Clinical Significance of Central Corneal Thickness in the Management of Glaucoma

Carolyn Y. Shih, MD; Joshua S. Graff Zivin, PhD; Stephen L. Trokel, MD; James C. Tsai, MD

Objective: To evaluate the effect of central corneal thickness determination on the clinical management of patients with glaucoma and glaucoma suspect.

Methods: A cross-sectional retrospective study was performed on 188 consecutive patients. Mean ultrasound pachymetry measurements of central corneal thickness and corresponding Goldmann applanation tonometry measurements were obtained. Intraocular pressures (IOPs) were corrected using linear and mathematical (Orssengo-Pye) algorithms. Measurement-significant outcomes were defined as an IOP adjustment of 1.5 mm Hg or greater and outcomes-significant results as an IOP adjustment of 3.0 mm Hg or greater. Changes in therapy such as the use of eyedrops and addition or cancellation of laser therapy or surgery were then noted for those individuals with measurement- or outcomes-significant changes.

Results: Using the linear correction scale, 105 (55.9%) of 188 patients had at least a measurement-significant adjustment in their IOP measurements: 67 (35.6%) had adjustments between 1.5 and 3.0 mm Hg, while 38 (20.2%) had an outcomes-significant IOP adjustment (≥3.0 mm Hg). Among the 188 patients, 16 (8.5%) had a change in eyedrop therapy, 4 (2.1%) had a change regarding laser therapy, and 6 (3.2%) had a change in the decision regarding glaucoma surgery. Using the exponential correction (Orssengo-Pye) scale, similar percentages were obtained.

Conclusion: Pachymetry-measured central corneal thickness has a significant effect on the clinical management of patients with glaucoma and glaucoma suspect.

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OVER THE PAST 50 YEARS, central corneal thickness (CCT) measurement has been an important variable in the assessment of intraocular pressure (IOP) values in patients undergoing refractive and corneal transplant surgery, as well as in contact lens wearers. Studies by Ehlers and Hansen2 and Whitacre et al3 stressed that IOP measurements should be adjusted for CCT. However, the incorporation of CCT-adjusted IOP measurements into daily clinical practice was limited until recently, when the Ocular Hypertension Treatment Study4 reported that CCT was a strong predictor for the development of primary open-angle glaucoma in patients with ocular hypertension. In particular, this study demonstrated that subjects with decreased CCT measurements had an increased risk of developing primary open-angle glaucoma (for every 40-µm decrease in CCT, the relative risk was 1.71). Moreover, individuals with CCTs of 555 µm or less had a 3 times greater risk of developing glaucoma compared with patients with CCTs of greater than 588 µm. Moreover, with millions of individuals having undergone laser in situ keratomileusis surgery,5,6 there is a growing concern that the process of removing corneal tissue during this surgery (with resulting thinner corneas) will lead to an increased difficulty in diagnosing glaucoma, because this surgery tends to alter IOP measurements and may in turn require greater emphasis on the assessment of the optic disc and visual fields for the diagnosis and treatment of glaucoma.7,8

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As summarized in a meta-analysis by Doughty and Zaman9 on the effect of CCT on IOP measurements, studies9,10 have hypothesized that CCT and IOP are related to or interdependent on one another, except at gross extremes. Furthermore, variations in mean CCT have been observed in patients with different types of glaucoma.11-13 Altogether, these studies suggest that IOP measurements are affected...
by CCT values. In fact, misdiagnosis often occurs when CCT is not considered, because generally patients with normal-tension glaucoma have thinner corneas and those with glaucoma suspect have thicker corneas. According to manometric data from Ehlers and colleagues, 44% of patients with normal-tension glaucoma would be reclassified as having primary open-angle glaucoma, and 35% of patients with ocular hypertension would be reclassified as having normal IOPs. Furthermore, Hendon et al found that as many as 65% of patients with ocular hypertension could be reclassified as having normal IOPs.

Believing corneal pachymetry to be essential to the care of patients, Tanaka stated that... performing pachymetry may influence the management of all patients by allowing clinicians to (1) observe or pursue less aggressive treatment of patients with pseudo-ocular hypertension; (2) modify the target intraocular pressure in patients with glaucoma; and (3) detect an elevated intraocular pressure in otherwise normal patients with thin corneas and "normal" applanation readings.

There is growing consensus that routine measurement of CCT may be critical for the proper management of patients with glaucoma and glaucoma suspect not only for cost reasons, but most important, for effective quality care. Therefore, we hypothesized that CCT has a significant effect on the clinical management of patients with the diagnoses of glaucoma and glaucoma suspect. To evaluate the effect of incorporating CCT measurements into daily clinical practice, we performed a cross-sectional retrospective study of consecutive patients seen for glaucoma care.

