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RESEARCH REPORT

Predictive Analysis Between Topographic, Pachymetric and Wavefront Parameters in Keratoconus, Suspects and Normal Eyes: Creating Unified Equations to Evaluate Keratoconus

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ABSTRACT

Purpose: To perform prediction analysis between topographic, pachymetric and wavefront parameters in keratoconus, suspects, and normal cases and to look at the possibility of a unified equation to evaluate keratoconus.

Methods: This cross-sectional, observational study was done in cornea services of a specialty hospital. Fifty eyes of 50 candidates with a diagnosis of normal, keratoconus suspect, and keratoconus were included in each group (total 150 eyes). All eyes underwent detailed analysis on Scheimplug + Placido device (Sirius, CSO, Italy). Main parameters evaluated were topographic [maximum keratometry (Max K_m), average keratometry and astigmatism at 3, 5, and 7 mm], pachymetric [central and minimum corneal thickness (MCT) and their difference, corneal volume] and corneal aberrations [higher order aberrations root-mean-square (HOARMS), coma, spherical, residual].Central tendency, predictive fits and regression models, were computed.

Results: The measured variables had a significant difference in mean between the three groups (Kruskal–Wallis, $p < 0.001$). Max K_m, MCT, and HOARMS had significant fits with other topographic, pachymetric and wavefront parameters, respectively. Inter-relations between these three (Max K_m, MCT, and HOARMS) were also stronger for keratoconus (R^2 from 0.75 to 0.33) compared to suspect/normal eyes (R^2 from 0.15 to 0.003). These three variables (Max K_m, MCT and HOARMS) were used as representative variables to create the unified equations. The equation for the pooled data was ($K\text{max} = 59.5 + 2.3 \times \text{HOARMS} - 0.03 \times \text{MCT}$; $R^2 = 0.7$, $p < 0.001$).

Conclusions: Major variables used for grading keratoconus (MaxKm, MCT, HOARMS) can be linked by linear regression equations to predict the pathology's behavior.

Keywords: Classification, higher order aberrations, keratoconus, pachymetry, predictive analysis, topography

INTRODUCTION

Keratoconus is a progressive, non-inflammatory disorder causing corneal thinning and ectasia.[1] However, recent attempts have shown the possibility to grade the keratoconus also on the pachymetric and corneal wavefront changes.[2–7] Authors have included a combination of these factors such as topography & pachymetry, topography & corneal aberrations/biomechanics to create composite grading scales.[4,6–9]

However, the ideal result would be to create a combined, multifactorial grading scale. This seems biologically plausible because the changes seen in progressive keratoconus, such as increase in the corneal steepness, worsening of the wavefront profile and decreased corneal thickness are the manifestations of a same disease process.

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In the current study, first we evaluate the interrelationship between keratometric, pachymetric and wavefront changes in normal, suspect, and keratoconic eyes. Then we attempt to create unified equations from the data to predict the progressive relationship between these factors and their changes with progressive ectasia. To the best of our knowledge, this is the first study in published literature attempting to create these equations between all the three major factors: topography, pachymetry and higher order aberrations.

METHODS

This cross-sectional, comparative study was performed at the cornea and refractive surgery services of a specialty hospital. Informed consents were taken from all the candidates. The study had the approval of the institutional review board and followed all tenets of the Declaration of Helsinki. Consecutive young (15–35 years) candidates presenting to our hospital for topographic analysis were included in the study. The inclusion criteria were either of the following: screening for elective vision correction including lasik, high astigmatism, frequent change of glasses and suspicion or clinical diagnosis of primary keratoconus. Those with a history of any ocular surgery or morbidity including dry eyes were excluded. Patients with history of hydrops were also excluded. All contact-lens wearers were asked to be off soft contact lenses for a minimum of 3 weeks and rigid gas-permeable lenses for a minimum of 5 weeks. All the candidates underwent rotating Scheimpflug analysis plus Placido disc assessment-based topography with Sirius topographer (Costruzione Strumenti Oftalmici (CSO), Scandicci FI, Italy). All the scans were performed by a single experienced examiner (M. S.) and evaluated for satisfactory scanning by two different observers (G. P., D. S.).

The KISA% index was used to classify the eyes as normal, keratoconus suspects or keratoconus. The index and its derivation has been described in detail elsewhere in the literature.[2,10]

Sample Size Calculation

Sample size determination was done earlier based on the previous study where the corneal pachymetry was 524.2 ± 49.5, and $449.3 \pm 73.7\,\mu m$ for suspect versus keratoconic corneas.[7] The required sample size was more than 15 for each group considering a desired power of 0.8 and alpha of 0.5.

