Central Corneal Thickness and Glaucoma in East Asian People

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Purpose. To examine the association between central corneal thickness (CCT) and glaucoma.

Methods. This was a nested case-control study using 1090 subjects from an eye disease population survey in Singapore and 243 participants from a hospital glaucoma surgery clinical trial in Singapore.

Results. Mean CCT in 938 community subjects was 539 µm ± 32 µm, and in 12 community subjects with primary open angle glaucoma (POAG) the mean CCT was 545 µm ± 38 µm. In the hospital cohort, mean CCT was 552 µm ± 38 µm in 136 patients with POAG and 551 µm ± 35 µm in 105 patients with primary angle closure glaucoma (PACG). No individuals had undergone previous intraocular surgery or had other significant ocular pathology. Regression models showed POAG diagnosis was not associated with CCT (P = 0.42) or age (P = 0.062) in community subjects but was associated with IOP (P = 0.005). Similar analyses for hospital cases showed CCT to be significantly higher in both POAG and PACG (both P = 0.001), but this became nonsignificant after controlling for IOP and age (P = 0.26, POAG; P = 0.08, PACG). Both age (P = 0.043) and IOP (P = 0.001) were highly associated with hospital POAG; only IOP (P = 0.001) was associated with hospital PACG. Further regression analyses for community subjects showed diabetic status and pseudophakia had no significant effect on CCT (P = 0.33 and P = 0.11, respectively).

Conclusions. The authors found no evidence to support the previous observation that thinner corneas may be independently associated with POAG or PACG. Age and IOP are significantly associated with CCT, and this should be taken into account by future studies investigating CCT as an independent risk factor for glaucoma diagnosis. (Invest Ophthalmol Vis Sci. 2011;52:8407–8412) DOI:10.1167/iovs.11-7927

Interest in central corneal thickness (CCT) and glaucoma was renewed by the publication of the Ocular Hypertension Treatment Study (OHTS), which suggested CCT to be an independent risk factor for the development of primary open angle glaucoma (POAG).1 There is, however, marked racial variation in CCT2 and it remains unclear whether CCT is indeed an independent predictor of progression to glaucoma, a phenotypic marker of different ethnic groups with differing inherent glaucoma risk, or just a source of error in clinical tonometry.3 We have examined this further by exploring the association between central corneal thickness (CCT) and glaucomatous optic neuropathy using data from a population study of eye disease and a randomized trial of glaucoma surgery in Singapore.

Methods

Subjects were examined in accordance with the World Medical Association’s Declaration of Helsinki, and informed consent was obtained in all cases. The Ethical Review Board of Singapore National Eye Centre approved this research.

Community Subjects

The sampling strategy has been described previously.4 In summary, 2000 Chinese people aged 40 to 79 years residing in the Tanjong Pagar district of Singapore were selected from the electoral register (13% of 15,082 registered), using a disproportionate, stratified, clustered, random sampling procedure. A total of 1717 were considered eligible for examination, after exclusion of those who were moribund, had moved from the area, or had died. A total of 1090 people were examined in the research clinic (63.5% of the total).

All patients underwent full clinical examination including gonioscopy, as previously described. CCT was measured using an optical pachymeter (Device I; Haag-Streit, Bern, Switzerland) mounted on the slit lamp. The “touch” method of measuring CCT was used throughout. CCT was measured from the anterior epithelial surface to the posterior endothelial surface using ×1.6 objective magnification with +2.5 D eyepiece addition, read to the nearest 0.01 mm. CCT was measured three times in each eye, and the median was taken as the representative value for that eye. Each subject was instructed to maintain a steady gaze in the primary position. The brightest, narrowest illumination beam possible was used. Measurements of axial CCT were made using the pupil margin as a point of reference to ensure accurate centration. Because there is a well-recognized systematic difference between right and left eyes (left > right, 20 µm) attributed to alignment of the instrument with the visual axis (not the geometric axis),5,6 data for normal subjects is given for right eyes only.

