Role of Corneal Epithelial Measurements in Differentiating Eyes with Stable Keratoconus from Eyes that Are Progressing

Marcony R. Santhiago, MD PhD,[1] *Larissa R. Stival, MD,*[1,2] *Daniella C. Araujo, PhD,*[3]
Newton Kara-Junior, MD, PhD,[1] *Marcia C. Toledo, MD*[2]

Purpose: To evaluate measures of corneal epithelium in eyes that showed documented signs of keratoconus (KC) progression and compare with stable eyes and healthy controls. Also, to determine the correlation of these epithelial parameters with maximum keratometry (K max) and pachymetry.

Design: Prospective, observational, comparative study.

Participants: One-hundred and fifty eyes from 150 patients. The study included 50 eyes from patients with documented KC progression, 50 eyes with stable KC, and 50 clinically normal eyes to serve as controls.

Methods: A spectral−domain (SD)-OCT imaging was obtained in all eyes, and mean values were compared between the groups. The correlation of epithelial parameters with K max and thinnest pachymetry was also investigated.

Main Outcome Measures: For the purposes of this study, the epithelial measures maximum, minimum, superior, and inferior values as well as the difference between the minimum and maximum (min−max) and epithelial standard deviation were considered, obtained from SD-OCT and compared between groups. Measurements of the thinnest point and min−max in pachymetry were also recorded.

Results: The only epithelial parameter that presented a statistically significant difference between stable and progressive KC was epithelium min−max. Although stable KC presented epithelium min−max mean values of -18.2 ± 6.6, progressive KC eyes presented mean values of -23.4 ± 10.3 ($P < 0.0001$). Epithelial maximum ($P = 0.16$), minimum ($P = 0.25$), superior ($P = 0.28$), inferior ($P = 0.23$), and standard deviation ($P = 0.25$) values were not significantly different between stable and progressive eyes. Difference min−max pachymetry points in stable (-108.3 ± 33.5) and progressive KC (-115.2 ± 56.0) were not significantly different ($P = 0.723$). There was no significant correlation between epithelium min−max with corneal thinning ($P = 0.39$) or K max ($P = 0.09$) regardless of disease progression.

Conclusions: Epithelial measures are useful to identify KC eyes that are progressing; the parameters that measure the difference between min−max epithelium points were significantly different between stable and progressive groups, unlike this difference in pachymetry. Finally, this epithelial parameter seems to be independent of corneal thinning and K max.

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Keratoconus (KC) is a structural and progressive disease, leading to changes in curvature and thickness and poor visual acuity.[1] A collective international effort group has been engaged in developing and validating new tools for diagnosing this disease at an increasingly early stage.[2,3] With the advent and popularization of measures that interrupt its progression, avoiding or at least postponing a corneal transplant, it has become essential to better understand these new parameters in eyes that are progressing, making viable intervention before the disease has more clinical severe repercussions.[4]

Studies show that there are marked epithelial changes in eyes with KC, and therefore, the analysis of this layer can be helpful in the early diagnosis of this disease.[5−10] From modifications in protein expression to structural alterations

that ultimately represent thinning in steeper areas and adjacent thickening, it has recently been shown that the incorporation of epithelial analysis can increase the sensitivity for early diagnosis.[11,12] An epithelial apoptosis process may explain the thinning of this corneal layer.[11]

Recently, relevant factors on the KC natural history of the disease have been identified in a more methodologically appropriate design.[1] A steepening in the maximum keratometry (K max) > 1 diopter (D) over 1 year is higher than expected for the natural history, being an essential sign of active progression.[1] Although little or so is known about the behavior of the epithelial layer in KC that is actively progressing.

With wider mapping through spectral−domain (SD)-OCT, it is currently possible to reproducibly measure

parameters of the epithelial thickness.[13,14] This study aimed to identify measures of corneal epithelium that behave differently in stable KC from those in progression.

Methods

Study Design and Subjects

This is a prospective comparative observational study approved by the institution's ethics committee (University of Sao Paulo) and the Brazilian National ethics and research committee. This study also followed the tenets of the Declaration of Helsinki. Informed consent was obtained from all patients.