For the regression analysis, we used an *a priori* calculation of multiple regression fit between maximum curvature and pachymetric factors (two predictors, minimum pachymetry and difference in central & minimum pachymetry). This best-fit curve had an *R*-squared of 0.2.[7] With an estimated power of 0.8, and the minimum sample size was 48 for a maximum of three predictors. Therefore, a sample size of 50 each was finalized for the subgroups.

Case Selection Methodology

All the normal and suspect cases were from the pool of candidates who had come for refractive surgery screening. As our practice is primarily referral based, most of the cases with keratoconus were patients who were referred for screening of keratoconus and found to be having the disease.

Fellow eyes of patients with keratoconus may have subtle changes not visible on early testing. Therefore to avoid any relative bias, only cases with no evidence of keratoconus or suspect in both eyes were included in the 50 cases of the group ''normal''. In cases with similar grade in both eyes (OU Keratoconus or OU Keratoconus suspect or OU normal), one eye was randomly selected using a computer-generated binary response sequence (OD/OS—0/1). In patients with a diagnosis combination of Keratoconus suspect and Keratoconus, one eye was randomly selected using a computer generated binary response sequence (OD/OS—0/1). Cases with unilateral keratoconus or keratoconus suspect eye were included in the study without the randomization of the eye to be included. First 50 cases reached in the three groups were included in the analysis.

Data Retrieval and Statistical Analysis

The four map display was used for pachymetry and topography outcomes using corneal thickness and tangential anterior maps, respectively. Other parameters noted were maximum keratometry (at the apex and confirmed using real-time cursor controlled display), Average Keratometry at 3 mm, 5 mm and 7 mm, minimum corneal thickness (MCT) and corneal volume at 10 mm. The corneal wavefront display was used for wavefront measurements. All the wavefront data were measured at 6 mm diameter. Total corneal (combined anterior + posterior) aberration was noted. Wavefront error (WFE), higher order aberrations root-mean-square (HOARMS), astigmatism, coma, spherical aberration and residual (non-coma, non-spherical HOARMS) were noted. The images were saved as exported screenshots and pdfs files. The data were manually entered into an MS Excel (Microsoft, Richmond, VA) sheet. The data were then transferred to SPSS 16.0 (SPSS Inc., Chicago, IL) for the analysis. Measures of central were used to for the descriptive data. Best-fit curves and linear regression plots were drawn using SPSS.

TABLE 1 Demographic distribution of the study population.

	Normal ($n=50$)	Suspect ($n=50$)	Keratoconus ($n=50$)	Pooled ($n=150$)	p Value
Age (years) in mean ± SD (range) format	24.4 ± 6.3 (15–35)	24.3 ± 5.8 (15–35)	26.3 ± 5.9 (15–34)	24.9 ± 6.1 (15–35)	0.18 (ANOVA)
Gender (M:F ratio)	23:27	20:30	19:31	62:88	0.6 (χ^2)
Eye (OD: OS ration)	30:20	24:26	22:28	76:74	0.4(χ^2)

TABLE 2 Topographic parameters: comparison between the three groups.

