Evaluation of keratoconus progression

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ABSTRACT

Aim To define variables for the evaluation of keratoconus progression and to determine cut-off values.

Methods In this retrospective cohort study (2010–2016), 265 eyes of 165 patients diagnosed with keratoconus underwent two Scheimpflug measurements (Pentacam) that took place 1 year apart ±3 months. Variables used for keratoconus detection were evaluated for progression and a correlation analysis was performed. By logistic regression analysis, a keratoconus progression index (KPI) was defined. Receiver-operating characteristic curve (ROC) analysis was performed and Youden Index calculated to determine cut-off values.

Results Variables used for keratoconus detection showed a weak correlation with each other (eg, correlation r=0.245 between RPImin and Kmax, p<0.001). Therefore, we used parameters that took several variables into consideration (eg, D-index, index of surface variance, index for height asymmetry, KPI). KPI was defined by logistic regression and consisted of a Pachymin coefficient of −0.78 (p=0.001), a maximum elevation of back surface coefficient of 0.27 and coefficient of corneal curvature at the zone 3 mm away from the thinnest point on the posterior corneal surface of −12.44 (both p<0.001). The two variables with the highest Youden Index in the ROC analysis were D-index and KPI: D-index had a cut-off of 0.4175 (70.6% sensitivity) and Youden Index of 0.606. Cut-off for KPI was −0.78196 (84.7% sensitivity) and a Youden Index of 0.747; both 90% specificity.

Conclusions Keratoconus progression should be defined by evaluating parameters that consider several corneal changes; we suggest D-index and KPI to detect progression.

INTRODUCTION

Keratoconus is an ectatic corneal disease that leads to a cone-shaped cornea. It is characterised by corneal thinning, protrusion and scarring, finally leading to a loss of vision and astigmatism.[1] This has been known for many years, and yet there is still no recognised medication for its treatment.[2] The current goal is to stop disease progression, rather than trying to heal the disease. Cross-linking leads to a higher degree of stiffness of the cornea and inhibits further progression.[3] Therefore, labelling the disease as progressive is a critical point as it defines further treatment.

Many studies have been performed to identify improvements, particularly early diagnosis and in detecting keratoconus in its early stages.[4 5] A recent review showed that although many studies have analysed how to detect keratoconus, there are very few that describe how the progression can be evaluated and to date, there is still no reliable definition of ectatic progression.[6 7] Typical changes of the cornea when affected by keratoconus are an increase in corneal elevation, decrease in corneal curvature and a decrease in corneal thickness, but not all of these changes have to occur within one patient; this is what makes defining progression remarkably difficult.[6] This lack of consensus in how to define the progression of the disease endangers treatment occurring in time to stop the natural history of keratoconus and also carries the risk of possibly unnecessary treatment of non-progressive eyes. Since interventions like cross-linking entail that due to their specific risks of complications such as infections or endothelial cell loss, patients should not be unnecessarily put at risk and indications for cross-linking should be strictly evaluated, which again leads to the need of a consistent definition of progression.[7–9]

The purpose of our analyses was to test different definitions of keratoconus progression, defined by multiple variables, and then to identify the most suitable variables with reliable cut-off values to clearly identify the patients whose disease is worsening. We analysed Scheimpflug measurements to find variables that can be used for the evaluation of keratoconus progression. Our hypothesis was that the D-index used for the detection of keratoconus is also the best parameter for evaluation of keratoconus progression.

MATERIAL AND METHODS

A total of 265 eyes of 165 patients diagnosed with keratoconus were examined in this cohort study in the Department of Ophthalmology at the Goethe-University in Frankfurt, Germany. The study was approved by the local ethics committee and conducted in accordance with the Helsinki Declaration.

Patients presented at our clinic with the question of whether they required corneal cross-linking. Any patients with previous ocular surgery of any kind, for example severe trauma or other corneal pathology as well as history of corneal hydrops, were excluded. All stages of keratoconus, including subclinical keratoconus, were incorporated in the study. Differentiation between subclinical and clinical keratoconus was performed using Scheimpflug tomography. Eyes that only showed changes at the corneal back surface and were not symptomatic were classified as subclinical keratoconus (the other eye needed to show clear signs of clinical keratoconus). Patients with very advanced disease (usually with corneal thickness at its thinnest point <380 µm) often were not able to be included because as

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a group there were no images labelled 'OK' after the internal scan check.

