Imaging and aberrometric analyses of diseases affecting biomechanical properties of the cornea
Modern disgnostic methods of keratoconus

Ph.D. thesis

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Introduction

The most frequently occurring disease affecting corneal biomechanics is keratoconus. Keratoconus is a bilateral, noninflammatory, progressive disorder characterized by corneal ectasia, thinning and protrusion. The disease induces myopia, irregular astigmatism and has well defined slit lamp findings. The diagnosis of more advanced keratoconus is not complicated, because of the typical biomicroscopic and topographic findings, but the detection of subclinical or forme fruste cases may impose difficulty. It is particularly important to detect the disease among refractive surgery candidates, as keratorefractive procedures may worsen their condition. Measurement of Placido disk based corneal topography and central corneal thickness are widely used methods in the diagnosis of keratoconus, however they are of limited use. Placido disk based corneal topography only examines the anterior surface of the cornea and alteration in the reference point or viewing angle may result in inaccuracy of curvature measurement. Ultrasound pachymetry is a contact device and precise measurement depends on correct probe alignment and centration. With the advent of the Pentacam Comprehensive Eye Scanner (Oculus, Wetzlar, Germany) anterior and posterior corneal surface elevation data measurement and pachymetry map detection have become possible. Height data give a more accurate representation of the true shape of the corneal anterior and posterior surface. The machine also provides topographic and pachymetric map of the cornea, thus providing a great help in the early diagnosis of keratoconus.

Understanding the characteristics of ocular higher order aberrations owing to keratoconus might be very useful to differentiate early cases from simple myopia or myopic astigmatism. It is particularly important to detect the disease among refractive surgery candidates, because patients complaint, glare and distorted vision may be qualitatively and quantitatively explained by aberrometry. The advantage of measuring corneal aberrations relates to their ability to analyze most of the anterior corneal surface, which allows a better understanding of the optical behavior of the cornea. It is known that keratoconic patients have significantly more higher order aberrations (HOA) than normal population, the most relevant of these HOAs is vertical coma, which can be observed already in the early stage of the disease and can be used for screening. Corneal higher order aberrations are calculated from corneal topographic elevation data and do not take into account the internal ocular

aberrations. The limitation of this method is that it neglects the pupil area and position and it is not aligned to the line of sight (LoS), which is the most relevant reference axis for defining retinal image quality at the point of fixation. The characteristics of the position of LoS relative to the pupillary center in keratoconus has not been observed before.

Purposes

We have aimed to examine the following characteristics of keratoconus based on the above mentioned theories:

1. To describe the diagnostic efficacy of the Scheimpflug camera in keratoconus.
2. To determine the most sensitive topographic, elevation and pachymetric parameters in keratoconus and to define cutoff values for disease screening.
3. To compare anterior chamber parameters of normal to keratoconic corneas measured by rotating Scheimpflug camera and to evaluate trends in progression of corneal protrusion.
4. To evaluate rate of corneal protrusion progression in keratoconus
5. To evaluate ocular wavefront aberrations due to keratoconus compared to normal controls.
6. To describe the changes in the axis of line of sight among keratoconic patients.

Methods

Scheimpflug camera measurements

Pentacam measurements were performed on 41 eyes of 24 patients with keratoconus and 68 eyes of 41 normal subjects. Control subjects were refractive surgery candidates of our clinic. Diagnosis was based on classical corneal biomicroscopic and topographic findings, in accordance with the criteria established by the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study Both eyes of every subject were used in the study, except for those with previous ocular surgery, trauma or other pathology. Severe cases were excluded, because of potential stromal haze or scar formation, which may alter the optical transparency of the cornea and image acquisition of the Pentacam. Control subjects were age matched and had a refractive error of less than ± 5 diopters sphere, and/ or astigmatism less than 3 diopters. Patients who wear rigid contact lenses, were asked to stop using them for 3 weeks, and soft contact lenses were ceased for at least one week before assesment.

