Central Corneal Pachymetry and Visual Field Progression in Patients with Open-Angle Glaucoma

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**Purpose:** To investigate the association between corneal pachymetry and visual field progression in patients with chronic open-angle glaucoma.

**Design:** Retrospective case–control study.

**Participants:** Eighty-eight patients with primary open-angle glaucoma, pseudoexfoliative glaucoma, pigmentary glaucoma, or normal-tension glaucoma, followed for an average of 8 years, who had visual field loss and progression as defined by modified Anderson criteria. Cases with progression were matched for race, diagnosis, and age at pachymetry with controls who did not have progression.

**Methods:** Progression was defined by use of the modified Anderson criteria. Central corneal thickness (CCT) was determined by ultrasound pachymetry.

**Main Outcome Measures:** Visual field progression and corneal pachymetry.

**Results:** The mean CCT in patients with visual field progression was significantly lower than the mean CCT in patients who did not progress (529.36 μm vs. 547.35 μm; P = 0.02). Those with thinner CCT were more likely to progress than those with thicker CCT as identified by Cox proportional hazards regression analysis (P = 0.01; hazard ratio, 1.44 for a 40-μm thinner CCT; 95% confidence interval, 1.12–1.80), and CCT was the only risk factor identified to be significantly associated with visual field progression.

**Conclusions:** In this case–control patient population, visual field progression in patients with open-angle glaucoma was significantly associated with thinner CCT.

Since the introduction of applanation tonometry by Goldman and Schmidt in 1957, the relationship between central corneal thickness (CCT) and intraocular pressure (IOP) has been of interest. The average CCT for “normal” eyes was found to be 534 μm in a meta-analysis of 300 data sets that acquired CCT by both optical-based and ultrasound pachymetry; however, the average increased to 544 μm when only ultrasound-based studies were evaluated (80 data sets). Ultrasound pachymetry generally yields slightly higher CCT estimates than slit-lamp–based optical pachymetry. An acceptable population variance of ± 1 standard deviation will yield “normal” ultrasound CCT values between 510 μm and 578 μm.

Elevated IOP remains the most important risk factor for the development of glaucomatous optic neuropathy. Accurate IOP measurements are important for glaucoma patient care, and this has prompted investigations of CCT in patients with different forms of open-angle glaucoma (OAG). Those diagnosed with normal-tension glaucoma (NTG) may exhibit lower than average CCT values, whereas those patients with ocular hypertension (OHT) are more likely to show higher than average CCT. Patients with primary open-angle glaucoma (POAG) show a normal or only marginally different CCT.

The Ocular Hypertension Treatment Study (OHTS) found thinner CCT to be a powerful predictor for the development of primary OAG, as measured by development of reproducible visual field defects and optic disc changes in those with OHT. However, an association between CCT and progression was not found in those with OAG in the Early Manifest Glaucoma Trial (EMGT). We investigated CCT and its relationship to visual field progression in patients with and without visual field progression.

**Patients and Methods**

The Human Subjects Division of the University of Washington approved this retrospective study. All patients were selected from a database of patients seen between April and November 2000, which served as the basis of a previous report. All patients who met the following inclusion criteria were enrolled in this study: (1) at least 2 years of follow-up with Humphrey visual fields; (2) the patient demonstrated visual field progression with criteria modified...
from Anderson and described below; (3) CCT by ultrasound pachymetry was available.

Diagnoses of POAG, pseudoexfoliative glaucoma (PXG), pigmentary glaucoma (PGD), and NTG were included in this study. Patients with NTG were diagnosed on the basis of an IOP no greater than 21 mmHg at diagnosis or during follow-up; some patients had daytime diurnal IOP curves recorded, but most did not. Patients were excluded if they had a history of nonsurgical ocular trauma, chronic uveitis, history of glaucoma drainage device surgery, proliferative diabetic retinopathy or other retinal disease or retinal surgery that would affect visual field testing, nonglaucomatous optic neuropathy or other neuro-ophtalmic disease, central corneal opacity or scarring, known corneal edema or Fuchs’ dystrophy, refractive surgery, or penetrating keratoplasty. Patients with consistently unreliable visual fields were also excluded. If both eyes of 1 patient showed progression, only 1 eye was chosen (the worse eye).