For each patient, a Scheimpflug (Pentacam; Oculus, Wetzlar, Germany) measurement was performed. Patients stopped wearing contact lenses at least 2 weeks prior to measurement. A trained resident from the Department of Refractive Surgery at our clinic took the Scheimpflug images. In cases where the automated image quality check was not labelled with 'OK', the assessment was repeated.

Only imaging with a quality check resulting in 'OK' was included in this study. This approach ensured higher reliability of measurements. After a follow-up of 12±3 months, the Scheimpflug measurement was repeated for evaluation of progression. Variables used for keratoconus detection and their resulting differences determined between the first and second measurement after 12 months were analysed. We used Belin/Ambrósio Enhanced Ectasia Software integrated into the Oculus Pentacam System to generate the D-index, consisting of five subgroups: Df (deviation of front surface elevation difference), Db (deviation of back surface elevation difference), Dp (deviation of pachymetric progression), Dt (deviation of thinnest point) and Da (deviation of ARTMax/Ambrósio relational thickness maximum).[10–12]

We also analysed maximum keratometry (Kmax), minimum pachymetry (Pachymin), minimum pachymetric progression index (RPImin), elevation of the corneal surface front and back (ELEF and ELEB). Furthermore, we analysed the recently introduced ARC and PRC, which reflect the corneal curvature at the zone 3 mm away from the thinnest point on the anterior corneal surface (ARC) and posterior corneal surface (PRC).

DATA AND STATISTICAL ANALYSES

Statistical analyses to compare first to second measurements were performed with SPSS V.24 (IBM) and Stata V.13 (Statacorp). The Kolmogorov-Smirnov test was used to test for normal distribution of the data. For data fitting a normal distribution, Pearson's correlation analysis was performed. If normal distribution was not confirmed, Spearman's correlation analysis was used. A p value <0.05 was considered statistically significant. Data are presented as mean±SD.

After a first analysis of mean values and SD, all parameters were correlated with each other to find out whether it makes sense to use single variables as references for progression.

All calculations performed to define progression and correlations were executed with the values of the differences between the first baseline and the second measurement after 12±3 months.

We set up five different and possible ways of defining keratoconus progression consisting of several criteria (as seen below) and analysed the behaviour of the variables D-index, index of surface variance (ISV), index for height asymmetry (IHA), keratoconus index (KI) and keratoconus progression index (KPI) in a receiver operating characteristic (ROC) curve to see which ones are the most suitable for detecting progression. Progression criteria were defined with a difference between the two measurements (first baseline and second after 12 months) >0 in ELEB or values <0 in ARC, PRC and Pachymin. These four variables were set up in five different combinations to define progression: in our first ROC differences in ARC, PRC and Pachymin were set to define progression; in ROC2 ELEB, PRC and Pachymin; in ROC3 PRC and ELEB; in ROC4 Pachymin and ELEB; and in ROC5 Pachymin and PRC values defined progression.

Table 1 Mean, SD and range of variables, which are commonly used for keratoconus evaluation

