Comparing Corneal Variables in Healthy Subjects and Patients with Primary Open-Angle Glaucoma

Federico Saenz-Frances, Julian Garcia-Feijó, Luis Jañez, Lara Borrego-Sanz, Jose M. Martinez de la Casa, Ana Fernandez-Vidal, Carmen Mendez-Hernández, Enrique Santos-Bueso, Juan Reche-Frutos, and Julian Garcia-Sánchez

PURPOSE. This study was designed to identify possible differences between healthy subjects and patients with primary open-angle glaucoma (POAG) in keratometry, central corneal thickness, overall corneal thickness, mean thickness of a circular zone centered at the corneal apex of 1-mm radius (zone I), and mean thickness of several concentric rings also centered at the apex of 1-mm width (zones II to VI, respectively).

METHODS. These variables were recorded in 126 healthy subjects and 130 patients with POAG. Corneal thicknesses and the power of the flattest and steepest axes were compared between the two populations using a t-test and the position of the flattest axis using a Mann-Whitney U-test. A binary logistic regression procedure was used to determine the diagnostic capacity of the corneal variables using the area under the receiver operator characteristic curve (AUC) to select the best regression equation.

RESULTS. Significant differences between subjects and patients were detected in mean central corneal thickness and in mean thicknesses of zones I to VI. The logistic regression model included as predictors the mean central corneal thickness and the mean thicknesses of zones IV and VI; for this model, the AUC was 0.711, sensitivity was 67.7%, and specificity was 65.5%.

CONCLUSIONS. Healthy subjects and glaucoma patients differ significantly in terms of mean overall corneal thickness and thicknesses of the corneal zones I to VI defined here. The variables mean central corneal thickness and mean thicknesses of zones IV and VI are able to discriminate between subjects with or without glaucoma. (Invest Ophthalmol Vis Sci. 2011;52:3683–3688) DOI:10.1167/iovs.10-6660

Primary open-angle glaucoma (POAG) is defined as an optic neuropathy of multifactorial origin whose main characteristic feature is optic nerve disc damage caused by a loss of ganglion cells. Elevated intraocular pressure (IOP) is the principal risk factor known for this disease to develop and progress. Today’s criterion standard for determining IOP is Goldmann applanation tonometry. However, it is precisely the limitations of this tonometry system, such as the dependence of its measurements on central corneal thickness (CCT), that have determined, on one hand, the development of new tonometers that are less affected by corneal variables and, on the other, a growing interest in corneal structure. Effectively, characterization of CCT has revealed its role both as a confounding factor when measuring IOP and as a risk factor for the development and progression of glaucoma.

The most widespread method used to determine CCT is ultrasound pachymetry, in which the examiner places a probe on the approximate center of the cornea. The Pentacam (Oculus, Lynwood, WA), based on the Scheimpflug principle, captures images of the cornea and, with keratometry, calculates corneal thickness across the entire cornea by taking perpendicular measurements to the surface every 1 µm. It also has the added benefit of automatically locating the corneal apex.

This study was designed to identify differences between healthy subjects and patients with POAG in terms of the power of the flattest and steepest axes of the cornea, their position, and the thickness of several defined corneal zones, all determined using the Pentacam.

MATERIALS AND METHODS

We performed a cross-sectional study in 126 healthy volunteers and 130 patients with primary open-angle glaucoma. The patients were recruited from the Glaucoma Unit of the Hospital Clínico San Carlos in Madrid, Spain, and control subjects among the patients’ relatives and hospital staff. The study protocol was approved by our institution’s review board and complied with the guidelines of the Declaration of Helsinki. Informed consent was obtained from each participant before inclusion in the study. All study participants were Caucasian. Eyes were considered to be glaucomatous if they had shown abnormal results in at least two consecutive visual field examinations (Octopus TOP-G1X; Interzeag, Geneva, Switzerland) and if there was evidence of glaucomatous damage, as determined by the appearance of the optic nerve head. Glaucoma patients were required to show a gonioscopic evidence of an open angle. Subjects with nonprimary open-angle glaucoma (e.g., pseudoexfoliation, pigment dispersion, neovascularization) were excluded. Control subjects had to have an IOP <21 mm Hg, a normal visual field, and a nonglaucomatous-appearing optic disc.