Review of the patients’ charts included medical history, including presence of diabetes mellitus, hypertension, cardiovascular disease, and thyroid disease. Other variables documented included age at diagnosis, age at pachymetry readings, race, gender, follow-up time, number of visual fields, glaucoma type, eye involved, and family history of glaucoma in first-degree relatives. Noncompliance as recorded by treating physician, or as indicated by multiple missed clinic appointments, was noted, as was refraction. The IOP was averaged over each 3-month to 4-month period to derive a mean IOP. Ocular history was also recorded, including visual acuity, laser and incisional surgeries, optic disc hemorrhages, and changes in lens clarity. Cup-to-disc ratio was calculated as the mean of the horizontal and vertical cup-to-disc ratio recorded in the chart. The subjects were matched 1:1 with control subjects from the same database who met the same criteria as the subjects but did not demonstrate visual field progression. Subjects were matched in the following variables in this order: race (white, African American, Asian, and Hispanic); diagnosis of glaucoma (POAG, PXG, NTG, and PDG); and age at the time of pachymetry. If an exact match of glaucoma type was not available, then POAG, PXG, and PDG were used interchangeably; however, NTG was always matched to those with NTG.6,12,13,17 In addition, if an exact race match was not available, then white, Asian, and Hispanic were interchanged, but African American was always matched to African American.32 Age was matched within 10 years, but in 7 cases the limited number of control eyes available for matching resulted in a larger difference in age of up to 12 years.

If the eye with progression was the eye with more visual field loss at presentation (the worse of the 2 eyes), it was matched with a control eye that was the worse of the 2 eyes for the control patient, and the same relationship was maintained if the eye with progression was the better of the 2 eyes at presentation.33

Patients underwent visual field testing with either the Humphrey 30-2 or 24-2 full-threshold programs (Humphrey-Zeiss, Dublin, CA). If a learning effect was exhibited, the baseline visual field used took this into account. Visual field global indices were recorded, including mean deviation (MD), pattern standard deviation (PSD), and corrected pattern standard deviation. Advanced Glaucoma Intervention Study (AGIS) scores24 were calculated.

Visual field progression was defined by criteria modified from Anderson.25 Progression from a normal field to an abnormal one was possible (5 patients had normal visual field tests at initial testing). A visual field was considered abnormal if 2 of the following 3 criteria were met on at least 2 consecutive visual fields: (1) an abnormal glaucoma hemifield test (borderline was not considered abnormal); (2) 2 contiguous nadir points (allowing the 2 nasal step edge points) on a Humphrey program 30-2 full-threshold visual field with P<0.05 on the total deviation plot, with at least 1 point at P<0.01 in the same area on both tests; and (3) corrected pattern standard deviation P<0.05 on full-threshold tests, or PSD P<0.05 on Swedish Interactive Threshold Algorithm (SITA) Standard tests.

Progression for visual fields that were already abnormal at baseline was also modified from Anderson,25 after taking into account the initial AGIS score to adjust for greater fluctuation seen in eyes with more advanced glaucomatous damage.26,27 In eyes with an initial AGIS score of 1 to 5 (mild visual field loss),24 progression was defined as 3 adjacent points depressed 5 dB or more from the initial level of loss on the total deviation plot, with at least 1 point depressed 10 dB, at the same locations on 2 consecutive fields. For those with an initial AGIS score of 6 or greater, progression was defined as 3 adjacent points depressed 10 dB or more from the initial level of loss on the total deviation plot at the same locations on 2 consecutive fields.

Before 1998, patients were followed with full-threshold testing; beginning in 1997, SITA Standard testing was used in some patients, and most patients were followed with the SITA Standard algorithm by 1999. Because AGIS scoring uses total deviation values of the visual field, and because SITA Standard testing has been noted to improve overall MD by approximately 1 dB,28-31 all total deviation values were reduced by 1 dB on SITA examinations for the purposes of AGIS scoring and for the determination of progression by modified Anderson criteria. In addition, the MD was reduced by 1 dB on all SITA Standard tests for data analysis.

