Corneal Properties in Primary Open-angle Glaucoma Assessed Through Scheimpflug Corneal Topography and Densitometry

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Purpose: The purpose of this study was to compare corneal topography and densitometry measurements in patients with primary open-angle glaucoma (POAG) and healthy subjects.

Patients and Methods: A total of 200 eyes of 75 patients with POAG and 125 healthy controls underwent corneal topography and densitometry (Oculus Pentacam HR). The data compared in the 2 groups were: anterior chamber angle, anterior chamber depth, and anterior chamber volume, keratometry ($K_{\text{minimum}}$, $K_{\text{maximum}}$, and $K_{\text{mean}}$), central corneal thickness, central anterior elevation, anterior elevation apex, maximum anterior elevation, and posterior elevation apex. Densitometry measurements were made at 3 depths on a 12-mm-diameter circle divided into 4 concentric rings (0 to 2, 2 to 6, 6 to 10, and 10 to 12 mm). The diagnostic capacity of the corneal variables was assessed through the areas under the receiver operating characteristics curve.

Results: The corneal density of practically all depth layers and total corneal density were significantly higher in the POAG than the control group ($P<0.05$). Total corneal density was positively correlated with age ($r=0.623$; $P<0.001$) and also showed a good diagnostic capacity for glaucoma [area under the curve $=0.617$; 95% confidence interval (CI): $0.541-0.697$; $P<0.001$]. In a multiple linear regression designed to assess its relationship with age, sex, central corneal thickness, and $K_{\text{mean}}$, age emerged as a significant confounder both in controls (coefficient $=0.315$; $P<0.001$; 95% CI: $0.246-0.384$) and patients (coefficient $=0.370$; $P<0.001$; 95% CI: $0.255-0.486$).

Conclusion: Corneal densitometry measurements showed a good diagnostic capacity for POAG suggesting this type of examination could have clinical applications in the diagnosis and management of glaucoma.

Key Words: corneal densitometry, primary open-angle glaucoma, corneal topography, Scheimpflug

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Primary open-angle glaucoma (POAG) is a progressive optic neuropathy and the second leading cause of blindness worldwide.

Intraocular pressure (IOP) is the only modifiable risk factor for POAG, so measurements must be reliable and reproducible. However, the current gold standard procedure for IOP measurement, Goldmann applanation tonometry, is considerably influenced by several well-defined variables such as central corneal thickness (CCT) and keratometry ($K$).

With the new devices that we have today, several new variables can be determined that give a good idea of individual corneal biomechanics (hysteresis and resistance factor) and the state of the cornea (corneal densitometry).

The Pentacam HR (Oculus, Wetzlar, Germany) is a noninvasive device that offers good predictability and reproducibility of measures. It is based on a Scheimpflug imaging system and its new software allows for the rapid and objective assessment of corneal densitometry. This measurement correlates with corneal light scatter and transparency. Readings provide information on corneal clarity and are provided as a grayscale units (GSU) that goes from 0 (full transparency) to 100 (full opacity or clouding), depending on luminance per unit volume.

Corneal densitometry has been used in the study of both systemic diseases (eg, diabetes mellitus, mucopolysaccharidosis) and eye diseases (eg, keratoconus, pseudoxfoliation syndrome) and also for the follow-up of refractive surgery or bacterial keratitis.

Some studies have examined corneal densitometry in patients with glaucoma other than POAG such as pseudoxfoliative glaucoma (PEG) or primary congenital glaucoma. Sekeroglu et al found no significant differences in corneal densitometry between patients with PEG and healthy control subjects. In contrast, Morales-Fernandez et al detected higher corneal densitometry measurements in patients with primary congenital glaucoma compared with controls, and densitometry was found inversely correlated with best-corrected visual acuity (BCVA).

The purpose of this study was to examine corneal densitometry in patients with POAG and to determine the diagnostic capacity of differences in its measurements in relation to healthy control subjects.