The study included patients with documented KC progression, patients with stable KC, and clinically normal eyes to serve as controls evaluated at private practice from January 2018 to January 2020. The inclusion criteria for cases comprised all patients with a documented diagnosis of KC. We excluded patients who presented with allergic processes that were active.[15] It is known that acute ocular allergic processes are related to the increase in inflammatory cytokines in tears, so acute allergy could be a confounding factor for epithelial measurements because the levels of inflammatory cytokines could be even higher depending on the severity of the allergy.[12] The most prominent signs and symptoms were the following:

1. Eyelids: severe eczema of the eyelids and periorbital skin, prominent, periorbital darkening (allergic "shiners"), or the absence of the lateral eyebrow.
2. Conjunctiva: papillary hypertrophy of the upper and lower tarsal conjunctiva. Gelatinous hypertrophy of the limbal conjunctiva (Limbal Horner-Trantas dots).
3. Cornea: punctate epithelial keratitis, persistent epithelial defects, pannus formation, neovascularization, subepithelial scarring, and lipid keratopathy.
4. Symptoms: pain, redness, itching, burning of the eyes, foreign body sensation, and watery to thick ropy mucous discharge.

Patients with any other ocular pathologies, systemic inflammatory or autoimmune diseases, diabetes mellitus, with a history of medications that increase hormone levels, pregnancy, or with recent (< 6 months) systemic/ocular allergy or infection history were excluded from the study. Patients using contact lenses were instructed to discontinue their use for a minimum of 4 weeks before the eye examination.

Patients using any type of antiinflammatory/antiallergic ocular or systemic medications or who had undergone any ocular surgical intervention for both eyes were also excluded. Patients who had undergone a surgical intervention in only 1 eye were included in the study, and the eye without surgery was included. All subjects also underwent a dry eye evaluation using the Schirmer test, corneal staining with green lissamin, and tear film breakup time. Subjects with concurrent symptoms of dry eye were excluded.

Patient Selection

The progressive KC group included eyes with an increase in K max of 1.00 D within 1 year.[1] The corneal topographic imaging was obtained using a Dual Scheimpflug device (Galilei G6, Ziemer Ophthalmic Systems AG) and were the same indicated for corneal cross-linking.

The stable KC group consisted of patients with KC that did not meet the objective criteria for progression.

Additionally, a group of clinically normal eyes, paired by age, was also included to control. Although we used only 1 eye, clinically normal eyes had both eyes within normal standards. In this group, the presence of subclinical ectatic corneal disease was excluded bilaterally. Data collected included gender, age, the patient's ocular, and medical history. Again, careful attention was paid to evaluate and exclude the presence of a clinical history of atopy. In addition, all patients were requested to answer a questionnaire on eye rubbing, irritation, and pain in their eyes to rule out ocular allergy.

For all groups, only 1 eye per patient was included in the study. When the patient had 1 eye in progress, and the other eye stable, only the eye in progress was considered for this study.

All patients underwent a complete ophthalmic examination, including uncorrected distance visual acuity, best spectacle-corrected visual acuity, and manifest refraction. The same examiner (L.R.S.) carefully performed the refraction. Uncorrected distance visual acuity and best spectacle-corrected visual acuity were measured in decimal Snellen and converted to the logarithm of the minimum angle of resolution for statistical analysis.

The stage of the disease was defined by the Krumeich[16] classification using the parameters of corneal curvature (average curvature in the central 3 mm of the cornea), refractive error (degree of myopia/astigmatism), pachymetry (central corneal thickness), and biomicroscopy (transparent cornea or with opacities and perforation). This classification is not associated with any specific device and allows comparison with previous studies.

Corneal curvature and power, thickness maps, and elevation parameters were evaluated using the same Dual Scheimpflug analyzer device previously described and according to the manufacturer's guidelines. Only measurements that satisfied the minimum quality required by the system were included. The same experienced examiner acquired all the images (M.R.S.).

An SD-OCT system (Avanti; OptoVue, Inc.) with a corneal adaptor lens was used to acquire pachymetry (corneal thickness) and epithelial thickness maps. It has a working wavelength of 840 nm and operates at a scan speed of 70 000 axial scans per second. Equipped with an add-on lens, this system makes corneal measurements with the "pachymetry wide" scan mode, consisting of B-scans evenly in 8 radial directions at a length of 9 mm centered at the pupil center. The device was used according to the user's manual. The scans were triggered manually after the alignment procedure was completed. Participants were asked to sit back to ensure the measurement independence, and the scan unit was thoroughly reset before each subsequent scan. The data were valid if the measurement outcomes showed sufficient image signals and good quality. According to the device display, the epithelial data were obtained within the 7-mm zone.

Epithelial measurement (μm) parameters obtained from SD-OCT and compared between groups for this study were as follows:

1. Epithelial min: minimum epithelial thickness of the map.
2. Epithelial max: maximum epithelial thickness of the map.
3. Epithelial minimum and maximum: difference between minimum and maximum (min−max) epithelial thickness of the map.
4. Epithelial standard deviation (Std Dev): Std Dev of the epithelial thickness of the map.
5. Epithelial superior: average epithelial thickness of the superior region of the map.
6. Epithelial inferior: average epithelial thickness of the inferior region of the map.

