Influence of eye tilt on corneal densitometry

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ABSTRACT

Purpose: To investigate whether Pentacam densitometry readings are affected by corneal tilt.

Methods: In a prospective study, the right eyes of 86 healthy participants aged 42.8 ± 20.0 years (range 18–79 years) were imaged using Scheimpflug tomography. Elevation maps were exported to calculate corneal tilt using custom-made software, and densitometry readings were acquired directly from the corneal densitometry analysis add-on to the standard software Oculus Pentacam HR. Simple mediation analysis was applied to study age as a confounding factor in the correlation between corneal tilt and corneal densitometry.

Results: Corneal tilt and corneal densitometry are not independent from one another because age is statistically significant correlated with both corneal tilt (r=0.50, p<0.001) and corneal densitometry (r=0.91, p<0.001). Only 3.8% of the correlation between tilt and densitometry operates directly, while the remaining 96.2% of that correlation depends on age.

Conclusions: Corneal tilt plays a role on corneal densitometry readings, even though that interaction is strongly influenced by age. Age is a well-known factor in densitometry readings that should be taken into consideration when interpreting Scheimpflug densitometry.

Keywords: cornea, densitometry, corneal tilt, corneal transparency, Pentacam

KEY POINTS

- Corneal tilt plays a role on corneal densitometry readings, even though that interaction is strongly influenced by age.
- Results suggest strong eye tilt could influence corneal densitometry readings, independently of the origin of that corneal tilt.
- Age is a major confounding factor in corneal densitometry readings that should be taken into consideration when considering a corneal densitometry analysis in a given patient.

INTRODUCTION

Corneal densitometry measures how much light is backscattered from corneal tissue and can be used as a surrogate for corneal tissue density or corneal transparency.[1] Different techniques exist to measure corneal transparency, the most popular one being the traditional slit-lamp examination.[2] Backscatter analysis has demonstrated higher sensitivity in detecting slight transparency changes compared to subjective observation,[3] and more sophisticated methods, such as spectrophotometry, custom scatterometers, anterior segment–optical coherence tomography (AS-OCT), confocal microscopy, or Scheimpflug imaging,[4] are therefore needed to objectively quantify changes in corneal transparency.

In the last decade, Pentacam HR (Oculus Optikgeräte GmbH, Wetzlar, Germany) has become a benchmark in evaluating corneal densitometry thanks to its availability in clinics worldwide.[5] This forms a powerful tool to investigate both healthy corneas,[6] as well as eye diseases such as keratoconus,[7-12] Fuchs endothelial dystrophy,[13] dry eye,[14] pellucid marginal degeneration,[15] high myopia,[16] or glaucoma.[17] Slight hypoxia induced by contact lens wear has also been associated with transient increased backscatter.[18-20] An association of corneal densitometry with disease has also been established in multiple myeloma,[21] Fabry disease,[22] and other rare disorders.[23,24] Corneal densitometry has also been helpful to evaluate corneal integrity after refractive surgery,[25,26] corneal crosslinking,[13] and trabeculectomy.[27] Beyond eye disorders and disease, it was reported that while corneal densitometry increases with age,[6,28-30] no correlations have been found with corneal keratometry and refractive parameters.[29]

During a Pentacam eye scan, patients are instructed to focus on an internal target. As a result of the miss-match between optical and visual axes,[31] topography and tomography maps are systematically tilted.[32-33] Furthermore, the level of eye tilt depends on age[35] and eye dominancy.[32]

Corneal light scattering, including strong limbal backscatter, is affected by eye orientation relative to the slit-light source, and consequently, corneal tilt with respect to the visual axis could influence corneal densitometry readings. Consequently, this study aims to investigate whether Pentacam densitometry readings are affected by corneal tilt under natural fixation, measured with a validated, custom algorithm.[33,36]

METHODS

Participants

This study was approved by the Antwerp University Hospital Research Ethics Committee and adhered to the tenets of the Declaration of Helsinki. Subjects signed informed consent before enrolment. Fully anonymized records from 86 healthy Caucasian subjects (66% women and 34% men) aged between 18 and 78 years, (mean ± SD = 42.8 ± 20.0 years) were collected for this prospective study.