Glaucoma was diagnosed as previously described,1 with cases divided into primary angle-closure glaucoma (PACG) and POAG according to the presence or absence of an occludable drainage angle, defined as one where the posterior half (usually pigmented) of the trabecular meshwork could be seen for <90° of the angle circumference. All clinical data were confirmed by the same investigator (PJF).

Hospital Trial Patients

Baseline examination data from 243 patients previously recruited for a placebo-controlled randomized clinical trial assessing the benefit of
5-fluorouracil–augmented trabeculectomy in the management of primary angle-closure glaucoma constituted the hospital cohort. All patients were for primary angle-closure surgery and had no previous history of intraocular surgery. Full inclusion and exclusion criteria are as previously published. Standardized criteria were used to identify eligible cases of angle-closure glaucoma, as follows: glaucomatous optic neuropathy, defined as a focal or diffuse area of optic disc rim loss to 10% of disc diameter at any point, combined with a reproducible defect on automated perimetry (using the 24–2 test pattern on a Humphrey Field Analyzer). A minimum of two points reduced by 5 decibel (dB) or one point reduced 10 dB perimetry (using the 24–2 test pattern on a Humphrey Field Analyzer). A minimum of two points reduced by 5 decibel (dB) or one point reduced 10 dB perimetry (using the 24–2 test pattern on a Humphrey Field Analyzer). A minimum of two points reduced by 5 decibel (dB) or one point reduced 10 dB perimetry (using the 24–2 test pattern on a Humphrey Field Analyzer). A minimum of two points reduced by 5 decibel (dB) or one point reduced 10 dB perimetry (using the 24–2 test pattern on a Humphrey Field Analyzer).

**Statistical Analysis**

The relationship between CCT and IOP was examined by scatter plots and univariate linear regression across the groups. All scatter plots used a jitter option to enable coincident points to be plotted close together, rather than superimposed, to allow a truer impression of the quantity of data included without affecting the regression calculations. Multivariate regression models were then used to account for the possible modifying effects of age and sex on the relationship between CCT and IOP at diagnosis. Univariate and multivariate logistic analyses were used to assess any relationship between CCT and POAG diagnosis, PACG diagnosis, diabetic status, and previous pseudophakia after accounting for age and IOP at diagnosis.

Estimates of the appropriate regression coefficients, with 95% confidence intervals (CIs) are given. The corresponding $t$-test, calculated from the ratio of the regression coefficient to its SE, was used to obtain the $P$ values.

**RESULTS**

Of the 1333 persons identified, 1090 constituted the community cohort and 243 the hospital-based clinical trial patients (Table 1). Among the community subjects, 55 persons who had previously undergone intraocular surgery or who had ocular pathologies thought to influence CCT were excluded (Table 2), as were 12 in whom CCT was not assessed. Community PACG cases were excluded because of insufficient case numbers for analysis. There remained 938 normal subjects (849 without and 89 with diabetes mellitus), 73 pseudophakic subjects, and 12 subjects with POAG. Information on the diabetic status of the 138 POAG and 105 PACG hospital patients was not available. Demographic and clinical details of both community and hospital subjects are shown in Table 1.

Mean CCT in all community normal subjects was 539 μm ± 32 μm. Subanalyses of community normal subjects by diabetic status showed mean CCT to be 536 μm ± 32 μm for those without diabetes, respectively. Mean CCT was 545 μm ± 38 μm in community subjects with POAG and 545 μm ± 29 μm in pseudophakic, but otherwise normal, community subjects. In hospital cases with POAG, the mean CCT was 552 μm ± 38 μm; for those with PACG, the mean CCT was 551 μm ± 33 μm.

