

Detection of the early keratoconus based on corneal biomechanical properties in the refractive surgery candidates

Zofia Pniakowska, Piotr Jurowski

Context: Subclinical keratoconus is contraindication to refractive surgery. The currently used methods of preoperative screening do not always allow differentiating between healthy eyes and those with subclinical keratoconus. **Aim:** To evaluate biomechanical parameters of the cornea, waveform score (WS), and intraocular pressure (IOP) as potentially useful adjuncts to the diagnostic algorithm for precise detection of the early keratoconus stages and selection of refractive surgery candidates. **Settings and Design:** Department of Ophthalmology and prospective cross-sectional study. **Patients and Methods:** Patients enrolled in the study were diagnosed with refractive disorders. We assessed parameters of corneal biomechanics such as corneal hysteresis (CH), corneal resistance factor (CRF), Goldman-correlated IOP (IOPg), corneal compensated IOP, WS, and keratoconus match index (KMI). They were classified into one of three groups based on the predefined KMI range: Group 1 (from 0.352 to 0.757) – 45 eyes, Group 2 (from –0.08 to 0.313) – 52 eyes, and Group 0 - control group (from 0.761 to 1.642) – 80 eyes. **Results:** In both study groups, IOPg, CRF, and CH were decreased when compared to control ($P < 0.0001$). In control group, there was positive correlation between CH and KMI ($P < 0.05$), with no correlations in any of the two study groups. CRF correlated positively with KMI in control ($P < 0.0001$) and in Group 2 ($P < 0.05$). **Conclusions:** CH and CRF, together with WS and IOPg, consist a clinically useful adjunct to detect subclinical keratoconus in patients referred for refractive surgery when based on KMI staging.

Key words: Corneal hysteresis, corneal resistance factor, intraocular pressure, keratoconus, keratoconus match index, ocular response analyzer, refractive surgery, waveform score

Subclinical keratoconus (also called forme fruste keratoconus) is the early form of the most common corneal ectasia.^[1,2] Clinical manifestation occurs in the later stages of the disease, including a progressive protrusion and conical shape of the corneal curvature.^[3] The changes in corneal biomechanical properties correspond with the altered histological features of the cornea. Pathomechanism of the disease includes progressive thinning of the corneal stroma, breaks in Bowman's layer, and deposition of iron in the basal layers of corneal epithelium.^[4]

In the clinical setting, early diagnosis plays an important role in the preoperative screening for patients referred to refractive surgery.^[5,6] Here, subclinical keratoconus is a contraindication to surgical treatment to avoid the most feared complications of refractive procedures (i.e., LASIK- Laser-assisted in-situ keratomileusis) such as iatrogenic ectasia.^[7-10] Preoperative screening is based on several widely known methods, including morphological classification with pachymetry, disease evolution classifications with the use of keratometry, videokeratography, or slit-lamp examination.^[11-15] However, those methods do not always allow to differentiate between healthy eyes and those with subclinical stages of keratoconus.

Therefore, to properly assess the keratoconus stage, the index-based systems such as the Pentacam (Oculus, Germany) or the Ocular Response Analyzer (ORA) (Reichert, USA) became

Department of Ophthalmology and Visual Rehabilitation, Veterans Central Hospital, Lodz, Poland

Correspondence to: Dr. Zofia Pniakowska, Department of Ophthalmology and Visual Rehabilitation, The Veterans Central Hospital, Zeromskiego 113 Street, Lodz 90-710, Poland. E-mail: zofia.pniakowska@gmail.com

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recently the preferred diagnostic methods. ORA determines so-called "keratoconus match index" (KMI). KMI assess corneal biomechanical properties, which may be helpful in defining the keratoconus stage and monitoring progression of the disease.

The aim of the study was to evaluate the biomechanical parameters of the cornea, waveform score (WS), and intraocular pressure as a potentially useful adjunct to the diagnostic algorithm for precise detection of the early keratoconus stages and the resulting selection of refractive surgery candidates.