	Mean	SD	Minimum	Maximum
Age	34.74	10.31	19	58
ISV	77.95	38.5	10	186
ISV*	2.14	11.17	−35	53.25
IHA	23.67	21.32	0.1	96.4
IHA*	0.48	16.48	−67	57.6
D	7.62	3.96	1.08	19.97
D*	0.254	1.03	−1.96	6.51
Df	8.88	6.81	−1.8	41.85
Df*	−1.01	3.6	−21.80	8.32
Db	6.91	5.44	−0.9	26.14
Db*	0.47	1.65	−5.88	9.87
Dp	7.23	4.83	−0.45	28.64
Dp*	0.19	2.04	−11.23	7.11
Dt	2.25	1.789	−1.39	9.44
Dt*	0.25	0.56	−1.76	2.74
Da	2.53	0.88	−0.49	4.13
Da*	0.06	0.3	−1.1	1.39
RPImin	1.42	0.65	0.29	4.97
RPImin*	0.01	0.36	−1.79	1.39
ARTmax	187.86	86.99	46	504
ARTmax*	−7.45	26.94	−138.5	104.33
Pachymin (µm)	474.53	46.73	334	591
Pachymin (µm)*	−6.57	12.77	−58	27.5
Kmax (D)	53.11	6.52	42.4	73.8
Kmax (D)*	0.4	1.64	−4.3	12.53
KI	1.21	0.12	0.92	1.6
KI*	0.01	0.04	−0.09	0.25
BFSF	7.63	0.36	6.57	8.6
BFSF*	−0.01	0.07	−0.41	0.25
BFSB	6.3	0.31	5.21	7.2
BFSB*	−0.003	0.08	−0.41	0.52
EBFSB	6.49	0.24	5.74	7.34
EBFSB*	0.004	0.07	−0.33	0.37
EBFSF	7.76	0.31	6.81	8.72
EBFSF*	1.47	0.18	0.85	2.15
ELEFmax (µm)	25.75	14.05	2	78
ELEFmax (µm)*	1.19	3.88	−15.5	22.67
ELEBmax (µm)	52.65	25.25	7	137
ELEBmax (µm)*	2.03	7.17	−21	49.83
ARC (mm)	6.79	0.73	5.59	8.03
ARC (mm)*	−0.03	0.16	−0.78	0.51
PRC (mm)	5.25	0.612	4.09	6.47
PRC (mm)*	−0.04	0.17	−1	0.37

*Difference of the variable between two measurements
ARC, corneal curvature at the zone 3 mm away from the thinnest point on the anterior corneal surface; ARTmax, Ambrósio relational thickness maximum; BFSB, best fit sphere back; BFSF, best fit sphere front; D, D-index; Da, deviation of ARTMax/Ambrósio relational thickness maximum; Db, deviation of back surface elevation difference; Df, deviation of front surface elevation difference; Dp, deviation of pachymetric progression; Dt, deviation of thinnest point; EBFSB, enhanced best fit sphere back; EBFSF, enhanced best fit sphere front; ELEBmax, maximum elevation of back surface; ELEFmax, maximum elevation of front surface; IHA, index of height asymmetry; ISV, index of surface variance; KI, keratoconus index; KM, mean keratometry front/back surface; Kmax, maximum keratometry; Pachymin, minimum pachymetry; PRC, corneal curvature at the zone 3 mm away from the thinnest point on the posterior corneal surface; RPImin, minimum pachymetric progression index.

The variables we tested in each ROC were D-index, ISV, IHA and KI to determine cut-off values and their sensitivity and specificity. In addition, in ROC3 we tested Pachymin and Kmax, in ROC4 PRC, ARC and Kmax, and in ROC5 ELEB, ELEF and Kmax. We established a KPI consisting of Pachymin, PRC and ELEBmax considering that these are the variables that define the

disease and tested it using ROC as well. KPI was created with a linear logistic regression analysis. For each ROC curve, the Youden Index was calculated. We wanted to find cut-off values with a specificity of 90%.

RESULTS

The mean age was 34.7 years (range 19–58 years), 38 eyes were staged as subclinical keratoconus and 227 eyes as clinically manifest keratoconus. Mean average values, minimum, maximum and SD of the measurements, and the difference between the first and the second measurement after 12 months can be found in table 1.

The results of correlation analysis of the variables' differences between first and second measurement (after 12 months) showed that the highest and at the same time statistically significant correlation is r=0.776 between ELEBmax and ELEFmax. The correlation coefficient varies highly within this analysis from r=0.726 for PRC and D-index to −0.375 between PRC and KI, both with p <0.001. Only a weak, yet significant correlation (after Bonferroni correction) was found between the main parameters currently used in the definition of keratoconus progression (Kmax and Pachymin r=0.386, Kmax and elevation back r=0.353, Pachymin and elevation back r=0.357), emphasising that in progressive cases not all parameters change at the same time.

Logistic regression analysis to calculate KPI was set up with progression defined as Pachymin <0, ELEB >0 and PRC <0. In this regression, Pachymin had a coefficient of −0.78 (p=0.001), whereas ELEB had a coefficient of 0.27 and PRC −12.44 (both p<0.001), consequently KPI=−0.78 (difference in Pachymin)+0.27 (difference in ELEB)−12.44 (difference in PRC)–2.48.

ROC analysis with the highest Youden Index for D-index was found in ROC2 where we used ELEB, Pachymin and PRC as definition for progression (table 2).

