Complementary Keratoconus Indices Based on Topographical Interpretation of Biomechanical Waveform Parameters: A Supplement to Established Keratoconus Indices

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Purpose. To build new models with the Ocular Response Analyzer (ORA) waveform parameters to create new indices analogous to established topographic keratoconus indices. Method. Biomechanical, tomographic, and topographic measurements of 505 eyes from the Homburger Keratoconus Centre were included. Thirty-seven waveform parameters (WF) were derived from the biomechanical measurement with the ORA. Area under curve (ROC, receiver operating characteristic) was used to quantify the screening performance. A logistic regression analysis was used to create two new keratoconus prediction models based on these waveform parameters to resample the clinically established keratoconus indices from Pentacam and TMS-5.

Results. ROC curves show the best results for the waveform parameters p1area, p2area, h1, h2, dive1, mslew1, aspect1, aplhf, and dslope1. The new keratoconus prediction model to resample the Pentacam topographic keratoconus index (TKC) was $WF_{TKC} = -4.068 + 0.002 \times p2area - 0.005 \times dive1 - 0.01 \times h1 - 2.501 \times aplhf$, which achieves a sensitivity of 90.3% and specificity of 89.4%; to resample the TMS-5 keratoconus classification index (KCI) it was $WF_{KCI} = -3.606 + 0.002 \times p2area$, which achieves a sensitivity of 75.4% and a specificity of 81.8%. Conclusion. In addition to the biomechanically provided Keratoconus Index two new indices which were based on the topographic gold standards (either Pentacam or TMS-5) were created. Of course, these do not replace the original topographic measurement.

1. Introduction

Keratoconus is an ectatic corneal disorder, in which the cornea assumes a conical shape due to deficits of structural integrity. This loss of structural components results in a thinning and protrusion of the cornea [1], inducing irregular astigmatism and myopia and leading to a mild to marked deterioration of visual acuity [2]. Vision-specific quality of life is significantly affected by keratoconus [3]. In most cases the disease is bilateral and mostly diagnosed in the second or third decade of life with an incidence of 55:100,000 [2, 4, 5]. In current clinical practice, corneal tomography or topography systems are being used to assist the examiner in classifying and monitoring the disease. Since 2005 the evaluation of biomechanical properties has extended the diagnostic spectrum [6].
The Ocular Response Analyzer (ORA, Reichert, Depew, USA) provides data about corneal hysteresis, corneal resistance factor, and intraocular pressure and—in an additional keratoconus tool—a Keratoconus Match Index and Keratoconus Match Probabilities Index.

The ORA software provides a “cornea corrected intraocular pressure” (IOPcc), which is based on the pneumotonometer measurement of the ORA and calibrated to the classical intraocular pressure measurement which is derived with a Goldmann applanation tonometer (IOPg), which is currently the gold standard in a clinical setup.

As topography is the gold standard in keratoconus screening, data from the TMS-series or the Pentacam have primarily been used for helping to diagnose keratoconus.

Our aim was to create a “topography correlated Keratoconus Index” analogous to the IOPg, which is based firstly on TMS data and secondly on Pentacam data.

2. Patients and Methods

This retrospective study was conducted at the Department of Ophthalmology, Saarland University Medical Centre in Homburg/Saar (UKS), Germany. The study adhered to the tenets of the Declaration of Helsinki. Each subject provided informed written consent to participate in this research study.

Patients were recruited from the database of the Homburg Keratoconus Centre (HKC). In the HKC, patients with keratoconus were included. The HKC includes also patients without obvious corneal abnormalities but with dysfunction of the thyroid gland, as thyroid disorders are suspected of leading to corneal biomechanical changes [7]. The diagnostic methods and goals of the HKC have been previously described in detail [8–10].

Inclusion criteria for the calculations for this study were no ocular surgery, no other ocular diseases than keratoconus, complete data of the complete ophthalmological examination, including tomography measurements using Scheimpflug imaging (Pentacam, Oculus Optikgeräte GmbH, Wetzlar, Germany), Placido disk video topography (TMS-5, Tomey Corporation, Nagoya, Japan), and biomechanical examination using the Ocular Response Analyzer (ORA).

The classification into normal or keratoconus patients was based on the Keratoconus Index (KCI ≥ 5%) by TMS-5 and on the Topographic Keratoconus Classification (TKC ≥ 1) by Pentacam. An additional control group of normal eyes was not established, as the main aim is to compare screening results of different devices and not to test the screening capacity of the devices.

The HKC includes in total 8195 data sets, of which each eye and each measurement made at a different time point is a separate data set. Selecting only the most current measurement of only one eye of a patient and with complete examination we were able to evaluate the data of 505 patients.

2.1. Ocular Response Analyzer. The ORA acts as an air-puff tonometer and assesses the kinetics of the cornea during inward and outward movement. The deformation dynamics of the cornea, such as height, slope, and width, were described with more than 40 parameters, so-called waveform parameters. The Keratoconus Match Index (KMI) is a composite value of the seven waveform parameters (CRF, p2area, dslope1, h2, p2area1, h21, and waveform score). The explanations of the waveform parameters are presented in Figure 1 and the Supplementary Table, available online at https://doi.org/10.1155/2017/5293573.

2.2. Statistical Analysis. Statistical analysis was performed using SPSS software (SPSS version 19.0, International Business Machines Corporation, New York, United States of America). The binary decision for healthy versus keratoconus was tested.

The following steps were performed using the TMS-5 based and using the Pentacam based keratoconus index as reference to create a waveform index based on KCI (WFKCI) and a second index based on TKC (WFTKC).