METHODS

A cross-sectional retrospective study was performed on 188 consecutive patients seen at an academic medical center glaucoma practice between June 20, 2002, and August 20, 2002. Patients with known corneal pathologic conditions (eg, with corneal edema or those who had undergone penetrating keratoplasty) were excluded from the study. However, patients who had undergone refractive surgery were not excluded from the study. Three consecutive ultrasound pachymetry (Sonomed, Inc, Lake Success, NY) measurements of CCT were obtained from each eye, and a mean value was then computed. Measurements were performed under topical anesthesia. The corresponding Goldmann applanation tonometry (GAT) measurements were obtained at each of these visits with the use of fluorescein solution (in most cases, only one measurement was taken). These GAT measurements were performed by one of us (J.C.T.). In most cases, the CCT measurements were performed before applanation tonometry. In all cases, the CCT measurements were done before gonioscopy.

Given the small number of patients in the study, variables such as the number and type of glaucoma medications taken by each patient were not considered in subset analysis (eg, to determine whether differences were observed in CCT for patients taking topical carbonic anhydrase inhibitors). Analyses included the mean CCT and GAT values of the right eye of patients. If reliable CCT or GAT values were unobtainable from the right eye, then the corresponding measurements from the left eye were collected. Institutional review board approval was obtained for the retrospective data collection and analysis.

The recorded IOP measurements were then adjusted for CCT using 545 µm as the reference value (in a review of 80 studies using ultrasound pachymetry, the mean ± SD CCT was 544 ± 34 µm). The IOP data were corrected using a linear algorithm and a mathematical model. The linear correction scale (based on extensive literature review) added or subtracted 2.5 mm Hg for every 50-µm difference in CCT from the reference value of 545 µm (ie, a 1.0-mm Hg change for every 20-µm difference in CCT from the reference value of 545 µm). A correction factor (CF) of 2.5 mm Hg (for every 50-µm deviation from the reference CCT value) was used, because various CFs in the literature have ranged from approximately 1.00 to 3.57 mm Hg for every 30-µm deviation. In fact, in the study by Ehlers and Hansen, the CF reported was 3.57 mm Hg per 50-µm deviation (ie, about 5 mm Hg for every 70 µm), and the meta-analysis of 134 studies by Dougherty and Zaman found that the slope of the regression line created by the data resulted in 3.33 mm Hg per 50-µm deviation. Furthermore, in a cannulation study of 125 patients undergoing phacoemulsification cataract surgery with corresponding manometric water column and Perkins tonometry measurements, Pillunat and colleagues calculated an approximate 2.5-mm Hg change in IOP for every 50-µm difference in corneal thickness.

Adjustments of IOP were made according to the following linear formula: Corrected IOP = Measured IOP – (CCT – 545)/50 × 2.5 mm Hg.

Analytical measures of the model were performed, substituting 2.0 and 3.0 mm Hg as the CFs (for every 50-µm deviation from the reference CCT of 545 µm).

To provide a comparison, a mathematical formula derived by Orssengo and Pye was used, because the formula accounts for factors such as the anterior radius of curvature, thickness, and Poisson ratio of the cornea. The formula is as follows: True IOP = Goldmann applanation IOP + K, where K is a complex CF dependent on anaplted area, radius of curvature of the anterior cornea, center thickness of the cornea, and Poisson ratio of the cornea. A standard radius of curvature of the anterior cornea (7.74 mm) was used for the purpose of this study as it was not calculated for individual patients.

In regard to CCT-adjusted IOP values, measurement significant adjustments were defined as IOP corrections of 1.5 mm Hg or greater (in either direction). Although there may be differences in opinion regarding the value of key CFs, our analysis suggests that 1.5 and 3.0 mm Hg are appropriate cutoff values for determining potential outcome effects. Although results of the Early Manifest Glaucoma Trial and the Ocular Hypertension Treatment Study suggest a 10% difference in outcome for each millimeter of mercury, this figure was derived from extrapolated data. As a conservative measure, we opted to set our first cutoff slightly higher at 1.5 mm Hg.

The 1.5-mm Hg figure was arrived at because a change as small as 1.0 mm Hg is noted to be measurement significant in clinical trials; the Early Manifest Glaucoma Trial reported that “each higher (or lower) millimeter of mercury of IOP on follow-up was associated with an approximate 10% increased (or decreased) risk of progression” in patients with early manifest glaucoma. Furthermore, Parrish et al defined a 1.5-mm Hg difference as significant in their randomized clinical trial comparing the IOP-lowering effects of topical prostaglandin analogues. Other authors have defined similar differences in IOP (eg, 1.75 mm Hg) as being significant between study groups.