Measurements of the thinnest point and difference between min−max in pachymetry points were also recorded from OCT for comparative purposes. Three consecutive measurements were performed by an experienced operator (M.R.S.). The correlation of epithelial parameters with K max and thinnest pachymetry was also investigated.

Statistical Analysis

The results obtained were expressed as mean $\pm$ Std Dev. Analysis of variance was used to compare mean results in the same group and Tukey multiple pairwise comparisons were performed for comparison between groups (Tukey Honest Significant Differences, R function: Tukey HSD). All statistical analyses were performed using the JMP 16 statistical software. The mean values, Std Dev, and 95% confidence intervals were determined. To correct for multiple comparisons performed in this study ($\sim$18) using the Bonferroni method, only individual P values of < 0.003 were considered significant. Graphic expressions were elaborated by box plots and the density distribution of values. The sample size calculation was performed to detect differences of at least 2 µm in epithelial thickness measurements between stable and progressive KC, at a significance level of 5% and a power of 80%, assuming a Std Dev of 10%. The minimum sample size of this study was 50 eyes per group.

Although epithelial min−max is a continuous variable, an analysis of the receiver operating characteristic curve was also made to determine potential cut-off values with their respective sensitivity and specificity.

Pearson correlation (r) was used to measure linear dependence between 2 different variables (x and y). The plot of $y = f(x)$ is represented by the linear regression curve. The direction and strength of the Pearson correlation were interpreted as follows: 0.9 to 1.00 (-0.90 to -1.00), very highly positive (negative) correlation; 0.70 to 0.89 (-0.70 to -0.90), highly positive (negative) correlation; 0.40 to 0.69 (-0.40 to -0.69), moderately positive (negative) correlation; 0.20 to 0.39 (-0.20 to -0.39), and low positive (negative) correlation; 0.00 to 0.19 (0.00 to -0.19) negligible correlation. A P value of < 0.05 was considered statistically significant for the correlation.

Categorical variables were compared using either chi-square or Fisher exact tests as appropriate. Categorical variables were expressed as percent (%).

Results

This study included 150 eyes of 150 patients, being 50 with progressive KC, 50 stable, and 50 clinically normal eyes (controls). There were no significant differences between groups for age (22.7 ± 4.09 years in the progressive KC group vs. 23.3 ± 4.31 years in the stable KC group vs. 23.6 ± 6.13 years in the control group; $P = 0.811$) or sex distribution (51% male patients in the progressive KC group: 52% male patients in the stable KC group, 54% male patients in the control group; $P = 0.762$).

The groups were comparable in terms of disease stage: 58% (29 eyes) stable group versus 50% (25 eyes) in the progressive group were classified as stage I ($P = 0.654$); 22% (11 eyes) stable group versus 24% (12 eyes) in the progressive group were classified as stage II ($P = 0.813$); 4% (2 eyes) stable group versus 4% (2 eyes) in the progressive group were classified as stage III ($P = 1.0$), and 16% (8 eyes) stable group versus 22% (11 eyes) in the progressive group were classified as stage IV ($P = 0.446$).

Table 1 shows mean values and Std Dev of epithelial measurements in all groups. The only parameter that presented a statistically significant difference between stable and progressive KC was epithelium min−max. Although stable KC presented epithelium min−max mean values of -18.2 ± 6.6 µm, progressive KC eyes presented mean values of -23.4 ± 10.37 µm ($P < 0.0001$) (Fig 1A).

The receiver operating characteristic curve analysis to separate eyes with stable KC and eyes that are progressing through the epithelial min−max variable revealed some cut-off values and their respective sensitivity and specificity. For example, for a value of 23.4 µm, the sensitivity was 84%, whereas the specificity was 46%. The value of 31 µm min−max difference reached a sensitivity of 98% (Fig 2).

Measurements of difference between min−max in pachymetry points in stable (-108.3 ± 33.5 µm) and progressive KC (-115.2 ± 56.0 µm) were not significantly different ($P = 0.723$) (Fig 1B).

Table 2 shows the correlation of epithelial parameters with K max. In stable KC eyes, there is a significant correlation between measurements of epithelium min. (pearson $= -0.36$, $P = 0.0218$) and epithelium inferior (pearson $= -0.40$, $P = 0.0088$) with K max. Also, in progressive KC eyes, there is the same significant and negative correlation between epithelium min (pearson $= -0.40$, $P = 0.0041$) and epithelium inferior (pearson $= -0.46$, $P = 0.0008$) measurements with K max.