General exclusion criteria were spherical equivalent greater than 5 diopters, or 3 or more diopters of astigmatism, a best-corrected visual acuity lower than 20/25, opacities in the cornea or lens impairing optic nerve head visualization, and alterations in optic nerve head morphology, such as oblique discs or peripapillary atrophy. We also excluded subjects who had undergone previous eye surgery and those whose visual field defects were of causes other than glaucoma (e.g., demyelinating disease, nonglaucomatous neuropathy, or a central nervous system disorder). If both eyes of a patient or a subject fulfilled all the

From the 1Department of Ophthalmology, Hospital Clínico San Carlos, and the 2Instituto de Tecnología del Conocimiento, Universidad Complutense de Madrid, Madrid, Spain.

Supported in part by Instituto de Salud Carlos III Grant “Red temática de Investigación Cooperativa. Proyecto RD07/0062: Patología ocular del envejecimiento, calidad visual y calidad de vida.”

Submitted for publication September 30, 2010; revised November 22 and December 13, 2010; accepted December 28, 2010.

Disclosure: F. Saenz-Frances, None; J. García-Feijó, None; L. Jañez, None; L. Borrego-Sanz, None; J.M. Martínez de la Casa, None; A. Fernandez-Vidal, None; C. Mendez-Hernández, None; E. Santos-Bueso, None; J. Reche-Frutos, None; J. García-Sánchez, None.

Corresponding author: Federico Saenz-Frances, Department of Ophthalmology, Hospital Clínico San Carlos, Universidad Complutense de Madrid, Madrid, Spain 28040; federicosaenzfrancessb@gmail.com.

Copyright 2011 The Association for Research in Vision and Ophthalmology, Inc.
FIGURE 1. Example of the information provided by the Pentacam. The box in the lower right-hand corner shows the corneal thickness map, which is accompanied in the right-hand column by a color-coded key to the corresponding thicknesses.

FIGURE 2. The figure shows the spreadsheet onto which the Pentacam exports the corneal thicknesses. Using this diagram, we defined zones I to VI centered at the corneal apex (in this case, for a right eye). Note that though zones II, III, IV, and V are complete rings, zone VI is a crescent shape because in the nasal zone (right) the limbus is reached.
determined by ultrasound pachymetry. Table 2 provides the differences in the variables observed between the two groups and their confidence intervals. Figure 3 shows the distributions of the variables that varied significantly between the two populations. The Mann-Whitney U test indicated no significant differences in the flattest corneal axis (U = 1100; P = 0.73).

Using the AUC of the ROC to select the best regression equation able to discriminate between the presence or absence of POAG, the variables revealed as significant were the mean thicknesses of the entire cornea and of corneal zones IV and VI. The variables included in this regression model and the parameters of the logistic regression equation are provided in Table 3; the area under the ROC curve (Fig. 4) for this model was 0.711 (95% confidence interval, 0.622–0.801). The sensitivity of this model for diagnosing POAG was 67.7%, and its specificity was 63.5%.

This regression model revealed that first-order interactions (products) between the predictive variables were not significant and that stratification into quartiles indicated a lack of confounding factors among the predictive variables.

**DISCUSSION**

The role of the cornea in glaucoma is becoming ever more evident since it was established that CCT conditions IOP measurement\(^2\)–\(^7\) and that greater corneal thickness is a protecting factor for the onset and advance of glaucoma.\(^1\)–\(^5\) Most of the recent studies in this area have addressed the effects of CCT and other new parameters, such as corneal hysteresis,\(^2\)–\(^5\) on the different tonometry systems.\(^7\)–\(^10\) In contrast, in the present study, we considered different ring-shaped zones of the cornea of preestab-

