Corneal Biomechanical Properties in Normal, Forme Fruste Keratoconus, and Manifest Keratoconus After Statistical Correction for Potentially Confounding Factors

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Purpose: To evaluate the difference in corneal biomechanical properties, after controlling for potentially confounding factors, along the spectrum of keratoconic disease as measured by the keratoconus severity score.

Methods: The corneal biomechanical properties of 73 keratoconic (KCN) eyes of 54 patients, 42 forme fruste keratoconic (FFKCN) eyes of 32 patients, and 115 healthy eyes of 115 age- and sex-matched patients were reviewed retrospectively. The main outcome measures were corneal hysteresis (CH) and corneal resistance factor (CRF).

Results: In the normal group, the mean CH was 11.0 ± 1.4 mm Hg and mean CRF was 11.1 ± 1.6 mm Hg. The FFKCN mean CH was 8.8 ± 1.4 mm Hg and mean CRF was 8.6 ± 1.3 mm Hg. The KCN mean CH was 7.9 ± 1.3 mm Hg and mean CRF was 7.3 ± 1.4 mm Hg. There were statistically significant differences in the mean CH and CRF in the normal group compared with the FFKCN and the KCN groups ($P < 0.001$) after statistically controlling for differences in central corneal thickness, age, and sex.

Conclusions: There is a significant difference in the mean CH and CRF between normal and FFKCN corneas after controlling for differences in age, sex, and central corneal thickness. However, there is a significant overlap in the distribution of CH and CRF values among all groups. The biomechanical parameters CH and CRF cannot be used alone but may be a useful clinical adjunct to other diagnostic tools, such as corneal tomography, in distinguishing normal from subclinical keratoconic corneas.

Key Words: keratoconus, forme fruste keratoconus, keratoconus severity score, ocular response analyzer, corneal biomechanics, corneal resistance factor, corneal hysteresis

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Keratoconus (KCN) is an asymmetric, bilateral, progressive ectatic disease of the cornea that is a well-accepted contraindication to refractive surgery, particularly laser in situ keratomileusis (LASIK).[1–5] This disease is easily diagnosed clinically by a skilled physician in its fulminate stages. However, keratoconus has a wide spectrum of disease severity and clinical onset. The more subtle or preclinical forms, usually termed "forme fruste" or "subclinical" keratoconus (FFKCN), may be missed using even the most sophisticated topographic and tomographic analysis. This is particularly true in the younger population who commonly present for refractive surgery screening. In individuals in their late teens and twenties, topographic and tomographic abnormalities may not be present yet, simply because of the relatively late onset of clinical disease. Performing surgery on these individuals can have disastrous consequences causing progressive ectasia and significant vision loss.[5–11]

Keratoconic corneas are known to possess altered collagen fibril orientation that may lead to impaired biomechanics.[12–14] It is hypothesized that the creation of the LASIK flap and excimer ablation of the corneal stroma cause a mechanical weakening of the cornea that could convert a FFKCN cornea into a manifest KCN cornea.[1,6] Keratoconus and FFKCN are frequently diagnosed by clinical observation, corneal topography, and corneal tomography (eg, scanning slit beam or Scheimpflug imaging).[15–21] Several studies have suggested topographic indices to quantify the "keratoconic nature" of a cornea under evaluation.[15,19–22] Unfortunately, some patients with normal topographic (eg, anterior corneal), and tomographic (eg, anterior, posterior corneal, and pachymetric) findings go on to develop ectasia even after only modest excimer laser ablation.[23–27] Although other factors may be involved (eg, unexpected thick flap and aggressive laser ablation), keratectasia may develop in such a cornea because of biomechanical instability for which no preoperative abnormalities were detectable with existing technology.

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The ocular response analyzer (ORA; Reichert ophthalmic instruments, Buffalo, NY) measures the biomechanical properties of the cornea. Using current software, the ORA system describes these properties using 2 metrics: corneal hysteresis (CH) and corneal resistance factor (CRF). The system uses an air puff to produce a dynamic bidirectional indentation process from which a biomechanical waveform is produced. From this "biocorneagram," the CH and CRF metrics are derived.[28] KCN eyes are known to be more elastic and less rigid than normal eyes.[14] Multiple studies have identified statistically lower CH and CRF values for KCN eyes compared with normal eyes with fairly consistent values.[29–33] However, in FFKCN, this difference between diseased and normal corneas seems less strong with much more varied data.[34–37]

The main purpose of this study was to identify whether parameters obtained from the ORA are useful in differentiating normal corneas from those with the earliest preclinical forms of keratoconus, if these biomechanical values are correlated with the severity of ectatic disease and if the CH and CRF parameters provide unique information, independent of potential confounding factors such as central corneal thickness (CCT), patient age, and sex.