					95% confidence interval for mean		Range		
Parameter (units)	Group	N	Mean	SD	Lower bound	Upper bound	Minimum	Maximum	p Value (Kruskal–Wallis test)
Maximum keratometry (D)	Normal	50	43	1.4	42.6	43.4	40.1	46.4	<0.001
	Suspects	50	47.8	0.8	47.6	48	45.3	49.1	
	Keratoconus	50	55.8	5.1	54.3	57.2	47.5	70.7	
	Total	150	48.9	6.1	47.9	49.8	40.1	70.7	
Average keratometry at 3 mm (D)	Normal	50	42.5	1.4	42.1	42.9	39.5	46.2	<0.001
	Suspects	50	46	1.2	45.7	46.4	41.1	48.2	
	Keratoconus	50	48.5	4.5	47.2	49.8	41.2	66.5	
	Total	150	45.7	3.7	45.1	46.3	39.5	66.5	
Average keratometry at 5 mm (D)	Normal	50	42.5	1.4	42.1	42.9	39.4	46.1	<0.001
	Suspects	50	45.9	1.2	45.5	46.2	41.2	47.9	
	Keratoconus	50	48	4	46.9	49.1	41.3	64.9	
	Total	150	45.4	3.4	44.9	46	39.4	64.9	
Average keratometry at 7 mm (D)	Normal	50	41.9	3	41.1	42.8	23.4	45.8	<0.001
	Suspects	50	45.6	1.1	45.3	45.9	41.1	47.6	
	Keratoconus	50	47.2	3.5	46.2	48.2	41.3	63.1	
	Total	150	44.9	3.5	44.4	45.5	23.4	63.1	
Astigmatism at 3 mm (D)	Normal	50	1.1	1.9	0.6	1.7	0	11.3	<0.001
	Suspects	50	2.9	1.6	2.4	3.3	0.4	10.3	
	Keratoconus	50	3.9	2.4	3.3	4.6	0.3	12.7	
	Total	150	2.6	2.3	2.3	3	0	12.7	
Astigmatism at 5 mm (D)	Normal	50	1	1.3	0.6	1.4	0	7.9	<0.001
	Suspects	50	2.7	1.4	2.3	3.1	0.5	8.3	
	Keratoconus	50	3.3	2	2.7	3.9	0.2	10.3	
	Total	150	2.3	1.9	2	2.6	0	10.3	
Astigmatism at 7 mm (D)	Normal	50	0.9	1.1	0.6	1.2	0	5.8	<0.001
	Suspects	50	2.5	1.2	2.1	2.8	0.4	6.5	
	Keratoconus	50	2.8	1.8	2.3	3.4	0.2	8	
	Total	150	2.1	1.6	1.8	2.3	0	8	

RESULTS

Demographics

The mean age, gender (males/females) and the laterality (OD/OS) ratio were comparable in the three groups (Table 1).

Topographic Characteristics

The topographic characteristics, including maximum keratometry, average keratometry and astigmatism at 3, 5 and 7 mm were considered. Means, standard deviations, 95% confidence intervals of mean were computed (Table 2). The means were significantly different between the three groups, normal, suspects, and keratoconus ($p<0.001$, Kruksal–Wallis one-way analysis of variance test) (Table 2).

Pachymetric Characteristics

Mean, standard deviation, and 95% confidence interval of mean were computed for central corneal thickness (CCT), MCT and the numerical difference between central and minimum corneal thickness (δCT). The means were significantly different between the three groups, normal, suspects and keratoconus ($p<0.001$, Kruskal–Wallis test) (Table 3).

TABLE 3 Pachymetric and corneal wavefront criteria: difference between the three groups.

Parameter (units)	Group	Mean	SD	95% confidence interval for mean		Range		*p* Value (Kruksal–Wallis test)
				Lower bound	Upper bound	Minimum	Maximum	
Corneal volume at 10 mm (mm^3)	Normal	57.2	3.3	56.3	58.2	51.3	64.9	<0.001
	Suspect	55.4	4.6	54.1	56.8	42.8	62.9	
	Keratoconus	53	7.7	50.8	55.1	5.7	60.6	
	Total	55.2	5.8	54.3	56.1	5.7	64.9	
Minimum corneal thickness (MCT) (μ)	Normal	548	31.3	539.1	556.9	501	616	<0.001
	Suspect	496.9	47.8	483.3	510.5	382	627	
	Keratoconus	447.6	45.2	434.7	460.4	291	529	
	Total	497.5	58.6	488	506.9	291	627	
Central corneal thickness (CCT) (μ)	Normal	551.6	31.2	542.7	560.5	510	619	<0.001
	Suspect	502.9	46.8	489.6	516.2	401	651	
	Keratoconus	467.3	41.4	455.5	479.1	304	533	
	Total	507.3	53	498.7	515.8	304	651	
Corneal thickness difference (δCT) (μ)	Normal	3.6	2.5	2.9	4.4	1	13	<0.001
	Suspect	6	6.3	4.2	7.8	1	28	
	Keratoconus	19.7	15.6	15.3	24.2	0	93	
	Total	9.8	12.1	7.8	11.7	0	93	
Total wavefront error (μ)	Normal	0.8	0.4	0.7	0.9	0.4	2	<0.001
	Suspect	2.3	1	2	2.6	0.5	4.8	
	Keratoconus	4.8	3.4	3.9	5.8	1.6	18.8	
	Total	2.6	2.6	2.2	3	0.4	18.8	
HOARMS (μ)	Normal	0.4	0.1	0.4	0.5	0.2	0.7	<0.001
	Suspect	0.8	0.4	0.7	0.9	0.3	1.9	
	Keratoconus	3	2.2	2.4	3.6	0.6	13.3	
	Total	1.4	1.7	1.1	1.7	0.2	13.3	
Astigmatism $Z_2^{\pm 2}$ (μ)	Normal	0.6	0.4	0.5	0.7	0.1	1.9	<0.001
	Suspect	2.1	1	1.9	2.4	0.4	4.7	
	Keratoconus	3.6	3	2.7	4.4	0.3	14.4	
	Total	2.1	2.2	1.7	2.4	0.1	14.4	
Coma $Z_3^{\pm 1}$ (μ)	Normal	0.3	0.1	0.2	0.3	0	0.6	<0.001
	Suspect	0.5	0.3	0.4	0.6	0.2	1.6	
	Keratoconus	2.1	1.3	1.8	2.5	0.3	4.8	
	Total	1	1.1	0.8	1.1	0	4.8	
Spherical Z_4^0(μ)	Normal	0.2	0.1	0.2	0.3	0.1	1	0.003
	Suspect	0.2	0.1	0.2	0.2	0	0.5	
	Keratoconus	0.5	0.6	0.3	0.7	0	3.4	
	Total	0.3	0.4	0.2	0.4	0	3.4	
Residual HOARMS (non-coma, non-spherical) (μ)	Normal	0.2	0.1	0.2	0.2	0.1	0.5	<0.001
	Suspect	0.5	0.3	0.4	0.6	0.1	1.5	
	Keratoconus	1.7	2	1.1	2.3	0.3	12.2	
	Total	0.8	1.3	0.6	1	0.1	12.2	

