Effect of Corneal Arcus on Central Corneal Thickness, Intraocular Pressure, and Primary Open-angle Glaucoma

The Singapore Malay Eye Study

Renyi Wu, MD, PhD; Tien-Yin Wong, MD, PhD; Seang-Mei Saw, PhD; Howard Cajucom-Uy, MD; Mohamad Rosman, MD; Tin Aung, PhD

Objectives: To examine the association of corneal arcus with central corneal thickness (CCT), intraocular pressure (IOP), and the prevalence of primary open-angle glaucoma.

Methods: This was a population-based cross-sectional study of Malay participants aged 40 to 80 years living in Singapore. Participants underwent a standardized interview and systemic and ocular examinations, including CCT, IOP, and corneal curvature radius measurements. Corneal arcus, assessed using a slitlamp, was defined as gray-white or yellow opacity located near the periphery of the cornea but separated from the limbus by a clear zone.

Results: Corneal arcus was found in right eyes among 1747 (57.9%) of 3015 participants. After adjusting for age, sex, and systemic factors, IOP was higher (15.87 vs 14.86 mm Hg, \( P < .001 \)) and CCT was thinner (540.6 vs 543.4 \( \mu m \), \( P = .03 \)) in eyes with vs without corneal arcus. In multiple linear regression models, eyes with corneal arcus had on average 1.14 mm Hg higher IOP than eyes without corneal arcus. In the presence of corneal arcus, the linear correlations of \( CCT \times IOP \) and of corneal curvature radius \( \times IOP \) were altered. The prevalence of ocular hypertension, but not primary open-angle glaucoma, was significantly higher among participants with corneal arcus than among participants without corneal arcus (\( P = .02 \)).

Conclusions: Corneal arcus was associated with higher IOP and lower CCT independent of age, sex, and systemic and ocular factors. Further research is required to investigate the clinical implications of these findings for IOP assessment in eyes with corneal arcus.


Glaucoma is the leading cause of irreversible blindness worldwide, with primary open-angle glaucoma (POAG) the most common form of glaucoma. Intraocular pressure (IOP) is the only treatable risk factor associated with the onset and progression of glaucoma.\(^1\) The accuracy of IOP measurement is crucial in the diagnosis and management of glaucoma. Corneal structural characteristics, such as central corneal thickness (CCT), corneal curvature radius (CCR), and corneal biomechanical properties are known to affect the accuracy of IOP measurement by Goldmann applanation tonometry (GAT),\(^2\) the current gold standard for IOP measurement. Studies\(^8\) have shown that, with GAT, thinner corneas yield a falsely low IOP reading, while thicker corneas yield a falsely high IOP reading. A negative correlation between CCR and GAT-measured IOP readings has been shown in some studies\(^7\) but not in other studies.\(^6\) Other studies showed that corneal biomechanical properties such as corneal hysteresis and corneal resistance factor, which are measured by the ocular response analyzer, affect GAT-measured IOP measurement,\(^6,11\) with low corneal hysteresis leading to underestimation of IOP.\(^11\)

Corneal arcus is an area of lipid deposition near the corneoscleral limbus but separated from the limbus by a lipid-free zone called the lucid interval of Vogt. Corneal arcus often begins in the superior and inferior parts of the cornea and progresses to form a complete ring without visual impairment. It is a recognized sign of hyperlipidemia when observed in individuals younger than 50 years\(^2,13\) and is reported to be associated with some systemic disorders, such as cardiovascular disease.\(^19\) The effect of corneal arcus on the structure and function of the cornea is not fully understood. In this population-based study of
adult Malays in Singapore, we describe the effect of corneal arcus on CCT, CCR, IOP, and the prevalence of POAG.

METHODS

STUDY POPULATION

The Singapore Malay Eye Study was a population-based cross-sectional study of 3280 Malay participants (78.7% response rate) aged 40 to 80 years living in Singapore. The study methods have been described previously. Approval for the study protocol was granted by the local institutional review board, and the study was conducted in accord with the Declaration of Helsinki. Written informed consent was obtained from all individuals before study enrollment.