Patients and Methods

A prospective study was carried out in the Department of Ophthalmology. Informed consent was obtained from all participants of the study. Patients enrolled in the study were diagnosed with refractive disorders with classical methods, such as computerized corneal topography, central corneal thickness measurement, axial length, white-to-white measurement of the limbus, confocal microscopy, anterior chamber depth and pupil size, and referred for surgical treatment (keratoplasty or phakic intraocular lens exchange).^[16-20] Patients with history of corneal surgery procedures, past or existing corneal trauma

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independent of its etiology, other corneal dystrophies, thyroid orbitopathy, glaucoma, and diabetes mellitus were excluded from the study.

Preoperatively, both eyes of each patient were assessed with ORA. The measurement process provided by ORA is based on the production of air pulse, which concaves corneal surface for a few milliseconds. Then, the air pump switches off, so that the applied force diminish slightly, letting the cornea recur to its normal shape. Cornea passes through the phase of applanation 2-fold during the time of the measurement. Deformation of the elastic corneal surface is proportional to the pressure applied by the air-puff. ORA records the pressure twice, at a time of first and second corneal applanation point. The average of two obtained pressure values is Goldmann-correlated intraocular pressure (IOPg), and their difference is exactly corneal hysteresis (CH).

During the measurement, the device generates 38 mathematical waveform parameters, including the quantitative parameters such as CH, corneal resistance factor (CRF), intraocular pressure (IOPg and corneal compensated IOP [IOPcc]), and WS. CH is the parameter describing elasticity of the corneal tissue whereas CRF represents viscoelastic response of cornea, i.e., corneal "resistance." IOPcc describes IOP accurately, by eliminating the measurement error caused by corneal biomechanical characteristics such as thickness or elasticity. In turn, the WS value corresponds with measurement quality presented on a scale from 0 to 10.

KMI classified the measured parameters into five model stages, embedded in the ORA database – normal: KMI ranging from 0.761 to 1.642, keratoconus suspect: KMI ranging from 0.352 to 0.757, mild keratoconus: KMI ranging from -0.08 to 0.313, moderate keratoconus: KMI ranging from -0.345 to -0.091, and severe keratoconus: KMI ranging from -1.003 to -0.359.^[21,22]

In our study, patients were classified into one of the three groups based on KMI value. Group 1 (keratoconus suspect group) consisted of 45 eyes with KMI from 0.352 to 0.757, Group 2 (mild keratoconus group) consisted of 52 eyes with KMI from -0.08 to 0.313, and the control group (Group 0) included 80 eyes with KMI from 0.761 to 1.642.

The WS reflects the quality of measurement, taking the value from 0 to 10. WS value provides information about reliability of data obtained with ORA and information about condition of the patient's cornea. Low WS results from asymmetrical corneal applanation, which can be caused by corneal dystrophy, ectasia, or keratoconus. In addition, IOPcc values measured with ORA are unaffected by the corneal factors. Four consecutive measurements were taken for each eye. We selected the best value of WS to statistical analysis, and measurements of WS below acceptable 3.5 score were excluded.

For all measurable variables, we tested the compatibility of their distribution with a normal distribution using λ -Kolmogorov test. For comparison between two measurements of the same parameter in both groups, we used Student's *t*-test for independent samples. The relationship between the two variables was calculated with the rectilinear correlation coefficient *r*. The coefficient of determination, which is the square of the coefficient, assessed the impact of two variables.

We found the differences between the mean values and the dependencies between attributes as statistically significant where the error of probability was $P < 0.05$.