Central corneal thickness was measured by ultrasound pachymetry (model 500 Pachette, DGH Technology, Exton, PA), with an average of 3 to 5 readings obtained from the central cornea after instillation of topical anesthetic drops.

Univariate analysis was performed with variables compared between those with and without visual field progression with the independent sample 2-tailed t test and Mann–Whitney U test. Categorical variables were analyzed with the chi-square test and Fisher exact test. Multivariate analysis was performed with Cox proportional hazards regression analysis and is expressed as hazard ratio (HR) with 95% confidence intervals (95% CI). Variables that were candidates for multivariate testing included all variables that might be considered to be associated with visual field progression, including age at diagnosis and at pachymetry; compliance; myopia; CCT; mean and maximum IOP; months of follow-up; years of disease; presence of optic disc hemorrhage; presence of PXG; and initial characteristics including cup-to-disc ratio, MD, PSD, AGIS score, and history of trabeculectomy. The final model included those variables with an upper limit of the univariate analysis 95% CI greater than 1.5, regardless of the P value, along with variables deemed clinically important such as mean IOP and visual field MD.

Follow-up time was defined as the time over which chart notes and visual field testing were available for review. For Kaplan–Meier survival analysis and Cox regression, the end point in the progressing group was the first worsened visual field, and in the nonprogressing group the end point was the last available visual field. A cutoff point of CCT that provided the best discrimination between progressors and nonprogressors was sought and evaluated with the chi-square test with Yates continuity correction, then evaluated with Kaplan–Meier survival analysis. A statistical spreadsheet software program was used for all calculations.32

Results

Forty-four eyes of 44 patients met inclusion criteria and were matched with 44 eyes of 44 control subjects. Demographic data and initial characteristics are listed in Table 1. The diagnosis of glaucoma was made in 3 patients between 1975 and 1980, in 4 patients between 1981 to 1985, in 14 patients between 1986 and
1990, and in 24 patients after 1990. There was no significant difference between the subjects and the matched control group in age at diagnosis, age at pachymetry, follow-up time, duration of disease, race, diagnosis, gender, family history, eye involved, compliance, initial cup-to-disc ratio, presence of optic disc hemorrhage, change in visual acuity, and refraction (Table 1). Initial visual field indices between the 2 groups were similar (Table 1). In addition, the factors noted from the medical history did not significantly differ between the 2 groups (hypertension, diabetes mellitus, cardiovascular disease, and thyroid disease) (data not shown). Four eyes had worsened visual acuity by more than 2 Snellen lines in the progressing group, 3 from glaucoma and 1 from macular degeneration. No progression was considered to be due to lens opacification. In the control group, 1 eye had worsened visual acuity from macular degeneration.

The mean CCT in those with visual field progression was significantly lower than the mean CCT in patients who did not progress (529±36 μm vs. 547±35 μm; P = 0.02). Thinner CCT was the only variable identified by multivariate Cox proportional hazards regression as significantly associated with progression (P = 0.01, HR, 1.44/40 μm decrease in CCT; 95% CI, 1.12–1.80) (Table 2). With Kaplan–Meier survival analysis, a CCT ≤520 μm (N, 26; mean CCT, 498 μm) was significantly associated with progression compared with a CCT >520 μm (N, 42; mean CCT, 555 μm) (P = 0.01, log-rank test) (Figure 1). The Kaplan–Meier estimate of progression at 90 months was 79% in the group with CCT ≤520 μm versus 43% in the group with CCT >520 μm.

The mean IOP was significantly lower in the group with progression in univariate analysis (16.2±2.6 mmHg vs. 17.9±3.1 mmHg; P = 0.01). The group with progression underwent more trabeculectomy surgery (sometimes in combination with cataract surgery) than the nonprogressing group (14 of 44 eyes [32%] vs. 6 of 44 eyes [14%]; P = 0.08). Neither of these was significantly associated with progression in the multivariate analysis. The group with visual field progression had more visual fields during follow-up (9.7±4.9 vs. 7.0±2.6; P = 0.02). Neither of these was significantly associated with progression in the multivariate analysis.