Any CCT-associated IOP adjustments of 3.0 mm Hg or greater (in either direction) were designated as outcomes significant. A 3.0-mm Hg decrease in the initial IOP corresponded to an almost 50% reduction in the risk of glaucoma progression in the population-based Baltimore Eye Survey. Moreover, per findings in the Early Manifest Glaucoma Trial (in which each 1.0-mm Hg reduction in IOP corresponded to a 10% decreased risk of progression of glaucoma), a 3.0-mm Hg reduction in IOP would result in an approximate 30% decreased risk of glaucoma progression.
The medical charts were reviewed, and notations that indicated the effect of CCT evaluation on the treatment plan were evaluated. Alterations in the glaucoma treatment plan were then noted for patients with measurement- and outcomes-significant IOP adjustments (ie, ≥1.5 and ≥3.0 mm Hg, respectively). These changes in therapy included (1) addition or discontinuation of antiglaucoma medications, (2) recommendation or deferment of glaucoma laser procedures, or (3) recommendation or deferment of glaucoma incisional surgery.

Linear regression calculations were performed to ascertain the effect of variables such as age, race, and sex on adjustments in IOP following CCT measurements.

Table 1. Demographics of Study Population

<table>
<thead>
<tr>
<th>Demographic</th>
<th>No. (%)</th>
</tr>
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<tbody>
<tr>
<td>Age, mean ± SD, y</td>
<td>71.4 ± 13.8</td>
</tr>
<tr>
<td>Men</td>
<td>69 (36.7)</td>
</tr>
<tr>
<td>Women</td>
<td>119 (63.3)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>26 (13.6)</td>
</tr>
<tr>
<td>White</td>
<td>151 (80.3)</td>
</tr>
<tr>
<td>Asian</td>
<td>11 (5.9)</td>
</tr>
<tr>
<td>Right eye</td>
<td>185 (98.4)</td>
</tr>
<tr>
<td>Left eye</td>
<td>3 (1.6)</td>
</tr>
<tr>
<td>No. of glaucoma medications used by patient, mean ± SD</td>
<td>1.8 ± 1.4</td>
</tr>
<tr>
<td>Central corneal thickness, mean ± SD, µm</td>
<td>554.5 ± 53.8</td>
</tr>
<tr>
<td>Intraocular pressure, mean ± SD, mm Hg</td>
<td>15.8 ± 4.8</td>
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</tbody>
</table>

Table 2. Measurement and Clinically Significant Changes Made After Central Corneal Thickness Measurements*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Orssengo-Pye Model</th>
<th>Linear Model†</th>
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</thead>
<tbody>
<tr>
<td>Measurement-significant changes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥1.5 mm Hg</td>
<td>119 (63.3)</td>
<td>105 (55.9)</td>
</tr>
<tr>
<td>Measurement-significant changes &lt;3.0 mm Hg</td>
<td>39 (20.7)</td>
<td>67 (35.6)</td>
</tr>
<tr>
<td>Outcomes-significant changes ≥3.0 mm Hg</td>
<td>80 (42.6)</td>
<td>38 (20.2)</td>
</tr>
<tr>
<td>Change in glaucoma medical therapy</td>
<td>19 (10.1)</td>
<td>16 (8.5)</td>
</tr>
<tr>
<td>Change in recommendation for glaucoma laser surgery</td>
<td>4 (2.1)</td>
<td>4 (2.1)</td>
</tr>
<tr>
<td>Change in recommendation for glaucoma incisional surgery</td>
<td>5 (2.7)</td>
<td>6 (3.2)</td>
</tr>
</tbody>
</table>

*Data are expressed as number (percentage) among 188 subjects. † ±2.5 mm Hg per 50-µm deviation from 545 µm.

**RESULTS**

One hundred eighty-eight subjects were included in the study. The CCT and GAT were analyzed from the right eye; when neither of these readings was reliable, the CCT and GAT from the left eye were used (3/188 [1.6%]).

**Table 1** gives the demographic characteristics of the study population. Sixty-nine men (36.7%) and 119 women (63.3%) were enrolled. The mean ± SD age of the subjects was 71.4 ± 13.8 years. One hundred fifty-one (80.3%) of the patients were white, 26 (13.8%) were African American, and 11 (5.9%) were Asian. The mean ± SD CCT was 553.0 ± 53.6 µm for women and 557.0 ± 54.0 µm for men (P > .50). The mean ± SD CCT for African Americans was 539.3 ± 53.0 µm, and it was 562.2 ± 53.5 µm and 572.4 ± 56.5 µm for whites and Asians, respectively (P > .15).

