Central Corneal Thickness in the Central Retinal Vein Occlusion Fellow Eyes†

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Objective: To investigate the central corneal thickness (CCT) in the central retinal vein occlusion fellow eye (CRVO-fellow eye) patients.

Material and Method: A cross-sectional study with 97 CRVO-fellow eye patients and 112 healthy subjects. Three measurements of CCT were obtained with ultrasonic pachymetry.

Results: Mean age of CRVO-fellow eye was higher than controls, 59.7 ± 10.3 vs. 46.4 ± 5.8 years, (p < 0.001). Males were more prevalent in CRVO-fellow eye than in the controls, 47.4% vs. 25%, (p = 0.001). In CRVO-fellow eye group, systemic diseases were more prevalent. Glaucoma and ocular hypertension were detected in 23 eyes (23.7%) of CRVO-fellow eye. Mean CCT of CRVO-fellow eye was thinner than controls, 529.2 ± 30.3 vs. 543.3 ± 31.8 μm, (p = 0.001). Multiple linear regression models adjusted for age, sex, diabetes, hypertension, cup-to-disc ratio, IOP, and axial length revealed that mean CCT of CRVO-fellow eye was 16.9 μm thinner than controls.

Conclusion: CRVO-fellow eye patients have thinner CCT than controls. The pathophysiology of this association is unclear. It may be related to less lamina cribosa rigidity in the thin corneal eye. Lamina cribosa displacement may compress central retinal vein, leading to CRVO.

Keywords: Central retinal vein occlusion, Central corneal thickness, Optic nerve head, Lamina cribosa, Ocular biomechanics, Corneal biomechanics, Glaucoma

Central corneal thickness (CCT) has been investigated in various entities of glaucoma, e.g., ocular hypertension(1-5), primary open-angle glaucoma(6-8), and primary angle-closure glaucoma(9). Thin cornea is an important risk factor of glaucoma conversion regarding Ocular Hypertension Treatment Study (OHTS)(10), and European Glaucoma Prevention Study (EGPS)(11). The true mechanism of thin CCT and glaucoma conversion is unclear. It is thought that thin cornea relates to underestimated intraocular pressure (IOP) measurement. However, multivariate analysis of the predictive factors reveals that CCT is an independent risk factor to IOP. Other reports emphasized CCT indicates a risk of glaucoma progression(12,13) and the advance stages of glaucoma(14). Because the cornea connects to sclera and lamina cribosa (LC) in the back of the eye, the corneoscleral shell of the cornea may be relevant to scleral and LC rigidity.

Central retinal vein occlusion (CRVO) is known to be associated with open-angle glaucoma. The Central Retina Vein Occlusion Study reports that 11% of 725 CRVO patients are under treatment for glaucoma(15). Hayreh et al reported that 26% of 674 CRVO/Hemi CRVO have glaucoma/ocular hypertension (OHT)(16). In that article, they noted that glaucoma and CRVO associations vary by 6-69%. On the other hand, glaucoma indicates a risk factor of CRVO(17). In a hospital-based prospective survey, Hirota et al reported a higher incidence of CRVO in 433 glaucoma patients than in those with other diseases, 4.2% vs.
In Beaver Dam Eye Study, incidence of CRVO increased 29% for each 0.1 increment in cup-to-disc ratio\(^{(19)}\). The mechanism of the association is unclear. The common mechanism may be related to LC compression. LC is displaced backward by increased IOP, and it will compress and collapse the retinal vein, and will lead to subsequent intimal proliferation; then CRVO occurs\(^{(20-22)}\).

To the best of the authors’ knowledge, CCT has never been investigated in CRVO. No instrument can be used for measurement of LC rigidity in the living eye. The authors’ thus hypothesize that CRVO has less LC rigidity, as indicated by an indirect evidence of thin cornea.