METHODS

This was a retrospective case review study. Institutional review board approval was obtained. Charts of patients evaluated by a single physician (D.R.H.) at the University of California, Los Angeles Laser Refractive Center, Jules Stein Eye Institute, between April 2005 and April 2009 were reviewed. Those patients diagnosed with keratoconus or FFKCN using clinical evaluation and topographic and tomographic analysis (Orbscan II; Bausch & Lomb, Rochester, NY) were included in the study. All eyes with previous ocular surgery, corneal scarring, history of other ocular disease, or any corneal pathology other than keratoconus were excluded. The eyes that met inclusion criteria were then graded according to the keratoconus severity score (KSS), as defined by the Collaborative Longitudinal Evaluation of Keratoconus study group.[19] The KCN group included eyes with a KSS score ≥3. The FFKCN group consisted of two subgroups: FFKCN A, defined as the fellow eye in a patient with a clinically manifest KCN eye (KSS could be 0, 1 or 2 as long as KCN eye had KSS ≥ 3), and FFKCN B which included eyes with KSS of 1 or 2, regardless of the status of the fellow eye. A control group of normal, healthy eyes was selected from a database of patients who had cleared the LASIK pro-operative screening process. Eyes for the control group were selected by age and sex matching to eyes in the diseased groups.

The ORA device was used to obtain a biomechanical waveform from which the CH and CRF are obtained.[28] All ORA measurements were taken at least twice and averaged for statistical analysis. All ORA waveforms were reviewed to ensure that they showed adequate amplitude and shape. Corneal thickness was obtained by choosing the thinnest pachymetry measurement off the Orbscan pachymetric map. The Orbscan device had been previously calibrated to ultrasound pachymetry using an acoustic factor of 0.92 by performing linear regression on the CCT of 50 normal eyes measured with both Orbscan and ultrasound pachymetry. The main outcome measures were CH and CRF. The effects of CCT, age, and sex were also evaluated in each group.

Statistical analysis was performed using statistical software SAS version 9.1 (Cary, NC). Paired *t* test and analysis of variance (ANOVA) were used to compare the mean values of the study groups. Multivariate and univariate linear regression analysis and Spearman correlation coefficient were used to evaluate the linear best-fit relationship between variables and to control for CCT, age, and sex. An alpha level of <0.05 was set a priori to determine statistical significance.

RESULTS

Table 1 summarizes the demographic data and the CH and CRF values obtained for each of the groups. There were no significant differences between the groups for all parameters except CH, CRF, and CCT. The normal group consisted of 115 eyes of 115 patients, age and sex matched, based on the demographics of the KCN and FFKCN groups. Box and whisker plots comparing CH and CRF between all groups are shown in Figures 1 and 2. Mean CH was 11.0 ± 1.4 mm Hg (range: 8.1–14.9 mm Hg). Mean CRF was 11.1 ± 1.6 mm Hg (range: 7.4–14.7 mm Hg). Mean CCT was 546 ± 31 μm (range: 459–610 μm). CH and CRF were not

TABLE 1. Summary Data for Normal, FFKCN, and Keratoconic Eyes

Characteristics	Normal	FFKCN	FFKCN A	FFKCN B	KCN
No. eyes (patients)	115 (115)	42 (32)	19 (19)	23 (13)	73 (54)
Male gender (%)	77 (67)	25 (60)	15 (79)	9 (39)	52 (71)
Age, mean ± SD (range) (yrs)	36 ± 10 (20–57)	37 ± 10 (18–61)	36 ± 13 (18–61)	37 ± 9 (24–56)	37 ± 11 (18–64)
Caucasian (%)	84 (73)	31 (74)	15 (79)	16 (70)	53 (73)
KSS, mean ± SD (range)	0.0 ± 0.0 (0)	1.4 ± 0.7 (0–2)	1.3 ± 0.8 (0–2)	1.5 ± 0.5 (1–2)	3.0 ± 0.0 (3)
CH (range) (mm Hg)*	11.0 ± 1.4 (8.1–14.9)	8.8 ± 1.4 (6.0–11.8)	8.6 ± 1.4 (6.0–11.4)	8.7 ± 1.4 (7.0–11.8)	7.9 ± 1.3 (4.9–11.6)
CRF (range) (mm Hg)*	11.1 ± 1.6 (7.4–14.7)	8.6 ± 1.3 (6.4–11.1)	8.4 ± 1.4 (6.4–10.5)	8.7 ± 1.1 (6.7–11.1)	7.3 ± 1.4 (3.7–10.8)
Corneal thickness, mean ± SD (range) (μm)*	546 ± 31 (459–610)	494 ± 31 (424–554)	492 ± 30 (431–542)	497 ± 32 (424–554)	464 ± 47 (335–559)

*$P < 0.05$ by ANOVA.