STUDY MEASUREMENTS

All participants underwent a standardized interview and systemic and ocular examinations, including collection of blood samples at a centralized study clinic. Relevant portions of the examination are presented herein. Blood pressure was measured with a digital automatic blood pressure monitor (Dinamap Pro Series DP110X-RW 100V2; GE Medical Systems Information Technologies, Inc, Milwaukee, Wisconsin) after the participants were seated for at least 5 minutes. Nonfasting venous blood samples were drawn and sent that day to the National University Hospital Reference Laboratory, Singapore, for analysis of the following levels: glucose, creatinine, glycated hemoglobin, and serum lipids (total, high-density lipoprotein cholesterol [HDL-C], and low-density lipoprotein cholesterol [LDL-C]). Total, HDL-C, and LDL-C levels were directly measured from assays. The refraction (sphere, cylinder, and axis) of each eye was measured using an autorefractor machine (Canon RK-H11003 10 magnification was used to obtain an overall view of the cornea, and the presence of corneal arcus was assessed by the authors). Corneal arcus was defined as gray-white or yellow opacity located near the periphery of the cornea but separated from the limbus margin by a clear zone. Five CCT measurements were obtained, which was used for analysis. Gonioscopy was performed using a Goldmann 2-mirror gonioscope (model 903; Haag-Streit, Koniz, Switzerland). After pupil dilation, the optic disc was evaluated using a 78-diopter lens at ×16 magnification with measuring graticule. The vertical cup-disc ratio (VCDR) was then calculated. Disc hemorrhage, notching of the neuroretinal rim, and thinning of the retinal nerve fiber layer were documented. Finally, automated perimetry (SITA 24-2, Humphrey Visual Field Analyzer II; Carl Zeiss Meditec, Inc, Dublin, California) was performed using near refractive correction by trained study technicians on 1 in 10 participants before examination by study ophthalmologists and on all participants suspected of having glaucoma. The visual field test was repeated if the test reliability was not satisfactory (fixation loss >20%, false-positive rate >33%, or false-negative rate >33%) or if there was a glaucomatous visual field defect.

DIAGNOSTIC DEFINITION OF GLAUCOMA

Glaucoma was defined according to International Society Geographical and Epidemiological Ophthalmology criteria based on the following 3 categories: (1) Subjects with category 1 had optic disc abnormality (VCDR or VCDR asymmetry ≥97.5 percentile or neuroretinal rim width between 11- and 1-o’clock position or between 5- and 7-o’clock position <0.1 VCDR) with a corresponding glaucomatous visual field defect. (2) Subjects with category 2 had a severely damaged optic disc (VCDR or VCDR asymmetry ≥99.5 percentile) in the absence of adequate performance on a visual field test. In diagnosing category 1 or 2 glaucoma, it was required that there was no other explanation for the VCDR finding (dysplastic disc or marked anisometropia) or visual field defect (retinal vascular disease, macular degeneration, or cerebrovascular diseases). (3) Subjects with category 3 had no visual field or optic disc data, were blind (corrected visual acuity <3/60), and had previous glaucoma surgery or an IOP exceeding the 99.5 percentile. Final identification, adjudication, and classification of glaucoma cases were reviewed by one of us (T.A.). In addition, ocular hypertension (OHT) was defined as an IOP exceeding 21 mm Hg in the absence of glaucoma.

DATA MANAGEMENT AND STATISTICAL ANALYSIS

Excluded from the analysis were participants with uveitis, secondary glaucoma, pseudoexfoliation syndrome, a history of any ocular surgery, primary angle closure or glaucoma, and current use of ocular hypotensive medication, as well as those with conditions that interfered with accurate IOP assessment by GAT (such as corneal scar, significant pterygium, and others). Statistical analysis was performed using commercially available software (SPSS, version 11.5; SPSS Inc, Chicago, Illinois). Proportions were compared using the χ² test, and means were compared using the t test. Analysis of covariance models were used to estimate the mean CCT, CCR, IOP, and axial length adjusted for covariates. Multiple linear regression models were developed to assess the change in IOP by the presence or absence of corneal arcus. Nonstandardized and standardized coefficients were provided, and the absolute magnitude of the standardized regression coefficient indicates the relative importance of a factor as a predictor of IOP. The effect of corneal arcus on the linear correlations of CCT × IOP and of CCR × IOP was accessed by variance analysis. Finally, Lowest estimation curves were constructed to demonstrate the relationship between IOP and the prevalence of POAG by the presence or the absence of corneal arcus. The difference in slopes was compared in a multivariate model after log transformation.

RESULTS

Baseline characteristics of the study population are summarized in Table 1. Excluded subjects were older and
had higher systolic and diastolic blood pressures and blood

glucose and total cholesterol levels.

The mean (SD) IOP readings were normally distrib-
uted and were consistent between right and left eyes (15.
4 [3.6] and 15.4 [3.8] mm Hg, respectively; Pearson prod-
uct moment correlation coefficient, 0.815); hence, only
data in right eyes among 3015 participants (91.9%) were
used for analysis. The mean IOPs of the participants by
age group and by sex are given in Table 2. In general,
the mean IOP was higher in women than in men, with a
statistically significant difference observed in groups aged
40 to 49 years (P = .02), 50 to 59 years (P < .001), and 60
to 69 years (P = .007).

