Towards a New Keratoconus Screening Paradigm: Correlating Known Risk Factors with the Corneal Spatial Thickness Profile and Biomechanical Properties Obtained from the Ocular Response Analyzer

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Introduction

Keratoconus (KCN) is a non-inflammatory, progressive disease characterized by thinning of the cornea, steepening of the anterior corneal surface, and corneal warpage leading to compromised vision in individuals affected (Figure 1). KCN affects millions of individuals worldwide with an estimated prevalence of 1 per 2000 in the general population.[1,2] While it is relatively easy to diagnose advanced KCN, identification sub-clinical disease and those at increased risk of KC remains a challenge.[2] Additionally, patients whom undergo refractive surgery and have undetected sub-clinical KCN, are at increased risk of developing post LASIK corneal ectasia – a serious vision threatening complication. To this point, there has been no clear way of determining who is at risk of developing keratoconus or post refractive ectasia until the changes in the cornea begin to manifest in the corneal topographic imaging.

Figure1. Patient with advanced Keratoconus

The Ocular Response Analyzer (ORA) (Reichert Inc., Depew, New York) measures corneal resistance to deformation by air puff applanation, giving us a corneal hysteresis (CH), and an empirically derived intraocular pressure-independent corneal resistance factor (CRF) (Figure 2).

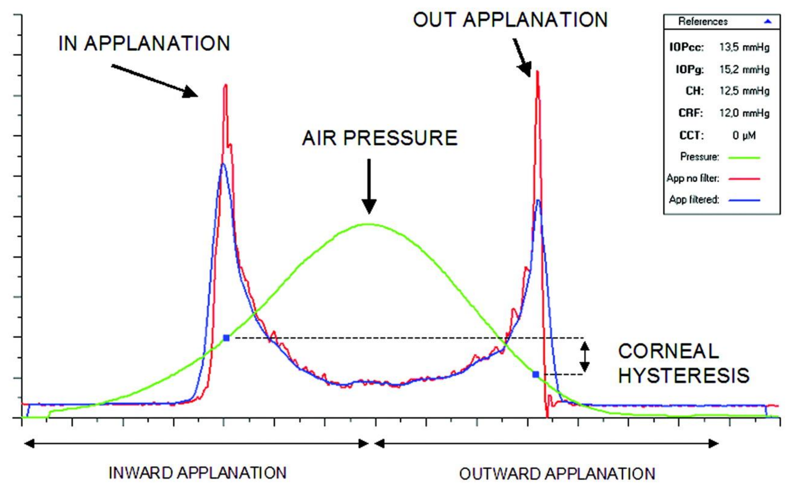

Figure 2. Sample ORA waveform.[3]

The Pentacam (Oculus, Wetzlar, Germany) is an anterior segment tomographer capable of collecting corneal thickness and steepness measurements through use of a rotating Scheimpflug camera. By taking the average thickness of the cornea from concentric rings placed around the thinnest point, the corneal spatial thickness profile (STP) can be derived. Using the STP and ORA data, we compared normal eyes with keratoconic eyes to determine if there is a correlation between the STP and biomechanical parameters (CH and CRF) of the cornea, as well as between these variables and more established risk factors.

Methods

Pentacam and ORA data was collected from 100 normal eyes of 50 patients, and from 32 eyes of 19 patients with keratoconus. Demographics data is presented in Table 1 below.

	KCN (N=19)	Normal (N=50)
Age, mean(sd)	29.5 (3.1)	29.8 (3.3)
Sex		
F	11 (58%)	23 (46%)
M	8 (42%)	27 (54%)

Table 1. Patient demographics data.

Using the spatial thickness profile, a third order polynomial equation was computed using Microsoft Excel (Figure 3). The coefficients of the best fit curve as well as the ORA data were then analyzed using a multilevel, multivariable analysis to determine which variables demonstrated a statistically significant difference between groups of patients

In looking at differences in coefficients, sex and age were not included since they had no bearing on the coefficients themselves, whereas thinnest corneal thickness (thinnest CT), steepest central curvature (steep K), and group status (KCN, normal) did have significant bearing and were therefore included in the multivariate analysis.

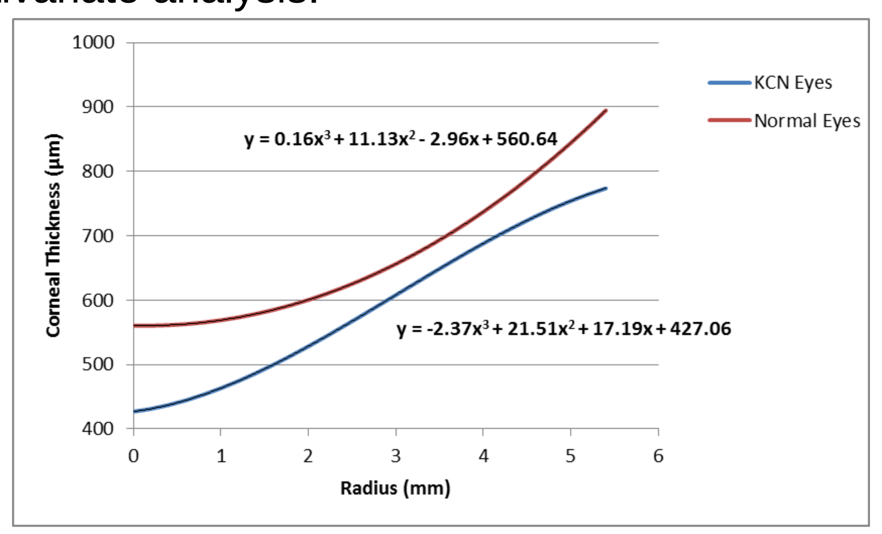

Figure 3. Average cornea spatial thickness profile fit to a 3rd order polynomial.