All eyes were examined with the Pentacam HR (Oculus Inc.), used by three trained examiners. The readings were taken as recommended in the instruction manual. In each eye keratometric values, central and minimal pachymetry, anterior and posterior elevation and posterior Q value were evaluated. For height data measurement, the best fit sphere (BFS) and toric ellipsoid was used as a reference body.

Aberrometric analysis

In this study, 55 eyes of 30 patients with mild to moderate keratoconus and 100 eyes of 50 refractive surgery candidates with normal corneas were included. Both eyes of each patient have undergone a complete ophthalmologic evaluation including slit-lamp biomicroscopy, keratometry, retinoscopy, ophthalmoscopy, and Placido disk based videokeratography. Keratoconic patients included in the study were either mild or forme fruste cases. The criteria for diagnosing keratoconus were defined as the existence of central thinning of the cornea with Fleischer ring, Vogt's striae, or both by slit-lamp examination. Forme fruste keratoconus was diagnosed when an abnormal, localized steepening was observed by corneal topography without any slit-lamp findings. Subjects with corneal scarring, previous ocular surgery, trauma, or any other ocular diseases except for keratoconus

and refractive errors were excluded from the study. Both eyes of subjects were used in the study if they met these criteria. Control subjects were age matched and had a mostly myopic refractive error (spherical equivalent, −2.36±1.72 diopters). Patients who wore rigid contact lenses were asked to stop using them for 4 weeks, and soft contact lenses were abandoned for ≥1 week before assessment.

All eyes were examined with the WASCA Hartmann-Shack wavefront sensor (Carl Zeiss Meditec AG, Jena, Germany). Wavefront aberration measurements were standardized to a 4.5-mm pupil. We used no dilating drop, because the aberration profile of a pharmacologically dilated pupil is less relevant to the natural pupil view normally experienced by the patient and to avoid instrument myopia. Wavefront measurements were performed in a dark room. We used the right-hand coordinate reference frame and the double-index convention for naming the Zernike coefficients and polynomials recommended by the OSA/VSIA Standards Taskforce. The signs of bilaterally asymmetrical Zernike coefficients of the left eyes affected by enantiomorphism were reversed to allow comparison between right and left eyes. Both topographic and wavefront aberration images were taken at 5 to 10 seconds after a complete blink, when the tear film layer is the most stable. To calculate the axis of the LoS relative to the pupil center, vector analysis following the recommendations of the Astigmatism Project Group of the American National Standards Institute and the method suggested by Alpins was applied.

Statistical analyses

Statistical analyses were performed with Statistica 8.0 software (StatSoft Inc., Tulsa, OK, USA). Bootstrap method was used to overcome the correlated nature between eyes of the same subject by treating each subject as a cluster. Normal distribution assumption was tested by the Shapiro-Wilks' W test. For group comparisons of continuous variables the Mann-Whitney nonparametric test was used. A p value less than 0.05 was considered statistically significant. Receiver operating characteristic (ROC) curves were obtained using SPSS 15.0 (SPSS Inc., Chicago, Il, USA). Area under the ROC curve (AUROC) was calculated to describe the predictive accuracy of the different indices and to determine the cutoff point for the most sensitive parameter. Logistic regression analysis and generalized estimating equation (GEE) analysis was performed to investigate predictors of classical topographic and central pachymetric findings contrasted with keratometric, pachymetric and elevation data obtained by the Pentacam with calculation of r^2, positive and negative predictive values. Confirmatory

factor analysis (CFA) was performed in the keratoconic group for quantification of the validity of parameters characterizing the disease.

Results

Results of Scheimpflug camera measurements

All following parameters were significantly higher in the keratoconus group compared to the normal control group: steep and flat keratometry, central and minimal and relative pachymetry, posterior corneal surface asphericy (Q), anterior and posterior elevation values. ROC curve analyses showed best predictive accuracy for posterior and anterior elevation (area under the curve, AUROC: 0.97 and 0.96) followed by minimal and central pachymetry (0.89 and 0.88). Optimal cutoff point for posterior elevation was found to be 15.5 μm for the discrimination of keratoconus corneas from normals. Logistic regression analysis showed best fit to the data for the model completed with the height data of the Pentacam (minimal pachymetry, anterior and posterior elevation). The goodness-of-fit of this model was: r^2: 0.67, positive predictive value was: 0.92, negative predictive value was: 1.0. Confirmatory factor analysis explained a three factor model satisfactorily showing minimal pachymetry (-0.99), anterior elevation (0.98) and keratometry (0.95) as the most representative clinical variables of the disease.