All wavefront measurement are at 6 mm diameter.
HOARMS, higher order aberrations root mean square.

Corneal Wavefront Analysis

Mean, standard deviation, 95% confidence interval of mean was computed for four components Astigmatism, total HOARMS, total Wavefront error and following higher order terms: coma, spherical aberration and residual (non-coma, non-spherical HOARMS) higher order aberrations. The means were significantly different between the three groups, normal, suspects and keratoconus ($p < 0.001$, Kruskal–Wallis test) (Table 3).

Inter-relation Between Topographic, Wavefront and Pachymetric Variables within Class Categories

Topographic Factors

The topographic factors keratometry at 3 mm, 5 mm and 7 mm (AvgKm at 3 mm, AvgKm at 5 mm, AvgKm at 7 mm, respectively), and astigmatism at 3 mm, 5 mm and 7 mm (Astigmatism at 3 mm, Astigmatism at 5 mm, Astigmatism at 7 mm, respectively) were entered into a regression model to analyze their

TABLE 4 Intra-class predicting factors and their linear regression equations.

Dependent variable (class, units)	Group	R-squared (R^2), p value for the fit	Intra-class predicting factors (δR^2)	Linear regression equation with the significant predictors and the given R^2
Maximum keratometry (topography, D)	Pooled	$R^2 = 0.64$, $p < 0.001$	AvgKm at 5 mm ($\delta R^2 = 0.54$) Ast at 3 mm ($\delta R^2 = 0.04$) Ast at 7 mm($\delta R^2 = 0.02$)	Kmax = (−9.9) + 1.3 × AvgKm at 5 mm + 1.6 × Ast at 3 mm + 1.6 × Ast at 7 mm.
	Normal	$R^2 = 0.94$, $p < 0.001$	AvgKm at 3 mm	Kmax = 0.75 + 0.99 × AvgKm at 3 mm.
	Suspects	none	–	–
	Keratoconus	$R^2 = 0.20$, $p = 0.01$	AvgKm at 7 mm	Kmax = 24.4 + 0.67 × AvgKm at 7 mm
HOARMS (corneal wavefront at 6 mm, μ)	Pooled	$R^2 = 0.99$, $p < 0.001$	ResAb ($\delta R^2 = 0.84$) coma ($\delta R^2 = 0.15$) SphAb ($\delta R^2 = 0.0003$)	HOARMS = 0.009 + 0.77 × ResAb + 0.73 × coma + 0.16 × SphAb.
	Normal	$R^2 = 0.91$, $p < 0.001$	Coma ($\delta R^2 = 0.63$) ResAb ($\delta R^2 = 0.26$) SphAb ($\delta R^2 = 0.03$).	HOARMS = 0.07 + 0.61 × coma + 0.69 × ResAb + 0.15 × SphAb.
	Suspects	$R^2 = 0.99$, $p < 0.001$	Coma ($\delta R^2 = 0.75$) ResAb ($\delta R^2 = 0.23$) SphAb ($\delta R^2 = 0.10$).	HOARMS = (−0.11) + 0.73 × coma + 0.71 × ResAb + 0.36 × SphAb.
	Keratoconus	$R^2 = 0.99$, $p < 0.001$	ResAb ($\delta R^2 = 0.84$) Coma ($\delta R^2 = 0.15$	HOARMS = 0.001 + 0.81 × ResAb + 0.74 × coma.
Minimum corneal thickness (Pachymetry, μ)	Pooled	$R^2 = 0.96$, $p < 0.001$	CCT	MCT = (−53.4) + 1.08 CCT.
	Normal	$R^2 = 0.99$, $p < 0.001$	CCT ($\delta R^2 = 0.994$) corVol ($\delta R^2 = 0.001$).	MCT = (−8.28) + 0.95 × CCT − 0.49 × CorVol
	Suspects	$R^2 = 0.98$, $p < 0.001$	CCT ($\delta R^2 = 0.98$) CorVol ($\delta R^2 = 0.003$)	MCT = (−25.5) + 0.91 × CCT− 1.1 × CorVol
	Keratoconus	$R^2 = 0.87$, $p < 0.001$	CCT	MCT = (−31.2) + 1.02 × CCT