Results

Table 2 compares the coefficients of the 3rd order polynomial and selected other variables between KCN eyes and normal eyes.

Eye Variables	KCN (N=32)	Normal (N=100)	Difference	p-value
Coefficient				
Third Order	-2.37 (3.67)	0.16 (0.95)	133.5	<0.001
Second Order	21.51 (18.06)	11.13 (6.01)	10.4	0.003
First Order	17.19 (29.56)	-2.96 (8.18)	20.2	<0.001
Constant	427.1 (80.59)	560.6 (33.72)	-133.5	<0.001
Pentacam				
steepest K	51.86 (8.09)	44.09 (1.39)	7.8	<0.001
thinnest CT	433.3 (81.50)	559.8 (33.51)	-126.5	<0.001
ORA				
CH	8.61 (1.87)	10.80 (1.66)	-2.19	<0.001
CRF	7.48 (2.35)	10.72 (1.69)	-3.24	<0.001

Table 2. Comparison of coefficients and other selected variables between normal and KCN eyes.

The results of the multivariate analysis, adjusting for Pentacam steepest K are presented in Table 3. The multivariate model with thinnest CT, did not converge.

	Average Difference Between KCN and Normal	P-Value
Third order Coeff	13.9 times higher in KCN	0.08
Second order Coeff	26.3 (7.8)	<0.001
First Order Coeff	38.3 (7.8)	<0.001
Constant	-121.9 (7.8)	<0.001

Table 3. Multivariate analysis results accounting for Pentacam Steep K.

The association between ORA measurements and the other variables in the model are presented in tables 4 and 5. There was a significant difference in both CH and CRF between groups when adjusted for central steepness as well as a significant difference in CH when adjusted for thinnest CT, however there was no significant difference in CRF between groups when adjusted for thinnest CT.

CRF Outcome		Estimate	SE	p-value
Model 1	Group	-3.1	0.5	<0.001
Model2	Group	20.79	7.4	0.07
	Steep K	0.44	0.16	0.01
	Group*Steep K	-0.53	0.17	0.003

Table 4. Comparison of CRF between groups adjusted for steep K

CH Outcome		Estimate	SE	p-value
Model 1	Group	-2.07	0.44	<0.001
Model2	Group	15.13	6.96	0.03
	Steep K	0.38	0.15	0.02
	Group*Steep K	-0.39	0.16	0.02
Model 3	Group	7.01	3.52	0.05
	Thinnest CT	0.02	0.006	0.004
	Group*Thinnest CT	-0.01	0.007	0.03

Table 5. Association between CH and Steep K and Thinnest CT

Correlation coefficients for the 3rd order polynomial coefficients and Pentacam steep K, thinnest CT, CH and CRF are presented in Table 6 below. In the KCN group, the constant value, first, and third order coefficients were significantly correlated with the Pentacam steep K and thinnest CT, however only the constant value correlated well with one of the biomechanical variables (CRF).

	Pentacam Steep K	Pentacam Thinnest CT	CH	CRF
	KCN Group			
Constant	**-.72*** **	**.98*** **	.34	**.48***
First	**.44***	**-.58** **	-.04	-.35
Second	.28	-.25	-.29	-.12
Third	**-.43***	**.44***	.32	.19
	Normal Group			
Constant	.11	**.99*** **	**.44*** **	**.55*** **
First	.17	.01	.13	.08
Second	-.17	.05	-.09	-.05
Third	**.26***	.02	.12	.10

Note: *** *p* < .001, ** *p* < .01, and * *p* < .05

Table 6. Correlations between Coefficients and selected variables.

Conclusion

- The initial analysis comparing STP between keratoconic and normal eyes validates its diagnostic value[5], but to date little time has been spent attempting to quantify the differences in order to determine whether a screening protocol can be derived from the coefficients of the best fit curve[2]. The fact that all the coefficients and the constant are significantly different is likely secondary to the severity of KCN in a significant portion of the cohort, and more subtle differences would most likely be observed with milder keratoconus.
- CH and CRF were significantly different between groups even when adjusted for central corneal steepness, and with CH even when adjusted for corneal thickness. This provides further evidence that the biomechanical weakness inherent in keratoconic eyes is in large part independent of the shape of the cornea, making warpage simply a marker of disease progression at the microscopic level. This understanding of keratoconus is in line with the popular theories behind the disease's etiology, including collagen disorganization from enzymatic processes, mechanical stress, and oxidative stress[6].
- While it is of interest that the first and third order coefficients in the KCN group correlated well with corneal steepness and the thinnest point, the most important finding was that only the constant value was significantly correlated with one of the biomechanical markers.
- Future comparisons of early KCN eyes to normal eyes with similar corneal thicknesses and curvature, will help elucidate whether the coefficients of the STP can be useful in predicting mechanical function in subclinical disease. Ultimately, the goal is to identify and treat these patients before the disease progresses to requiring surgical intervention.

References

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