Table 3 shows the correlation of epithelial parameters with the thinnest pachymetry. Although in stable eyes there is a significant correlation between measurements of epithelium max. (pearson $= -0.33$, $P = 0.0327$), epithelium min−max (pearson $= 0.33$, $P = 0.0331$), epithelium superior (pearson $= -0.46$, $P = 0.0025$), and epithelium Std Dev (pearson $= -0.41$, $P = 0.0071$) with the thinnest pachymetry, in progressive eyes the significant correlation is only with epithelium min. (pearson $= 0.45$, $P = 0.0010$), and epithelium inferior (pearson $= 0.44$, $P = 0.0014$).

There was no significant correlation between epithelium min−max with corneal thinning ($P = 0.39$) or K max ($P = 0.09$) regardless of disease progression. Epithelium min. and inferior presented a significant correlation with corneal thinning ($P = 0.0010$ and $P = 0.0014$, respectively) and K max ($P = 0.0041$ and $P = 0.0008$, respectively) in eyes that are progressing.

Figure 3 is an illustrative picture revealing epithelial min−max values according to different stages in both groups, eyes with stable KC and eyes that are progressing.

Discussion

The main findings of this study are that epithelial measures are useful to identify eyes with actively progressing KC; the difference between the min−max epithelial points were significantly different between stable and KC groups and some cut-offs can potentially differentiate eyes with progression, unlike this difference in pachymetry; and that this epithelial change seems to be independent of changes in the K max and the thinnest pachymetric point of the cornea (Fig 4).

Findings of previous studies had already revealed the importance of epithelial parameters in the diagnosis of KC,[6−10,17,18] probably relating to the fact that these alterations are associated with early microbiologic

Table 1. Comparison of Epithelial Parameters between Control, Stable, and Progressive Keratoconus

Epithelial Parameters (μm) (Mean Values ± Standard Deviation)	Patient Group			Comparisons (P Value)		
	Healthy Subjects	Stable Keratoconus	Progressive Keratoconus	Healthy vs. Stable	Healthy vs. Progressive	Stable vs. Progressive
Epithelium minimum	47.6 ± 4.9	42.7 ± 5.7	40.5 ± 7.1	0.0005*	< 0.0001	0.252
Epithelium maximum	56.0 ± 3.5	60.9 ± 6.5	63.9 ± 7.1	0.0002	< 0.0001	0.166
Epithelium min−max	−8.4 ± 3.6	−18.2 ± 6.6	−23.4 ± 10.37	< 0.0001	< 0.0001	< 0.0001
Epithelium superior	51.7 ± 3.6	53.0 ± 5.6	53.6 ± 5.6	0.277	0.016	0.285
Epithelium inferior	53.1 ± 4.1	53.7 ± 3.8	53.9 ± 5.7	0.632	0.440	0.234
Epithelium standard deviation	1.6 ± 0.4	4.5 ± 1.8	5.0 ± 2.3	< 0.0001	< 0.0001	0.255

*Statistically significant difference.

disturbances.[11,12] Therefore, we hypothesized that there could be noticeable differences in this layer in eyes that showed active disease progression compared with stable eyes, regardless of their stage.

A possible explanation for the role of the more expressive min−max epithelial difference in eyes with progression is that the corneal epithelium has rapid cell turnover and is highly reactive to asymmetries in the shape of the underlying stromal surface.[19] Direct measurements of the remodeling of the epithelial layer can, therefore, suggest progression. This study also confirms that more meaningful than punctual values, such as epithelial thinnest point, metrics associated with the asymmetric reactive capacity of the epithelium are capable of detecting subtle differences between groups.

The meaningful difference in the min−max variable between stable and progression eyes is even more interesting because there is no significant correlation between this epithelial parameter and corneal thinning or K max regardless of disease stage. In other words, this variable behaves independently and, therefore, can be a valuable tool in monitoring these patients. Although receiver operating characteristic curve analysis shows that the combination of sensitivity and specificity is limited for values < 23 μm, values > 23 μm and especially > 31 μm are more sensitive in the possible detection of eyes that may be actively progressing.

Although not evaluating progression, previous studies found that epithelial thickness measurements from OCT have value in early diagnosis of forme fruste KC. Hwang et al[10] showed that epithelial thickness variability metrics (epithelial min−max and epithelial Std Dev) were among the most valuable parameters distinguishing eyes with early stages of KC from normal populations. Li et at[17] found epithelial thickness Std Dev to be a strong predictor of early KC, and Temstet et al[18] found epithelial thickness in the corneal thinnest location useful in the diagnosis of early subclinical KC.