HOARMS, higher order aberrations root mean square at 6 mm; ResAb, residual aberration (non-coma, non-spherical); SphAb, spherical aberration; MCT, minimum corneal thickness; CCT, central corneal thickness; CorVol, corneal volume at 10 mm.
Kmax, maximum keratometry; avgKm, average keratometry; Ast, astigmatism
At 3 mm, at 5 mm, at 7 mm: at diameters of 3 mm, 5 mm and 7 mm, respectively.
δR^2, change in total R^2 by inclusion of the mentioned variable in the regression model, used only in cases with at least two predicting factors.

prediction of maximum keratometry. Initially, the data were assessed for the entire study cohort ($n = 150$) and then for the subgroups ($n = 50$ each) (Table 4).

For the pooled data of the entire cohort, Maximum Keratometry (Kmax) had a predictive linear equation ($R^2 = 0.64$, $p < 0.001$) as follows: $K\text{max} = (-9.9) + 1.3 \times$ Avg K at 3mm $+ 1.6 \times$ Astigmatism at 3mm $+ 1.6 \times$ Astigmatism at 7mm. Subgroup analysis is given in Table 4.

Corneal Higher Order Aberration Factors

Factors measured in corneal higher order wavefront were kept at three so as to minimize chances of spurious association and dilution of clinical relevance when using multiple small Zernike terms. The aberrations terms were coma, spherical aberration (SphAb) and the residual aberration (ResidualAb) (consisting of the root-mean-square of all the non-coma, non-spherical aberration terms). These were entered in a predictive model to analyze the component of role they played on the total HOARMS. First the data were assessed for the entire study cohort ($n = 150$), and then for the subgroups ($n = 50$ each) (Table 4).

For the pooled data of the entire cohort, HOARMS was expectedly predicted significantly ($R^2 = 0.99$, $p < 0.001$) the linear equation HOARMS $= 0.009 + 0.77 \times$ ResidualAb $+ 0.73 \times$ coma $+ 0.16 \times$ SphAb. Subgroup analysis is given in Table 4.

Pachymetric Factors

For the corneal thickness parameters, MCT, CCT, difference in central and minimum corneal thickness (δCT) and the corneal volume at 10 mm (CorVol) were assessed. First the data were assessed for the entire study cohort ($n = 150$), and then for the subgroups ($n = 50$ each) (Table 4).

For the pooled data of the entire cohort, MCT was predicted significantly ($R^2 = 0.96$, $p < 0.001$) only by the CCT. The predictive linear equation was MCT $= (-53.4) + 1.08$ CCT. Subgroup analysis is given in Table 4.

Best-Fit Analysis between Maximum Topography (MaxK), Minimum Corneal Thickness (MCT) and Total HOARMS

As stated above in the methods section, MCT, MaxK and HOARMS were identified as the three primary pachymetric, keratometric and wavefront parameters based on previous studies. Predictive plots were drawn to compare the inter-relation between these three variables. Data for pooled ($n = 150$), normal ($n = 50$), suspects ($n = 50$) and keratoconus ($n = 50$) were used. Non-linear (quadratic, cubic, exponential) models were tried in case the linear fit was not strong or non-significant. Best-fit models were computed and constants were included in all of the equations to maintain the relevance and comparability of R^2 statistic. The predictive equations and figures showed interesting trends towards strong and significant fits between these three variables in keratoconic eyes and the pooled data.