Table 1. Participant Demographic and Clinical Details

<table>
<thead>
<tr>
<th>Reason</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aphakia</td>
<td>10</td>
</tr>
<tr>
<td>Previous serious ocular trauma</td>
<td>5</td>
</tr>
<tr>
<td>POAG</td>
<td>2</td>
</tr>
<tr>
<td>Previous intraocular surgery</td>
<td>2</td>
</tr>
<tr>
<td>PACG</td>
<td>2</td>
</tr>
<tr>
<td>Previous intraocular surgery</td>
<td>2</td>
</tr>
<tr>
<td>End stage with corneal decompensation</td>
<td>2</td>
</tr>
<tr>
<td>PACG either eye, no surgery</td>
<td>4</td>
</tr>
<tr>
<td>PACG either eye, no surgery</td>
<td>25</td>
</tr>
<tr>
<td>Other</td>
<td>33</td>
</tr>
<tr>
<td>Secondary glaucoma</td>
<td>2</td>
</tr>
<tr>
<td>Mixed mechanism</td>
<td>1</td>
</tr>
<tr>
<td>Significant corneal pathology</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>55</td>
</tr>
</tbody>
</table>
munity normal subjects without diabetes showed greater CCT in those with higher IOP (1.38 μm/1 mm Hg; \( P \leq 0.00001 \)). After accounting for age, the difference in CCT attributable to IOP increased to 1.69 μm/1 mm Hg (\( P \leq 0.00005 \)). Older age was associated with lesser CCT of 6.8 μm per decade age (\( P \leq 0.00001 \)). Similar analyses in the 73 community pseudophakic subjects and 89 community normal subjects with diabetes showed no significant association between CCT and IOP, even after accounting for age (which was associated with a 9.8-μm reduction in CCT per decade for diabetic community normal subjects; \( P = 0.009 \)) (Table 3).

Regression analysis of the hospital POAG group showed a CCT difference of 1.29 μm/1 mm Hg in IOP, although this was not significant (\( P = 0.060 \)). After adjustment for age, mean CCT difference per 1 mm Hg IOP was 1.20 μm (\( P = 0.067 \)), with a reduction in mean CCT of 9.8 μm per decade (\( P = 0.001 \)). For the hospital PACG group, a CCT decrease of 0.59 μm/1 mm Hg increase was found (\( P = 0.14 \)). This steepened to 0.68 μm reduction in CCT per 1 mm Hg increase but remained statistically nonsignificant (\( P = 0.08 \)) after adjustment for age (10.3 μm CCT reduction per decade age; \( P = 0.003 \)). Comparison of the CCT and IOP regression slopes for hospital POAG

![Figure 1](http://iovs.arvojournals.org/pdfaccess.ashx?url=/data/journals/iovs/933458/)  
**Figure 1.** Scatter plots of CCT (μm) against IOP for community normal subjects (with and without diabetes) and hospital POAG and PACG patients with univariate regression lines, as indicated.
and PACG patients confirmed these to be significantly different ($t = 2.53; P = 0.012$).

Logistic regression showed community POAG diagnosis was not associated with CCT ($P = 0.42$) or age ($P = 0.062$), but was associated with IOP ($P = 0.005$) (Table 4). For hospital glaucoma cases, univariate logistic regression showed POAG diagnosis was significantly associated with CCT (per 10 μm, $P = 0.001$; OR, 1.14; 95% CI, 1.08–1.20); however, after accounting for age (age per decade, $P = 0.043$; OR, 1.33; 95% CI, 1.01–1.75) and IOP (per 1 mm Hg, $P = 0.001$; OR, 1.78; 95% CI, 1.63–1.94), this became insignificant ($P = 0.26$; OR, 1.05; 95% CI, 0.96–1.14). Similar analysis for the hospital PACG cohort showed CCT to be significantly associated with PACG diagnosis ($P = 0.001$; OR, 1.13; 95% CI, 1.06–1.20); however, after accounting for age, which was significantly associated with PACG diagnosis ($P = 0.001$; OR, 1.80; 95% CI, 1.63–1.99), this again became insignificant ($P = 0.11$; OR, 1.09; 95% CI, 0.98–1.20). In contrast to the hospital POAG group, age (per decade) was not associated with PACG diagnosis ($P = 0.35$; OR, 1.18; 95% CI, 0.84–1.66).

