The Role of Ocular Response Analyzer in Differentiation of Forme Fruste Keratoconus From Corneal Astigmatism

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Purpose: To determine the diagnostic accuracy of corneal biomechanical factors in differentiating patients with forme fruste keratoconus (FFKC) from astigmatic and normal cases.

Methods: A total of 50 eyes with FFKC, 50 with astigmatism and 50 normal eyes, were included in this study. All patients had a detailed ophthalmologic examination including slit-lamp evaluation, Goldmann tonometry, indirect fundoscopy, topography by Scheimpflug imaging biomicroscopic anterior and posterior segment examination, and corneal biomechanical and intraocular pressure evaluation with ocular response analyzer (ORA).

Results: All topographic findings were statistically significant among the three groups ($P>0.05$). Although there was no statistically significant difference in the corneal-compensated intraocular pressure (IOPcc) among the three groups, the Goldmann-correlated intraocular pressure (IOPg), corneal hysteresis (CH), and corneal resistance factor (CRF) were statistically significantly lower in the FFKC group, compared with the other groups ($P<0.001$). There were no statistically significant difference in the IOPg, CH, and CRF between astigmatism and control groups ($P=0.99$, 0.79, and 0.86, respectively). The area under the receiver operating characteristic (AUROC) curve was greater than 0.85 for IOPg (0.80), CH (0.85), and CRF (0.90) for discriminating between FFKC and controls; whereas the AUROC was greater than 0.85 for IOPg (0.80), CH (0.79), and CRF (0.85) for discriminating between FFKC and astigmatism groups.

Conclusion: Based on our study results, in differentiation of patients with FFKC from normal control cases or astigmatic patients, corneal biomechanical parameters play a role particularly in patients with suspicious results. We suggest using ORA in combination with corneal topography for better and more accurate diagnosis of FFKC.

Key Words: Corneal biomechanical properties—Corneal hysteresis—Forme fruste keratoconus—Anterior segment parameters—Astigmatism—Ocular response analyzer.

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Keratoconus is a progressive, noninflammatory, usually bilateral corneal ectasia characterized by corneal thinning and protrusion.[1] Most of the cases can be diagnosed with corneal topography because of the presence of a typical topographic pattern.[2] However, in some cases, mild changes in keratoconic corneas cannot be detected using the most sophisticated topographic modalities. The main problem is the detection of these subclinical forms that may be indicative of early stage keratoconus. Although there is no establish consensus on the definition of this condition, it refers to suspicious keratoconus or forme fruste keratoconus (FFKC).[3,4] Although FFKC often has a keratoconus-like asymmetric bow tie pattern as assessed by corneal topography, astigmatic eyes may also have this pattern rather than symmetric pattern.[5] Therefore, the corneal steepening and astigmatism formation may be found in the topographic maps of both FFKC and astigmatism cases. Although all astigmatic patients do not have keratoconus, distinction of patients with FFKC and astigmatism may be challenging.[6] In refractive surgery, diagnosing patient with FFKC is critical, as these patients are at risk of ectasia.[7–9] In addition, early diagnosis of keratoconus is essential in follow-up and treatment of these patients.[3]

Ocular response analyzer (ORA) (Reichert Ophthalmic Instruments, Buffalo, NY) is a noninvasive device that measures corneal biomechanics and strength. It is used to determine the corneal biomechanical properties in vivo, through air pulse pressure to the central cornea with inward and outward movements.[10,11] In particular, pathologies such as keratoconus characterized by weakened corneal structure have shown to impair corneal biomechanics.[12–14] Because keratoconus is a progressive disease, biomechanical properties of corneas with FFKC may also show early additional diagnostic clues. In addition, the data about the role of ORA in differentiation of FFKC from normal or astigmatic eyes are limited in literature.

In this study, we aimed to determine the diagnostic accuracy of corneal biomechanical factors in differentiating patients with FFKC from astigmatic and normal cases.

MATERIALS AND METHODS

In this prospective study, a total of 150 eyes of 150 patients including, 50 with FFKC, 50 with astigmatism, and 50 normal eyes, between November 2015 and July 2016 at Bagcilar Education and Research Hospital, Istanbul, Turkey, were investigated. The study was approved by the local ethics committee and was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from each participant.