Corneal arcus was found in 1747 (57.9%) of 3015 par-
ticipants. Figure 1 shows a typical ring-form corneal
arcus in a male participant. The distribution of corneal arcus by age group and by sex is given in Table 2. The
prevalence of corneal arcus increased with age and was
consistently higher among men than among women. Sig-
ificant differences in the prevalence of corneal arcus be-
tween men and women were seen among groups aged
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to 69 years (P = .007).

Figure 1. A circular corneal arcus was present on the right eye of a Malay
adult in the Singapore Malay Eye Study.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Included (N=3015)</th>
<th>Excluded (n=265)</th>
<th>P Value(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex, No. (%)</td>
<td>1447 (48.0)</td>
<td>132 (49.8)</td>
<td>.80</td>
</tr>
<tr>
<td>Corneal arcus, No. (%)</td>
<td>1747 (57.9)</td>
<td>173 (65.3)</td>
<td>.10</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>57.9 (10.9)</td>
<td>67.7 (8.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Body mass index, mean (SD)(^b)</td>
<td>26.8 (6.5)</td>
<td>26.3 (6.1)</td>
<td>.10</td>
</tr>
<tr>
<td>Blood pressure, mean (SD), mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>146.4 (23.7)</td>
<td>154.5 (23.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diastolic</td>
<td>77.2 (11.0)</td>
<td>80.0 (11.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Blood glucose level, mean (SD), mg/dL</td>
<td>121 (65)</td>
<td>141 (76)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Total cholesterol level, mean (SD), mg/dL</td>
<td>211 (47)</td>
<td>218 (45)</td>
<td>.02</td>
</tr>
<tr>
<td>Intraocular pressure, mean (SD), mm Hg</td>
<td>15.4 (3.6)</td>
<td>15.1 (5.2)</td>
<td>.24</td>
</tr>
<tr>
<td>Central corneal thickness, mean (SD), µm</td>
<td>541.3 (33.5)</td>
<td>538.0 (34.7)</td>
<td>.13</td>
</tr>
<tr>
<td>Corneal curvature radius, mean (SD), mm</td>
<td>7.65 (0.22)</td>
<td>7.65 (0.25)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Axial length, mean (SD), mm</td>
<td>23.6 (1.1)</td>
<td>23.2 (0.9)</td>
<td>.14</td>
</tr>
</tbody>
</table>

SI conversion factors: To convert glucose to millimoles per liter, multiply by 0.0555; cholesterol to millimoles per liter, multiply by 0.0259.

\(^a\) Independent-samples t test or \(\chi^2\) test as appropriate.

\(^b\) Calculated as weight in kilograms divided by height in meters squared.

Table 2. Characteristics of the Study Population in the Singapore Malay Eye Study

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</tr>
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<td>67.7 (8.6)</td>
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<td>&gt;.99</td>
</tr>
<tr>
<td>Axial length, mean (SD), mm</td>
<td>23.6 (1.1)</td>
<td>23.2 (0.9)</td>
<td>.14</td>
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</table>

Table 1. Age-Specific and Sex-Specific Intraocular Pressure and Corneal Arcus in the Singapore Malay Eye Study

<table>
<thead>
<tr>
<th>Age Group, y</th>
<th>No.</th>
<th>All Participants</th>
<th>Men</th>
<th>Women</th>
<th>P Value(^a)</th>
<th>All Participants</th>
<th>Men</th>
<th>Women</th>
<th>P Value(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-49</td>
<td>809</td>
<td>15.1 (3.4)</td>
<td>14.9 (3.4)</td>
<td>15.4 (3.3)</td>
<td>.02</td>
<td>355 (43.9)</td>
<td>193 (54.4)</td>
<td>162 (45.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>50-59</td>
<td>926</td>
<td>15.6 (3.3)</td>
<td>15.1 (3.2)</td>
<td>16.0 (3.4)</td>
<td>&lt;.001</td>
<td>553 (57.8)</td>
<td>264 (49.3)</td>
<td>271 (50.7)</td>
<td>.001</td>
</tr>
<tr>
<td>60-69</td>
<td>696</td>
<td>15.6 (3.5)</td>
<td>15.2 (3.6)</td>
<td>16.0 (3.3)</td>
<td>.007</td>
<td>446 (64.1)</td>
<td>248 (55.6)</td>
<td>198 (44.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>70-80</td>
<td>584</td>
<td>15.4 (4.2)</td>
<td>15.1 (4.4)</td>
<td>15.7 (4.0)</td>
<td>.11</td>
<td>411 (70.4)</td>
<td>226 (55.0)</td>
<td>185 (45.0)</td>
<td>.17</td>
</tr>
<tr>
<td>Total</td>
<td>3015</td>
<td>15.4 (3.6)</td>
<td>15.1 (3.6)</td>
<td>15.8 (3.5)</td>
<td>&lt;.001</td>
<td>1747 (57.9)</td>
<td>931 (53.3)</td>
<td>816 (46.7)</td>
<td>&lt;.001</td>
</tr>
</tbody>
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Figure 1. A circular corneal arcus was present on the right eye of a Malay
adult in the Singapore Malay Eye Study.