Further logistic regression models to investigate the effect of diabetes and pseudophakia in the community subjects showed neither to have any significant association with CCT ($P = 0.33$, diabetes; $P = 0.11$, pseudophakia). Age (but not IOP) was significantly associated with a diagnosis of diabetes or pseudophakia (both $P = 0.001$) (Table 4).

### Table 3. Univariate and Multivariate Regression Analyses of CCT (μm) against IOP and Age by Group

<table>
<thead>
<tr>
<th>Community</th>
<th>Intercept</th>
<th>Coefficient</th>
<th>95% CI</th>
<th>$P$</th>
<th>Age (decade)</th>
<th>Coefficient</th>
<th>95% CI</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal without diabetes</td>
<td>849</td>
<td>519.10</td>
<td>1.38</td>
<td>0.70 to 2.05</td>
<td>&lt;0.0001</td>
<td>553.35</td>
<td>1.69</td>
<td>1.03 to 2.35</td>
</tr>
<tr>
<td>Normal with diabetes</td>
<td>89</td>
<td>514.62</td>
<td>1.40</td>
<td>-0.68 to 3.47</td>
<td>0.19</td>
<td>578.74</td>
<td>1.23</td>
<td>-0.78 to 3.24</td>
</tr>
<tr>
<td>Pseudophakic</td>
<td>73</td>
<td>549.82</td>
<td>-0.34</td>
<td>-1.94 to 1.27</td>
<td>0.68</td>
<td>585.14</td>
<td>-0.25</td>
<td>-1.87 to 1.37</td>
</tr>
<tr>
<td>Hospital</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>POAG</td>
<td>158</td>
<td>522.30</td>
<td>1.29</td>
<td>-0.05 to 2.63</td>
<td>0.060</td>
<td>586.01</td>
<td>1.20</td>
<td>-0.09 to 2.49</td>
</tr>
<tr>
<td>PACG</td>
<td>105</td>
<td>566.15</td>
<td>-0.59</td>
<td>-1.38 to 0.20</td>
<td>0.14</td>
<td>632.04</td>
<td>-0.68</td>
<td>-1.44 to 0.99</td>
</tr>
</tbody>
</table>

Adjusting these analyses for sex made little impact on the value of the respective regression coefficients or on their interpretation.

### Table 4. Univariate and Multivariate Logistical Regression Analyses by Diagnosis

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>CCT per 10 μm</th>
<th></th>
<th></th>
<th>IOP per 1 mm Hg</th>
<th></th>
<th></th>
<th>Age per Decade</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>OR</td>
<td>95% CI</td>
<td>$P$</td>
<td>OR</td>
<td>95% CI</td>
<td>$P$</td>
<td>OR</td>
<td>95% CI</td>
<td>$P$</td>
</tr>
<tr>
<td>Community POAG</td>
<td>1.07</td>
<td>0.89–1.28</td>
<td>0.49</td>
<td>1.27</td>
<td>1.11–1.46</td>
<td>0.001</td>
<td>1.74</td>
<td>0.97–3.10</td>
</tr>
<tr>
<td>Hospital POAG</td>
<td>1.05</td>
<td>0.87–1.23</td>
<td>0.71</td>
<td>1.23</td>
<td>1.06–1.42</td>
<td>0.005</td>
<td>1.74</td>
<td>0.97–3.10</td>
</tr>
<tr>
<td>Hospital PACG</td>
<td>1.08</td>
<td>0.90–1.30</td>
<td>0.42</td>
<td>1.79</td>
<td>1.64–1.96</td>
<td>0.001</td>
<td>1.53</td>
<td>1.01–1.75</td>
</tr>
<tr>
<td>Diabetes (community normals)</td>
<td>1.14</td>
<td>1.08–1.20</td>
<td>0.001</td>
<td>1.78</td>
<td>1.63–1.94</td>
<td>0.001</td>
<td>1.18</td>
<td>0.84–1.66</td>
</tr>
<tr>
<td>Pseudophakia (community)</td>
<td>1.03</td>
<td>0.94–1.11</td>
<td>0.55</td>
<td>1.80</td>
<td>1.63–1.99</td>
<td>0.001</td>
<td>1.93</td>
<td>1.38–2.70</td>
</tr>
<tr>
<td></td>
<td>1.05</td>
<td>0.96–1.14</td>
<td>0.26</td>
<td>1.79</td>
<td>1.62–1.98</td>
<td>0.001</td>
<td>1.93</td>
<td>1.38–2.70</td>
</tr>
<tr>
<td></td>
<td>0.97</td>
<td>0.90–1.04</td>
<td>0.33</td>
<td>1.04</td>
<td>0.97–1.12</td>
<td>0.29</td>
<td>4.14</td>
<td>2.97–5.79</td>
</tr>
</tbody>
</table>