Anterior chamber was significantly deeper in keratoconic patients measured centrally, 1,2 and 3 mm paracentrally and at minimum pachymetry ($p<0.05$). In the keratoconic group, posterior elevation significantly correlated with anterior chamber depth in the center ($r=0.72$), at the miminum pachymetry ($r=0.52$), 1 and 2 mm paracentrally ($r=0.64$ and $r=0.34$, respectively). In the multivariable GEE model posterior elevation was a highly significant predictor (OR: 1.31), central anterior chamber depth was marginally significant (OR: 4.54) of keratoconus, however average keratometry was not significant. Linear piecewise model identified thresholds for posterior elevation (40 μm) and for minimal pachymetry (450 μm) beyond which points corneal protrusion is accelerated by 5-7 times. These cut-off values were confirmed by GEE also.

Results of aberrometric analysis

We found no significant difference between the two groups in the value of spherical equivalent, RMS and defocus (Z_2^0). The following parameters were significantly higher in the keratoconus group compared to the control group: HORMS ($p<0.001$), vertical coma Z_3^{-1} ($p<0.001$), trefoil: Z_3^{-3} ($p<0.002$), Z_3^3 ($p=0.001$), secondary astigmatism: Z_4^{-2} ($p<0.001$), Z_4^2($p<0.001$), tetrafoil Z_4^4 ($p=0.016$), pentafoil Z_5^{-5} ($p=0.03$), secondary coma Z_5^{-1} ($p=0.04$) and secondary trefoil Z_5^3 ($p=0.01$), and y offset value between LoS and papillary axis ($p<0.001$).

In keratoconic patients there was a significant correlation between the axis of the shift in the LoS and the steepest keratometric axis on topography ($r=0.59$, $p<0.001$), the distance of the LoS from pupil center and vertical coma ($r=-0.39$, $p=0.004$), and spherical aberration ($r=0.29$, $p<0.04$). There was also a significant correlation between the average keratometry value (aveK) measured by topography and spherical aberration ($r=-0.49$, $p<0.001$). A factorial regression model testing the interactive effects of vertical coma and spherical aberration on the shift of LoS had a good fit on our data ($r^2=0.69$, $p<0.001$).

Discussion

Measurements with the Scheimpflug camera

In this study ROC curve analysis showed, that posterior elevation was the most effective parameter in the diagnosis of keratoconus. A cutoff value of 15.5µm had 95.1% sensitivity and 94.3% specificity for discriminating normal eyes from keratoconus. In contrast to ROC curve analysis, confirmatory factor analysis (CFA) is not used for discriminating keratoconus from normal corneas, but it tries to identify and rank the underlying mechanisms leading to the corneal shape disorder observed in the disease. To our knowledge, this is the first application of CFA in the evaluation of keratoconus. In the CFA model, we examined three topographic parameters [(flat and steep keratometry, cylinder) characterizing corneal curvature factor], two pachymetric parameters [(minimal and central pachymetry) the corneal thinning factor] and two elevation parameters [(anterior and posterior elevation at the apex of the cone) cone apex elevation]. All these parameters have been shown to affect corneal morphological alteration observed in keratoconus. In our model best results were obtained for the minimal pachymetry (-0.99), followed by anterior elevation (0.98), keratometry results

(0.95), central pachymetry (-0.94), posterior elevation (0.92) and corneal cylinder (0.38). These results show, that elevation measurements and localization of the apex of the cone by corneal pachymetric map play an important role in the detection of disease progression. Before the advent of Orbscan and Pentacam, these data could not be measured. The same hypothesis is supported by the results of the logistic regression analysis, according to which the model completed with the height data of the Pentacam shows a better ability for disease prediction.