Another relevant finding of this study is that although there is a significant difference in the min−max
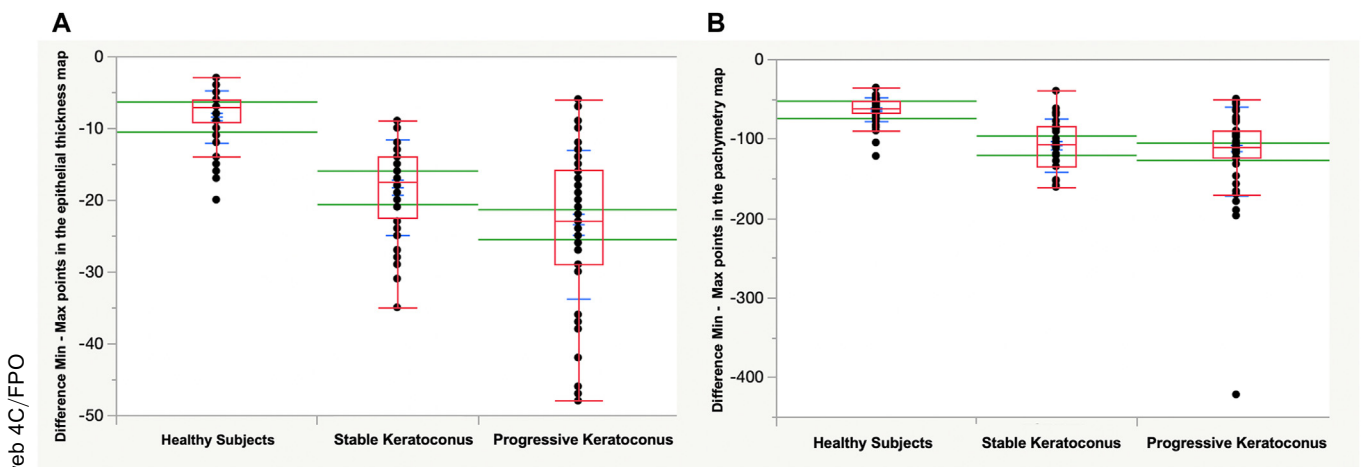

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Figure 1. Box-plot graph. A, Difference between minimum and maximum (min−max) epithelial thickness of the map (epithelial min−max) values comparing progressive keratoconus (KC), stable KC, and healthy controls. The medium of the epithelial min−max values of the progressive group is significantly higher than stable group and controls (P < 0.0001). B, Measurements of difference between min−max in pachymetry points in stable and progressive KC were not significantly different (P = 0.723). The bar inside each box represents the median, and each box extends from the 25th percentile to the 75th percentile of the distribution in each group.
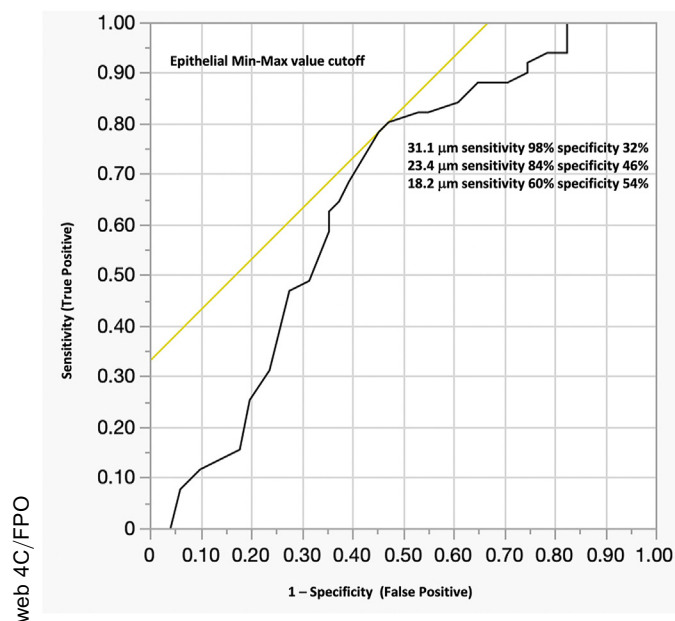
Figure 2. Receiver operating characteristic curve: analysis of the receiver operating characteristic curve to separate eyes with stable keratoconus and eyes that are progressing through the epithelial minimum and maximum (min−max) variable revealed some cut-off values and their respective sensitivity and specificity. For example, for a value of 23.4 μm, the sensitivity was 84%, whereas the specificity was 46%. The value of 31 μm min−max difference reached a sensitivity of 98%.

measurement of the epithelial layer, the same does not occur in the min−max of pachymetry, emphasizing that pachymetric map (stromal + epithelial) measurement is not sensitive to structural changes that occur as KC progresses.