### DISCUSSION

We found no association between CCT and glaucoma diagnosis for both community and hospital cohorts in east Asian people. IOP was significantly associated with glaucoma diagnosis for community POAG, hospital POAG, and hospital PACG cases. Increasing age was associated with hospital POAG diagnosis. Age and IOP are significantly associated with CCT, and this should be taken into account when examining any association between CCT and glaucoma diagnosis. Our findings confirm those of the Singapore Malay Eye Study, which found no association between CCT and POAG diagnosis.8

Investigation of the effect of CCT on glaucoma risk is complicated by the relationship between CCT and IOP measurement. In 1957, Goldmann9 assumed a CCT of 500 μm for the calibration of the Goldmann applanation tonometer (GAT) and suggested that theoretically the IOP reading could be affected by CCT. Later, Ehlers10 found GAT IOP values to be correct for a CCT of 520 μm and reported error magnitudes may be up to ±5 mm Hg for CCTs within 460 to 580 μm. It is now well recognized that CCT is a measurement error factor in the estimation of IOP by GAT, with thin and thick corneas giving incorrectly low and high values, respectively.10–14

IOP remains the most significant modifiable risk factor for glaucoma, and its control has been shown to influence both glaucoma development15 and glaucoma progression.16–19 The
concept that CCT is an independent risk factor for POAG was brought to the forefront by the OHTS.1 This reported that subjects with a corneal thickness of 555 μm or less were at threefold higher risk for POAG than subjects with a corneal thickness of >588 μm. When race was entered into a multivariate analysis for the OHTS, it was no longer a statistically significant predictor of progression to glaucoma, however CCT was.2 As Afro-Caribbean subjects are known to have thinner CCT compared to Caucasian subjects,2-20 and age-adjusted prevalence rates for POAG are 4–5 times higher in black persons than white persons,21 it is unclear whether CCT is an independent predictor of glaucoma risk, a phenotypic marker of different ethnic groups with differing inherent glaucoma risk, or a source of error in tonometry.

In contrast to the inconsistent association between CCT and glaucoma diagnosis, the relationship between CCT and glaucoma outcomes appears stronger. Thinner CCT is associated with more severe functional and anatomic glaucomatous damage on initial examination,2 higher cup/disc ratio at the most recent examination,22 and visual field progression23 (including patients with chronic angle closure glaucoma).24 The Early Manifest Glaucoma Trial, however, reported thinner CCT to be independently related to progression only in patients with higher baseline IOP.25

Numerous studies have compared CCT in patients with glaucoma with normal controls; however, the results are inconsistent. Some reports show CCT to be significantly thinner in POAG patients26-27 or in normal pressure glaucoma patients (but not in POAG patients),15,20 whereas most have found no significant difference.20-29-34

