPg were not related in healthy individuals (P = 0.89) and were inversely related in the EXG and POAG patients (P = 0.005 and P = 0.05, respectively). CRF and IOPcc were not related in the POAG and control groups (P = 0.07 and P = 0.46, respectively) but were positively correlated in the EXG patients (P = 0.01). The CH and CRF were also positively correlated in all groups (P = 0.02 in the EXG group and P < 0.001 in the POAG and control groups). The IOPg and IOPcc were directly related in all groups (P < 0.001). The correlation coefficients of the ORA parameters for all groups were outlined in Table 3.

The mean number of glaucoma medications used by the EXG group was 1.91 ± 0.86 and the POAG group used 1.81 ± 0.80 medications. In total, 29 EXG patients (63%) and 36 POAG patients (54%) were using prostaglandin analogues. The mean

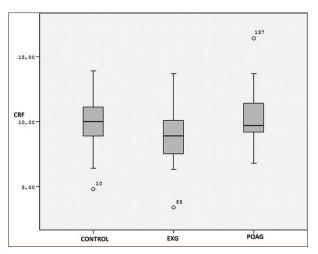


Figure 2: Box-and-whisker plots of the corneal resistance factors (CRF) of the control and study groups. The middle line in each box indicates the median. The bars indicate the range of the results. The height of the box indicates the upper and lower quartiles. The circles indicate the participants with outlier values that exceeded 1.5 times the first or the third interquartile range

durations of glaucoma were 3.24 years in the EXG group and 2.93 years in the POAG group. There were no significant differences between the glaucoma groups regarding the numbers of glaucoma medications, prostaglandin analogues use and the duration of glaucoma (P > 0.05).

Discussion

CH, also known as the corneal damping response, is thought to primarily reflect corneal viscoelasticity. [8,9] It has previously been shown that low CH values are more likely to be associated with progressive glaucomatous changes more than changes in CCT because CH provides information about the eye responsiveness to mean IOP or changes in IOP. [10] Other studies have also concluded that reduced CH could be an important marker of increased susceptibility of the optic nerve to glaucomatous damage. [11] Therefore, low CH levels likely increase the risk for developing glaucomatous optic neuropathy. [12]

In this study, we compared the CH levels of patients with two different types of glaucoma (EXG and POAG) and healthy subjects. To the best our knowledge, this is the first report of a comparison between CH in EXG and POAG patients. Previous work has shown that CH is significantly lower in glaucomatous patients than in with healthy subjects. [9,13] Studies that have examined POAG patients have found that CH levels are lower in these patients than in healthy subjects[13] and that CH is significantly lower in patients with exfoliative eyes than those without.[14] In the current study, CH was markedly decreased in EXG patients compared with POAG patients and healthy controls (P < 0.001), and CH levels were only slightly lower in the eyes of POAG patients compared to healthy controls (P = 0.46). It is well known that EXG has a more serious clinical course and that the progression of optic neuropathy in EXG is more rapid than in POAG.[14] Deposition of exfoliation material might itself change biomechanical properties of tissues; for example, the deposition of exfoliation material in zonular fibres may lead to instability of the zonules.[14,15] Cankaya et al. found

P1: Significance between control and exfoliative glaucoma group,

 $[\]ensuremath{\mathsf{P}}^2\!\!:$ Significance between control and primary open angle glaucoma group,

P³: Significance between primary open angle glaucoma and exfoliative glaucoma group