A good, significant quadratic fit in pooled data ($R^2 = 0.45$, $p < 0.001$) was found when MCT and maximum keratometry were compared (Figure 1). On group-wise evaluation, the keratoconic eyes had a fair, significant quadratic fit ($R^2 = 0.20$, $p = 0.005$). Compared to this suspects had a poorer linear fit ($R^2 = 0.08$, $p = 0.04$). The normal eyes had a no significant predictive fit between MCT and maximum keratometry.

For comparisons between HOARMS and maximum keratometry, there was a good, significant quadratic fit in pooled data ($R^2 = 0.75$, $p < 0.001$) (Figure 2). On group-wise evaluation, the keratoconic eyes had a fair, significant quadratic fit ($R^2 = 0.59$, $p = 0.005$). Compared to this both the subgroups of suspects (and normal eyes) had no significant predictive fit between HOARMS and maximum keratometry.

For comparisons between HOARMS and MCT, there was a good, significant cubic fit in pooled data ($R^2 = 0.46$, $p < 0.001$) (Figure 3). On group-wise evaluation, the keratoconic eyes had a fair, significant linear fit ($R^2 = 0.33$, $p < 0.001$). Suspects showed a mildly significant linear fit ($R^2 = 0.10$, $p = 0.03$) and the normal eyes showed a mildly significant quadratic fit ($R^2 = 0.15$, $p = 0.02$) between HOARMS and MCT.

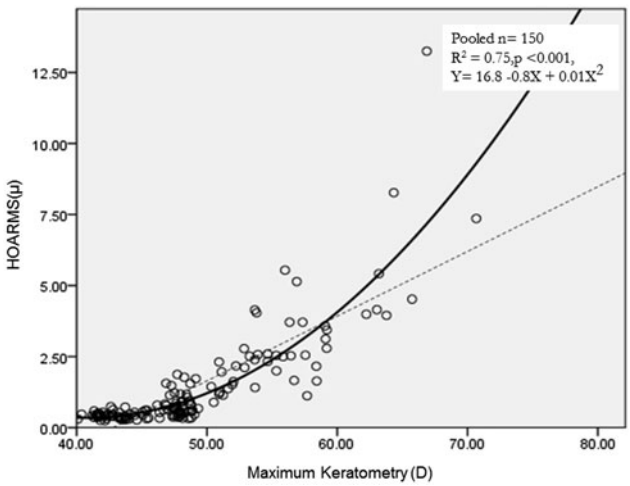

FIGURE 2 Predictive best-fit curve between maximum keratometry (x-axis) and higher order aberrations (y axis) for all the candidates ($n = 150$). The R^2 statistic, p value for the fit and the equation are given in the box. The solid line shows the best-fit equation's plot (quadratic, significant) and the dotted line shows the linear plot in comparison.

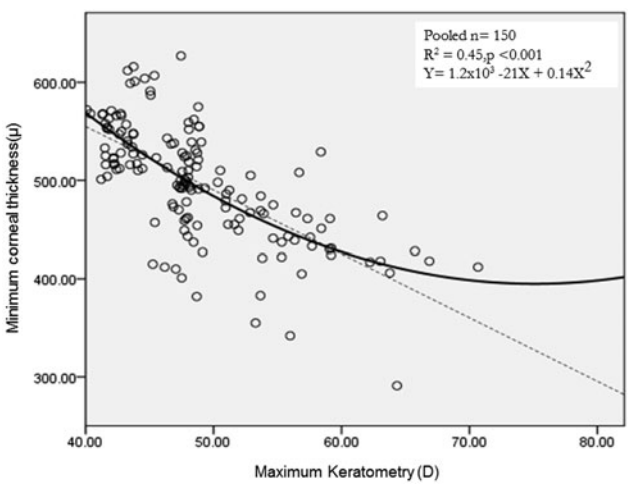

FIGURE 1 Predictive best-fit curve between maximum keratometry (x-axis) and minimum corneal thickness (y axis) for all the candidates ($n = 150$). The R^2 statistic, p value for the fit and the equation are given in the box. The solid line shows the best-fit equation's plot (quadratic, significant) and the dotted line shows the linear plot in comparison.

