Relationship of Central Corneal Thickness with Optic Disc Parameters: The Singapore Malay Eye Study

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PURPOSE. To examine the relationship of central corneal thickness (CCT) with optic disc parameters measured by confocal scanning laser ophtalmoscopy in a Malay population.

METHODS. This was a population-based cross-sectional study of Asian Malay adults aged 40–80 years living in Singapore. Participants had a standardized interview, examination, and imaging at a study clinic. CCT was measured with an ultrasound pachymeter. Confocal scanning laser imaging was performed on all participants to obtain optic disc parameters. Multivariate regression analyses controlling for age, sex, intraocular pressure, and other potentially confounding factors were conducted separately for disc area, rim area, cup-to-disc ratio, and mean cup depth.

RESULTS. Of the 3280 participants in the study, 2525 (77.0%) right eyes with reliable confocal scanning laser tomography images were included in this analysis, with 48 eyes defined to have primary open-angle glaucoma (POAG). In POAG subjects, CCT was positively correlated with rim area (regression coefficient of 0.372 mm² per 100 μm CCT increase; P = 0.035) and negatively correlated with cup-to-disc area ratio (−0.160 per 100 μm CCT increase; P = 0.024). There was no relationship between CCT and disc size (P = 0.088). In the 2468 subjects without glaucoma, there were no associations between CCT and confocal scanning laser tomography parameters.

CONCLUSIONS. In this population-based study, decreased CCT was associated with lower rim area and greater cup-to-disc area in subjects with POAG, but not in subjects without glaucoma.


The association between corneal properties and susceptibility to glaucoma is an area of recent interest.1–5 Central corneal thickness (CCT) is regarded as a risk factor for the development of primary open-angle glaucoma (POAG) among ocular hypertensive patients1 and visual field progression in POAG patients.2–5 The reasons for this increased risk have not been elucidated. Many researchers have focused on the concept that thinner-than-average corneas may underestimate the true intraocular pressure (IOP), and thicker-than-average corneas may overestimate IOP.4–6 However, this factor alone seems not sufficient to explain the increased susceptibility to glaucoma found in those with thinner corneas. For example, in the Ocular Hypertension Treatment Study, CCT was a risk factor for the conversion of patients with ocular hypertension to POAG, after statistical adjustment for IOP and other risk factors.7

Another hypothesis is that CCT may reflect sclera and lamina cribrosa changes associated with glaucomatous optic neuropathy because of the anatomic continuity of the cornea, sclera, and optic disc lamina. It has been shown that CCT is correlated with anterior scleral thickness in POAG patients.10 Several studies have assessed the relationship between CCT and objectively measured optic disc parameters, but these have provided inconsistent results. When measured with confocal scanning laser ophthalmoscopy (Heidelberg Retina Tomograph; Heidelberg Engineering, Heidelberg, Germany), several hospital-based studies on glaucoma patients suggested correlations of CCT with optic disc area11,12 and nasal rim volume,13 while in the population-based Tajimi study from Japan, these correlations could not be confirmed in normal subjects.14 Instead, correlation of CCT to cup volume was observed in that study.14 In another population-based survey, the Bridlington Eye Assessment Project,15 no significant relationship of CCT with any parameter obtained with retinal tomography was demonstrated.

In view of the clinical importance of CCT and the controversy about the relationship between CCT and glaucomatous optic neuropathy, we examined the relationships of CCT with optic disc parameters measured quantitatively with confocal scanning laser ophthalmoscopy (HRT II; Heidelberg Engineering) in a population-based study in Singapore.

METHODS

Study Population

The Singapore Malay Eye Study was a population-based cross-sectional study of 3280 (78.7% response rate) Malay subjects aged 40 to 80 years living in Singapore. The study methodology has been described previously.16,17 This study was conducted in accordance with the Declaration of Helsinki, and ethics approval was obtained from the Institutional Review Board.

Study Measurements

All participants underwent a standardized interview, systemic and ocular examinations, and ocular imaging at a centralized study clinic.16 Relevant portions of the examination are presented here. Height was measured using a wall-mounted tape and weight with a digital scale. Body mass index (BMI) was calculated as weight (in kilograms) divided
Table 1. Characteristics of Participants Included and Excluded in the Study