Table 3: Correlations among ORA parameters

	EXG	POAG	Control
CH*** and CCT [†]	P<0.001 r=0.585	<i>P</i> =0.70 <i>r</i> =0.047	P<0.001 r=0.588
CH*** and CRF****	<i>P</i> =0.02 <i>r</i> =0.331	<i>P</i> <0.001 <i>r</i> =0.648	P<0.001 r=0.808
CH*** and IOPcc*	<i>P</i> <0.001 <i>r</i> = −0.625	<i>P</i> <0.001 <i>r</i> = −0.648	<i>P</i> <0.001 <i>r</i> = −0.500
CH*** and IOPg**	<i>P</i> =0.005 <i>r</i> = -0.405	P=0.05 r = -0.236	<i>P</i> =0.89 <i>r</i> =0.019
CRF**** and IOPcc*	<i>P</i> =0.01 <i>r</i> =0.360	P=0.07 r=0.221	<i>P</i> =0.46 <i>r</i> =0.106
CRF*** and IOPg**	<i>P</i> <0.001 <i>r</i> =0.576	<i>P</i> <0.001 <i>r</i> =0.535	P<0.001 r=0.604
CRF**** and CCT†	<i>P</i> =0.008 <i>r</i> =0.385	P=0.08 r=0.217	P<0.001 r=0.710
IOPg** and IOP cc*	<i>P</i> <0.001 <i>r</i> =0.954	<i>P</i> <0.001 <i>r</i> =0.925	P<0.001 r=0.856
IOP (GAT) ^{††} and IOPg**	<i>P</i> <0.001 <i>r</i> =0.769	<i>P</i> <0.001 <i>r</i> =0.736	P<0.001 r=0.745
IOP (GAT) ^{††} and IOPcc*	<i>P</i> <0.001 <i>r</i> =0.501	<i>P</i> <0.001 <i>r</i> =0.696	P<0.001 r=0.501

*Cornea-compensated intraocular pressure, ***Corneal hysteresis, ****Corneal resistance factor, †Central corneal thickness, †Intraocular pressure measured with Goldmann applanation tonometry

that corneal visco-elasticity is decreased in exfoliative eyes compared to healthy eyes. [14] Ocular tissues are coated with a sclerocorneal sheet and the sclera and cornea are essentially composed of similar extracellular matrix constituents. Changes in corneal viscoelasticity might reflect the viscoelasticity of the peripapillary scleral tissues. [14] It is reasonable to speculate that decreased viscoelasticity of the corneoscleral sheet of the eyes due to exfoliation might reduce scleral biomechanical damping capacity during IOP fluctuations and resulting in increased pressure on the optic nerve. [16] The lower CH observed in exfoliative glaucoma patients may result in decreased support of the laminar and peripapillary scleral structure for the optic nerve during increased IOP. This speculation may explain why the progression of optic neuropathy in EXG eyes is more rapid than that in POAG eyes when IOP levels are similar.

It had been shown that reduced CH is directly related to visual field deterioration in patients with glaucoma. [10,12] However, in these studies, CH levels were measured during follow-ups or after visual field deterioration had occurred. Based on these studies, we were unable to determine whether CH was a cause or result of glaucomatous progression. Lower CH might be the result of glaucomatous progression or hypotensive therapy.[17,18] Mederios and colleagues conducted a prospective study that examined the relationship between CH and glaucomatous progression.^[19] These authors acquired the baseline CH levels of patients and performed follow-ups of those patients to determine the degrees of visual field deterioration. According to this study, lower CH is a risk factor for glaucomatous visual field deterioration. Cankaya et al. found that eyes with exfoliation exhibit lower CHs when compared to healthy eyes and that CH levels are significantly lower in EXG patients than in patients with exfoliation without glaucoma. [14] Lower CH might be a risk factor for glaucomatous progression in EXG patients. It is not known whether CH is an independent risk factor for glaucomatous progression in EXG patients. Mederios et al. found a significant relation between IOP and CH and these authors suggested that the effect of higher IOP levels on visual field deterioration is significantly increased in patients with lower CH.[19]

It has been shown that IOP is directly related to CH and that patients receiving hypotensive treatments have lower CH levels.^[18] We found a significant relationship between IOP and CH, which suggests that the effect of IOP on the rate of

glaucoma progression is dependent on CH. This finding is similar to those of other investigations. [19,20] Further prospective and longitudinal studies with multivariate models should be performed to prove that CH is an independent risk factor.

Similar to CH levels, the mean CRF levels were the lowest in the EXG eyes. There was a significant difference in CRF levels between the EXG and healthy eyes. A previous study also reported that CRF levels are reduced in in EXG patients, but the difference was not statistically significant in that study. [14] Decreased CRF, which is a measure of overall corneal rigidity, in EXG patients may also contribute to the more rapid progression of optic neuropathy in these patients.