In this study, three groups (astigmatic, FFKC, and control) were compared. The patients having a topographic cylindrical value of greater than 0.75 diopters in topographic analysis were included in the astigmatism group. The patients who were diagnosed with "suspicious keratoconus" (defined as an anterior asymmetry index [SIf]

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TABLE 1. *Topographic Findings of the Subjects*

	FFKC Group (n:50), Mean±SD	Astigmatism Group (n:50), Mean±SD	Control Group (n:50), Mean±SD	P[a]
Thinnest point (mm)	476.9±29.25	530.3±35.04	552.46±32.34	<0.001
CCT (mm)	488.66±30.46	556.42±38.31	579.72±37.62	<0.001
Kmax (D)	48.05±1.77	47.13±2.16	44.13±1.31	<0.001
avgK (D)	44.47±1.21	44.72±1.97	42.98±1.17	<0.001
Cyl (D)	2.27±1.45	2.6±1.05	0.45±0.19	<0.001
SIf	1.8±0.74	0.70±0.45	0.33±0.26	<0.001
SIb	0.53±0.28	0.13±0.08	0.10±0.07	<0.001

[a] One-way ANOVA and post hoc Tukey test.

CCT, central corneal thickness; Cyl, topographic cylindrical value; FFKC, forme fruste keratoconus; avgK, average keratometry value; Kmax, maximum keratometry value; SIb, symmetry index back; SIf, symmetry index front.

of >0.50 and/or a posterior asymmetry index [SIb] of >0.30 in combination with corneal thinning) with the topography device, those having mild steepening on topography, and no clinical signs of keratoconus such as Vogt striae, Fleischer rings, and ruptures in Bowman were included in the FFKC group. Normal eyes were selected from the patients who were admitted to the ophthalmology department for routine controls without any symptoms and who had completely normal topographic results. Exclusion criteria were as follows: corneal scarring or severe dry eye, a history of corneal surgery, or pregnancy or breastfeeding during the course of the study.

All patients had a detailed ophthalmologic examination including biomicroscopic anterior and posterior segment examination, topography by Scheimpflug imaging (Sirius, Costruzione Strumenti Oftalmici, Florence, Italy), corneal and intraocular pressure (IOP) evaluation using a biomechanical waveform analysis device (Ocular Response Analyzer, software version 1.02, Reichert, Inc.), and Goldmann tonometry.

Anterior segment parameters were obtained using a rotating Scheimpflug camera, Sirius, a topography device consisting of a combination of two rotating Scheimpflug cameras, and a Placido disk. All measurements were in compliance with the manufacturer's instructions by a single trained examiner. Maximum keratometry (K) value (Kmax), average K value (avgK), topographic cylindrical value (topographic astigmatism) (Cyl), symmetry index front (SIf), symmetry index back (SIb), central corneal thickness (CCT), and thinnest point of the cornea were recorded from the topography data generated by the Scheimpflug system. The Kmax was defined as the steepest point of the anterior corneal surface. The SIf was the symmetry index of the anterior curvature and defined as the difference of the mean anterior tangential curvature of two circular zones centered on the vertical axis in the inferior and superior hemispheres. The SIb was the symmetry index of the posterior curvature and defined as the difference of the mean posterior tangential curvature of two circular zones centered on the vertical axis in the inferior and superior hemispheres.

TABLE 2. *Comparison of Ocular Response Analyzer Findings Among Groups*

	FFKC Group (n:50), Mean±SD	Astigmatism Group (n:50), Mean±SD	Control Group (n:50), Mean±SD	P[a]
IOPcc (mm Hg)	14.33±2.45	15.72±2.89	15.29±3.6	0.06
IOPg (mm Hg)	11.26±2.96	15.06±3.19	15.13±3.47	<0.001
CH	8.56±1.39	10.29±1.51	10.47±1.2	<0.001
CRF	7.56±1.71	10.19±1.76	10.36±1.2	<0.001

[a] One-way analysis of variance and post hoc Tukey test.

CH, corneal hysteresis; CRF, corneal resistance factor; FFKC, forme fruste keratoconus; IOPcc, corneal-compensated intraocular pressure; IOPg, Goldmann-correlated intraocular pressure.