The cut-off value with our required specifity of at least 90% for D-index was 0.4175 with a sensitivity of 70.6% and a Youden Index of 0.606. The cut-off we calculated for KPI was −0.78196, with 84.7% sensitivity, 90% specificity and Youden Index of 0.747. In

Table 2 ROC analysis with different definitions of progression and the Youden Indices are shown

Scenario	Test result variable	Area	SE	Lower bound*	Upper bound*	Cut-off	Sensitivity	Specifity	Youden index
ROC1	ISV	0.706***	0.036	0.636	0.777	2.533	0.596	0.761	0.357
	IHA	0.517	0.038	0.441	0.592	10.317	0.258	0.841	0.099
	D	0.785***	0.031	0.724	0.847	0.318	0.685	0.818	0.503
	KI	0.644***	0.037	0.572	0.716	0.0238	0.36	0.847	0.207
	KPI	0.814***	0.027	0.76	0.868	–1.909	0.843	0.642	0.485
ROC2	ISV	0.654***	0.039	0.579	0.73	2.533	0.565	0.739	0.304
	IHA	0.602**	0.039	0.527	0.678	0.983	0.659	0.55	0.209
	D	0.897***	0.02	0.858	0.936	0.318	0.812	0.867	0.679
	KI	0.622***	0.038	0.548	0.697	0.0238	0.365	0.844	0.209
	KPI	0.946***	0.013	0.921	0.971	–0.986	0.894	0.872	0.766
ROC3	ISV	0.635***	0.036	0.564	0.705	2.533	0.523	0.753	0.276
	IHA	0.574*	0.036	0.503	0.644	0.925	0.617	0.538	0.155
	D	0.879***	0.021	0.838	0.919	0.198	0.776	0.816	0.592
	KI	0.621***	0.035	0.552	0.691	0.008	0.533	0.671	0.204
	KPI	0.947***	0.013	0.922	0.972	–1.772	0.963	0.816	0.779
	Pachymin	0.321***	0.034	0.255	0.388	NA			
	Kmax	0.623***	0.036	0.553	0.692	0.383	0.533	0.69	0.223
ROC4	ISV	0.622***	0.036	0.553	0.692	2.2	0.509	0.752	0.261
	IHA	0.587*	0.036	0.518	0.657	9.583	0.31	0.859	0.169
	D	0.793***	0.028	0.739	0.847	0.274	0.638	0.826	0.464
	KI	0.609**	0.035	0.54	0.679	0.021	0.353	0.852	0.205
	KPI	0.875***	0.021	0.833	0.916	–1.729	0.845	0.785	0.63
	Kmax	0.589*	0.036	0.519	0.659	0.279	0.543	0.658	0.201
	ARC	0.394**	0.036	0.325	0.464	NA			
	PRC	0.301***	0.033	0.237	0.365	NA			
ROC5	ISV	0.606*	0.036	0.536	0.676	6.167	0.319	0.904	0.223
	IHA	0.552	0.036	0.482	0.622	10.317	0.261	0.863	0.124
	D	0.824***	0.026	0.772	0.875	0.318	0.655	0.897	0.552
	KI	0.581*	0.036	0.511	0.651	0.024	0.303	0.842	0.145
	KPI	0.873***	0.022	0.831	0.916	–1.025	0.723	0.897	0.62
	Kmax	0.598**	0.035	0.528	0.667	1.042	0.311	0.877	0.188
	Elevation front	0.575**	0.036	0.504	0.646	3.071	0.277	0.904	0.181
	Elevation back	0.672***	0.034	0.605	0.739	1.708	0.613	0.726	0.339

In our ROC1, ARC, PRC and Pachymin were set to define progression; in ROC2, ELEB, PRC and Pachymin; in ROC3, PRC and ELEB; in ROC4, Pachymin and ELEB; and in ROC5, Pachymin and PRC values defined progression.
*P<0.05.
**P<0.01.
***P<0.001.
ARC, corneal curvature at the zone 3 mm away from the thinnest point on the anterior corneal surface; D, D-index; IHA, index of height asymmetry; ISV, index of surface variance; KI, keratoconus index; Kmax, maximum keratometry; KPI, keratoconus progression index; NA, not applicable; Pachymin, minimum pachymetry; PRC, corneal curvature at the zone 3 mm away from the thinnest point on the posterior corneal surface; ROC, receiver operating characteristic.