The IOP, CCT, CCR, and axial length were com-
pared in eyes with and without corneal arcus (Table 3). Eyes with corneal arcus had significantly higher IOP than eyes without corneal arcus. In contrast, CCT was sig-
ificantly thinner in eyes with corneal arcus than in eyes
without corneal arcus. In a multivariate model adjusted
for age, sex, body mass index, systolic and diastolic blood
pressures, and blood glucose and total cholesterol lev-
eels, significant differences in IOP and CCT were seen be-
tween eyes with and without corneal arcus (ie, eyes with corneal arcus had significantly higher IOP and lower
CCT). The difference in the mean CCR or axial length
was not significant between eyes with and without corneal arcus.
For all participants, Table 4 gives the results of multiple linear regression models adjusted for age, sex, body mass index, systolic and diastolic blood pressures, blood glucose and total cholesterol levels, corneal arcus, central corneal thickness, corneal curvature radius, and axial length. Among participants with corneal arcus, IOP was higher by 1.14 mm Hg in all participants, higher by 0.97 mm Hg in men, and higher by 1.27 mm Hg in women compared with participants without corneal arcus, IOP was higher by 1.14 mm Hg in all participants, higher by 0.97 mm Hg in men, and higher by 1.27 mm Hg in women compared with participants without corneal arcus. A comparison of the slopes after log transformation revealed that the prevalence of POAG was significantly different among participants with and without corneal arcus (3.1% and 3.5%, respectively; P = .35), and no significant association of corneal arcus with the prevalence of POAG was found (Table 6).

Table 5 summarizes the effect of corneal arcus on the linear correlations of CCT, CCR, and axial length to IOP. A multiple linear regression model adjusted for age, sex, body mass index, systolic and diastolic blood pressures, blood glucose and total cholesterol levels, corneal arcus, central corneal thickness, corneal curvature radius, and axial length. A multiple linear regression model adjusted for age, sex, body mass index, systolic and diastolic blood pressures, blood glucose and total cholesterol levels, corneal arcus, central corneal thickness, corneal curvature radius, and axial length. A similar interaction was observed for the correlation of CCR × IOP (P < .001, test for interaction).

In the present study, 101 participants were diagnosed as having POAG based on International Society Geographical and Epidemiological Ophthalmology criteria (87 category 1 eyes and 14 category 2 eyes). In general, the prevalence of POAG was not significantly different among participants with and without corneal arcus (3.1% and 3.5%, respectively; P = .35), and no significant association of corneal arcus with the prevalence of POAG was found (Table 6). Figure 2 shows the Lowess curves for the relationship between IOP and the prevalence of POAG stratified by the presence or absence of corneal arcus. A comparison of the slopes after log transformation revealed that the prevalence of POAG was slightly higher among participants with corneal arcus (P = .15).

Among 79 participants diagnosed as having OHT, corneal arcus was noted in 57 (72.2%). The prevalence of OHT was significantly higher among participants with corneal arcus (3.2%) than among participants without corneal arcus (1.8%) (P = .02). The association of cor-
neal arcus with the prevalence of OHT was nonsignificant among all participants ($P = .05$) and among men ($P = .09$) but was significant among women ($P = .03$).