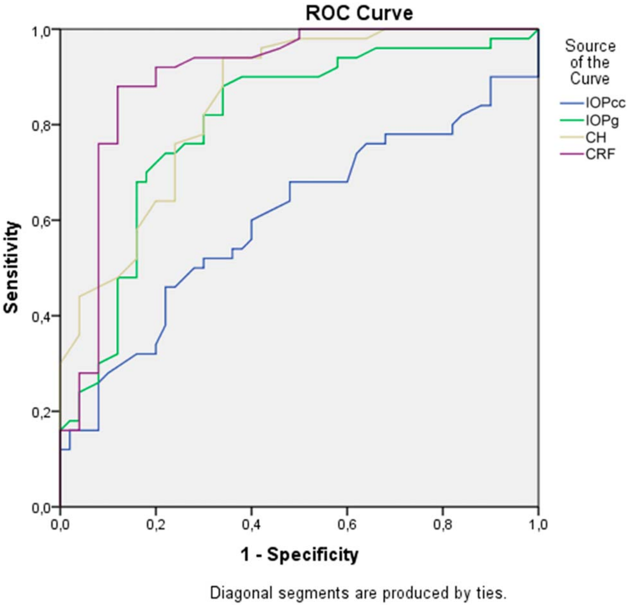
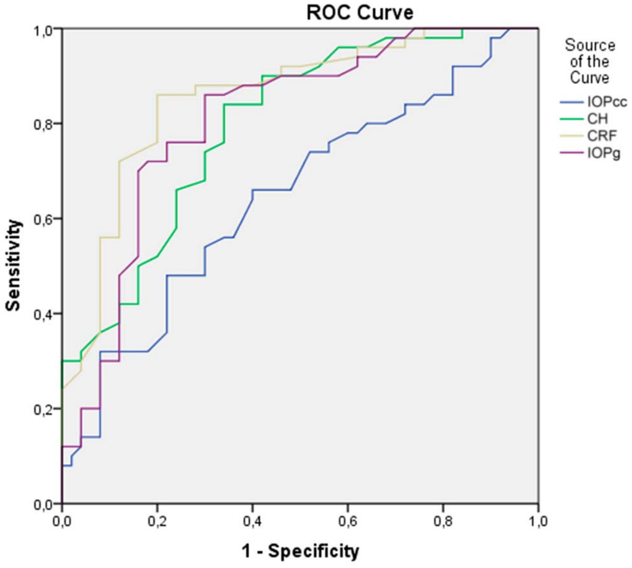


FIG. 1. Receiver operating characteristic (ROC) curves drawn for the ORA findings of control-FFKC groups. CH, corneal hysteresis; CRF, corneal resistance factor; FFKC, forme fruste keratoconus; IOPcc, corneal-compensated intraocular pressure; IOPg, Goldmann-correlated intraocular pressure; ORA, ocular response analyzer. full color online

The ORA was used by a single examiner. Minimum four measurements were performed in each eye. The highest waveform score was recorded for the statistical analysis.[11] The ORA reports two IOPs: Goldmann-correlated IOP (IOPg) and corneal-compensated IOP (IOPcc). Corneal hysteresis (CH) and corneal resistance factor (CRF) were also evaluated with ORA. Two different bidirectional (inward and outward) applanation pressure measurements are recorded by the ORA device, and the difference between these two pressures is the CH, which is an indicator of corneal viscosity. Corneal resistance factor is considered as the indicator of the overall resistance of the cornea, which is mainly associated with the elastic properties of the cornea.

Statistical Analysis

Statistical analyses were performed using the Number Cruncher Statistical System (NCSS) 2007 statistical software (NCSS, LLC, Kaysville, UT). Descriptive statistics were expressed as mean and SD. One-way analysis of variance was used to compare the groups, whereas the Tukey variance analysis was performed for the subgroup analyses, and the chi-square test was performed for the qualitative data. For the diagnosis of FFKC, the area under the curve (AUC) was calculated using the receiver operating



Diagonal segments are produced by ties.

FIG. 2. Receiver operating characteristic (ROC) curves drawn for the ORA findings of astigmatism-FFKC groups. CH, corneal hysteresis; CRF, corneal resistance factor; FFKC, forme fruste keratoconus; IOPcc, corneal-compensated intraocular pressure; IOPg, Goldmann-correlated intraocular pressure; ORA, ocular response analyzer. full color online

characteristic (ROC) curves for ORA variables, and sensitivity, specificity, positive and negative predictive values, and odds ratio were determined. A P value of ≤ 0.05 was considered statistically significant.