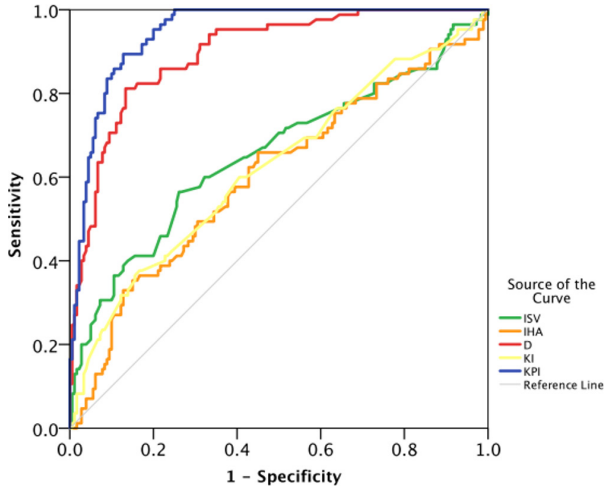

Figure 1 Receiver operating characteristic curve shows that high sensitivity and specifity levels are achieved with KPI and D-index for determination of keratoconus progression. D, D-index; IHA, index of height asymmetry; ISV, index of surface variance; KI, keratoconus index; KPI, keratoconus progression index.

figure 1, ROC curve for the variables ISV, IHA, D-index, KPI and KI is shown. D-index and KPI show a rapidly increasing slope, whereas the other variables show a more moderate and gradually increasing slope meaning a higher false-positive rate. The reference line symbolises the line of no discrimination, meaning the false-positive and true-positive rate is equal.

DISCUSSION

In this study, we wanted to define reliable cut-off values to define keratoconus progression. We used variables that other groups had already evaluated for keratoconus detection[13–15] and sought to prove if they are suitable for detecting progression as well. Muftuoglu *et al* extensively analysed the various parameters measured by Scheimpflug tomography (such as corneal thickness, curvature, elevation etc.) and compared them with the D-value in terms of applicability for detection of keratoconus in its early stages. They found that the D-value has the highest area under the curve and recommended its use in early detection of keratoconus. Similarly, we found that it is superior to single parameters in terms of evaluation of progression of the disease.[15]

If we take a first look at our preceding correlation analysis, we can see that there is only a weak correlation between the tested variables. This means, for example, in some eyes the cornea has become thinner, signifying progression; however, Kmax did not increase. If we would now only use Kmax, which did not change for the definition of progression in this eye, we would then be marking wrongly—as non-progressive. Therefore, our general recommendation for the evaluation of keratoconus progression is to also use parameters that include several variables, for example the D-index, or to use at least two different parameters affected by keratoconus, for example, steepening of the front or back surface and corneal thinning.[6] Recently, other groups such as Wonneberger *et al* evaluated the repeatability of Scheimpflug imaging for diagnosing progression. What they found was that three consecutive measurements at each visit at the clinic and control examination after 3 to 6 months with an increase of 1 D of patient's astigmatism makes a true progression of disease more likely.[16] With this definition, up to 20% of the patients showed a progression; considering the weak correlation between our tested variables, this rate might be too little and progression could have been overseen. The area under the curve for established parameters like Pachymin or Kmax in our analysis were low as expected, and as a consequence we do not recommended for the evaluation of progression.

The D-index and the KPI showed the best results in all cases of our ROC analysis. Here, it is important to point out that the definition we used for disease progression consisted of Pachymin, PRC, ARC and ELEB, while KPI consisted of Pachymin and PRC as well. Of course, this index has to show the best results, given that progression was defined by the same variables but nevertheless, elevation, steepening and corneal thinning are typical corneal changes when the cornea is affected by keratoconus, and so it makes sense to use these characteristics as well as use them for the definition of progression and detection of progression. Furthermore, previous groups, for example Duncan *et al*, found the CI for ARC and PRC to be very small in a normative cohort, suggesting that these parameters are suitable for detecting ectatic progression.[6] D-index and KPI are a combination of several variables that can all be affected by the disease's progression, and their meaning and suitability as a marker for progression is emphasised.