All participants underwent a comprehensive ophthalmologic examination, including corneal Scheimpflug imaging using Pentacam. Corneal disease, previous corneal or intraocular surgery, diabetes mellitus, multiple sclerosis, or uncontrolled hypertension were considered exclusion criteria, while subjects presenting exclusively peripheral limbal degenerations associated with ageing such as arcus senilis were included. Only right eyes were considered in this study to avoid any artefact in the study outcomes as a result of the natural correlation between fellow eyes.[37]

Estimation of corneal tilt

Raw anterior and posterior corneal height maps were exported for further analysis. A previously validated methodology,[33,36] was applied to calculate the three-dimensional angle between visual and optical axes. This angle (known as angle alpha) was used as a measure of corneal tilt in the current study. The estimation of visual and optical axes is summarized in the following.

Earlier theoretical analysis and clinical studies demonstrated that eye orientation during a Pentacam exam corresponds to the best approximation of the visual axis.[38,39] Accordingly, the axis of the Pentacam Scheimpflug camera was considered the visual axis.

To determine the corneal optical axis, defined as the path of light that goes through the ocular system without refraction,[40] a raytracing algorithm was custom coded in MATLAB (MathWorks, Natick, MA, USA) and graphically validated using AutoCAD (Autodesk, McInnis Parkway San Rafael, CA, USA). In short, the methodology consists of simulating parallel light rays directed towards the cornea and refracted through the anterior and posterior surfaces according to Snell's law.[41] The angle of incidence was calculated for each ray with respect to the normal line to the anterior and posterior corneal surfaces using ray tracing to provide a measure for the local focal length. The corneal topography of each eye was rotated in three dimensions in an optimization loop based on the Levenberg-Marquardt nonlinear least-squares algorithm to maximize the focal length of a central light ray that was selected as the optimal optical axis. The full description of optical axis determination can be found in previous literature.[33]

Estimation of corneal densitometry

Figure 1 illustrates two examples of raw corneal imaging with Pentacam. The corneal densitometry screen is provided as an add-on to the standard software of the Pentacam Scheimpflug device. The Pentacam measurement protocol takes a series of 25 images over equally distributed meridians. In the post-measurement processing, data are interpolated to create a densitometry map via the Pentacam software package. The output is expressed in standardized grayscale units (GSU). The standardized grayscale unit measure is calibrated by proprietary software, which defines a minimum light scatter of 0 (maximum transparency) and a maximum light scatter of 100 (minimum transparency). For consistency with the previous literature, the densitometry measurement protocol was performed in a manner described previously.[6] This is provided by the Pentacam software in the form of a regional densitometry assessment, with four independent concentric zones: the central zone of 2 mm diameter, the annulus extending from 2 to 6 mm diameter, the annulus extending from 6 to 10 mm diameter, and the one that extends from 10 to 12 mm diameter. Therefore, the overall cornea was considered over a diameter of up to 12 mm. Moreover, the software performs a depth analysis over 3 layers: the anterior layer includes the anterior 120 µm, the central layer, and the posterior layer which corresponds to the most posterior 60 µm of the cornea. In addition, the whole corneal depth was also considered.

Statistical analysis

The statistical analysis was performed using SPSS software for Windows version 25.0 (SPSS Inc., Chicago, Illinois, United States), supported by the PROGRESS 4.0 package by Andrew F. Hayes. The normality of all sets of data was not rejected (Shapiro–Wilk test, $p > 0.05$). Pearson correlation coefficients (r) were used to assess relationships within the continuous variables under investigation. Age was considered a confounding factor for corneal tilt and corneal densitometry by means of simple mediation analysis. A simple mediation model is any causal system in which at least one causal antecedent variable X is proposed as influencing an outcome Y through a single intervening variable M.[42] Two cases were investigated: 1). Corneal tilt (X) influences corneal densitometry (Y) through age as mediator (M), and 2). Age (X) influences corneal densitometry (Y) through corneal tilt as a mediator (M). The level of significance was set to 0.05.