RESULTS

A total of 150 eyes of 150 patients were included in this study. There was no significant difference in the mean age and sex of the study groups (Table 1). The topographic data of the study participants are summarized in Table 1. All topographic findings were statistically significant among the three groups. In the FFKC group, the CCT was significantly lower, whereas symmetry indices back and front were significantly higher, compared with normal and astigmatism groups. When astigmatism and FFKC groups were compared separately, there was a statistically significant difference, except avgK ($P=0.70$) and Cyl ($P=0.27$).

The ORA findings of the three groups are summarized in Table 2. Although there was no statistically significant difference in the IOPcc among the groups, the IOPg, CH, and CRF were statistically significantly lower in the FFKC group, compared with other two groups ($P<0.001$). When control and astigmatism groups were compared separately, there was no statistically significant difference in the IOPg ($P=0.99$), CH ($P=0.79$), or CRF ($P=0.86$).

The ROC curves were drawn for the ORA findings of control-FFKC (Fig. 1) and astigmatism-FFKC groups (Fig. 2), and the AUC values were calculated. Accordingly, in differentiation of FFKC patients from control or astigmatic cases, the IOPg, CH, and CRF results were above 0.80. The ROC curves were analyzed to define the best cutoff values having the highest sensitivity and specificity results (Tables 3 and 4).

DISCUSSION

In this study, we evaluated the diagnostic accuracy of ORA parameters in differentiation of FFKC from astigmatic or normal eyes. We found that IOPg, CH, and CRF were statistically significantly different in the FFKC group than the astigmatic and control patients. In the ROC curve analysis, the AUC for the IOPg, CH, and CRF was also statistically significant in differentiation of FFKC from both astigmatic and control patients. To the best of our knowledge, this is the first study in literature reporting that ORA and corneal biomechanical factors may be useful in differentiation of patients with astigmatism and FFKC.

The corneal steepening and astigmatism formation are the characteristics of both simple astigmatism and FFKC. Our topographical data also support this condition with significantly increased Cyl and Kmax values. However, the CCT was significantly lower in the FFKC group, compared with normal and astigmatism groups. According to the results of ORA, in patients with FFKC, CH and CRF were lower than astigmatism and control groups. These results support the findings of previous reports suggesting that as the elasticity and the resistance of cornea decrease, protrusion and low tensile strength may occur, even at the very early phases.[1,15] However, in the astigmatism group, the corneal skeleton was preserved, which is helpful in differentiation of FFKC and astigmatism based on the biomechanical features.

Although the diagnosis of keratoconus depends on the topographic findings, the ability of the ORA to distinguish between normal eyes and eyes with keratoconus was also studied previously.[10] Shah et al.[16] reported significantly decreased CH, CRF, and CCT values in patients with keratoconus, compared with the control cases. Fontes et al.[17] also reported that CH and CRF were statistically lower in keratoconic eyes than that of healthy thin corneas with a CCT of <505 μm; however, they found very low sensitivity and specificity for discriminating the groups. Wolffsohn et al.[12] reported that additional corneal biomechanical metrics might improve the detection and severity prediction of keratoconus

TABLE 3. *Comparison of Area Under the Receiver Operating Characteristic Curve, Selected Parameter Cutoff, Sensitivity, and Specificity for Ocular Response Analyzer Variables Between Forme Fruste Keratoconus and Control Groups*

Parameter	AUROC	SE	*P*	Sensitivity	Specificity	Cutoff	95% CI
IOPcc (mm Hg)	0.60	0.058	0.076	60	60	14.45	0.49–0.71
IOPg (mm Hg)	0.80	0.045	<0.001	82	70	11.75	0.71–0.89
CH	0.85	0.037	<0.001	76	76	9.45	0.77–0.92
CRF	0.90	0.033	<0.001	88	88	9.25	0.83–0.96

AUROC, area under the receiver operating characteristic curve; CH, corneal hysteresis; CI, confidence interval; CRF, corneal resistance factor; IOPcc, corneal-compensated intraocular pressure; IOPg, Goldmann-correlated intraocular pressure.