PATIENTS AND METHODS

This was a descriptive cross-sectional study carried out at the Ophthalmology Department of the Hospital Clinico San Carlos, Madrid, Spain. All patients gave their consent to participate and also for results to be published in accordance with the tenets of the Declaration of Helsinki. Over the period from January to September 2019, we recruited 200 consecutive white subjects. Of these, 125 were healthy individuals and 75 were patients with POAG. In
turn, patients were divided into 3 groups of 25 patients according to the Glaucoma Staging System (GSS2), which considers the state of the visual field measured as the mean defect (MD) as the most important reference: early POAG MD < 6, moderate POAG MD 6 to 12, and advanced POAG MD > 12.15,16 Subjects with other types of glaucoma were excluded.

For the control group, inclusion criteria were healthy volunteers older than 18 years, no eye disease, IOP < 21 mm Hg, normal optic disc, normal visual field, BCVA > 0.8 (Snellen), spherical refractive defect < 5 D, and cylinder < 3 D. Exclusion criteria were a history of corneal, macular, or optic nerve disease as well as eye surgery or ocular trauma.

For the study group, inclusion criteria were patients diagnosed with POAG showing an open angle on gonioscopy, narrowing of the neuroretinal rim, visual defects through Octopus TOP perimetry (Haag-Streit, Koenig, Switzerland), and optic nerve damage in the retinal nerve fiber layer as determined by spectral-domain optical coherence tomography (Heidelberg Engineering Inc., Heidelberg, Germany). Exclusion criteria were a BCVA of < 0.3 (Snellen), spherical refractive defect > 5 D, cylinder > 3 D, or incapacity to collaborate with the tests required.

For analysis, one eye per subject was randomly selected using a sequence generated at www.randomization.com. The data obtained in each patient were age, sex, eye examined, IOP (Perkins hand-held Goldmann tonometer; Clement-Clarke, Columbus, OH), and Pentacam HR topography and densitometry data.

The Pentacam examination was conducted by a single experienced investigator (M.M.-S.) who was masked to the study group of the subject tested. In each participant, the same device was used in the same room and under constant dim-light conditions. The test was performed in automatic mode to minimize human error. Measurements were taken once per patient, checking the “examination quality specification” OK index, given the good reproducibility and repeatability of this device. IOP was measured after the Pentacam examination to avoid altering the ocular surface, and thus corneal measurements.

The data compiled in each patient were: sex, age, IOP, keratometry (K minimum, K maximum, and K mean), cylinder, and CCT. In addition, corneal densitometry measurements were obtained over a 12-mm-diameter circle centered at the apex of the cornea divided into 4 concentric rings (0 to 2, 2 to 6, 6 to 10, and 10 to 12 mm) and also at 3 depths or layers: anterior (120 µm thickness from the surface), mid-stroma (thickness 120 to 60 µm) and posterior (thickness 60 µm). Other variables recorded were central anterior elevation (CAE), anterior elevation apex, maximum anterior elevation, and posterior elevation apex (PEA) and the anterior segment measurements such as anterior chamber depth (ACD), anterior chamber volume (ACV), and anterior chamber angle (ACA). Finally, we also collected data on the treatment received and previous surgeries for POAG. As the literature lacks information on correlations between total densitometry and age, sex, CCT, and K mean, we could not perform a sample size calculation. Hence, we consider this to be a pilot study whose findings will provide the grounds for sample size determinations in further studies.

Statistical Analysis

All statistical tests were performed using the software package SPSS 25.0 for Windows (SPSS Inc., Chicago, IL). The Kolmogorov-Smirnov test was used to check the normality of the distribution of quantitative variables, which were expressed as mean and SD. Corneal parameters were compared with the Student t test for independent samples. The possible effects of age, CCT, keratometry, and glaucoma stage on densitometry were assessed through the Pearson correlation. The level of significance for each contrast was set at P-value <0.05.

Receiver operating characteristic curves were constructed and areas under the curve (AUCs) were used to assess the capacity of each variable to distinguish between glaucomatous and healthy eyes. AUCs were compared for the different variables using the DeLong Method to provide the sensitivity and specificity of each model (Fig. 2).