### Discussion

In our study of the association of CCT and visual field progression in patients with OAG, we found that those eyes...
with progression had a thinner mean CCT than those who did not progress (529 vs. 547 μm; P = 0.02) (Table 1). Thinner CCT was significantly associated with progression in the multivariate analysis also (Cox regression, P = 0.02). We found a HR of 1.44 per 40 μm thinner CCT (95% CI, 1.12–1.80).

To place this figure in perspective, for a 40-μm decrease in CCT, the OHTS found a relative risk of 1.71 (95% CI, 1.40–2.09). In the OHTS, the mean CCT in the progressing versus the nonprogressing group was 553 versus 574 μm. Medeiros et al. have recently reported that patients with glaucomatous optic neuropathy and normal standard automated perimetry who had abnormal visual fields develop during follow-up had a significantly thinner CCT than those who did not (543 vs. 565 μm), with HR of 1.62 (95% CI, 1.07–2.45). Other authors have reported that patients with OHT and with thinner corneas have been found more likely to have early glaucomatous function damage as measured by frequency doubling technology perimetry. Our findings reinforce the importance of CCT as a marker for glaucomatous eyes that may have progression develop during follow-up.

However, this relationship was not seen in the EMGT, a prospective, randomized clinical trial, which, like our study, included patients with visual field defects on standard automated perimetry and which had visual field progression as an end point. Possible reasons for this discrepancy include differences in patient populations, including initial IOP levels, mean age, and racial characteristics. In addition, differences in criteria for progression may also play a role. Our criteria were designed for use in retrospective studies that required comparison between different Humphrey visual field testing strategies and were specifically intended to reduce false-positive progression, with the result that relatively large changes were required but could be confirmed with 1 repeat test. A previous study in a larger population (from which our study patients were drawn) showed fluctuation of 5.3% of eyes with these criteria, which is acceptable for clinical use. Prospective trials such as the EMGT, which include patients randomly assigned to no treatment, must necessarily be designed for maximum sensitivity and can require multiple confirmations of change to ensure optimum specificity while also taking advantage of uniformity of testing strategies and pointwise regression analysis. Our findings may reflect a tendency toward thinner CCT among patients at risk for larger increments of progression than those measured in the EMGT. In addition, the EMGT was a trial in which all patients in the treatment group received similar treatment (laser trabeculoplasty and betaxolol drops), whereas in our retrospective study, treatment was not standardized. It is possible that cases with