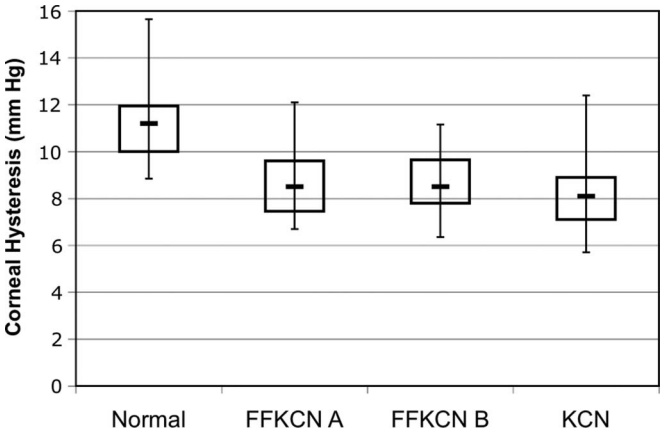

FIGURE 1. Box and whisker plot (with whiskers representing the range of data) comparison of CH in normal eyes, fellow eyes of manifest KCN (FFKCN A), eyes with FFKCN (FFKCN B), and eyes with manifest KCN.

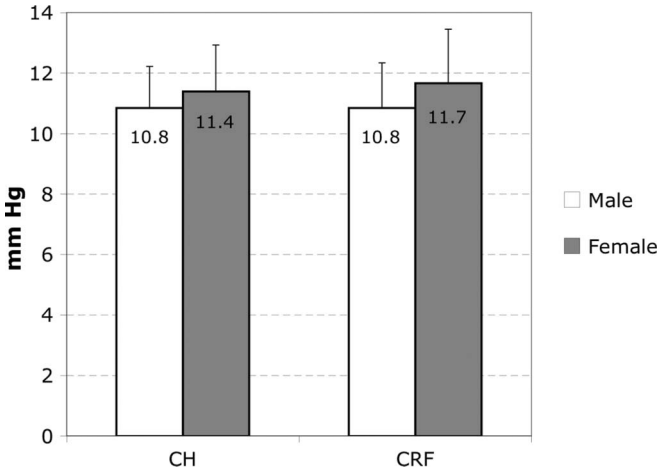

FIGURE 3. In the normal group, mean CH for men (10.8 ± 1.4 mm Hg) significantly differs from women (11.4 ± 1.5 mm Hg, $P = 0.048$). In addition, CRF is statistically significantly lower for men (10.8 ± 1.5 mm Hg) compared with women (11.7 ± 1.8 mm Hg, $P = 0.008$).

correlated with CCT ($P = 0.247$ and 0.196, respectively) or age ($P = 0.396$ and 0.277, respectively). Figure 3 shows the difference in mean CH and CRF between the 2 sexes in the normal group. CH correlated with sex, with men having an average value of 0.5 mm Hg lower than women ($P = 0.048$). CRF was significantly correlated with sex, with men having an average value of 0.7 mm Hg lower than women ($P = 0.008$). There was no significant difference in CCT between men and women in the normal group (men: 547 ± 31 μm and women: 541 ± 29 μm; $P = 0.30$).

The FFKCN group consisted of 42 eyes of 32 patients. Mean CH was 8.8 ± 1.4 mm Hg (range: 6.0–11.8 mm Hg). Mean CRF was 8.6 ± 1.3 mm Hg (range: 6.4–11.1 mm Hg). Mean CCT was 494 ± 31 μm (range: 424–554 μm). Further analysis of the FFKCN group was performed by separating the fellow eye of manifest keratoconic eyes (FFKCN group A) from FFKCN eyes with no manifest keratoconus in the fellow eye (FFKCN group B). Data for these subgroups can be seen in Table 1. CH and CRF showed no significant correlation between CCT, age, or sex neither in the FFKCN group nor in the 2 subgroups.

The manifest keratoconus group consisted of 73 eyes of 54 patients. Mean CH was 7.9 ± 1.3 mm Hg (range: 4.9–11.6 mm Hg). Mean CRF was 7.3 ± 1.4 mm Hg (range: 3.7–10.8 mm Hg). Mean CCT was 464 ± 47 μm (range: 335–559 μm). CH and CRF were not significantly correlated with age or sex. CH and CRF were significantly correlated with CCT ($P = 0.012$ and 0.005, respectively).