RESULTS

Participants were 200 consecutive white subjects seen at our center, of whom 125 were healthy controls and 75 were POAG patients. The mean ages were 64.16 (± 1.34) years for the control group and 72.20 (± 1.38) years for the POAG group. Proportions of men were 35.2% in the control group was 42.66% in the POAG group. Both groups were comparable in terms of age (P = 0.063), sex (P = 0.290), and eye examined (P = 0.100) (Table 1). The MDs in each group (mean ± SD) used to grade glaucoma severity are displayed in Figure 1. In the early POAG group, MD was 2.85 (± 1.23); in the moderate POAG group, MD was 8.26 (± 1.90); and in the advanced POAG group, MD was 15.66 (± 3.46).

Treatment received by the POAG patients was monotherapy in 20% (15/75), combined therapy with 2 drugs in 8% (6/75), and 3 drugs in 5% (4/75). The remaining patients were not under any medical treatment (66%, 50/75). Overall, 20% (15/75) of the patients had cataract surgery, 16% (12/75) trabeculectomy, 4% (3/75) microinvasive glaucoma surgery, and 1% (1/75) had undergone selective laser trabeculoplasty.

Among the topographic factors compared in the 2 groups, the only significant differences detected were a higher CAE (P = 0.004) and PEA (P = 0.042) in the POAG group (Table 2). Among the anterior chamber parameters examined, only the ACA emerged as significantly greater in the POAG group (P = 0.006) (Table 3). Corneal density was also found to be higher in POAG patients than healthy subjects in practically all layers: anterior, mid-stroma, and full thickness. In the posterior

### TABLE 1. Demographic and Clinical Characteristics of the Patients and Controls

| Variables         | Controls (N = 125) | POAG (N = 75) | P*  |
|-------------------|--------------------|--------------|-----|
| Age (y)           | 64.16 (± 1.34)     | 72.20 (± 1.38) | 0.063|
| Sex (% male)      | 35.2               | 42.66        | 0.290|
| Eye (% right eyes)| 48                 | 60           | 0.100|
| IOP (mm Hg)       | 16.37 (± 3.35)     | 16.38 (± 3.10) | 0.978|
| CCT (µm)          | 559.39 (± 48.36)   | 557.04 (± 42.42) | 0.720|
| MD (dB)           | —                  | —            | —   |
| Early (n = 25)    | 2.85 (± 1.23)      |              | —   |
| Moderate (n = 25) | 8.26 (± 1.90)      |              | —   |
| Advanced (n = 25) | 15.66 (± 3.46)     |              | —   |

*Student t test.
†Chi-squared test.
Significance < P < 0.05.
CCT indicates central corneal thickness; IOP, intraocular pressure; MD, mean defect; POAG, primary open-angle glaucoma.
Other factors also showing the discriminatory capacity to detect POAG were: ACA (AUC \( P = 0.034 \)) (Table 4).

A significant correlation was noted between corneal density and age \((r = 0.623; \ P < 0.001)\). Corneal density showed no correlation with keratometry \((K_{\text{maximum}}, K_{\text{minimum}}, \text{or} \ K_{\text{mean}}; \ P > 0.01)\) or with the severity of glaucoma according to the MD (Table 5).

The variable showing the best diagnostic capacity of all those examined was total corneal density referring to the full thickness of the total area examined \((\text{AUC} = 0.617; \ P < 0.001)\). Other factors also showing the discriminatory capacity to detect POAG were: ACA \((\text{AUC} = 0.607; \ P = 0.011)\), PEA \((\text{AUC} = 0.613; \ P = 0.006)\), the corneal density of rings 0 to 2 and 2 to 6 mm all layers (anterior, mid-stroma, and posterior) \((P < 0.001)\) and of the total area of the layers anterior and mid-stoma \((P < 0.001)\) and \(P = 0.016\), respectively) (Table 6).