The mean ± SD CCT measurement for the entire sample was 554.5 ± 53.8 µm (Figure). The mean ± SD IOP recorded was 15.8 ± 4.6 mm Hg. The most common initial diagnosis was primary open-angle glaucoma, in 87 patients (46.3%). The next most prevalent diagnoses were chronic angle-closure glaucoma in 26 patients (13.8%), normal-tension glaucoma in 21 patients (11.2%), glaucoma suspect in 18 patients (9.6%), and ocular hypertension in 11 patients (5.9%).

Using the Orssengo-Pye model, 119 patients (63.3%) had at least a measurement-significant adjustment in their IOP after CCT assessment (Table 2). Thirty-nine patients (20.7%) had adjustments between 1.5 and 3.0 mm Hg, while 22 (11.7%) had outcomes-significant IOP changes (≥3.0-mm Hg adjustment made to IOP). Of those patients who had at least a measurement-significant change to their IOP, 28 patients (14.9%) had a change in their treatment plan as a result of adjustments made to their IOP following CCT correction. Of these patients, 19 (10.1%) had a change in their medication regimen, 4 (2.1%) had a change in whether they had laser surgery, and 5 (2.7%) had a change in whether they had glaucoma surgery.

Similar percentages were obtained using the linear model (Table 2). One hundred five patients (55.9%) had...
at least a measurement-significant adjustment to their IOP, with 67 (35.6%) having less than a 3.0-mm Hg correction and 38 (20.2%) having an outcomes-significant correction (≥3.0 mm Hg in either direction). Among the 188 patients, 26 (13.8%) had a change in their treatment plan as a result of CCT-associated IOP correction. Sixteen patients (8.5%) had a change in medication therapy, 4 patients (2.1%) had a deferment or addition of laser surgery, and 6 patients (3.2%) had a change in whether they would receive glaucoma surgery.

Sensitivity analyses were performed following substitution of the linear CF (with 2.0-, 2.5-, and 3.0-mm Hg CFs; Table 3). With the more conservative CF of 2.0 mm Hg per 50-µm deviation in CCT, 43.6% of patients experienced at least a measurement-significant adjustment in their IOP measurements. With the less conservative adjustment of 3.0 mm Hg per 50-µm deviation, the percentage of patients with measurement-significant changes in IOP was 63.3%. Although the percentage of patients with measurement-significant changes less than 3.0 mm Hg remained relatively similar (33.5%-35.6%), the percentage of patients with outcomes-significant changes varied greatly depending on the adjustment used. 10.1% of the patients experienced outcomes-significant changes with the 2.0-mm Hg CF, compared with 29.4% of patients when using the 3.0-mm Hg CF.

The percentage of patients who experienced changes in medical or surgical therapy varied slightly based on the CF used (Table 3). The percentage of patients who had a change in medication therapy ranged between 8.0% and 9.1% (with the 2.0- and 3.0-mm Hg CFs, respectively), while the percentage of patients with a change in the recommendation of laser surgery ranged from 1.6% (with the 2.0- and 3.0-mm Hg CFs) to 2.1% (with the 2.5-mm Hg CF). The percentage of patients with a change in recommendation of glaucoma incisional surgery ranged between 2.7% (with the 2.0-mm Hg CF) and 3.2% (with the 2.5- and 3.0-mm Hg CFs) (Table 3).

Based on the Orssengo-Pye mathematical model, we compared the effects of IOP adjustment in regard to clinical management between different racial groups (Table 4). Measurement-significant IOP corrections were found in 69.3% of African Americans, 62.9% of whites, and 54.6% of Asians (P = .62). Of those patients with measurement-significant IOP adjustments, 30.6% of African Americans had a change in their therapy, compared with 13.3% of whites and 0% of Asians (P > .05). Furthermore, 15.3% of African Americans had a change in medication therapy, compared with 9.9% of whites; 11.5% of African Americans had a change in whether they had laser therapy, compared with 0.7% of whites; and 3.8% of the African Americans had a change in whether they had glaucoma surgery, compared with 2.7% of whites (P > .05 for all). The only statistically significant difference observed was that African Americans and whites were more likely to experience outcomes-significant IOP changes (≥3.0 mm Hg) than Asians (P < .05).

There were significant sex differences seen when using the Orssengo-Pye model (Table 5). As such, 73.9% of the men had a measurement-significant change in their IOP, compared with 57.1% of the women (P = .03). Furthermore, 14.5% of the men had a change in their medication therapy, compared with 7.6% of the women (P = .14). Among men, 4.3% had a change in whether they would have glaucoma surgery, compared with 1.8% of the women. The only category in which women had a greater change in therapy was laser surgery, in which 2.8% of the women had this change vs 1.4% of the men.