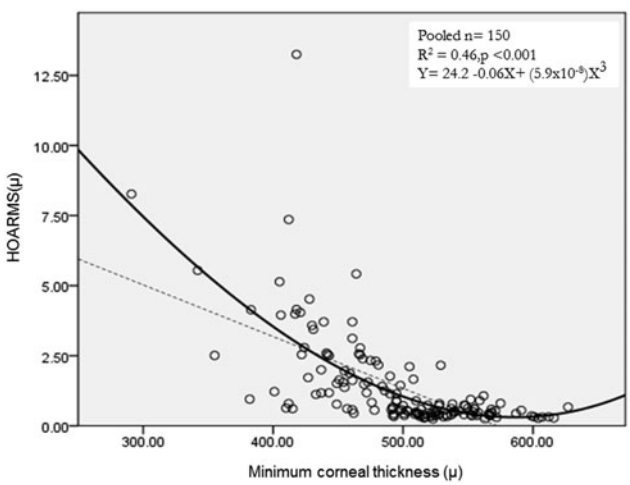

FIGURE 3 Predictive best-fit curve between minimum corneal thickness (x-axis) and higher order aberrations (y axis) for all the candidates ($n = 150$). The R^2 statistic, p value for the fit and the equation are given in the box. The solid line shows the best-fit equation's plot (cubic, significant) and the dotted line shows the linear plot in comparison.

Single-Unified Linear Regression Analysis to Predict the Combined Role of HOARMS and MCT on Kmax

For the overall data ($n = 150$), *K*max depend significantly ($R^2 = 0.71$, $p < 0.001$) on both HOARMS ($\delta R^2 = 0.67$) and MCT ($\delta R^2 = 0.04$), with the predictive linear equation being $K\text{max} = 59.5 + 2.3 \times \text{HOARMS} - 0.03 \times \text{MCT}$.

For the normal subgroup, there was no significant prediction seen. For the suspect group, there was weak but significant fit with only MCT ($R^2 = 0.08$, $p = 0.04$). For the keratoconic group, predictive linear fit was seen only with HOARMS and not with MCT ($R^2 = 0.56$, $p < 0.001$). The predictive linear equation was $K\text{max} = 50.5 + 1.8 \times \text{HOARMS}$. However, a two variable analysis between these two variables HOARMS and *K*max was done earlier and it showed a slightly better quadratic fit with a higher R ($R^2 = 0.59$, $p = 0.005$).

DISCUSSION

Our study first aimed at finding a predictive fit between these three major parameters used for keratoconus grading. All the topographic, wavefront and pachymetric parameters were found to be significantly different between the normal, suspect and keratoconic eyes. Therefore, the next objective was to identify those major parameters which were inter-predictive within their own types, i.e. pachymetric type factors, keratometric type factors and wavefront type factors.

Within the keratometric type factors, we looked at the prediction of maximum keratometry by other factors. Maximum keratometry (or the apical keratometry) is an important factor for grading keratoconus. It may also have implications in surgical treatment of keratoconus. A recent study has shown that eccentricity of the keratoconus cone (and hence the maximum keratometry) may have no role in outcomes with contact lens fitting; however, another study showed that it may have implications in surgical interventions such as collagen cross-linking.[11,12] We found that maximum keratometry (MaxK) was governed differently in normal, suspect and keratoconic eyes. It corroborated very well with central 3 mm keratometry in normal cases. This was probably because the steepest part of the cornea lies within or near the central 3 mm in the normal cases, as these corneas tend to maintain a normal aspheric profile. However, in the keratoconic cases, a larger zone (K_m at 7 mm) of corneal power was seen to predict the maximum keratometry. The cone in keratoconus is eccentric in a large majority of cases, and therefore this finding had a good clinical extrapolation.[13,14]

On evaluating the corneal wavefront factors, we found that coma and other asymmetrical aberrations played a major role in keratoconus. We found that the component of spherical aberration and its role becomes much lesser in keratoconic eyes (statistically non-significant) compared to the other two groups. These findings are in agreement with previous studies. Saad and Gatniel have noted that coma and trefoil can be used to differentiate between normal and suspect keratoconus.[15] Kosaki et al. found that larger amounts of trefoil, coma, tetrafoil, and secondary astigmatism exist in keratoconic eyes.[16] Alio and Shabayek have also demonstrated that coma plays a major role in keratoconic eyes.[8]

When evaluating the pachymetric factors, we found that the corneal thickness at the thinnest point (MCT) was strongly predicted by CCT in normal and suspects. However, this relationship tends to become weaker in the keratoconic group. This strongly suggests the fact that the area of thinning in keratoconus can be away from the center and thus reiterates the importance of doing a multiple slit-type of pachymetry rather than single, central touch pachymetry to detect the area of MCT.