<table>
<thead>
<tr>
<th>Differences (control minus glaucoma)</th>
<th>(P)</th>
<th>Mean Difference</th>
<th>Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Power steepest axis</td>
<td>0.307</td>
<td>–0.30</td>
<td>–0.87</td>
<td>0.28</td>
</tr>
<tr>
<td>Power flattest axis</td>
<td>0.290</td>
<td>–0.55</td>
<td>–1.56</td>
<td>0.47</td>
</tr>
<tr>
<td>CCT (ultrasound)</td>
<td>0.171</td>
<td>8.39</td>
<td>–3.66</td>
<td>20.45</td>
</tr>
<tr>
<td>Mean thickness</td>
<td>0.005</td>
<td>22.20</td>
<td>6.82</td>
<td>37.58</td>
</tr>
<tr>
<td>Thickness zone I</td>
<td>0.016</td>
<td>16.96</td>
<td>3.21</td>
<td>30.71</td>
</tr>
<tr>
<td>Thickness zone II</td>
<td>0.021</td>
<td>16.17</td>
<td>2.47</td>
<td>29.87</td>
</tr>
<tr>
<td>Thickness zone III</td>
<td>0.026</td>
<td>15.88</td>
<td>1.96</td>
<td>29.80</td>
</tr>
<tr>
<td>Thickness zone IV</td>
<td>0.016</td>
<td>18.51</td>
<td>3.51</td>
<td>33.11</td>
</tr>
<tr>
<td>Thickness zone V</td>
<td>0.009</td>
<td>22.00</td>
<td>5.63</td>
<td>38.38</td>
</tr>
<tr>
<td>Thickness zone VI</td>
<td>0.031</td>
<td>20.62</td>
<td>1.93</td>
<td>39.31</td>
</tr>
</tbody>
</table>

Powers of the corneal axes are expressed in diopters. All corneal thicknesses, including CCT, are expressed in micrometers. For definitions of the thickness zones, see Figure 2.

95% CI, 95% confidence interval.

**FIGURE 3.** Box plots illustrating mean corneal thickness and mean thicknesses of zones I to VI recorded in the study (in which significant differences were detected between the healthy subjects and glaucoma patients). In each box, the horizontal line indicates the median, the upper and lower limits, and the third and first quartiles, respectively. Outliers are indicated with circles and are those values that appear above the third or below the first quartiles at a distance greater than 1.5 times the distance of the interquartile range (Q3–Q1). The whiskers emerging from the boxes represent values appearing above the third or below the first quartiles at a distance lower than 1.5 times the distance of the interquartile range. Thicknesses are expressed in micrometers (microns).
lished size centered at the corneal apex. As far as we are aware, this approach has not been previously reported in the literature.

Our findings served to identify structural differences in the corneas of healthy subjects and of patients with POAG; all the subjects who participated in our study were Caucasian. In a study sample of 36 healthy Caucasians, Aghian et al. recorded a mean CCT of 562.8 μm compared to our mean of 555.08 μm. In the patients with glaucoma, these authors observed a mean of 542.2 μm, whereas our figure was 546.68 μm. However, unlike the difference in CCT between healthy controls and glaucoma patients detected in the study by Aghian et al., this difference was not significant in our study. Consistent with the present results, Shing et al. and Kitsos et al. reported similar CCT in their healthy subject and POAG patient groups. In the present study, we used ultrasound pachymetry to measure CCT because this is perhaps the most widely used method. Notwithstanding, other methods such as optical coherence tomography or even the Pentacam itself have provided highly reproducible results for this variable. It remains to be clarified why ultrasound pachymetry was unable to detect CCT differences between our glaucoma patients and controls in the present study. Ultrasound pachymetry has been described as a highly reliable and reproducible method by Gunvant et al., although authors such as Lackner et al. claim the Pentacam shows higher interobserver reproducibility. Perhaps this worse interobserver reproducibility, along with an inability to detect CCT differences between glaucoma-tous and healthy populations described by us and by Shing et al. and Kitsos et al., is the outcome of the fact that the clinician has to visually establish the center of the cornea, whereas other pachymetry systems, such as the Pentacam, automatically locate this center. Accordingly, we found high agreement between the Pentacam CCT measures of thickness at the pupil axis and minimum corneal thickness (the Pentacam estimates CCT as several measures, including thickness at the pupil axis and minimum corneal thickness) (intraclass correlation coefficient [ICC] = 0.98), whereas agreement was only moderate between ultrasound pachymetry-determined CCT and thickness at the pupil axis (ICC = 0.79) or minimum thickness (ICC = 0.77), determined using the Pentacam (Saenz-Frances F et al. IOVS 2009;51: ARVO EAbstract 579).