Table 2 summarizes comparisons between groups. On intergroup analysis, there was a statistically significant difference in mean CH and CRF in the normal group compared with all other groups, including both FFKCN subgroups ($P < 0.0001$). There was also a statistically significant difference in the mean CH and CRF between the FFKCN and

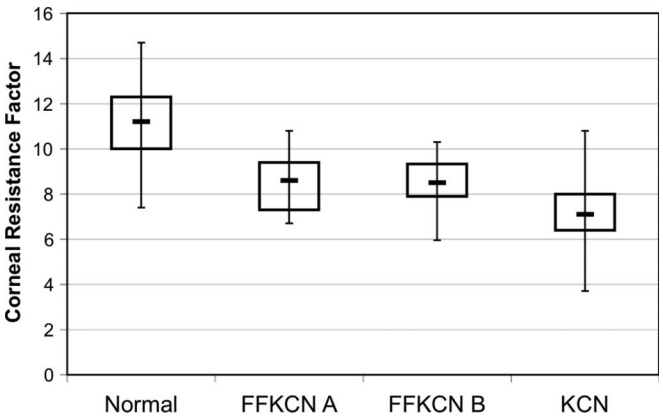

FIGURE 2. Box and whisker plot (with whiskers representing the range of data) comparison of CRF in normal eyes, fellow eyes of manifest KCN (FFKCN A), eyes with FFKCN (FFKCN B), and eyes with manifest KCN.

TABLE 2. Comparison of CH and CRF Between Groups Before and After Adjustment for Age, Sex, and CCT

Comparisons	Unadjusted	Adjusted
CH		
Overall (ANOVA)	$P < 0.0001$	$P < 0.0001$
KCN versus control	$P < 0.0001$	$P < 0.0001$
FFKCN versus control	$P < 0.0001$	$P < 0.0001$
FFKCN A versus control	$P < 0.0001$	$P < 0.0001$
FFKCN B versus control	$P < 0.0001$	$P < 0.0001$
FFKCN versus KCN	$P = 0.012$	$P = 0.13$
CRF		
Overall (ANOVA)	$P < 0.0001$	$P < 0.0001$
KCN versus control	$P < 0.0001$	$P < 0.0001$
FFKCN versus control	$P < 0.0001$	$P < 0.0001$
FFKCN A versus control	$P < 0.0001$	$P < 0.0001$
FFKCN B versus control	$P < 0.0001$	$P < 0.0001$
FFKCN versus KCN	$P = 0.001$	$P = 0.015$

KCN groups ($P = 0.012$ and 0.001, respectively). However, there was a significant difference in the mean CCT between the 3 groups as well (ANOVA, $P < 0.0001$). To address the potential confounding effect of corneal thickness, age, and sex on the association between biomechanical properties and keratoconic status, a multiple linear regression model was used to control these parameters. After adjustment, the difference in mean CH and CRF remained statistically significant when comparing normal controls with all other groups, including the 2 FFKCN subgroups ($P < 0.0001$ in all comparisons). The difference between the FFKCN and KCN groups in mean CRF remained significant ($P = 0.015$). The difference in mean CH, however, was no longer significant between the FFKCN and KCN groups ($P = 0.13$).

In further subgroup analysis, 10 FFKCN eyes with essentially normal topography (KSS scores of 0 or 1) whose fellow eye had manifest keratoconus were evaluated separately. These were compared with age-, sex-, and CCT-matched control normal eyes. Table 3 shows these results. The mean CH and CRF of the topographically normal FFKCN eyes (8.6 ± 1.4 and 8.7 ± 1.4 mm Hg, respectively) was statistically significantly different from the mean CH and CRF of the control eyes (10.4 ± 1.7 and 10.4 ± 1.7 mm Hg, respectively). Interestingly, there was no statistically significant difference in CCT, CH, or CRF between the manifest keratoconic eye and the fellow topographically normal eye (Fig. 4).

Correlations between the KSS and CH, CRF, and CCT are shown in Table 4. There was a strong Spearman correlation coefficient between all 3 parameters and severity of disease (CH: $r = -0.73$; CRF: $r = -0.78$; CCT = -0.73; ANOVA, $P < 0.001$). Student t test showed a significant difference in all parameters between KSS 2 and 3 (CH: $P = 0.014$; CRF: $P = 0.003$; CCT: $P = 0.023$). Comparison between KSS 1 and 2 showed a significant difference for CCT ($P = 0.013$) but not for CH or CRF ($P = 0.769$ and 0.136, respectively). Linear regression analysis showed a significant correlation between KSS and CRF, as well as CH ($P < 0.001$) with the R^2 value stronger with CRF ($R^2 = 0.57$, Fig. 4) as compared to CH ($R^2 = 0.48$) (Fig. 5).