### Table 2. Univariate and Multivariate Hazard Ratios and 95% Confidence Intervals for Progression of Glaucoma

<table>
<thead>
<tr>
<th></th>
<th>Univariate Hazard Ratio (95% Confidence Interval)</th>
<th>Multivariate Hazard Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at pachymetry per year greater</td>
<td>1.01 (0.98–1.04)</td>
<td>1.00 (0.97–1.00)</td>
</tr>
<tr>
<td>Age at diagnosis per year greater</td>
<td>1.00 (0.98–1.03)</td>
<td>0.99 (0.94–1.01)</td>
</tr>
<tr>
<td>Follow-up per months longer</td>
<td>1.00 (1.00–1.01)</td>
<td>1.00 (1.00–1.01)</td>
</tr>
<tr>
<td>Duration of disease per year greater</td>
<td>1.01 (0.96–1.07)</td>
<td>0.97 (0.90–1.04)</td>
</tr>
<tr>
<td>Family history of glaucoma</td>
<td>1.01 (0.53–1.91)</td>
<td>1.25 (0.62–2.35)</td>
</tr>
<tr>
<td>Poor compliance</td>
<td>1.29 (0.62–2.70)</td>
<td>1.38 (0.73–2.42)</td>
</tr>
<tr>
<td>Myopia</td>
<td>1.68 (0.89–3.14)</td>
<td>1.31 (0.65–2.64)</td>
</tr>
<tr>
<td>Pseudoexfoliative glaucoma</td>
<td>1.68 (0.83–3.42)</td>
<td>1.53 (0.73–3.21)</td>
</tr>
<tr>
<td>Initial cup-to-disc ratio per 0.1 larger</td>
<td>4.78 (0.81–28.1)</td>
<td>3.25 (0.54–19.5)</td>
</tr>
<tr>
<td>Initial visual field indices</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Mean deviation per dB greater</td>
<td>0.98 (0.93–1.03)</td>
<td>1.02 (0.95–1.09)</td>
</tr>
<tr>
<td>- Pattern SD per dB greater</td>
<td>1.02 (0.95–1.10)</td>
<td>0.99 (0.86–1.34)</td>
</tr>
<tr>
<td>- AGIS score per unit greater</td>
<td>1.03 (0.97–1.10)</td>
<td>1.07 (0.87–1.34)</td>
</tr>
<tr>
<td>- Mean IOP per mmHg greater</td>
<td>0.93 (0.84–1.02)</td>
<td>1.01 (0.88–1.15)</td>
</tr>
<tr>
<td>- Maximum IOP per mmHg greater</td>
<td>1.00 (0.96–1.04)</td>
<td>0.99 (0.95–1.04)</td>
</tr>
<tr>
<td>- Optic disc hemorrhage</td>
<td>1.71 (0.88–3.33)</td>
<td>1.44 (0.72–2.87)</td>
</tr>
<tr>
<td>- Trabeculectomy</td>
<td>1.41 (0.75–2.66)</td>
<td>1.17 (0.53–2.57)</td>
</tr>
<tr>
<td>- Corneal thickness per 40 μm thinner</td>
<td>1.44 (1.12–1.80)*</td>
<td>1.44 (1.12–1.80)*</td>
</tr>
</tbody>
</table>

AGIS = Advanced Glaucoma Intervention Study; dB = decibels; IOP = intraocular pressure; SD = standard deviation.

*P < 0.05.
thinner corneas may have not initially had sufficiently aggressive treatment to prevent progression, in part because of the effect of thinner CCT on IOP measurement.

No other baseline factors evaluated were related to progression in this study, although factors such as initial cup-to-disc ratio have confidence intervals indicative of likely influence on progression. Although we did not attempt to match patients by severity of disease, the 2 groups were not significantly different at the initial visit.

We matched African American patients cases to African American patient controls for our study, because several reports have noted that African Americans and Afro-Caribbean persons have thinner corneas than whites. The interracial differences in CCT among whites, Asians, and Hispanics are less clear, because there were not enough patients in the OHTS to evaluate for any differences between these groups. A retrospective analysis did not reveal any significant difference in the expected CCT when eyes of white patients were compared with those of Japanese patients. One study reported no difference in the mean CCT of 550 μm among whites, Asians, and Hispanics. Most of our patients were white (81.4%), and our study may be mostly applicable to whites.

The relationship between CCT and age is not entirely clear. We are not aware of published longitudinal reports on changes in CCT over time. In retrospective or cross-sectional studies, some authors have found no significant change in CCT with age, whereas other studies show an inverse relationship. We chose to match for age at the time of pachymetry in our study to reduce a potential confounding variable. In some cross-sectional studies, CCT was noted to decrease approximately 6.3 to 10 μm/decade, and we matched 74 of 88 eyes within 10 years (66 within 5 years), and all within 12 years. A meta-analysis of the literature did not indicate any obvious age-dependent difference in CCT for whites, but a clinically relevant age-dependent decline in CCT after 60 years was apparent in nonwhites.

We substituted diagnosis among POAG, PXG, and PDG, because studies have shown no significant difference in CCT among these groups. Some authors have noted that those with pseudoexfoliation syndrome, with and without glaucoma, may have thicker CCT or thinner CCT. Those with PDG and pigment dispersion syndrome have been shown to have CCT similar to normal controls. However, we matched subjects with NTG only to controls with NTG, because patients with NTG have been found to have thinner corneas than patients with other forms of chronic OAG in a preponderance of studies, although no difference in CCT between NTG and POAG was found by some authors.