The cut-off value we suggest for KPI is −0.78. In the available literature,[17] whole numbers rather than decimals are currently used, for example, for Kmax, a cut-off of 1 dpt and for Pachymin a cut-off of −10 µm. The KPI takes curvature as well as corneal thickness into consideration. We also decided to implement corneal elevation into the index, as we had seen a change in this variable, especially in the early stages of the disease, which is sometimes not reflected in curvature or corneal thickness measurements sufficiently.[18]

Besides KPI, the D-index showed reliable results in detecting progression. The cut-off value we recommend for the D-index is 0.42 to mark a keratoconus eye as progressive, so that further therapeutic steps can be made. D-index is proven to be a reliable parameter in detecting early and definite keratoconus and can highlight changes in the corneal surface earlier than, for example, Kmax.[6] It has already been tested as a parameter with which to diagnose keratoconus, but our results indicate that it is suitable to detect disease progression as well since it generated the highest result in our ROC analysis.

Of course our study had to face limitations. The only method used being Scheimpflug imaging, of course other technologies and examinations could have also been considered in detecting keratoconus progression. Furthermore, recent studies have shown that newer technologies such as biomechanical analysis can show changes in the cornea whereas tomography and topography are still unaffected.[19] In conclusion, further trials for a new and possibly more exact definition of keratoconus—detection and progression—have to be implemented. The technological development within recent years in ophthalmology has been fast and probably will continue at this pace or even more quickly in the future. However, the assessment of these new devices requires time, and subsequently, the introduction of new indices for example, for evaluation of disease detection or progression, needs time as well. Sometimes, to an extent, the technology becomes outdated before the proper instalment of indices has taken place. It is up to government to facilitate access to funding and research groups to set up more standardised approaches at a faster pace in order to keep up with industry and make the most positive use possible of the technological development.

We decided not to include visual acuity for evaluation of keratoconus progression. The reason for this was that too many factors might influence visual acuity. It could worsen for reasons that are not related to keratoconus for example. Also, patients with keratoconus have significantly better visual acuity wearing