Receiver operator characteristic (ROC) curve analysis for CH and CRF evaluating the FFKCN subgroup are shown in Figures 6 and 7. For CH, an optimal cutoff point of 9.1 mm Hg gave a sensitivity of 69.0%, specificity of 91.3%, and an accuracy of 85.4%. For CRF, the ROC curve analysis gave an optimal cutoff point of 9.1 mm Hg giving a sensitivity of 71.4%, specificity of 89.6%, and accuracy of 84.7%. The sensitivity and specificity of other cutoff points for CH and CRF are shown in Table 5.

TABLE 3. Comparison of Topographically Normal Fellow Eyes of Manifest Keratoconus to CCT/Age/Sex-Matched Controls

	Fellow Eye (n = 10), Mean ± SD	Controls (n = 20), Mean ± SD	*P*
Mean CCT (μm)	499 ± 34.9	500 ± 14.8	0.891
Mean CH (mm Hg)	8.6 ± 1.4	10.4 ± 1.7	0.006
Mean CRF (mm Hg)	8.7 ± 1.4	10.4 ± 1.7	0.010

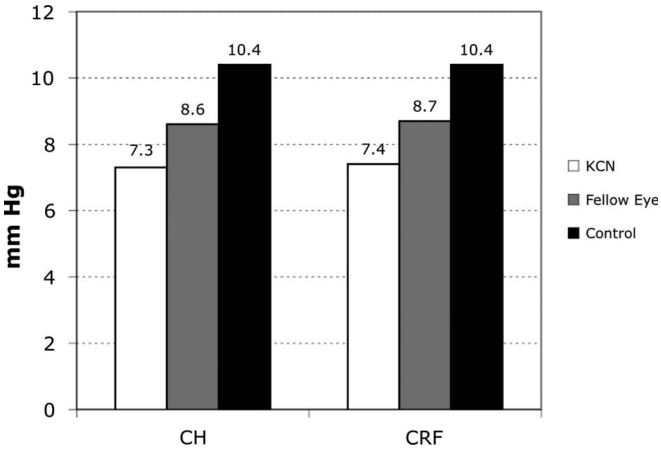

FIGURE 4. Bar graph representing the mean CH and CRF of a keratoconic eye (n = 10) and its topographically normal fellow eye (n = 10) compared with age-, sex-, and CCT-matched control eyes (n = 20). There were statistically significant differences between the control and fellow, as well as KCN groups, in both CH and CRF ($P < 0.001$). There was no significant difference between KCN and fellow groups ($P > 0.1$).

DISCUSSION

The detection of preclinical forms of keratoconus is essential in the screening of patients before laser refractive surgery to avoid the disastrous consequences of post-LASIK ectasia. Over the past few years, our ability to detect these cases using various topographic and tomographic analyses has improved; however, there continue to be new reports of ectasia after LASIK.[20,21] Understanding the biomechanical properties of these corneas before surgery may help us further reduce the incidence of ectasia after refractive surgery.

With current technology, the classic biomechanical properties of elasticity and viscosity can only be measured ex vivo. The ORA device offers the clinician the first opportunity to measure parameters that may relate to corneal biomechanics in vivo. From the "biomechanical waveform" obtained, the parameters "CH" and "CRF" are derived. How these parameters correlate, if at all, to classic viscoelastic properties such as stiffness, strength, extensibility, toughness, and hysteresis remains unknown. Yet, multiple studies have consistently shown CH and CRF to be, at a minimum, a "marker" for the keratoconus disease state.[29–33] Our study corroborated these findings and further found that, on average, the CH and CRF measurements are significantly lower in eyes with early subclinical keratoconus (FFKCN) when compared with measurements on normal corneas. There is, however, significant overlap between normal and diseased groups. This suggests that the CH and CRF values cannot be used alone but may be useful additional parameters, together with corneal tomographic analysis, to aid the clinician in the difficult task of identifying subtle forms of preclinical keratoconus. In particular, when faced with relatively normal topographic