RESULTS

When considering corneal tilt and corneal densitometry as independent variables, a statistically significant positive correlation was found between them (r=0.45; p<0.001), as shown in Figure 2. This statistically significant positive correlation exists independently of the corneal region or depth, (all, p<0.001), as indicated in Table 1. However, age is significantly correlated with both densitometry (r=0.91, p<0.001) and with corneal tilt (r=0.50, p<0.001). Consequently, corneal tilt and corneal densitometry cannot be considered independent.

Results from the simple mediation analysis (case 1: Tilt influences densitometry with age as a mediator) show that only 3.8% of the correlation between tilt and densitometry operates directly, while the remaining 96.2% of that correlation depends on age. The age mediation effect exists and is statistically significant (p<0.05). In other words, corneal tilt on its own does not significantly affect corneal densitometry.

The results from the second simple mediation analysis (case 2: Age influences corneal densitometry with corneal tilt as a mediator) show that 91.3 % of the correlation between age and densitometry operates directly, while the remaining 8.6 % of that correlation depends on corneal tilt. The tilt mediation effect exists and is statistically significant (p<0.05). Results from cases 1 & 2 simple mediation analyses are consistent. According to these results, there is a strong direct effect between age and corneal densitometry, and a minor, but statistically significant, indirect effect of corneal tilt.

Table 1: Correlation between corneal tilt and densitometry expressed by the Pearson correlation coefficient (r). The first two columns show mean densitometry values ± standard deviation and range (standardized GSU), respectively, considering different corneal regions and depths, according to Pentacam software.

	Mean ± SD	Range	Densitometry vs tilt (r)
Depth layers			
Anterior	23 ± 9	[11, 42]	0.35, p<0.001
Central	16 ± 6	[9, 31]	0.45, p<0.001
Posterior	13 ± 6	[7, 27]	0.43, p<0.001
Concentric regions			
0-2 mm	15 ± 4	[9, 21]	0.48, p<0.001
2-6 mm	14 ± 4	[8, 25]	0.49, p<0.001
6-10 mm	19 ± 9	[8, 45]	0.43, p<0.001
10-12 mm	26 ± 11	[9, 49]	0.41, p<0.001
Overall	17 ± 7	[9, 33]	0.45, p<0.001

The group mean value of corneal tilt was (5.8° ± 1.8°), ranging from 2.1° to 10.0°.

DISCUSSION

The current study showed that even though corneal densitometry seemed to be affected by corneal tilt (r=0.45; p<0.001) this is in reality an artefact caused by the strong influence of age on both densitometry (r=0.91, p<0.001) and corneal tilt (r=0.50, p<0.001). When considering age as a mediator, the direct correlation between corneal tilt and corneal densitometry greatly weakened. These results highlight the importance of considering age as a confounding factor in densitometry studies. Numerous scientific reports used corneal densitometry as a tool to investigate eye disease,[7-17,21-27] but few consider the potential confounding factors as they seem to take a statistically significant correlation between two parameters at face value (e.g., tilt and densitometry, Figure 2), while it can in fact be entirely explained by a third variable (e.g., age). Clinicians, therefore, need to be mindful of such confounding factors when using densitometry, or any other clinical test, as a discriminative parameter between groups and consider using mediation analyses where needed.

Unlike other well-established corneal biomarkers (corneal thickness, curvature, etc.), densitometry does not describe corneal shape but corneal tissue properties. To date, there are no other standardized and accessible methods to objectively quantify corneal clarity. Even though the use of densitometry as an eye health marker is still not widespread in clinical practice, many researchers have demonstrated the potential of densitometry as a key diagnostic parameter, for example, in subclinical keratoconus detection.[8,12] Due to its potential and increasing interest of the community in densitometry, it is of paramount importance to evaluate which potential co-founding factors could affect it.

A previous study based on bootstrap statistical analysis and an iterative statistical approach concluded that central corneal thickness was not a co-founding factor in corneal densitometry.[11] The independence of corneal densitometry and central corneal thickness was also acknowledged elsewhere.[24] Similarly, no correlations have been found with corneal keratometry and refractive parameters.[29] To date, age appears to be the strongest confounding factor in densitometry studies. However, further studies should deeply analyse the influence of anterior eye biometry on densitometry readings.