Results

Group 0 included healthy eyes (mean KMI = 1.1). The mean age was 28.68 ± 10.01 years [Table 1]. Group 1 consisted of eyes with suspect keratoconus (mean KMI = 0.55). The mean age was 32.11 ± 12.76 [Table 1]. In eyes with suspect of keratoconus, IOPg was significantly decreased, compared to control group ($t = 4.86$, $P < 0.0001$). Similarly, the significantly lower values, when compared to Group 0, were observed in Group 1 for CRF ($t = 7.13$, $P < 0.0001$) and CH ($t = 6.24$, $P < 0.0001$), respectively. However, IOPcc mean value in suspect keratoconus group did not differ from control group ($t = 1.13$, $P > 0.05$) [Table 1]. Group 2 included eyes with mild keratoconus (mean KMI = 0.1). The mean age was 34.81 ± 12.80 years [Table 1]. Patients with mild keratoconic eyes, included to this group, had significantly decreased IOPg ($t = 7.18$, $P < 0.0001$) when compared to healthy eyes. Mean values of CRF ($t = 11.41$, $P < 0.0001$) and CH ($t = 10.86$, $P < 0.0001$) were also significantly lower than in the control

Table 1: Characteristics of measured parameters and differences in corneal properties and intraocular pressure values between keratoconus suspect (Group 1), mild keratoconus (Group 2), and healthy eyes (Group 0)

Parameter	Study group	Mean values characterizing parameter	Differences between study groups and control Group (0)	
			<i>t</i>	<i>P</i>
KMI	0	1.1	-	-
	1	0.55		
	2	0.1		
Age	0	28.68	-	-
	1	32.11		
	2	34.81		
IOPg	0	14.94	-	-
	1	11.36	4.86	<0.0001
	2	9.91	7.18	<0.0001
IOPcc	0	14.2	-	-
	1	13.46	1.13	0.259
	2	13.77	0.71	0.473
CRF	0	11.27	-	-
	1	8.34	7.13	<0.0001
	2	6.69	11.41	<0.0001
CH	0	11.61	-	-
	1	9.45	6.24	<0.0001
	2	7.99	10.86	<0.0001
WS	0	7.92	-	-
	1	6.56	6.60	<0.0001
	2	4.41	17.78	<0.0001

KMI: Keratoconus match index, IOPg: Goldmann-correlated intraocular pressure, IOPcc: Corneal compensated intraocular pressure, CRF: Corneal resistance factor, CH: Corneal hysteresis, WS: Waveform score - the quality of ORA measurement, ORA: Ocular response analyzer

group. According to the results of ORA measurements, there was no difference in mean IOPcc observed between Group 2 and control group ($t = 0.71, P > 0.05$) [Table 1].

Statistical analysis of data revealed positive correlation between CH and IOPg in control group ($r^2 = 0.08, P < 0.05$) and Group 2 ($r^2 = 0.12, P < 0.05$). CH correlated negatively with IOPcc in Group 1 ($r^2 = 0.22, P < 0.05$) and Group 2 ($r^2 = 0.09, P < 0.05$) as well as in healthy eyes ($r^2 = 0.08, P < 0.05$) [Table 2]. Moreover, we observed positive relationship between CRF and IOPg in both study groups such as Group 1 ($r^2 = 0.38, P < 0.0001$), Group 2 ($r^2 = 0.53, P < 0.0001$), and control population ($r^2 = 0.55, P < 0.0001$). CRF correlated positively with IOPcc in normal eyes ($r^2 = 0.06, P < 0.05$). CRF correlated positively with CH in patients with keratoconus suspect ($r^2 = 0.69, P < 0.0001$), mild keratoconus ($r^2 = 0.77, P < 0.0001$), as well as in healthy participants ($r^2 = 0.74, P < 0.0001$) [Table 2]. Similarly, the positive correlation between IOPg and IOPcc in Group 1 ($r^2 = 0.69, P < 0.0001$), Group 2 ($r^2 = 0.61, P < 0.0001$), and control group ($r^2 = 0.69, P < 0.0001$) was noticed [Table 2].