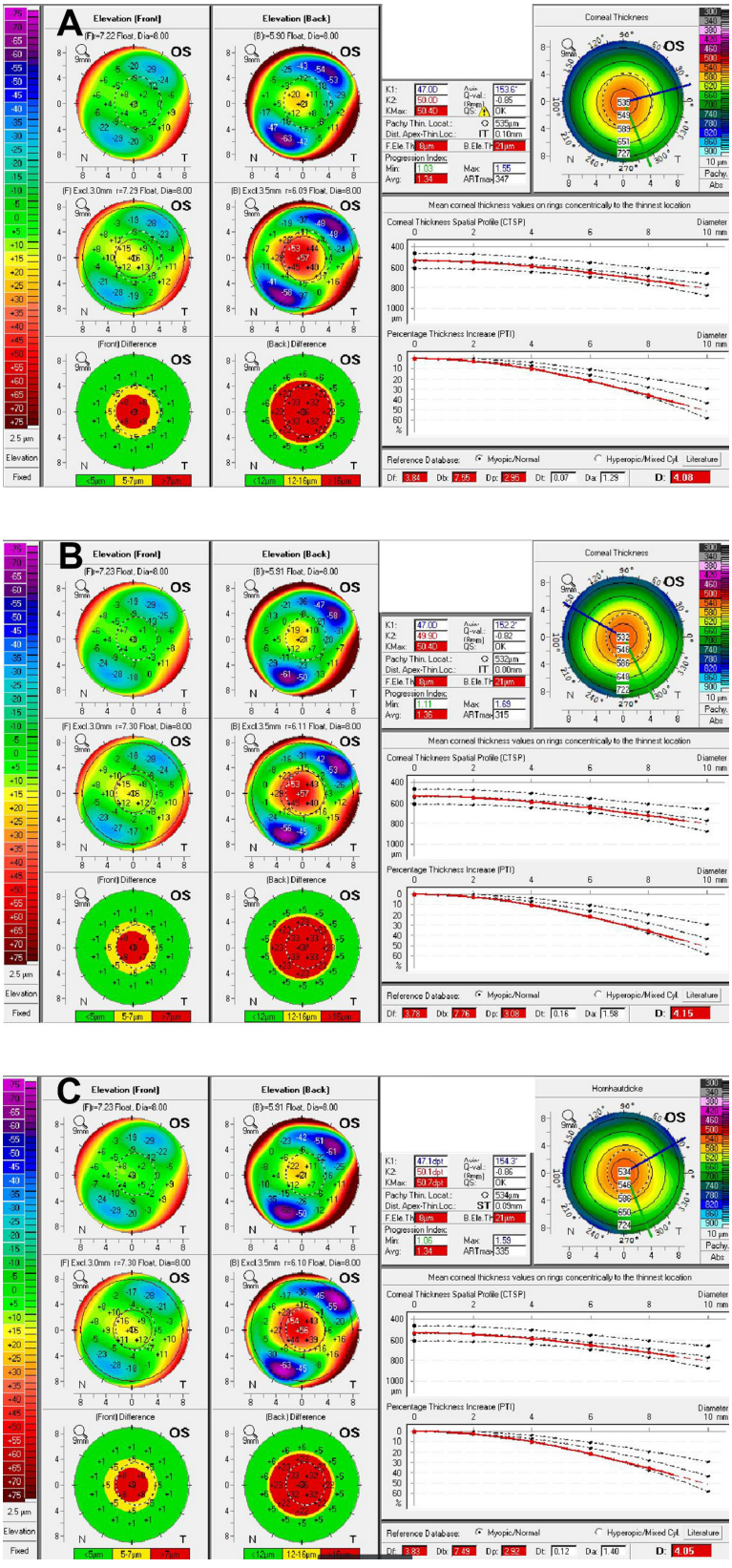

Figure 2 According to our definition, a non-progressing case is presented. This 27-year-old man presented with keratoconus in both eyes. We saw an initial D-value of 4.08 (A), which did not change substantially after 1 year (D-value 4.15). We decided not to perform corneal cross-linking and re-examined the patient after another year, where we saw that our decision was correct as still non-progression was found (D-value 4.05).