Results of linear piecewise regression suggest the existence of a specific threshold level of disease progression, at which level the rate of protrusion is significantly elevated. In both two cases of regression analyses, linear piecewise analysis could explain higher portion of variance than linear regression analysis did, confirming the separated nature of correlation across the dataset. According to this, the documentation of posterior elevation or central corneal thickness values are clinically important to assess protrusion rate during follow-up. Piecewise regression analysis showed better fit to the data of maximal posterior elevation than to the data of central pachymetry, proving previous results that posterior elevation is a better estimator of disease progression. Taken together these findings, the 40 μm threshold of maximal posterior elevation seems to be a better assessment of the real breakpoint than the 450 μm threshold of central pachymetry. Although linear piecewise regression analysis can explain only 24% of the variability in corneal ectasia with central corneal thickness, this breakpoint is an important finding since pachymetry is available in most of the cornea units. Better explanation coefficients of segments beyond threshold levels indicate closer correlation between corneal and anterior chamber parameters suggesting altered corneal rigidity as a more important determinant of corneal ectasia in advanced forms.

Aberrometric analysis

In our study we examined aberrometric properties of keratoconic and myopic eyes. Eyes with keratoconus had significantly more higher-order aberrations than normal control individuals. According to our findings, vertical coma was the dominant higher order aberration in keratoconus and there were significant differences in higher order astigmatic

polynomials, trefoil and secondary coma also. These aberrations can be attributed to the characteristic cone shape and the inferior shift of the cone's apex.

Our hypothesis, that the shift in the LoS is an internal compensation mechanism to reduce corneal coma caused by keratoconus was confirmed by result of vector analysis as the axis of the shift of the LoS showed a marked correlation with the steepest keratometric axis on topography. The negative sign of vertical coma means that there is a relative phase retardation of the wavefront in the inferior cornea due to the longer intraocular light path caused by inferior corneal protrusion. The displacement of the LoS also occurred inferiorly in most of cases.

We have also found evident correlation between the distance of the LoS from the pupil center and the spherical aberration. As progression in keratoconus occurs, the cone bulges anteriorly, the cornea thins and steepens, the cornea becomes more prolate, which explains why the spherical aberration becomes more negative as the average keratometry value increases. If the apex is not centered on the visual axis a prismatic effect, astigmatism from oblique incidence and coma occurs. These findings suggest that the decentration of the line of sight is an internal compensation mechanism of the eye in order to find the ideal balance between spherical aberration and coma.

List of publications

Publications attached to Ph.D. thesis

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1. Kovács I, Miháltz K, Ecsedy M, Németh J, Nagy ZZ. The role of reference body selection in calculating posterior corneal elevation and prediction of keratoconus using rotating Scheimpflug camera. Acta Ophthalmologica. (accepted for publication) doi: 10.1111/j.1755-3768.2010.02053.x

2. Miháltz K, Kovács I, Kránitz K, Erdei G, Németh J, Nagy ZZ. The mechanism of aberration balance and its effect on retinal image quality in keratoconus. J Cat Refr Surg. (accepted for publication)

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International:

1. Miháltz K, Kránitz K, Kovács I, Nagy ZZ. Evaluation of Wavefront Aberrations in Patients With Keratoconus Measured With a Hartmann-Shack Sensor. Invest Ophthalmol Vis Sci. 2009: ARVO E-Abstract 3541

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5. Kovács I, Miháltz K, Ecsedy M, Kránitz K, Németh J, Nagy ZZ. The role of reference body selection in calculating posterior corneal elevation and prediction of keratoconus using rotating Scheimpflug camera. Congress of the European Society of Cataract and Refractive Surgery (ESCRS), Budapest, 2010 February, free paper

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5. Miháltz K, Nagy ZZ. Wavefront analyses of keratoconic patients. Congress of the Hungarian Ophthalmologic Society, Szeged, 2010 June, course

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