**COMMENT**

In this cross-sectional study among the Malay population, IOP was significantly higher and CCT was significantly thinner in persons with corneal arcus, even after adjustment for age, sex, and systemic and ocular factors. In contrast, there was no significant difference in CCR or axial length observed between participants with and without corneal arcus. In GAT-determined IOP, a measured force is used to indent a standardized surface area of the cornea. Based on the Imbert-Fick law, the pressure inside the eye is proportional to the force required for indentation. However, a source of error is resistance of the cornea to indentation. Corneal resistance can be affected by thickness, elasticity, curvature, and perhaps other unknown factors. The effect of CCT on GAT-measured IOP has been well documented clinically and experimentally. A positive correlation has been established between CCT and GAT-measured IOP, ranging from 0.15 to 0.71 mm Hg per 10-µm increase in CCT. The effect of CCR on GAT-measured IOP or glaucoma progression is controversial. A negative correlation has been demonstrated in some studies, while other studies showed no correlation between CCR and GAT-measured IOP. In the present study, a positive linear correlation of CCT with GAT-measured IOP and a negative...
Corneal arcus is a common age-related abnormality. In the present study, corneal arcus was observed in 57.9% of the population. Compared with the prevalence among a population of white race/ethnicity, such as that in the Blue Mountains Eye Study,23 the prevalence of corneal arcus among the Malay adult population described herein was generally lower across groups aged 50 to 59, 60 to 69, and 70 to 80 years. Corneal arcus is considered a cardiovascular risk factor14; however, its effect on corneal and ocular structural properties is not fully understood. To our knowledge, this study is the first to report the correlation of corneal arcus with ocular biometric measurements. After adjustment for systemic and ocular factors, the mean GAT-measured IOP was significantly higher in eyes with corneal arcus. This could not be explained by CCT differences, as the mean CCT was significantly lower in these eyes, nor could it be explained by CCR or axial length differences. As summarized in Table 5, the linear correlations of CCT × IOP and of CCR × IOP were significantly stronger in eyes with corneal arcus (P < .001, test for interaction). These results suggest that corneal arcus may be independently associated with CCT and IOP.

There is no known explanation for the association of corneal arcus with higher IOP. There may be changes in biomechanical properties of the cornea in eyes with corneal arcus, as such mechanisms are emerging as important clinical variables that may affect IOP measurements.24,25 Corneal hysteresis and corneal resistance factor decrease with age26 and contribute to stiffening of the cornea.21 Because corneal arcus shares some similarities with the atherosclerotic process,3 we speculate that changes in corneal biomechanical properties may be induced during the formation of corneal arcus. However, evidence about corneal arcus is limited, and data are unavailable on biomechanical properties in eyes with corneal arcus. Further studies are warranted to confirm our hypothesis.

It is unclear why CCT was lower in eyes with corneal arcus. Some systemic and ocular factors, such as age, sex, body mass index, blood pressure, diabetes, chronic kidney disease, metabolic syndrome, CCR, IOP, and axial length are associated with CCT.28,29 However, even after adjustment for these factors, significantly lower mean (SD) CCT was seen in eyes with vs without corneal arcus (541.6 [1.5] vs 547.6 [1.9] µm, P = .01). Although the absolute difference in CCT was small, the clinical importance needs to be further evaluated given the importance of low CCT in glaucoma progression, which has been highlighted by the Ocular Hypertension Treatment Study30 and by the European Glaucoma Prevention Study.31 It was also observed that increased IOP among participants with corneal arcus was unassociated with higher prevalence of POAG among this group (Figure 2). In contrast, a significantly higher prevalence of OHT was noted among participants with corneal arcus. Because this was a cross-sectional study, the clinical implications of these findings are unknown. Although a 1–mm Hg difference in the mean IOP may not be critical enough to affect the prevalence of glaucoma or to determine visual field prognosis among patients with glaucoma,15,30 further studies should be conducted to examine the risk of progression to OHT and to glaucoma in eyes with corneal arcus.

Our study has several limitations. There may have been selection bias in our study with the exclusion of participants currently receiving ocular hypotensive agents or having a history of laser or surgical therapy for glaucoma. This may have eliminated some individuals with high baseline IOP, resulting in a lower mean IOP. However, without reliable data on the pretreatment baseline IOP of these subjects, the exclusion was considered necessary. Furthermore, as summarized in Table 1, the prevalence of corneal arcus and the ocular biometric measurements, including CCT, CCR, IOP, and axial length, among excluded subjects were not significantly different from those among participants included in the analysis, suggesting that exclusion of these subjects may not affect the relationships we observed in the study. Another limitation was the cross-sectional nature of the study, which makes causal inferences difficult relative to the associations among corneal arcus, higher IOP, and thinner CCT. An additional limitation of our study was that corneal arcus was described only as present or absent in a participant, without assessment of severity (eg, the number of quadrants affected). This prevented us from evaluating the association of corneal arcus severity with IOP and CCT. This is a potential area of future research.

In conclusion, the results from this population-based sample of Asian Malay adults in Singapore suggest that corneal arcus is associated with higher GAT-measured IOP and with lower CCT independent of age, sex, and systemic and ocular factors. Further studies are needed to confirm this, as well as the clinical importance of CCT and IOP differences between subjects with vs without corneal arcus.

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