TABLE 4. Correlations Between KSS and CH, CRF, and CCT

KSS Grade	CH, mm Hg	CRF, mm Hg	CCT, μm
0 (Control): n = 115, mean ± SD (range)	11.0 ± 1.4 (8.1–14.9)	11.1 ± 1.6 (7.4–14.7)	545 ± 30 (459–610)
0 (Fellow eye of KCN): n = 4, mean ± SD (range)	9.8 ± 1.0 (8.5–10.6)	10.0 ± 0.7 (9.1–10.5)	505 ± 39 (451–542)
1: n = 17, mean ± SD (range)	8.6 ± 1.6 (7.0–11.8)	8.8 ± 1.4 (6.4–11.1)	507 ± 29 (431–554)
2: n = 21, mean ± SD (range)	8.7 ± 1.2 (6.0–11.4)	8.2 ± 1.0 (6.5–10.4)	483 ± 27 (424–537)
3: n = 73, mean ± SD (range)	7.9 ± 1.3 (4.9–11.6)	7.3 ± 1.4 (3.7–10.8)	464 ± 47 (335–559)
Spearman correlation coefficient (ANOVA)	$r = -0.73$ ($P < 0.0001$)	$r = -0.78$ ($P < 0.0001$)	$r = -0.73$ ($P < 0.0001$)

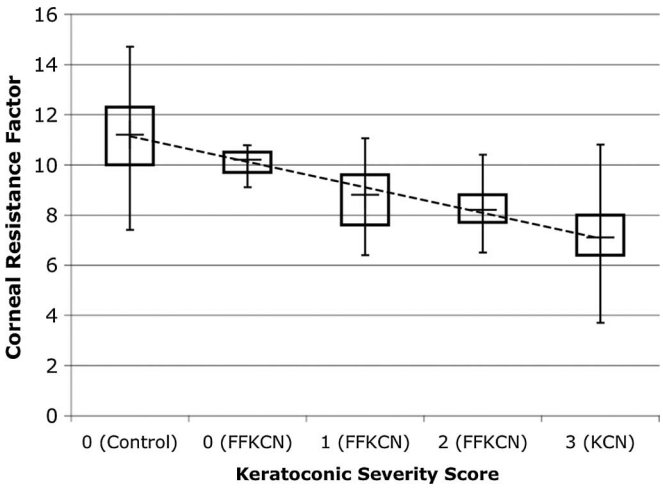

FIGURE 5. Box and whisker plot (with whiskers representing the range of data) comparison of CRF in study eyes separated according to KSS grade. For greater clarity, control eyes were separated from the FFKCN A eyes with a KSS of 0. The dashed line represents the linear regression analysis ($R^2 = 0.57$).

findings (KSS ≤ 1), the CH and CRF parameters may hold significant value in aiding the clinician in identifying these subtle cases.

Various other studies have evaluated the biomechanical properties of normal, FFKCN, and keratoconic corneas, with similar results to those of this study.[28–37] The results of our study compared with that of other published studies are shown in Table 6. The average CH (10.7 ± 1.7 mm Hg) and CRF (10.6 ± 1.8 mm Hg) of control eyes previously published (n = 1009) were very similar to those found in our study (11.0 ± 1.4 and 11.1 ± 1.6 mm Hg, respectively). The CH and CRF were also similar for all KCN eyes (n = 409) in previous studies (8.6 ± 1.6 and 7.3 ± 1.9 mm Hg, respectively) compared with those in our study (7.9 ± 1.3 and 7.3 ± 1.4 mm Hg, respectively).

There are fewer reports in the current literature examining subclinical or FFKCN eyes (n = 167). Our FFKCN findings were slightly lower (CH: 8.8 ± 1.4 mm Hg and CRF: 8.6 ± 1.3 mm Hg) than other published values (CH: 9.6 ± 1.7 mm Hg and CRF: 9.5 ± 1.8 mm Hg). This discrepancy is most likely because of differences in the definition of FFKCN used in the various studies.

Kirwan et al[35] (n = 30) used a vague definition of "clinically diagnosed" FFKCN using Orbscan topographic