This finding explains that the pachymetric map does not necessarily correspond to the stromal thickness because the epithelium is distributed irregularly in the KC.[6,7,19] The thinnest epithelium point follows the thinnest stroma only when this area coincides with the steeper curvature because one of the inducers of epithelial remodeling is the change in the shape gradient.[6,7,19]

The finding of greater min−max variability in eyes with progression than that in stable eyes is even more relevant given the concomitant finding of the absence of correlation of this parameter with K max. This dissociation is explained

by changes associated with the primary process of epithelial apoptosis in corneas with KC, regardless of curvature changes.[11,12]

Wang et al[11] investigated the histopathology of epithelia and its microRNA regulation in eyes with KC. They resolved the histologic structure of the keratoconic corneal epithelium and identified cell apoptosis, altered cell integrity, and downregulation of microRNA as potential mechanisms for keratoconic corneal epithelial degeneration. In addition, the apoptosis-related marker, p53 protein, was upregulated in the keratoconic corneal epithelium, suggesting degeneration of this layer.[11] Shetty et al[12] showed that the structural deformity of the KC cornea strongly correlates with reduced epithelial expressions of collagen fibril-maturating enzyme lysyl oxidase and that KC corneal epithelium expresses high levels of matrix metalloproteinase 9.

The process of apoptosis occurs asymmetrically in these corneas, so it makes sense that measures of epithelial variability play a role in differentiating early cases versus normal corneas and distinguishing eyes in active progression versus stable eyes, the main finding in our article.

Although it did not help differentiate between stable and progressive eyes, which is the objective of this study, we emphasize a correlation between the thinning of the epithelium, mainly in the cornea's inferior region, with the increase in the K max. This finding corroborates finding of previous studies, which were more oriented toward the epithelium as a diagnostic tool.[18,20]

Using an OCT apparatus whose epithelial measurements are derived from a smaller (5 mm) mapping diameter, Serrao et al[21] found the inferior paracentral region of the corneal epithelium to be significantly thinner in progressive than stable KC. Also utilizing a smaller diameter OCT mapping, Ouanezar et al[22] found no epithelial differences in progressing eyes compared with stable eyes. In addition to the smaller diameter that can influence the outcomes, it would have been critical that the authors had ruled out active allergic changes on the surface, as we did in our study, especially in stable eyes, because this could influence measures of epithelial variability. This way, we have access to epithelial alterations with a lower risk of bias. These methodologic differences explain the differences in findings. Our study went further by ruling out allergic bias and accessing a larger diameter OCT mapping. It detected the most significant variability

Table 2. Correlation of Epithelial Parameters with Maximum Keratometry

Epithelial Parameters	Stable Keratoconus				Progressive Keratoconus			
	Correlation	*Lower 95%*	*Upper 95%*	*P Value*	*Correlation*	*Lower 95%*	*Upper 95%*	*P Value*
Epithelium minimum	−0.36	−0.60	−0.05	0.0218*	−0.40	−0.61	−0.14	0.0041*
Epithelium maximum	−0.20	−0.49	0.11	0.19	−0.05	−0.32	0.23	0.73
Epithelium min−max	−0.10	−0.40	0.21	0.51	−0.24	−0.48	0.04	0.09
Epithelium superior	−0.12	−0.42	0.19	0.45	−0.03	−0.31	0.25	0.81
Epithelium inferior	−0.40	−0.64	−0.11	0.0088*	−0.46	−0.65	−0.20	0.0008*
Epithelium standard deviation	0.18	−0.13	0.46	0.27	0.15	−0.13	0.41	0.29

*Statistically significant difference

Table 3. Correlation of Epithelial Parameters with the Thinnest Pachymetry

Epithelial Parameters	Stable Keratoconus				Progressive Keratoconus			
	Correlation	Lower 95%	Upper 95%	P Value	Correlation	Lower 95%	Upper 95%	P Value
Epithelium minimum	0.00	−0.30	0.31	0.96	0.45	−0.61	−0.14	0.0010*
Epithelium maximum	−0.33	−0.59	−0.03	0.0327*	0.25	−0.02	0.50	0.07
Epithelium min−max	0.33	0.03	0.59	0.0331*	0.12	−0.15	0.38	0.39
Epithelium superior	−0.46	−0.68	−0.18	0.0025	0.21	−0.07	0.47	0.13
Epithelium inferior	0.11	− 0.20	0.40	0.49	0.44	0.18	0.64	0.0014*
Epithelium standard deviation	−0.41	−0.64	−0.12	0.0071*	−0.07	−0.34	0.21	0.61

*Statistically significant difference.

between the thinning of one area and the thickening of another in progressing eyes. Because of the nature of the disease, maps with a larger image capture diameter used in our study are more sensitive to these measures of epithelial variability.