The significant differences observed always indicated thinner corneal measurements in the glaucoma patients. However, given the lack of available literature data for the thicknesses of the corneal regions defined here, we do not know whether these differences could be clinically relevant in addition to being significant. To establish this relevance, we constructed a logistic regression model that revealed the variables mean thickness of the entire cornea and mean thicknesses of corneal zones IV and VI were able to discriminate between subjects with glaucoma and those without. Although not a diagnostic test in itself, the set of structural corneal variables identified showed considerable discriminatory capacity (AUC, 0.711; sensitivity, 67.7%; specificity, 65.5%). We are unaware whether these differences precede or result from the disease or its treatment. Brandt et al. observed that the CCT of a person is fairly stable over time such that we speculate that the thicknesses of the zones examined here will be similarly stable. On the other hand, the histologic architecture of the cornea is similar across its center and periphery yet varies in thickness (greater in the periphery) and cell density. In effect, Mimura et al. reported greater endothelial cell density in the corneal periphery. Moreover, Hamrah et al. detected phenotypic differences in the dendritic cells of the corneal stroma between the central and peripheral cornea and greater density in the periphery. Similarly, Pleyer et al. noted a greater density of IgM and complement molecules in the peripheral stroma, a factor correlated with autoimmune diseases of the peripheral cornea and with ulcers of noninfectious origin. Reinstein et al. described that the corneal epithelium was thicker at the inferior and nasal levels. Apart from these observations, no substantial differences seem to exist between the histologic architecture and cell composition of the central and peripheral cornea. Notwithstanding, Nagayasu et al. noted differences in the number of collagen fibers and their diameters between the central cornea and the periphery (more fibers of reduced diameter in the central zone), along with a greater density of proteoglycans in the central canine cornea. We do not know whether these differences between the central and peripheral cornea could somehow condition a change in corneal structure in response to high IOP or to the pressure-lowering medications used by glaucoma patients. However, given the subtle nature of these differences, we feel that our findings are perhaps more consistent with the idea that a primary structural difference exists between the cornea of a person with POAG and one without POAG. Indeed, the morphometric characteristics of the optic nerve head in glaucoma have been widely explored. Thus, when Lesk et al. examined the relationship between CCT and optic nerve disc topography, they found greater shallowness

| Table 3. Variables Entered in the Logistic Regression Equation and Their Corresponding Significance Values and Confidence Intervals |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
|                             | P              | Exp(B)       | Lower 95% CI Limit of Exp(B) | Upper 95% CI Limit of Exp(B) |
| Mean thickness              | 0.004          | 0.91         | 0.853                      | 0.97                      |
| Mean thickness zone IV      | 0.005          | 1.087        | 1.025                      | 1.152                     |
| Mean thickness zone VI      | 0.038          | 1.045        | 1.012                      | 1.079                     |
| Constant                    | —              | 408.054      | —                          | —                         |

AUC = 0.711. Exp(B) is the exponential of the coefficient of regression B.

![ROC Curve](image-url)  
**FIGURE 4.** ROC curve for the logistic regression model including, as predictors, the variables mean overall corneal thickness and mean thicknesses of corneal zones IV, V, and VI. AUC = 0.711.
and thinness of the corneas in patients with POAG and those with ocular hypertension. In addition, Insull et al. detected an inverse relationship between CCT and optic disc area. Wu et al. related a thinner CCT to a smaller area of the neuroretinal rim and greater cup-to-disc ratio in patients with POAG but not in healthy controls. Kourkoutas et al. observed a significant correlation between CCT and optic disc morphology, determined through the Heidelberg Retina Tomograph II according to a nonlinear regression model. All these data support a structural link between CCT and optic disc morphology, but we have yet to determine whether this relationship holds for the corneal zones described here. If such a relationship were confirmed, this would lend support to our hypothesis of an inherent difference in the corneal structure of glaucoma patients and healthy controls.

As revealed by our results, corneal structure, and especially corneal thickness, may play a role that goes beyond merely acting as a confounding factor for tonometry readings in the field of glaucoma. Our main finding that corneal features, in addition to central corneal thickness, are associated with glaucoma warrants further investigation. We have yet to determine whether other corneal zones, other dimensions of these zones, or a different centering point, may provide even more interesting information. Similarly, the effects of mean corneal thickness in zones I to VI on Goldman applanation tonometry and the new tonometers will also have to be examined, as has been reported for CCT.

References

35. Lackner B, Schmidinger G, Pich S, Funovic MA, Skorpik C. Repeatability and reproducibility of central corneal thickness mea-


44. Lesk MR, Hafez AS, Descovich D. Relationship between central corneal thickness and changes of optic nerve head topography and blood flow after intraocular pressure reduction in open angle glaucoma and ocular hypertension. *Arch Ophthalmol.* 2006;124:1568–1572.