In our study, KMI correlated negatively with age in eyes with mild keratoconus ($r^2 = 0.10, P < 0.05$) but did not correlate in Group 1 ($r^2 = 0.00, P > 0.05$) or in healthy eyes ($r^2 = 0.01, P > 0.05$) [Table 2]. In control group, we noticed positive correlation between KMI and CH ($r^2 = 0.12, P < 0.05$), however, with no significant correlations in any of the two study groups. KMI correlated positively with CRF in control ($r^2 = 0.17, P < 0.0001$) as well as in mild keratoconic eyes ($r^2 = 0.11, P < 0.05$).

Similarly, positive correlation was noticed between KMI and IOPg in control ($r^2 = 0.09, P < 0.05$) and study Group 2 ($r^2 = 0.08, P < 0.05$). KMI did not correlate with IOPcc in any of the analyzed groups.

Discussion

Detection of subclinical stages of keratoconus is still not easy; however, precisely made, early diagnosis is necessary because of the development of corneal refractive surgery. Estimation of corneal biomechanical properties plays an important role in excluding patients with subclinical keratoconus from refractive surgery procedures.^[5]

Our study revealed significant differences in IOPg between both study groups and control [Table 1]. Similarly, Touboul *et al.* demonstrated a higher average value of Goldmann-correlated IOP in normal eyes than in early keratoconic eyes.^[20] This fact may suggest that IOPg could be helpful parameter in the early keratoconus detection. On the other hand, IOPg value does not eliminate an IOP measurement error caused by biomechanical properties of the cornea, which in turn results in inaccurate IOP estimation. As previously found, it is likely in keratoconus that there is an artifact in IOP assessment using Goldmann-correlated IOP because of the lower elastic modulus, which causes underestimation of IOP despite similar corneal thicknesses.^[23,24]

In contrast, IOPcc allows us to estimate the real IOP, independently from the disease-related changes in the cornea.

Table 2: Comparison of relationship among keratoconus match index, corneal hysteresis, corneal resistance factor, Goldmann-correlated intraocular pressure and corneal compensated intraocular pressure in patients with keratoconus and control group

Group correlation	0			1-2			1			2		
	"+/-"r	r ²	P	"+/-"r	r ²	P	"+/-"r	r ²	P	"+/-"r	r ²	P
WS												
KMI	0.36	0.13	0.0010	0.73	0.53	0.0001	0.59	0.35	0.0001	0.33	0.11	0.0140
CH	-0.12	0.01	0.2660	0.03	0.00	0.7520	-0.41	0.17	0.0050	-0.28	0.08	0.0420
CRF	-0.19	0.04	0.0850	-0.01	0.00	0.9600	-0.48	0.23	0.0010	-0.32	0.10	0.0200
IOPg	-0.19	0.04	0.8800	-0.05	0.00	0.6130	-0.29	0.08	0.0530	-0.24	0.06	0.0830
IOPcc	-0.11	0.01	0.2990	-0.06	0.00	0.4970	-0.02	0.00	0.8610	-0.06	0.00	0.6600
KMI												
Age	-0.08	0.01	0.4670	-0.31	0.10	0.0360	0.01	0.00	0.9190	-0.31	0.10	0.0220
CH	0.35	0.12	0.0010	0.21	0.04	0.1490	0.12	0.01	0.4220	0.26	0.07	0.0580
CRF	0.41	0.17	0.0001	0.16	0.03	0.2650	0.01	0.00	0.9460	0.33	0.11	0.0170
IOPg	0.30	0.09	0.0060	0.02	0.00	0.8740	-0.14	0.02	0.3350	0.28	0.08	0.0380
IOPcc	0.10	0.01	0.3680	-0.15	0.02	0.3230	-0.19	0.04	0.2030	0.11	0.01	0.4250
CH												
CRF	0.86	0.74	0.0001	0.88	0.77	0.0001	0.83	0.69	0.0001	0.88	0.77	0.0001
IOPg	0.29	0.08	0.0070	0.30	0.09	0.0030	0.09	0.01	0.5490	0.34	0.12	0.0120
IOPcc	-0.28	0.08	0.0100	-0.36	0.13	0.0001	-0.47	0.22	0.0010	-0.30	0.09	0.0280
CRF												
IOPg	0.74	0.55	0.0001	0.70	0.49	0.0001	0.62	0.38	0.0001	0.73	0.53	0.0001
IOPcc	0.24	0.06	0.0300	0.09	0.01	0.3440	0.09	0.01	0.5410	0.16	0.03	0.2310
IOPg												
IOPcc	0.83	0.69	0.0001	0.77	0.59	0.0001	0.83	0.69	0.0001	0.78	0.61	0.0001