Surgical procedures can theoretically cause changes in CCT. In this study, potential subject and control eyes that had undergone glaucoma drainage device surgery were excluded, because corneal decompensation and edema are relatively common complications of such surgery. We included patients who had undergone laser trabeculoplasty, cataract surgery, and/or trabeculectomy, because several authors have noted no significant changes in CCT when the measurements are taken months after the surgery, as our measurements were.

In our study, the group that progressed had a significantly lower mean IOP than that of the group that did not progress (P = 0.01). Reasons for this discrepancy likely include more aggressive treatment with medications and a higher prevalence of trabeculectomy surgery (P = 0.08) in patients with progressive visual field defects in our study group. In addition, several authors have noted a relationship between IOP and CCT. The IOP may be underestimated in thinner corneas and falsely elevated in those with thicker corneas. Doughty and Zaman found a statistically significant correlation between CCT and IOP measurement in a meta-analysis that used both optical and ultrasound pachymetry data: a 10% difference in CCT resulted in a 2.5±1.1 mmHg change in IOP (P = 0.01, r = 0.45), and they recommended that eyes with glaucoma should be adjusted 2 or 3 mmHg for a 50-μm difference in CCT from 534 μm. Whitacre et al suggested a smaller correction of approximately 1 mmHg for each 50-μm difference. Ehlers et al described a slightly larger correction, when catalyzing eyes during cataract surgery, of approximately 5 mmHg change of IOP for a change of 70 μm in CCT; this is of a magnitude large enough to explain the difference in mean CCT between groups in our study.

Central corneal thickness has been significantly associated with age, race, gender, diagnosis of glaucoma, severity of glaucoma, refractive state, diabetes, and mean IOP. Our matched patient population negated many of these associations, and the limited number of patients in our study may not have allowed some associations to be noted. A stricter study of the effect of CCT might have matched patients for all known or putative risk factors for progression and then determined whether CCT both significantly differed between the 2 groups and added to the risk prediction. The relatively small number of patients in our database did not allow for such extensive matching. However, a benefit of our study design was that it did allow for evaluation of nonmatched risk factors, such as IOP level, optic disc hemorrhage, and initial severity of glaucoma as measured by cup-to-disc ratio and visual field defect, albeit in a small population.

Pseudoexfoliation glaucoma is known to be a risk factor for progressive glaucoma. In our study, a larger number of Progressors versus controls had PXG because of the difficulty of exactly matching cases to controls in all of the variables matched. In univariate and multivariate analysis of both our study group and of the larger database of patients from which our study group was culled, PXG was not significantly associated with increased risk of progression, but these are retrospective studies with relatively small numbers of total patients and of patients with PXG.

Is a statistically significant difference in mean CCT of 18 μm between groups also clinically significant? We know that there is a wide range of “normal” CCT, and 18 μm is within the realm of normal variation (510–578 μm for ±1 standard deviation). Still, we believe our results, when taken in consideration with other evidence, may be useful to clinicians in the management of patients with...
glaucoma; patients with OAG with thinner CCT may need closer follow-up and more aggressive treatment than those with thicker CCT to prevent visual field progression. We postulate that the difference in progression is attributable to CCT influences on IOP and/or other factors that may be associated with CCT that we did not measure and, as yet, may be unknown.

An understanding of the meaning of an HR of 1.44 per 40 µm of thinning in CCT is critical; this does not mean an absolute 44% certainty that progression will occur but rather is a 44% increase over the baseline likelihood of progression. For example, if the likelihood of progression for a patient with CCT at the average of 544 µm is 10% per year, that for a patient with CCT of 504 µm would be 14.4%. Ultimately, the clinician and patient must weigh the risks and benefits of more aggressive treatment to offset any increase in risk.

This was a retrospective case–control study performed with patients identified from a patient database. As with all case–control studies, there are limitations because of our reliance on previously recorded data, which is nonstandardized and may be incomplete. Multiple ophthalmologists were involved in the care of many of our patients, and most likely there were differences in practice patterns. Despite our best efforts, ensuring lack of bias between the cases and those chosen as controls is difficult. Other limitations include the small number of subjects in this study and the racial composition of our population. We await further study to corroborate our observations.

References