The receiver operating characteristic curve (AUC) constructed to determine the capacity of each variable to distinguish between glaucomatous and healthy subjects is provided in Figure 2. The variables identified as showing the most discriminating capacity were corneal densities recorded for the anterior, mid-stroma, and full-thickness layers of the 0 to 2 mm central ring.

Multiple linear regression analysis was used to assess the association between the dependent variable total corneal density and the independent variables age, sex, CCT, and \(K_{\text{mean}}\) in both the control and POAG groups (Table 7). In the control group, this model showed that after adjusting for age, for each year of age, total corneal density increased by 0.315 \(\mu\)m \((\text{slope:} \ 0.315; \ P < 0.001; \ 95\% \text{ CI:} \ 0.246-0.384)\). Similarly, for each micron of CCT increase, corneal density increased by 0.024 \(\mu\)m \((\text{slope:} \ 0.024; \ P = 0.030; \ 95\% \text{ CI:} \ 0.002-0.045)\). In the POAG group, for each 1 year increase in age, total corneal density increased by 0.370 \(\mu\)m \((\text{slope:} \ 0.370; \ P < 0.001; \ 95\% \text{ CI:} \ 0.255-0.486)\).

Also by multiple linear regression, we examined the relationship between CAE (Table 8) and PEA (Table 9) as dependent variables, and age, sex, CCT, and \(K_{\text{mean}}\) as independent factors. For CAE as the dependent variable in the control group, this model showed, after adjusting for age, for every 1 year increase in age, total corneal density decreased by 0.040 \(\mu\)m \((\text{slope:} \ -0.040; \ P = 0.023; \ 95\% \text{ CI:} \ -0.076 \text{ to} \ -0.005)\). Likewise, in the POAG group, each diopter increase in \(K_{\text{mean}}\) was associated with an increase in CAE of 0.651 \(\mu\)m \((\text{slope:} \ 0.651; \ P < 0.001; \ 95\% \text{ CI:} \ 0.308-0.994)\).

Similarly, when we assessed the effects of the predictors on PAE in the control group, each year of age increase was associated with an increase in PAE of 0.134 \(\mu\)m \((\text{slope:} \ 0.134; \ P = 0.009; \ 95\% \text{ CI:} \ 0.034-0.235)\). Further, in this model, each micron of CCT increase was associated with an increase in PEA of 0.034 \(\mu\)m /micron of CCT increase \((\text{slope:} \ 0.034; \ P = 0.034; \ 95\% \text{ CI:} \ 0.008-0.060)\).

### TABLE 2. Corneal Characteristics With Pentacam HR

| Variables       | Controls (N = 125) Mean (± SD) | POAG (N = 75) Mean (± SD) | P*   |
|-----------------|--------------------------------|---------------------------|------|
| \(K_{\text{mean}}\) (D) | 46.75 (± 33.15) | 44.40 (± 2.32) | 0.432 |
| \(K_{\text{maximum}}\) (D) | 44.41 (± 1.79) | 44.97 (± 2.57) | 0.099 |
| \(K_{\text{minimum}}\) (D) | 43.08 (± 1.90) | 43.68 (± 2.34) | 0.061 |
| AEA (µm)        | 1.14 (± 3.85) | 1.77 (± 3.75) | 0.285 |
| CAE (µm)        | 1.08 (± 2.98) | 2.46 (± 3.43) | 0.004 |
| PEA (µm)        | 11.83 (± 8.83) | 14.36 (± 8.22) | 0.042 |
| CPE (µm)        | 6.04 (± 6.43) | 6.69 (± 6.24) | 0.485 |

Corneal measurements made with the Pentacam HR.

*Student t test.

**Bold indicates significant differences between groups.**

### TABLE 3. Pentacam HR Anterior Segment Parameters

| Variables       | Controls (N = 125) Mean (± SD) | POAG (N = 75) Mean (± SD) | P*   |
|-----------------|--------------------------------|---------------------------|------|
| ACD (µm)        | 2.86 (± 0.69) | 3.04 (± 0.86) | 0.139 |
| ACV (µm³)       | 153.12 (± 38.38) | 153.29 (± 38.34) | 0.976 |
| ACA (deg.)      | 34.70 (± 9.26) | 38.48 (± 9.41) | 0.006 |

*Student t test.