This study has some limitations. First, there is significant variability among individuals who are actively progressing both in objective measures and in the speed of this progression. However, most of the variables and variable categories identified as critical in our study will prove essential in other analyses, even if possibly by varying degrees, as we investigate measures (epithelial) that have been proven to change early.

Furthermore, the publication of these findings would represent a positive first step toward directing future studies in this context. Another possible limitation is that representative tensile strength measurements or biomechanics were not performed. Future studies that include these analyses in a reproducible manner may contribute to identifying patients with a greater propensity for progression.[23]

One of the aspects highlighted in this article is that we must separate the groups into stable versus progression to investigate variables associated with progression adequately.[24] Staging is a static assessment, whereas "being in progression" indicates a dynamic evaluation. For example, there are stage I eyes that are progressing and stage IV eyes that are stable. In the article's illustrative (Fig 4), we present a grade I KC that is actively progressing. In other words, the stage does not represent a measure of active progression if used in isolation. Therefore, it does not allow for adequate correlations or identifying variables associated with dynamic changes. The main indication of cross-linking is not a disease stage, its active progression.[4]

Hence, determining a variable (difference between the min−max thickness of the corneal epithelium) associated with eyes that are progressing represents a step forward in our knowledge.

Moreover, that can even (as illustrated in Figure 4) be identified in eyes with early stages of the disease.

In conclusion, this study shows that although epithelial thinning measures are helpful in the diagnosis, it is a measure that reveals epithelial variability as the most useful in detecting eyes that are actively progressing compared with stable KC ones. Furthermore, some variability cut-offs can differentiate eyes with progression with relatively high sensitivity. The epithelium min−max measure can aid monitoring and eventually suggest the indication of corneal cross-linking before the significant visual loss.
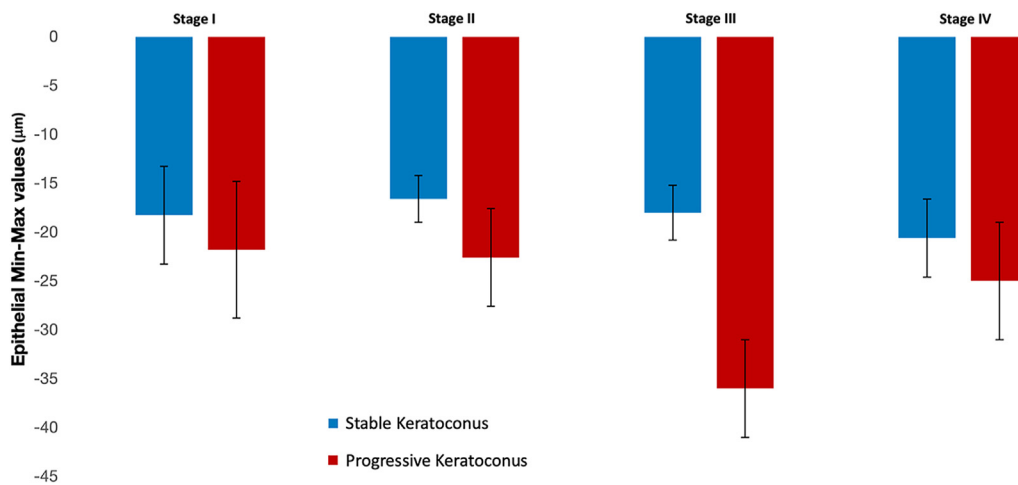