Group 0: Normal (control group), Group 1-2: Study groups, KMI: Keratoconus match index, IOPg: Goldmann-correlated intraocular pressure, IOPcc: Corneal compensated intraocular pressure, CRF: Corneal resistance factor, CH: Corneal hysteresis, WS: Waveform score

As a consequence, IOPcc measured in our series did not differentiate between keratoconus suspect eyes and normal eyes [Table 1]. Similarly, Touboul *et al.* reported that the IOPcc was significantly higher in normal eyes than in keratoconic eyes but with a smaller difference in corneal-compensated IOP than in Goldmann-correlated IOP.^[20]

The reliability of IOP measurement is described by WS. WS is recommended to be higher than 3.50 for its clinical utility in accurate IOP estimation in normal eyes.^[24,25] According to our results, WS was lower in study groups than in control; however, WS remained still higher than 3.50 in each group. In other words, only the results with WS above 3.50 can be considered in precise measurement of IOP in forme fruste keratoconus. Reliability of results measured with ORA is essential in detecting subtle differences between early keratoconus and normal eyes. On the other hand, our study can be affected by some limitations, due to the fact that the essential measurements were obtained by the ORA itself. The use of additional devices would certainly enhance the scientific value of the study. However, our results point out the necessity of further multi-center trials, regarding the early keratoconus detection in refractive surgery candidates.

Eyes with keratoconus have less elastic cornea, and thus parameters assessing its biomechanical changes can act as precise markers of the disease. Similarly to previous reports, our results showed higher values of CH and CRF in healthy eyes than in early keratoconic eyes [Table 1].^[6,26-30]

As widely proven before, KMI decreases with the increasing keratoconus severity.^[31-33] Therefore, KMI can act as the useful adjunct to the clinical evaluation and can be used for screening of early keratoconic changes in the cornea [Table 1]. In our study, WS correlated positively with KMI in control group as well as in both groups of early KC stage.

However, there was no relationship between KMI and CRF in KC-suspect as well as KMI and CH in both study groups [Table 2]. In our series, only CRF correlated positively with KMI in mild keratoconus group. Therefore, parameters assessing corneal biomechanical properties are weak quantitative parameters for differentiating between keratoconus suspect and normal corneas when considered without KMI.^[6] In addition, WS correlated negatively with CH and CRF in Group 1 and Group 2 with lack of relationship in control group.

In contrast, reliability of parameters assessing IOP was not proven in our clinical scenario. Our results showed positive relationship between IOPg and KMI in group with mild KC but not in KC-suspect [Table 2]. Therefore, IOPg cannot be used to assess subtle changes in the subclinical stages of keratoconus. Moreover, no correlations between KMI and IOPcc and between WS and IOPcc confirm that value of the IOPcc parameter assessing the IOP is free of any bias resulting from influence of the corneal biomechanics status. Therefore, IOPcc cannot be used in the clinical setting as marker assessing any biomechanical changes of the cornea, which in turn are seen in keratoconus.

Conclusion

A set of parameters assessing corneal biomechanical properties, including CH and CRF, together with WS and IOPg, consist

a clinically useful adjunct to detect subclinical keratoconus in patients referred for refractive surgery when based on KMI staging.

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Conflicts of interest

There are no conflicts of interest.

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