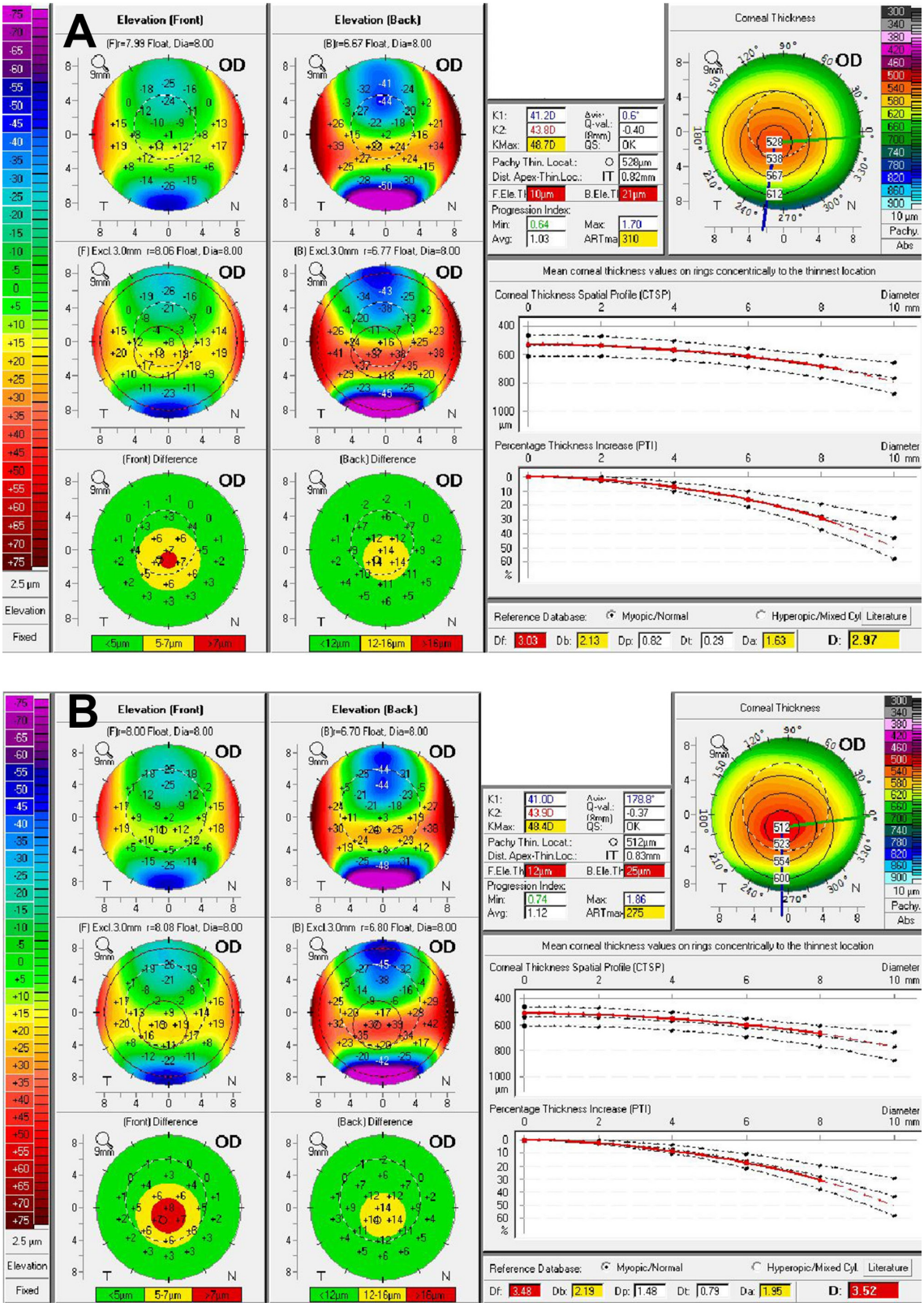

Figure 3 In this figure, a progressing case of a 22-year-old woman with keratoconus is presented. Although we saw a decrease in Kmax in this eye (48.7 to 48.4 D), we recommended corneal cross-linking as the overall situation worsened, the patient was rather young and had a more advanced stage in the other eye. The progress is visible by the decrease in corneal thickness, a further shift of the thinnest point in the direction of the inferotemporal, decrease of posterior corneal curvature (not shown) and an increase in the elevation parameters (D-value changed from 2.97 to 3.52).

contact lenses compared with spectacles. When performing subjective refraction to determine their corrected visual acuity, however, we used glasses that on the one hand can vary significantly with each examination in eyes with high astigmatism and on the other hand do not reflect their actual visual acuity potential as seen with contact lenses. Furthermore, many patients can develop corneal scarring. Unfortunately, scarring can also develop in the rather early stages of the disease. Depending on size and position of the scar, it can considerably affect visual acuity and make visual acuity testing for evaluation of keratoconus progression very unreliable.[20]

Other groups showed that the repeatability of Pentacam Scheimpflug imaging for keratoconus parameters, especially in the higher stages, decreases.[21] In eyes with higher stages of keratoconus (eg, when corneal thickness is <350 µm) such as scarring, irregular tear film and other factors, it is very difficult to receive an 'OK' from the internal quality check of the Scheimpflug system. In this analysis, we only included eyes where this criterion was met. We decided to use this approach to increase reliability of our analysis, and due to this factor, very few eyes in the higher stages of keratoconus were included. However, taking into consideration that corneal cross-linking is not recommended at the very advanced stages, there is less need for the evaluation of disease progression in the higher stages, and thus should not be a major drawback.

Nevertheless, it has been reported that Pentacam Scheimpflug imaging may overestimate anterior and posterior corneal elevation compared with other imaging techniques, but it offers excellent repeatability for corneal curvature variables. These facts should be kept in mind when evaluating patient's results acquired with Pentacam Scheimpflug imaging, in particular since our results are based on corneal elevation of the back surface (ELEB) being one of the main parameters defining progression.[22] Therefore, we support what Wonneberger *et al* have just recently published regarding performing more than one imaging at a time to create reliable results.[16]

When all these considerations are taken into account in patient examination, we recommend evaluating two parameters: KPI or D-index. If the patient's cornea shows a progression that reaches the cut-off values for D-index 0.42 or for KPI −0.78, further steps to stop progression should be taken (figures 2 and 3).

It is important to intervene early, before the progression of corneal ectasia goes too far as it results in a decrease in quality of life due to loss of vision.[23] Since progression can be extremely retarded or even halted with cross-linking,[24] the decision-making process should be shortened—our defined cut-off values should aid that.

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