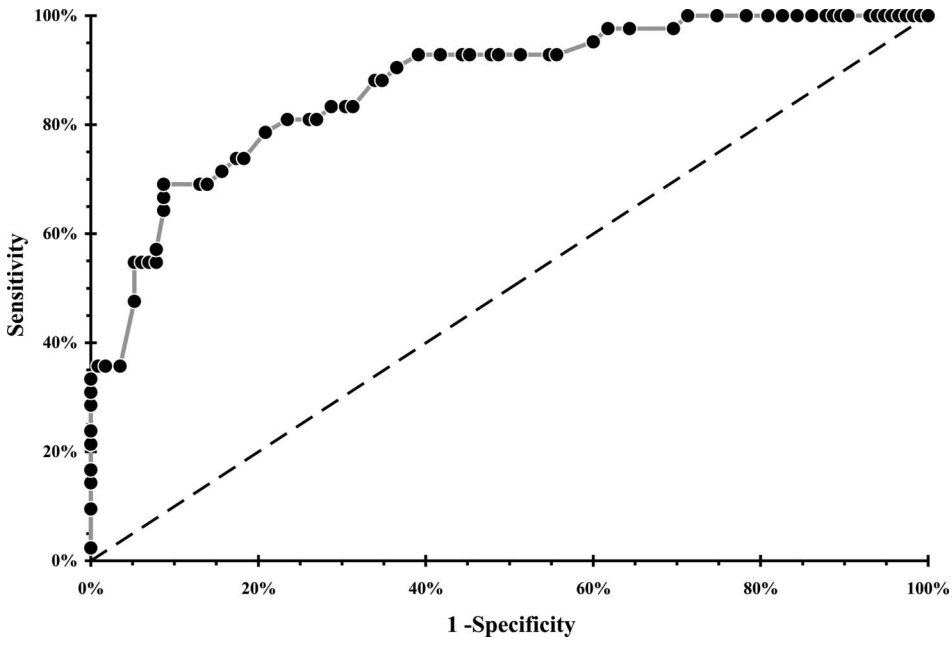

FIGURE 6. ROC curve for CH data in the FFKCN group. Optimal cutoff point for accuracy was 9.1 mm Hg giving a sensitivity of 69.0%, specificity of 91.3%, accuracy of 85.4%. Area under the curve: 0.872.

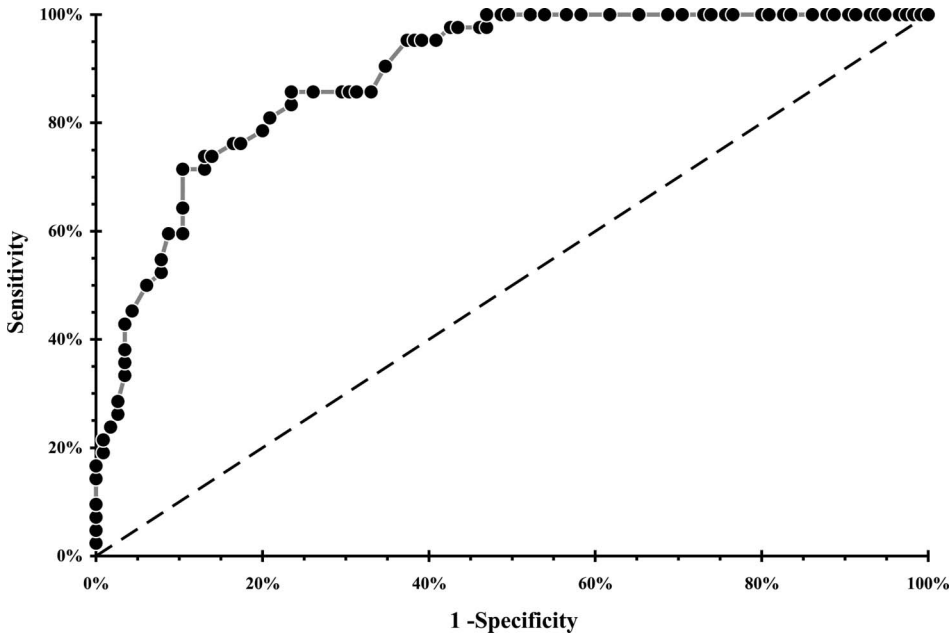

FIGURE 7. ROC curve for CRF data in the FFKCN group. Optimal cutoff point for accuracy was 9.1 mm Hg giving a sensitivity of 71.4%, specificity of 89.6%, accuracy of 84.7%. Area under the curve: 0.889.

analysis as the inclusion criteria. They simply state that the principle Orbscan criterion to identify FFKCN was a difference of 1.5 diopter or greater between superior and inferior corneal curvature. Using this definition, and without a quantifiable severity of subclinical disease, they found no difference in mean CH or CRF between the FFKCN and normal groups.

Saad et al[34] (n = 80) used a computer-based calculation from the Nidek OPD scan videokeratographer that provides a percentage similarity to 9 different clinical classifications including keratoconus and keratoconus suspect. Their inclusion criteria for keratoconus suspect eyes were a non-null score for keratoconus suspect and a null score for keratoconus. Their findings are interesting because their definition of FFKCN is completely objective. However, as noted by the authors in the discussion, their conclusions in this group are limited for this very reason. They still found a significant difference between groups. This difference failed to remain significant after an attempt to control for CCT because the number of eyes was too limited.

Schweitzer et al[36] (n = 55) used the normal fellow eye of a manifest keratoconic with a KISA index of $<60\%$.[15] The study by Schweitzer was the only other study to report the severity of FFKCN with a mean KISA index of 17.7%. They too found a significant difference between the groups, which remained after controlling for CCT in the thinner groups.