TABLE 4. *Comparison of Area Under the Receiver Operating Characteristic Curve, Selected Parameter Cutoff, Sensitivity, and Specificity for Ocular Response Analyzer Variables Between Forme Fruste Keratoconus and Astigmatism Groups*

Parameter	AUROC	SE	*P*	Sensitivity	Specificity	Cutoff	95% CI
IOPcc (mm Hg)	0.646	0.055	0.072	64	60	14.45	0.54–0.75
IOPg (mm Hg)	0.808	0.044	<0.001	86	70	11.60	0.72–0.89
CH	0.796	0.044	<0.001	74	70	9.24	0.71–0.88
CRF	0.857	0.038	<0.001	86	80	8.85	0.78–0.93

AUROC, area under the receiver operating characteristic curve; CH, corneal hysteresis; CI, confidence interval; CRF, corneal resistance factor; IOPcc, corneal-compensated intraocular pressure; IOPg, Goldmann-correlated intraocular pressure.

compared with traditional keratometric and pachymetric assessment of the corneal shape. Similarly, CH and CRF, and novel waveform-derived ORA parameters were reported to provide improved identification of keratoconus patients.[18] However, the data on the role of ORA in differential diagnosis of FFKC still remain limited.

Because FFKC is one of the main causes of corneal ectasia after refractive surgeries, its early diagnosis is critically important. In the recent literature, biomechanical data were shown to be valuable in the identification of FFKC. Touboul et al.[19] compared eyes with mild stages of keratoconus and control cases and reported that, using a threshold of 9.6, CH had a sensitivity of 66% with a specificity of 67%, and that, using a threshold of 9.7, CRF had a sensitivity of 72% and a specificity of 77%. Similarly, Ayar et al.[20] reported that CH and CRF were significantly lower in the FFKC patients, compared with normal control subjects, and the best cut-off values were reported as 9.3 and 8.8 mm Hg for CH and CRF, respectively. On the other hand, in a recent study, Luz et al.[21] reported that, not the CH or CRF, but ORA waveform parameters were able to better differentiate FFKC from normal corneas. In addition, the ORA waveform parameters were also reported to improve the predictive value in the differentiation of FFKC from normal eyes, when combined with topographic data.[22] However, Mohammadpour et al.[23] reported that although CH and CRF were helpful in differentiating keratoconus from normal eyes, they were not valuable for detecting suspicious keratoconus. Similarly, Ventura et al.[24] reported that the waveform-derived ORA parameters were able to better differentiate grades I and II keratoconus from normal corneas than the CH, IOPg, IOPcc, and CRF.

In this study, we found statistically significant AUC results regarding IOPg, CH, and CRF in the ROC analysis, in differentiation of FFKC cases from normal eyes. The best cut-off values for IOPg, CH, and CRF were reported as 11.75, 9.45, and 9.25, respectively. In addition, the AUC results regarding IOPg, CH, and CRF in the ROC analysis were also statistically significant, when FFKC and astigmatic groups were compared. Accordingly, the best cut-off values for IOPg, CH, and CRF were found to be 11.60, 9.24, and 8.85, respectively. To the best of our knowledge, this is the first study in the literature comparing FFKC cases with astigmatic patients using the ORA parameters.

In the literature, there are a limited number of data regarding the ORA findings in patients with astigmatism. Hagishima et al.[25] reported that there was no significant correlation between corneal astigmatism and IOPcc or IOPg as measured with ORA. Similarly, Wong et al.[26] reported that, at the default position, the IOPg and CRF had a weak correlation with corneal astigmatism, whereas the IOPcc and CH were not significantly correlated with corneal astigmatism. In our study, we also found no statistically significant difference between the control and astigmatism groups in the ORA findings including IOPcc, IOPg, CH, and CRF.

Nonetheless, there are some limitations of this study that should be mentioned. First, combination of different ORA parameters may increase the sensitivity or specificity of FFKC diagnosis, which may be a subject of another study. Second, sample size is small to generalize the study results to the overall population.

In conclusion, our study showed that corneal biomechanical parameters measured by ORA could be used in differentiation of patients with FFKC from normal control cases or astigmatic patients, particularly in patients with suspicious results. In addition, we suggest using ORA in combination with corneal topography for better and more accurate diagnosis of FFKC. However, further studies with larger groups are warranted to determine the exact role of ORA in the differential diagnosis of FFKC.

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