**Bold indicates significant differences between groups.**

**AEC indicates anterior elevation apex; CAE, central anterior elevation; CPE, central posterior elevation; K, keratometry; PEA, posterior elevation apex; POAG, primary open-angle glaucoma.**
In the present study, the mean corneal density in our control group of 125 healthy white individuals was 25.59 ± 7.52 GSU. In contrast, mean total corneal densities of 16.46 ± 1.85 GSU have been reported by Garzon et al17 for 338 white subjects and of 19.74 ± 3.89 GSU by Ni Dhubhghail et al18 for 445 Belgian subjects. The higher value obtained here could be explained by the younger age of the study participants of those studies (62.32 ± 6.61 and 48 ± 15.3 years, respectively) compared with our controls (64.16 ± 13.4 years).

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patients \( (P = 0.006) \). Sekeroglu et al.\(^9\) in their study in patients with PEG observed a smaller ACD, ACV along with a smaller ACA in the GPE group (29.87 ± 10.92 vs. 31.33 ± 12.12; \( P = 0.401 \)). In contrast, in our study, the POAG group showed a higher ACA than controls (38.48 ± 9.41 vs. 34.70 ± 9.26; \( P = 0.006 \)). These differences can be explained by the anatomic differences that characterize both types of glaucoma.

In a search of normative corneal densitometry data for adults with POAG, we only found one study from Turkey in which data obtained when POAG was diagnosed were 20.03 ± 5.42 GSU compared with 28.46 ± 7.45 recorded in our POAG group. This difference could be attributed to the corneal modifications induced by phacoemulsification or filtering surgeries in our patients as the participants of the Turkish study were naive patients.\(^19\)

In addition to changes in corneal structure derived from surgical procedures, the impacts of topical treatments on corneal density are remarkable. In the study by Sen et al.,\(^{19}\) a decrease in corneal density was noted from the third trimester of treatment with latanoprost \( (P = 0.08) \). In our study, the POAG pool was not divided according to treatment as these were long-term patients, so we cannot draw firm conclusions. In future work, it would be interesting to prospectively examine corneal density classification by groups of drugs.

**TABLE 7.** Multiple Linear Regression Analysis for the Dependent Variable Total Corneal Density (Full Thickness)

|        | Coefficient | 95% Confidence Interval | Significance \( (P) \) |
|--------|-------------|-------------------------|-----------------------|
| Control |             |                         |                       |
| Age    | 0.315       | 0.246-0.384             | < 0.001               |
| Sex    | -1.211      | -3.390 to 0.967         | 0.273                 |
| CCT    | 0.024       | 0.002-0.045             | 0.030                 |
| \( K_{\text{mean}} \) | -0.016 | -0.048 to 0.014 | 0.291 |
| POAG   |             |                         |                       |
| Age    | 0.370       | 0.255-0.546             | < 0.001               |
| Sex    | -2.701      | -5.575 to 0.173         | 0.065                 |
| CCT    | 0.016       | -0.017 to 0.050         | 0.326                 |
| \( K_{\text{mean}} \) | 0.269 | -0.369 to 0.908 | 0.404 |

Bold indicates significant differences between groups. Significance \( P < 0.05 \).

CCT indicates central corneal thickness; \( K \), keratometry; POAG, primary open-angle glaucoma.

**TABLE 8.** Multiple Linear Regression Analysis for the Dependent Variable CAE

|        | Slope     | 95% Confidence Interval | Significance \( (P) \) |
|--------|-----------|-------------------------|-----------------------|
| Control |           |                         |                       |
| Age    | -0.040    | -0.076 to -0.005        | 0.023                 |
| Sex    | 0.115     | -0.996 to 1.227         | 0.838                 |
| CCT    | 0.001     | -0.009 to 0.012         | 0.778                 |
| \( K_{\text{mean}} \) | 0.002 | -0.013 to 0.019 | 0.725 |
| POAG   |           |                         |                       |
| Age    | 0.008     | -0.053 to 0.070         | 0.781                 |
| Sex    | -1.075    | -2.616 to 0.465         | 0.168                 |
| CCT    | -0.002    | -0.021 to 0.015         | 0.747                 |
| \( K_{\text{mean}} \) | 0.651 | 0.308-0.994 | < 0.001 |

Bold indicates significant differences between groups. Significance \( P < 0.05 \).