Corneal densitometry values reported here agree with that from previous reports.[6,28,29] Similarly, the group mean value of corneal tilt agrees with that reported in previous work by Lopes et al.,[32] where the corneal tilt of the 347 Caucasian participants analysed was (5.9° ± 2.7°).

Results suggest strong eye tilt could influence corneal densitometry readings, independently of the origin of that corneal tilt. Corneal densitometry is based on the backscattering of light. Generally speaking, light from the source reaches the object to be imaged (the cornea), and is partially backscattered towards the detector to form an image. This final image, therefore, depends on how light travels inside the cornea and how much of it is backscattered.[30] When an object is tilted from its original position, the light will travel through it in a different manner, and consequently, backscattering will be affected.[43] Nowadays, alternative methodologies to estimate densitometry without using Pentacam software are available for Scheimpflug[43] and AS-OCT images.[44] However, these post-processing methods do not correct excessive brightness, highlighting the importance of an optimal data acquisition process.

As far as we can tell, current analysis does not suffer from major issues. We considered an alternative experimental design in which the densitometry would have been performed on eyes fixating under different angles. This idea was abandoned, however, in favour of the current approach as this would represent the natural fixating behaviour of the eye instead.

In conclusion, corneal tilt plays a role in corneal densitometry readings, even though that interaction is strongly influenced by age. Age is a major confounding factor in corneal densitometry readings that should be taken into consideration when considering a corneal densitometry analysis in a given patient.

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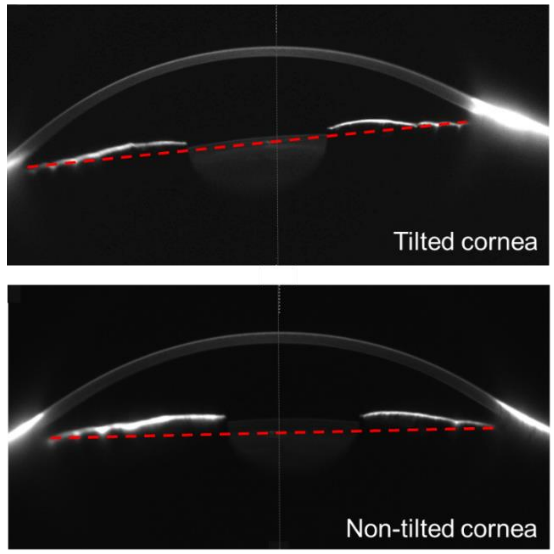

Figure 1. Examples of corneal tomography acquired with Pentacam. Images correspond to two subjects showing a different level of corneal tilt. Red dashed lines illustrate the level of tilt. The upper image (higher tilt) shows a brighter cornea and stronger limbal reflections than the bottom image (smaller tilt).

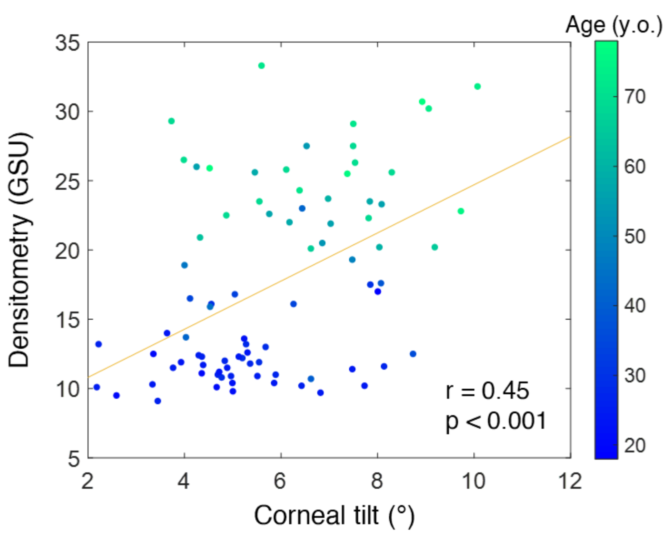

Figure 1: Correlation between corneal densitometry expressed in standardized grey scale units (GSU) and corneal tilt, calculated as the angle between visual and optical axes. Data points are coloured depending on the age of the subject, as indicated by the colour bar.