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Included (N = 2525)</th>
<th>Excluded (N = 755)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>57.0 ± 10.7</td>
<td>64.4 ± 10.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex; male, n (%)</td>
<td>1236 (49.0)</td>
<td>340 (45.0)</td>
<td>0.056</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>1643 (65.1)</td>
<td>603 (79.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>145.2 ± 22.7</td>
<td>153.7 ± 25.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>79.9 ± 11.0</td>
<td>79.2 ± 11.8</td>
<td>0.143</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>497 (19.7)</td>
<td>267 (35.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hemoglobin A1c (%)</td>
<td>6.36 ± 1.46</td>
<td>6.78 ± 1.79</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current smoking, n (%)</td>
<td>560 (22.2)</td>
<td>102 (13.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Axial length (mm)</td>
<td>23.6 ± 1.0</td>
<td>23.5 ± 1.1</td>
<td>0.458</td>
</tr>
<tr>
<td>Central corneal thickness (μm)</td>
<td>542.0 ± 33.1</td>
<td>538.4 ± 35.1</td>
<td>0.012</td>
</tr>
<tr>
<td>Myopia, n (%)</td>
<td>576 (22.8)</td>
<td>272 (36.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intraocular pressure (mm Hg)</td>
<td>15.37 ± 3.50</td>
<td>15.41 ± 4.20</td>
<td>0.784</td>
</tr>
</tbody>
</table>

Tomography Imaging

The tomograph used (HRT II; Heidelberg Engineering) employs a diode laser (670 nm wavelength) to sequentially scan the optic disc and parapapillary retina with the field of view set at 15°. Scans were conducted through dilated pupils. Corneal curvature radius was entered into the software for all subjects, and cylindrical lens power was adapted for those with astigmatism greater than or equal to 1 D. All examinations were performed by two trained operators.29,30

Images with a mean pixel height standard deviation of >50 μm were excluded. After completion of the study, the optic disc margin or contour line was defined and manually outlined by a trained ophthalmologist. This step was accomplished by plotting a series of six dots around the disc margin on the reflectance image. The disc margin was defined as the inner edge of Elschög's ring. The standard reference plane is defined at 50 μm posterior to the mean contour line height between 350° and 356° along the contour line. Global and regional optic nerve head parameters were measured and generated by the software (HRT II).

Glaucoma Diagnostic Definitions

Glaucoma suspects were defined as those participants fulfilling any of the following criteria: IOP greater than 21 mm Hg, VCDR > 0.6 or VCDR asymmetry > 0.2, abnormal anterior segment deposit consistent with pseudoxfoliation or pigment dispersion syndrome, occludable or closed anterior chamber angle (defined in the next section), peripheral anterior synechiae or other findings consistent with secondary glaucoma, and known history of glaucoma.31 As indicated, these participants underwent gonioscopy, visual field test, and a second IOP measurement, usually on another day.

Glaucoma cases were defined according to the International Society for Geographical and Epidemiologic Ophthalmology (ISGEO) criteria based on three categories. Category 1 cases were defined as optic disc abnormality (VCDR/VCDR asymmetry > 97.5 percentile or NRR width between 11 and 1 o’clock or 5 and 7 o’clock < 0.1 VCDR), with a corresponding glaucomatous visual field defect. Category 2 cases...
were defined as having a severely damaged optic disc (VCDR or VCDR asymmetry >99.5th percentile) in the absence of adequate performance in a visual field test. In diagnosing category 1 or 2 glaucoma, it was required that there should be no other explanation for the VCDR finding (dysplastic disc or marked anisometropia) or visual field defect (retinal vascular disease, macular degeneration, or cerebrovascular diseases). Category 3 cases were defined as subjects without visual field or optic disc data who were blind (corrected visual acuity, <3/60) and who had previous glaucoma surgery or have IOP >99.5 percentile.21

VCDR used in defining glaucoma suspects and glaucoma cases were based on clinical optic disc assessment during slit lamp biomicroscopy. Definition of glaucoma cases was performed by investigators masked to clinical data such as CCT.

To determine normative values for optic disc parameters (VCDR and VCDR asymmetry) and IOP, we used data from the one in five consecutive participants who were not glaucoma suspects and who had normal visual fields in both eyes on two separate occasions. A glaucomatous visual field defect was considered to be present if the following were found: a glaucoma hemifield test result outside normal limits and a cluster of three or more nonedge, contiguous points, not crossing the horizontal meridian, with a probability of <5% of the age-matched normal on the pattern deviation plot on two separate occasions. A narrow anterior chamber angle was diagnosed if the posterior trabecular meshwork was seen for 180° or less of the angle circumference during static gonioscopy.22 POAG was defined as an eye with an evidence of glaucoma as defined above with an open angle. Final identification, adjudication, and classification of glaucoma cases were reviewed by the senior glaucoma specialist (TA).