In the second part of the analysis, we looked at the best-fit predictive models between the three major parameters. This was an attempt to understand the relationship between these three. Corneas tend to get thinner and more aberrated with increasing maximum keratometry in the keratoconic eyes. This underlines the fact that more severe the keratoconus, steeper, distorted and thinner the cornea becomes. The normal and suspect corneas did not have a similar relationship between MCT and *K*max. Therefore, it can be derived that in our cohort, normal or suspects did not have this ''coupled'' association between these two factors.

Interestingly, the overall HOARMS had a moderate-linear fit with maximum keratometry. This could be because vertical coma produced due to the difference in location of the steepest cornea and the center of the cornea could be proportional to the numerical value of maximum keratometry.

The final aim of this study was to evaluate if these factors can be grouped into a single, predictive equation. The pooled data were used to create a single-unified regression equation which had a good fit ($\sim$71% data based on the R-squared statistic). For the cases that fit well to this equation, per unit change in *K*max was directly correlated to 2.3 units change in HOARMS and (-0.03) units change in the minimum corneal thickness. For the keratoconic cases itself, a change of 1.8 units of HOARMS caused 1 unit of increase in maximum keratometry in approximately 60% of the data based on the R-squared statistic.

It is also important to evaluate the finding of this study in terms of the clinical relevance of these equations. These dedicated equations provide an

insight to the practicing clinician on the pattern of keratoconic progression. Furthermore, they also give statistical importance about the association between different parameters. For example, the central zone's keratometry (K_m at 3 mm) almost completely governs the determination of maximum keratometry ($R^2 = 0.94$), but it has no statistical role in keratoconic corneas. Therefore, clinicians should not rely on central keratometry in the diagnosis of keratoconus. However, keratometry at 7 mm zone is much more useful for a clinician when suspecting keratoconus. This is so because maximum keratometry has a significantly predicting equation with the same in the keratoconic cohort. For higher order aberrations, there was a decreasing role of spherical aberration and increasing role of asymmetric aberrations with increasing ectasia. For clinicians with access to wavefront aberrometry, this finding can be clinically useful. For example, an increase in coma over follow-up can be sensitive sign for progression of keratoconus. The change in visual symptoms, for example, increase in the ''tailing of light'', especially during night driving, can suggest an increase in coma/asymmetric aberrations. Based on the knowledge derived from these predictive equations, this can raise a suspicion on worsening of the corneal ectasia. Some clinicians may not have access to Scheimpflug or Scanning slit facilities. For them, these equations can be used to calculate the predicted range of minimum corneal thickness by accessing the CCT using methods such as ultrasound pachymetry in cases with keratoconus. This would help them in referring a case timely. The equations combining the three parameters, HOARMS, keratometry, and thickness have useful insights for the clinician. The equation predicts that the decrease in minimum corneal thickness (measured clinically) and increase in HOARMS (deterioration of visual quality or worsened point spread function) are strongly suggestive factors for an increase in the corneal ectasia. The relationship was linear with approximately 60% data fitting the equation with maximum keratometry. The awareness of this relationship will give clinicians three different vantage points to assess keratoconus progression in their patients.

There are certain shortcomings in our study. We did not use the modern neural network-based keratoconus classification systems in our study. Rather, we used the KISA% index. This was done to ensure the uniformity in interpretation of data and increased reproducibility of the study as the KISA% is a very commonly available and simple index to use. Our sample size was not very large, and the equations would get more refined with larger sample sizes. The next step would be to incorporate more cases and also to validate these equations on a test population and determine their sensitivity and specificity. Our population base was predominantly South Asian and Arab, and it remains to be seen if racial variations would have an effect on the predictive capacity of these equations.

To conclude, our study provides insights into statistical interrelation between three major determinants for grading keratoconus. We were successfully able to create a unified regression equation between the major keratometric, pachymetric and wavefront factors in the overall data as well as the keratoconic subgroups. Further pooling of data from different databases into these regression curves would increase their predictive capacity.

DECLARATION OF INTEREST

The authors report no conflicts of interest. This manuscript has not been published elsewhere, and it has not been submitted simultaneously for publication elsewhere.

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