In our study, we used the KSS set forth by the Collaborative Longitudinal Evaluation of Keratoconus study group to grade the severity of FFKCN with an average value of 1.4 ± 0.7. No other studies stated the severity of the FFKCN groups, rendering direct comparison impossible. We feel that the use of a consistent grading scale for the range of subclinical and clinical keratoconus in reporting data will be helpful in assessing and comparing data in future studies. With the advent of new keratoconic detection paradigms using tomographic data, future studies of eyes examined with Scheimpflug systems may allow for more precise stratification of early keratoconus status, aiding the investigator to compare the biomechanical properties of early keratoconus with normals in a more meaningful way.[20,21]

In this study, there was a significant correlation between the severity of KCN as measured by KSS and CH, as well as CRF. There was, however, significant overlap with linear regression only accounting for approximately half of the variance (CH: $R^2 = 0.48$ and CRF: $R^2 = 0.57$). Indeed, the ROC curve analysis evaluating the ability of CH or CRF to properly

TABLE 5. Sensitivity and Specificity of CH and CRF for Different Cutoff Points in the FFKCN Group

Cutoff Point (mm Hg)	CH			CRF		
	Sensitivity (%)	Specificity (%)	Accuracy (%)	Sensitivity (%)	Specificity (%)	Accuracy (%)
≤8.0	35.7	99.1	82.2	35.7	96.5	80.3
≤8.5	54.8	94.8	84.1	50.0	93.9	82.2
≤9.0	64.3	93.3	84.1	64.3	89.6	82.8
≤9.5	73.8	82.6	80.3	76.2	82.6	80.9
≤10.0	81.0	73.9	75.8	85.7	73.9	77.1
≤10.5	90.5	63.5	70.7	95.2	62.6	71.3

TABLE 6. Comparison of the Weighted Average of Means for CH and CRF in Normal, KCN, and FFKCN Eyes Reported in Previous Studies Compared With the Current Study

	Normal[30–36]		FFKCN[34–37]		KCN[31–35]	
	CH (mm Hg)	CRF (mm Hg)	CH (mm Hg)	CRF (mm Hg)	CH (mm Hg)	CRF (mm Hg)
Weighted average	10.7 ± 1.7	10.6 ± 1.8	9.6 ± 1.7	9.5 ± 1.8	8.6 ± 1.6	7.3 ± 1.9
Our study	11.0 ± 1.4	11.1 ± 1.6	8.8 ± 1.4	8.6 ± 1.3	7.9 ± 1.3	7.3 ± 1.4

Data given as mean ± SD.

diagnose an abnormal cornea in the FFKCN group showed a relatively low area under the curve (0.872 and 0.889, respectively). Thus, CH or CRF alone is not sufficient but may be helpful in conjunction with other tests, particularly tomographic analysis, in the detection of early preclinical keratoconus.[20,21] More detailed analysis of the ORA raw data, or biocorneagram, may provide valuable information that can improve both the sensitivity and specificity of biomechanical abnormality detection beyond what is achievable with CH and CRF alone.

Fontes et al[37] published a report of 2 "unilateral" keratoconic eyes, comparing the biomechanics of the keratoconic eye to the normal fellow eye and normal controls. A trend toward lower CH and CRF was found, but the findings were not statistically significant because of the very small sample size. Schweitzer et al[36] had a much larger series of 55 eyes of unilateral keratoconus and found a significant difference between those eyes and controls. An important finding in our study is the statistically significant differences in CH and CRF between topographically normal fellow eyes in patients with manifest KCN compared with age- and CCT-matched normal controls.

A major confounding factor in comparing keratoconus to normal corneas is the difference of CCT between groups, as seen in this study. The differences are to be expected because KCN is a disease of progressive corneal thinning. The exact correlations between CCT and CH or CRF are still not well understood but there seems to be a weak positive correlation.[38,39] This correlation, however, was only seen in the KCN group in this study. This may be because of the fact that the correlation is weak, and this study did not have enough variation in CCT in the other groups to show a significant correlation. The correlation likely was seen only in the KCN group because this group had the widest range of corneal thickness.

FFKCN can be a subtle ectatic condition often missed by topographic/tomographic analysis. The long-term success of refractive surgery, particularly LASIK, depends on our ability to identify corneas at risk for ectasia. This study suggests that the corneal biomechanical parameters CH and CRF may be a useful adjunctive tool in further refining our ability to identify subtle FFKCN. New ORA software now allows detailed assessment of 38 separate parameters derived from the biomechanical waveform. Further analysis of these parameters may enhance our diagnostic capabilities. Ultimately, combining ORA metrics with tomographic parameters should lead us to improved exclusion criteria and, consequently, to a further reduction in the incidence of keratectasia after refractive surgery.

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