Previous work has found a positive correlation between CH and CCT.[21] It is known that corneas with thicker CCTs will have greater CHs, [22] and it is also known that CCT and CH are strongly related in non-glaucoma patients but only moderately related in glaucoma patients.[13] As in other recent studies, we found a positive correlation between CCT and CH in healthy subjects and EXG patients. However, this correlation was not significant in the POAG patients, which confirms previous work on POAG patients or suspected POAG patients.[10] Mean CCT levels were greater in POAG patients in our study, and this elevation in CCT level might led to increased CH level. Increased CH levels due to greater CCT in POAG patients might explain why there was no significant correlation between the healthy subjects and the POAG patients in terms of CH levels. The lack of a significant relationship between CH and CCT in the POAG patients might also be a result of IOP-lowering therapy. It has been shown previously that partial recovery of CH is observed after lowering IOP in chronic primary angle closure glaucoma patients.[18] We hypothesise that POAG patients might have lower CHs and higher IOP levels and that CH levels might begin to increase after the initiation of antiglaucomatous therapy to lower IOPs. The significantly lower CH levels of the EXG patients despite their reduced IOPs might be a result of the deposition of exfoliative material in corneoscleral tissues. This hypothesis should be further investigated in a longitudinal prospective study with age- and CCT-matched glaucoma subjects.

As with CH, there were significant relationships between CCT and CRF in the healthy subjects and EXG patients. Accurate IOP measurement is essential for the proper diagnosis

of glaucoma. It is evident that IOP measurements acquired via GAT are influenced by CCT.^[4] IOP measurements with GAT in patients with low CH values may be greatly underestimated. It can also be assumed that correcting IOPs according to CHs may be more accurate and could alter patients' diagnoses of glaucoma. There is a significant correlation between IOPg and CH in glaucoma patients, but this relationship is not significant in healthy subjects.^[9] In our study, we confirmed this finding and demonstrated the positive relationships between IOPg and CH in both EXG and POAG patients, and failed to find this relationship in healthy subjects. There were also significant relationships between CH and IOPcc in all groups as IOPcc is calculated from CH measurements by the ORA device.

One of the major limitations of our study is the significant difference in the age ranges of the groups. The mean age of the EXG patients was 68.6 ± 8.5 , the POAG patients averaged 58.9 ± 10.7 years old, and the healthy control group averaged 51.2 ± 11.6 years old. Corneal stiffness has been shown to increase with age due to changes in the collagen fibril properties of the cornea.^[23-25] Therefore, the aging process may have influenced our measurements of the biomechanical properties of the corneas, and corneal stiffness may have contributed to the decreased CH observed in the eyes of EXG patients. There are conflicting reports about the relation between CH and age in the literature. Kirwan et al. examined the mean CH levels of children with congenital glaucoma and healthy children. These authors found that the CH levels of the healthy children were similar to those of adults and stated that there might not be any correlation between CH and age. [26] In contrast, Kida et al. found that aging can cause significant changes in the biomechanical properties of the cornea and decrease CH and CRF levels in the cornea.[27] Another study showed that the stiffness of the cornea increases considerably with age and this change may be related to the non-enzymatic cross-linking of stromal collagen fibrils in the cornea. [28] Another limitation of this study is the risk that ocular medications affected the biomechanical properties of the corneas. The majority of our patients had been taking different types of glaucoma medications, and more research must be performed to determine how these medications may have ultimately affected our ORA measurements. Our patient groups exhibited a difference in CCT levels that may have affected the measurements of CH and CRF. Several studies have shown that CCT is positively correlated with CH,[21,22] and this relationship highlights another limitation of our study. In our study, we measured the biomechanical properties of the corneas of participants during a follow-up period while they were receiving hypotensive treatment. Therefore, we cannot actually determine whether lower CH levels were the cause or result of the rapid progression of glaucoma in EXG patients because we do not know the baseline CH levels. Therefore, a prospective study using age- and CCT-matched glaucoma patients with a longer follow-up period should be performed.

Finally, our findings suggest that corneal viscoelasticity is reduced in EXG eyes compared to POAG eyes. Altered corneal viscoelastic properties may explain the rapid progression of optic neuropathy in EXG eyes, and further studies should be performed to confirm this hypothesis. Further, longitudinal prospective studies are needed to determine the changes in visual field defects relative to baseline levels in patients with different corneal biomechanical properties to prove that

lower CH is associated with a more rapid progression of optic neuropathy in eyes with EXG than those with POAG.

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