### Statistical Analysis

Statistical analysis was performed using commercial software (SPSS, v. 17.0; SPSS, Chicago, IL). Since the correlations between the two eyes for optic disc parameters were high (e.g., correlation coefficients between right and left eyes for optic disc area = 0.85), only the data from right eyes are included in further analysis. An unpaired t-test or χ² test was used to test the differences of demographic characteristics between included and excluded participants. An unpaired t-test was performed to examine the differences in the tomography parameters (disc area, rim area, cup-to-disc ratio, and mean cup depth) between eyes of POAG and those without glaucoma. In a stepwise manner, three multiple linear regression models adjusted for age and sex; age, sex, BMI, spherical equivalent of refraction, and axial length; and age, sex, BMI, spherical equivalent of refraction, axial length, intraocular pressure, and disc area were used to estimate the relationships of CCT with each tomography parameter (disc area, rim area, cup-to-disc ratio, and mean cup depth). BMI was included in the regression models because it has been reported to be associated with the optic disc size and cup-to-disc ratio in our previous study on this population.23 These three regression models were constructed to avoid overadjusting of confounding factors. Significance level was set at $P < 0.05$.

### Results

Of 3280 participants, 224 were unable to complete the tomography test or had missing imaging data, and 281 had poor tomography image quality (SD > 50 μm). Of the remaining 2775 subjects, 194 with a history of intraocular surgery (including cataract, glaucoma, vitreoretinal surgery) or retinal laser photocoagulation, 48 with severe diabetic retinopathy and eight with retinal vein occlusion were further excluded, leaving 2525 right eyes (77.0%) for the final analyses. The demographic features and ocular biometric measurements of the included, and excluded participants are listed in Table 1. In general, excluded subjects were older and had higher levels of systolic blood pressure, hemoglobin-A1c, and higher prevalence of hypertension and diabetes, but lower prevalence of smoking. In addition, when compared with eyes included for analysis, excluded eyes had smaller mean CCT and higher proportion of myopia, but similar axial length and IOP.

### Table 3. Relationships of Central Corneal Thickness (per 100 μm) with Tomography Parameters, All Persons (N = 2525)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Regression Coefficient, Model 1</th>
<th>Regression Coefficient, Model 2</th>
<th>Regression Coefficient, Model 3</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disc area (mm²)</td>
<td>-0.034</td>
<td>0.253</td>
<td>-0.018</td>
<td>0.541</td>
</tr>
<tr>
<td>Rim area (mm²)</td>
<td>-0.005</td>
<td>0.797</td>
<td>0.005</td>
<td>0.802</td>
</tr>
<tr>
<td>Cup-to-disc area ratio</td>
<td>-0.009</td>
<td>0.305</td>
<td>-0.008</td>
<td>0.372</td>
</tr>
<tr>
<td>Mean cup depth (mm)</td>
<td>-0.008</td>
<td>0.124</td>
<td>-0.005</td>
<td>0.402</td>
</tr>
</tbody>
</table>

Linear regression models adjusted for the following: Model 1—age, sex; Model 2—age, sex, body mass index, spherical equivalent, and axial length; and Model 3—age, sex, body mass index, spherical equivalent, axial length, intraocular pressure, and disc area.
Among 2525 right eyes with eligible tomography data, 57 were diagnosed as glaucoma. Of these, 48 eyes were diagnosed as POAG (42 of category 1 and 6 of category 2). The tomography parameters of all eligible, nonglaucoma, and POAG eyes are shown in Table 2. When compared with those without glaucoma, POAG eyes had significant greater disc area, cup-to-disc area ratio, and mean cup depth but smaller rim area (all $P < 0.001$). No significant difference was observed in all tomography parameters between all eligible eyes and those without glaucoma.

The mean CCT was 536.1 ± 33.6 μm and 542.1 ± 33.0 μm for POAG eyes and eyes without glaucoma, respectively ($P = 0.213$). This difference of the means was statistically nonsignificant ($P = 0.954$, test of variance) after further adjustment for age and sex.

Figure 1 shows the distribution of CCT by optic disc area in persons without glaucoma (upper plot) and with POAG (lower plot). Linear regression revealed the relationships of CCT with disc area were nonsignificant in persons without glaucoma ($P = 0.383$) and in those with POAG ($P = 0.088$). Table 3 shows results of a linear regression test of CCT with tomography parameters in the study population. None of the correlations between CCT and tomography parameters were significant (all $P > 0.05$). Similar results were obtained in persons without glaucoma (Table 4). However, in POAG eyes (Table 5), increased CCT was significantly correlated with increased rim area ($P = 0.035$) but decreased cup-to-disc ratio ($P = 0.024$). Specifically, after adjustment for confounding factors of age, sex, BMI, spherical equivalent, axial length, IOP, and disc area, per 100 μm increase in CCT was associated with a 0.372 mm² increase in rim area, respectively, and a 0.160 decrease in cup-to-disc area ratio.