Most of these studies are case-control15,27-31,35 rather than population-based epidemiologic studies.8,20,26,32,34 Control selection bias may be an issue in some, in which the characteristics of the controls differ significantly from the characteristics of the population that is the target of inferences drawn from the study results. Of the five population studies investigating CCT, only one found CCT to be significantly thinner in patients with glaucoma, and this did not control for IOP or age.26

The 7 μm per decade reduction of CCT with age (P ≤ 0.00001) in community normal subjects is consistent with previous population studies (range, 4–7 μm per decade).3,5,37-38 We found no effect of sex on CCT, which is again consistent with previous study findings.26,35,38 although higher CCT in males has also been reported.36

For our community normal subjects, regression analysis showed an IOP change of 0.14 mm Hg/10 μm thicker CCT (95% CI, 0.01–0.20; P ≤ 0.0005). This is similar to that reported by previous population studies of CCT and IOP.5,20 A study by Foster et al.7 of CCT and IOP in a Mongolian population reported an IOP change of 0.18 to 0.24 mm Hg/10 μm CCT change, whereas in the Rotterdam population study by Wolfs et al.20 it was 0.19 mm Hg/10 μm CCT. Our results do not support those by Su et al.33 or the European Glaucoma Prevention Study39 that report diabetes is associated with higher CCT.

In hospital PACG patients, in contrast to the community normal subjects and the hospital POAG patients, we found an apparent change in CCT of −0.68 μm (95% CI, −1.44 to −0.09) for each 1 mm Hg higher IOP, although this was not statistically significant even after accounting for age (P = 0.08). The regression slope, however, was significantly different from that of both the community normal subjects and the hospital POAG subjects (P = 0.016 and P = 0.017, respectively) suggesting a distinct difference in the relationship of CCT with IOP in these subjects. Whether this was due to a congenital biomechanical difference in PACG subjects or was acquired is unknown. However, given that a similar difference was seen in the regression slope of community pseudophakic subjects compared with community normal subjects (P = 0.038), it would suggest the latter. As PACG patients had a greater range of IOPs compared to other groups (12-56 mm Hg) and these are also likely to be more labile, we hypothesize this may result in subclinical corneal stromal and epithelial edema (rather than a thicker normal cornea). This, in turn, might have resulted in the underestimation of IOP in these subjects, which is clearly of great clinical significance because this patient group already had the highest median and range of IOP values. For the pseudophakic subjects, it is possible that endothelial function might have been altered after phacoemulsification surgery such that corneal hydration was changed without CCT being increased. Regardless, it is difficult to explain otherwise why these highly statistically significant differences in the relationship between CCT and IOP may occur.

The primary strength of our study is the large group numbers for both the hospital cases and the community controls. There were insufficient numbers of community PACG cases who had not undergone previous surgical intervention to determine any relationship between CCT and early glaucoma diagnosis. One possible drawback in our study is that we used optical pachymetry. Although this provides repeatable, precise anatomic measures when readings are taken in a standardized manner, the readings are significantly different between left and right eyes by approximately 20 μm because of misalignment along the visual axis rather than the anatomic center of the cornea.5,6 Consequently, for the hospital cohort, adjustment of pachymetry values for left eyes with glaucoma to right eye equivalents could have introduced some error into our CCT values, although we believe this was unlikely. Another potential source of bias is that our hospital glaucoma subjects were not a randomly selected sample of hospital glaucoma subjects but were patients with uncontrolled IOP requiring surgery. Consequently, glaucoma disease stage may be important; however, because the multivariate CCT analyses had similar results in both the community and the hospital cohorts, we believe this is unlikely to have been significant.

We found no evidence to support the previous observation that thinner corneas may be independently associated with either POAG or PACG. Age and IOP are significantly associated with CCT, and these should be taken into account by future studies investigating CCT as an independent risk factor for glaucoma diagnosis.

References