Figure 3. Illustrative bar graph revealing difference between minimum and maximum epithelial (epithelial min−max) thickness values according to different stages in both groups, eyes with stable keratoconus and eyes that are progressing.
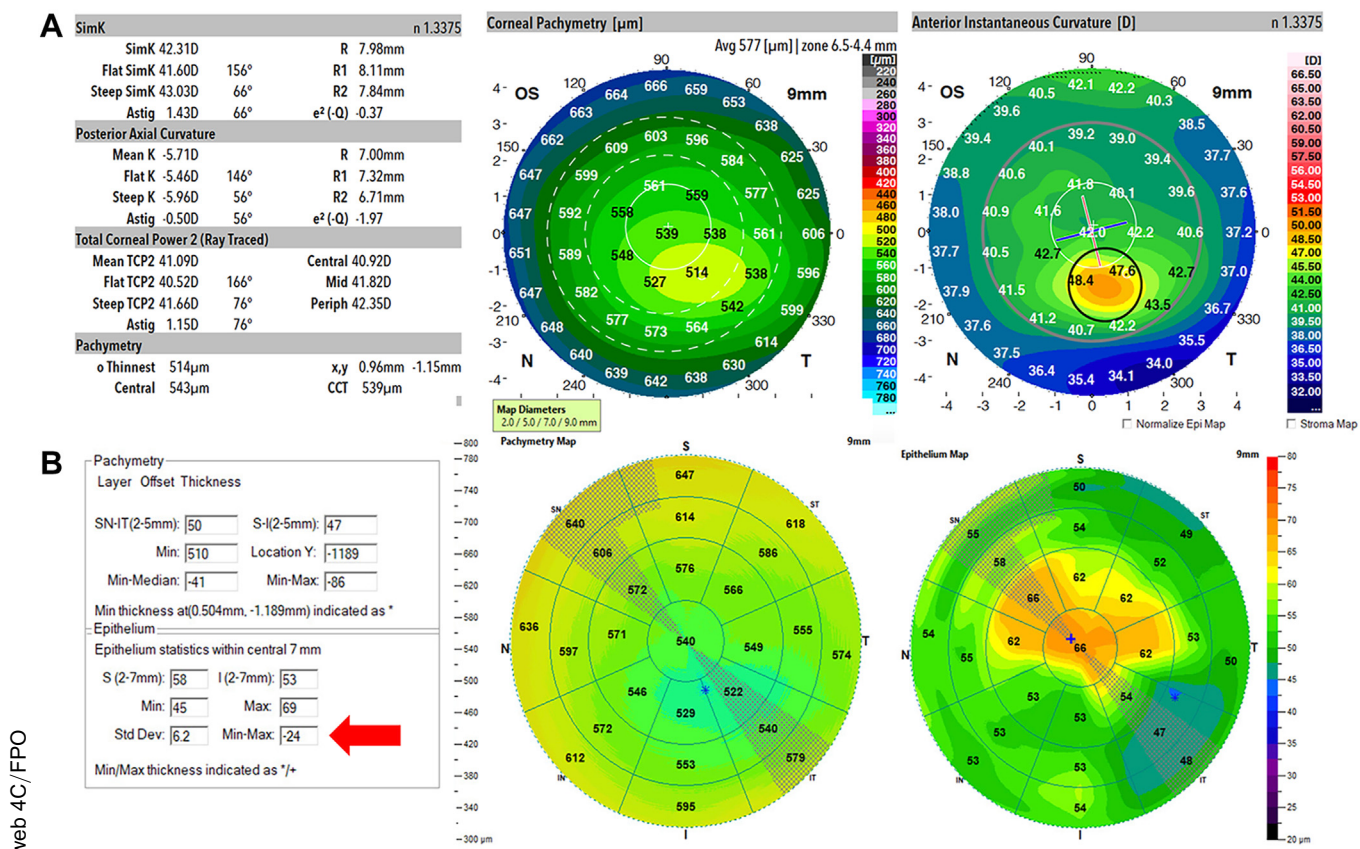
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Figure 4. Representative image of an eye with keratoconus (KC) progression of maximal keratometry documented in 1 year, with high variability of the epithelium minimum and maximum parameter (red arrow), although presenting epithelium minimum and standard deviation values similar to that of stable KC. Figure shows Dual Scheimpflug imaging with total corneal thickness pachymetric map and anterior curvature (top row), and SD-OCT with total corneal thickness pachymetric map and epithelial thickness map (bottom row). SD = spectral-domain.

Footnotes and Disclosures

[1] Department of Ophthalmology at University of Sao Paulo, Sao Paulo, Brazil.

[2] Department of Ophthalmology, Federal University of Goias, Goiania, Brazil.

[3] Department of Computer Science, Federal University of Minas Gerais, Belo Horizonte, Brazil.

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All authors have completed and submitted the ICMJE disclosures form.

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HUMAN SUBJECTS: Humans provided informed consent to use their corneal imaging.

This is a prospective comparative observational study approved by the institution's ethics committee (University of Sao Paulo) and the Brazilian National ethics and research committee. This study also followed the tenets of the Declaration of Helsinki. All patients provided informed consent to use their corneal imaging.

No animal subjects were used in this study.

Author Contributions:

Conception and design: Santhiago

Data collection: Santhiago, Stival, Araujo, Kara-Junior, Toledo

Analysis and interpretation: Santhiago, Stival, Araujo, Toledo

Obtained funding: N/A

Overall responsibility: Santhiago, Stival, Kara-Junior

Abbreviations and Acronyms:

min−max = minimum and maximum; **KC** = keratoconus; **K max** = maximum keratometry; **SD** = spectral-domain; **Std Dev** = standard deviation.

Keywords:

Epithelium, Keratoconus, Progression.

Correspondence:

Marcony R. Santhiago, MD, PhD, Instituto Central. 255 Enéas de Carvalho Aguiar AV.−Ophthalmology Department - Federal University of Sao Paulo, Sao Paulo, Brazil. E-mail: marconysanthiago@hotmail.com.

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