**DISCUSSION**

In this adult population of Malay ethnicity, no significant relationships between CCT and tomography parameters were observed in eyes without glaucoma. However, we found that CCT was correlated with rim area and cup-to-disc area ratio in POAG eyes. These associations persisted after adjusting for age, sex, and other confounding factors. Our study results provide interesting data addressing the relationship between CCT and glaucoma on a population level.

Our observation that CCT was not associated with tomography parameters in persons without glaucoma is in line with the finding in another population-based study, the Briddlington Eye Assessment Project, conducted on normal white subjects over 65 years of age (mean age of 73.3 years), in which glaucoma persons were also excluded. However, in the Tajimi study, CCT was found to be inversely correlated with cup volume in 1769 normal Japanese adults aged 40 years or more. It has to be noted that the correlation of CCT to cup volume shown in the Tajimi study was rather weak (partial correlation coefficient, $-0.05$; $P = 0.040$), so a chance finding cannot be excluded, and the clinical implication of such a weak correlation need to be confirmed. Furthermore, about one-fourth (23%) participants were excluded from the analysis in our study, whereas one-third were excluded in the Tajimi study for various exclusion criteria. Hence the discrepancy in the finding between the studies may reflect differences in the study design and sample size.

Several hospital-based studies on POAG patients have showed correlations of CCT with optic disc area and nasal rim volume. However, our study found that CCT was associated with decreased cup-to-disc ratio and increased rim area in POAG patients independent of age, sex, BMI, spherical equivalent, axial length, and disc area. One possible reason for the discrepancy could be that the definition of glaucoma was different in our study compared with those hospital-based studies. As the ISGEO scheme was used for glaucoma diagnosis in our study, eyes with “pseudonormal” small optic cups might have been misclassified as nonglaucomatous. On the other hand, there were six eyes with abnormally large disc VCDR but without visual field data that were classified as POAG (ISGEO category 2). Because of the cross-sectional nature of our study, the clinical significance of the correlations found in our study needs to be evaluated in longitudinal studies.

It is unclear why a significant correlation between CCT and HRT parameters was seen only in POAG patients. The possibility of a chance finding cannot be excluded because of the cross-sectional nature of the study, as well as the relative small POAG sample size ($n = 48$). One may speculate that our findings reflect a specific racial feature in this Malay population. However, the relation between CCT and glaucoma development has been found in various populations of different ethnicities. One possible explanation is that eyes with...
decreased CCT may have more chance of developing more advanced disease. This hypothesis needs to be confirmed by further longitudinal studies. Nevertheless, it is also possible that CCT decreases as glaucoma progresses; that is, a thinner CCT could be the result of the glaucomatous process that can be detected and measured in the anterior segment (i.e., cornea), whereas optic disc cupping and rim loss are the result of the glaucomatous process to the posterior segment (i.e., optic disc nerve head).

The strengths of our study include its large population-based design. In addition, reliable ocular measurements including optic disc parameters by tomography were obtained by standardized protocols. However, our study had several limitations. Firstly, the cross-sectional nature of the study prevented inferring causality or a chronological order of the correlation. In particular, the temporal relationship between CCT and optic disc parameters in POAG patients remains uncertain. Second, as mentioned above, like other population-based studies that have used the ISGEO scheme for glaucoma diagnoses, deviation in glaucoma classification seemed to be inevitable, especially those eyes with “pseudonormal” or “pseudoabnormal” optic cups but normal IOPs. Both conditions might have imposed bias on the correlation of CCT with rim area and mean RNFL thickness-related optic disc parameters. However, we believe that such errors have been minimized because each subject was carefully examined by experienced ophthalmologists, and all fundus images were reviewed by a senior glaucoma specialist. Third, about one-fourth of eyes were excluded because of unavailability or poor quality of tomography images or ocular abnormalities. When compared with those included, the excluded subjects were significantly older and had smaller CCT and a higher prevalence of myopia. It has been reported that age and refractive error are correlated with many tomography parameters. Although not influencing the final results, it is possible that these differences may have influenced the correlations tested in the study.

In summary, in a population-based study of Malay persons aged 40 to 80 years, CCT was found to be correlated with rim area and cup-to-disc ratio (tomography measurements) only in POAG patients, independent of axial length, IOP, disc area, and other confounding factors. No significant correlation between CCT and optic disc parameters was seen in subjects without glaucoma. The clinical significance of these findings requires further investigation.

References