CAE indicates central anterior elevation; CCT, central corneal thickness; \( K \), keratometry; POAG, primary open-angle glaucoma.
TABLE 9. Multiple Linear Regression Analysis for the Dependent Variable PEA

|         | Slope      | 95% Confidence Interval | Significance (P) |
|---------|------------|-------------------------|-----------------|
| Control |            |                         |                 |
| Age     | 0.134      | 0.034-0.235             | 0.009           |
| Sex     | 1.198      | −1.965 to 4.361         | 0.455           |
| CCT     | 0.046      | 0.014-0.077             | 0.004           |
| Kmean   | 0.008      | −0.037 to 0.054         | 0.720           |
| POAG    |            |                         |                 |
| Age     | 0.108      | −0.048 to 0.264         | 0.172           |
| Sex     | −0.308     | −4.201 to 3.585         | 0.875           |
| CCT     | −0.054     | −0.100 to −0.008        | 0.021           |
| Kmean   | 0.106      | −0.759 to 0.972         | 0.807           |

Bold indicates significant differences between groups. Significance P < 0.05.

CCT indicates central corneal thickness; K, keratometry; PEA, posterior elevation apex; POAG, primary open-angle glaucoma.

It should be noted that no other study has related by multiple linear regression total corneal densitometry with independent variables such as age, sex, CCT, or Kmean. In the present study, we found that age was a confounding factor for densitometry measurements in both the control (slope: 0.315; P < 0.001; 95% CI: 0.246-0.384) and POAG groups (slope: 0.570; P < 0.001; 95% CI: 0.255-0.486).

The diagnostic capacity of total corneal densitometry (whole area full thickness) was found to be intermediate (AUC = 0.617; P = 0.005). After determining differences between groups in both topographic and densitometry variables, the factor showing the best discriminatory capacity for glaucoma was the total corneal density of the 0 to 2 mm ring (AUC = 0.679; P < 0.001). Further, all the densitometry variables except values for the 10 to 12 mm ring anterior layer, 6 to 10 and 10 to 12 mm middle layer, 6 to 10 and 12 mm ring posterior layer, whole area posterior layer, and 10 to 12 mm ring full thickness showed significant diagnostic capacity.

Although the diagnosis of POAG is clinical and based on the tests mentioned earlier, our study shows that corneal density values differ between healthy subjects and POAG patients and that they have some discriminating capacity. Thus, besides for diagnostic purposes, these parameters might be also useful for patient follow-up, given the importance of these properties in corneal transparency and their influence on IOP measurements. These results support the use of these new variables in clinical practice. In this preliminary study, it is not possible to determine the influence of other variables such as previous surgeries, previous treatments, or the impact increased corneal density could have on the MD or visual acuity.

The limitations of our study are its small sample size, especially the size of the groups arising from patient stratification by the severity of glaucoma. In addition, there were several confounding factors such as age. Further work is needed to prospectively address corneal densitometry in POAG patients and the effects of hypotensive drugs or the different types of glaucoma filtering surgery. In the POAG group, we included patients with moderate and advanced glaucoma who had had prior surgery. In future studies, it should be clarified whether this factor could lead to changes in corneal density or if it is a primary alteration.

In conclusion, our findings indicate corneal densitometry differences in healthy subjects and patients with POAG besides known differences in other corneal properties. Some corneal density measurements showed a good diagnostic capacity for POAG suggesting a possible role of densitometry as a complementary test in the diagnostic and prognostic support of glaucoma. Further work is still needed, however, to determine if this corneal property is a primary or secondary alteration in patients with POAG.

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