Although some authors11,23 have reported that patients may be misdiagnosed because of the absence of CCT determination or the subsequent adjustment of IOP, we are not aware of any studies that have assessed the effect of CCT-associated IOP adjustments on glaucoma clinical management.

In our study, approximately half of the 188 eyes examined required an adjustment in IOP measurement of 1.5 mm Hg or greater. We chose 1.5 mm Hg as a key correction end point, because this value is often cited as a significant difference in clinical studies assessing IOP efficacy between medications. Furthermore, it is not known whether these calculated adjustments in IOP are relevant to clinical management. Based on our analysis, there appears to be clinical usefulness in these IOP corrections, as approximately 8% to 10% of the patients had a change in their medication therapy, about 2% had a change in the recommendation (or deferment) of laser procedures, and about 3% had a change in the recommendation (or deferment) of glaucoma incisional surgery. However, because our study was cross-sectional and there are no long-term data to support the clinical implications of these changes, it is impossible to extrapolate the true effect of these IOP adjustments and the resultant changes in clinical decisions on patient outcomes.
Because there is controversy regarding the IOP correction algorithm, we performed the CCT-associated adjustments based on the most prominent formulas used, a linear model derived based on a literature search and a mathematical model developed by Orssengo and Pye. A comparison of the 2 correction formulas yielded similar results. A sensitivity analysis yielded results that were nonmonotonic in 2 instances (ie, the percentage of patients with measurement-significant changes < 3.0 mm Hg and the percentage of patients with changes in laser surgery recommendation). Because the category-significant changes less than 3.0 mm Hg were an intermediate category between no change and changes greater than 3.0 mm Hg, as one moved from more to less conservative CFs (ie, 2.0-3.0 mm Hg per 50-µm change), there was an initial increase followed by a slight decrease as more patients were shifted into the 3.0-mm Hg range or greater (eg, the large increase to 29.4% with the 3.0-mm Hg CF). With regard to the recommendation for laser surgery, the move to less conservative CFs (ie, 3.0 mm Hg per 50-µm change) may have caused a shift in the need for glaucoma filtration surgery (rather than laser surgery) in the one patient affected. Regardless of the models and correction algorithms studied, adjustments for IOP based on CCT are critical for clinical management.

The only statistically significant difference between races was that Asians were less likely to experience outcomes-significant changes compared with whites and African Americans (when the Orssengo-Pye model was used). The lack of greater statistical significance between groups may be due to several factors, including that our patient sample (from a tertiary care practice) may not be representative of the general population. The patients analyzed were already diagnosed as having glaucoma or glaucoma suspect. Furthermore, sample sizes of the different races were not large enough to generate statistical power, with only 26 African Americans and 11 Asians included in the study. For example, the population-based Barbados eye studies of a predominantly black community (1142 participants) reported that black participants tended to have thinner corneas than white participants.

Limitations of this study include its retrospective analysis and its short duration. Patients were seen in an academic medical center glaucoma practice, with most having well-controlled glaucoma (mean IOP, approximately 16.0 mm Hg). Moreover, there was no way to confirm the true IOP of patients, because they were not taken to the operating room to have their anterior chambers cannulated for IOP assessment. Finally, we do not know whether our definitions of measurement-significant (≥ 1.5 mm Hg) and outcomes-significant (≥ 3.0 mm Hg) results are useful for accurately assessing the extent of the IOP adjustments.

Another limitation of this study is that it addresses CCTs obtained using ultrasound pachymetry, which is only one method of measuring CCT. Studies have shown that, depending on the method used, statistically
different CCTs may be obtained. Ventura et al noted that optical low coherence reflectometry represents the most precise pachymetric method available, with its measurements reproducible to 1 μm. In the future, appropriate refinement of the correction formula may need to be undertaken, depending on the corneal pachymetric method adopted.

This study presents preliminary data regarding the effects of CCT-adjusted IOP on clinical management of patients with glaucoma and glaucoma suspect. Because this was a cross-sectional study, further randomized controlled studies are needed to elucidate the effects of CCT on clinical management and consequent long-term patient outcomes. Given these future studies, it may be easier to delineate clear and effective treatment guidelines. Additional studies are needed to better test the consistency of these results across different racial and ethnic groups.

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Correspondence: James C. Tsai, MD, Edward S. Harkness Eye Institute, Department of Ophthalmology, College of Physicians and Surgeons, Columbia University, 635 W 165th St, New York, NY 10032 (jct2002@columbia.edu).

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