1. Finding the relevant waveform parameters. Receiver operating characteristic (ROC) curves were calculated for all 37 waveform parameters and quantified using the area under the curve (AUC) for each parameter. The 8 values with the AUC closest to 1 or 0 were selected for the subsequent analysis. A descriptive evaluation of data was performed using maximum, minimum, median, and mean along with respective standard deviation of the keratoconus and the healthy group.

2. Proving the predictability. Discriminant function analysis was used to prove the predictability of the selected values. Values which were considered as not significant were excluded from further calculations.

3. Creating a model. Logistic regression analysis was used to investigate the discriminatory effect of pre-specified model parameters on the outcome for normal (0) versus keratoconus (1) eyes. Model covariate effects were estimated with maximum likelihood and respective p values were given. The resulting model predicting probability of keratoconus was used to discriminate between the groups.

4. Proof of concept. To validate the prediction formulae derived from the logistic regression analysis, the AUC was calculated. The optimum cutoff points were calculated using Youden's J statistic as the sum of sensitivity and specificity minus 1 [11]. J lies within a range from −1 to +1. A diagnostic test can be considered to yield reasonable results for positive values of J. Higher values indicate better performance of the diagnostic test [11].

5. In absence of an external control group the validation of the logistic regression was done using cross validation. The study population was split randomly into 2 groups; for both groups a prediction model was derived and validation was done with both models for each study subpopulation.
3. Results

Five hundred and five eyes were selected for this study. The eyes were classified into keratoconus and normal using TKC and KCI. With TKC/KCI, 73.3%/67.3% was classified as keratoconus, respectively. Table 1 summarizes the ROC curve analysis results for all new waveform parameters.

4. Results Based on the Keratoconus Index TKC

For further calculations we selected the values with the highest AUC: \( p2area, p1area, h1, h2, \text{dive1}, \text{mslew1}, \text{aspect1}, \text{aplhf} \). All selected parameters correlated with each other. Table 2(a) shows descriptive statistics such as minimum, maximum, median, and mean with standard deviation of the selected parameters.

With logistic regression analysis, only four of these values were found to be statistically significant \((p < 0.05)\): \( p2area \), \( \text{dive1} \), \( h1 \), and \( \text{aplhf} \).

Logistic regression (Table 3(a)) resulted in a model based on TKC of

\[
WF_{TKC} = -4.068 + 0.002 \times p2area - 0.005 \times \text{dive1} - 0.01 \times h1 - 2.501 \times \text{aplhf}.
\]  

For \( WF_{TKC} \) we found an AUC with 0.944. The \( J \)-Index was highest with 0.78 at the threshold of 0.32. With this threshold, sensitivity was 90.3% and specificity was 89.4%.

5. Results Based on the Keratoconus Index KCI

For further calculations, we selected the values with the highest AUC:

\( p2area, p1area, h1, h2, \text{dive1}, \text{mslew1}, \text{aspect1}, \text{aplhf}, \text{dslope1} \).

All selected parameters correlated with each other. Table 2(b) shows descriptive statistics such as minimum, maximum, median, and mean with standard deviation of the selected parameters.

With logistic regression analysis, only \( p2area \) was statistically significant \((p < 0.05)\).

Logistic regression (Table 3(b)) resulted in a model based on KCI of

\[
WF_{KCI} = -3.606 + 0.002 \times p2area.
\]  

With the model for \( WF_{KCI} \) AUC is 0.821. The \( J \)-Index was highest with 0.57 at the new threshold of 0.36. With this threshold, sensitivity is 75.4% and specificity is 81.8%.

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**Figure 1:** Explanation of the parameters which were used for the model for \( WF_{TKC} \) and \( WF_{KCI} \): \text{dive1} as maximum single decrease in the fall of peak 1 or longest continuous line without a break, height 1 (\( h1 \)) as the distance from the lowest to the highest point in peak 1, \( p2area \) as area under the second peak, and \( \text{aplhf} \) as high frequency “noise” in region between peaks.
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Table 2: (a) Minimum, maximum, median, and (mean ± standard deviation) of the parameters of our selected variables, as well as their significance based on Topographic Keratoconus Classification from Pentacam for normal ($n = 135$) and keratoconus (Kc) eyes ($n = 370$). (b) Minimum, maximum, and mean of the parameters of our selected variables, as well as their significance based on keratoconus classification index, KCI, from TMS-5 for normal ($n = 165$) and keratoconus (Kc) eyes ($n = 340$).

(a)

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(b)

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Figure 2: Receiver operating characteristic curves for the new models based on TKC: WF_{TKC} (a) and based on KCI: WF_{KCI} (b). With the model for WF_{TKC} the area under the curve (AUC) is 0.944. With the model for WF_{KCI} AUC the area is 0.821.
In conclusion, currently, the Ocular Response Analyzer should be used as second line, as a complimentary device for detecting keratoconus. In addition to the proprietary biomechanical Keratoconus Match Index we created two new indices, which are based on Pentacam (TKC) and TMS-5.
(KCI) measurements: \( WF_{\text{TKC}} = -4.068 + 0.002 \times \text{p2area} - 0.005 \times \text{dive1} - 0.01 \times h1 - 2.501 \times \text{aplhf} \) and \( WF_{\text{KCI}} = -3.606 + 0.002 \times \text{p2area} \), which achieve a high sensitivity and specificity. Of course, these new indices do not replace the original topographic measurement.

**Competing Interests**

The authors report no conflict of interests and have no proprietary interest in any of the materials or instruments mentioned in this article.

**References**