Material and Method

The incidence of CRVO is uncommon (1.6%)\(^{(23)}\). Rajavithi is a tertiary eye care center, where patients are referred for further management of CRVO, such as panretinal photocoagulation, intravitreal drug injection, and vitreoretinal surgery. CCT may be altered with such treatment. If the authors’ had only new cases of CRVO, who never had any treatment before enrollment, the authors’ would have very limited number for statistic analysis. CRVO-fellow eye could be a validate representation of CRVO, because inter-eye CCT difference is small.

In this preliminary study, the authors used CRVO-fellow eye as a study group. The present study was cross-sectional study between CRVO-fellow eye and control subjects. Institution Review Board approved the protocol of the present study. Informed consent was read and signed by the participants.

Study group definition and selection

CRVO was defined as retinopathy with a combination of generalized hemorrhages, soft exudates, the presence of microvascular abnormalities, and dilated and tortuous retinal venules\(^{(19)}\). CRVO patients were searched from the hospital database (ICD 10, version 2006; codes H34.8: Other retinal vascular occlusions, and H34.9: Retinal vascular occlusion, unspecified) within the last 5 years of the first registration. Su et al\(^{(24)}\) described that mean CCT declined 5 \(\mu\)m per decade. Therefore, during the patient selection period (5 years), CCT might have declined approximately 2.5 \(\mu\)m.

Chart review was made. Fundus photography and angiogram, if existing, were reviewed by a retina specialist (SV). New CRVO patients were also enrolled to study from an out-patient clinic. CRVO associated with ocular inflammatory disease was excluded. Bilateral CRVO, contact lens wearer, corneal disease, and acute angle-closure attack were also excluded. Uncomplicated pseudophakia, after 6 months of the operation, was eligible. If patients met the entry criteria, they were contacted by telephone or postcard and invited to participate.

Control selection

Healthy control subjects, 35 years and older, were invited from among hospital staff and their friends or relatives. Exclusion criteria included having corneal disease, being a contact lens wearer, having glaucoma, and having a history of intraocular surgery. Those with uncomplicated pseudophakia, after 6 months of the operation, were eligible. Refraction, obtained with autorefractor (KR 3000, Topcon, Japan), was between -5 diopters and + 5 diopters. Best-corrected visual acuity was > 20/40. Ocular examination was obtained with slit-lamp. IOP, obtained with Goldmann applanation, was < 21 mmHg. Gonioscopy was Shaffer’s classification grade 2 or greater. Three measurements of CCT were obtained with ultrasonic pachymetry (Corneo-Gage Plus, Sonogage Inc., Cleveland, OH), and mean CCT was calculated for analysis. Dilated ophthalmoscopy and optic nerve head (ONH) evaluation were performed, and photographs were taken (KOWA VX-10, Kowa Optimed, Inc., Japan). Optical coherence tomography, Stratus version 4.0.2 (Carl Zeiss Meditec, Dublin, CA), was performed for fast retinal nerve fiber thickness, fast optic disc and fast macular thickness. Axial length was obtained with ultrasonography (OcuScan, Alcon, Forth Worth, TX). Data set of the right eye was enrolled for analysis. The study group undertook similar examinations as the controls. If the IOP, ONH were abnormal, Humphrey visual field test (Carl Zeiss Meditec, Dublin, CA) would be performed.

Glaucoma was defined as an optic neuropathy with typical glaucomatous visual field defect, regardless of IOP elevation. Ocular hypertension was defined as IOP > 21 mmHg with normal ONH and Humphrey visual field test.

Data analysis

Data was analyzed with SPSS for Windows, version 11.5 (SPSS Inc., Chicago, IL). Student t-tests were used to test for continuous variables. Chi-square tests or Fisher’s exact test were used to test categorical data. Multiple regression analysis was used to identify the predictive factors of CCT. Linear regression
analyses adjusting for possible confounding factors were also performed. Statistical significance is reached, if $p < 0.05$.

**Results**

There were 97 CRVO-fellow eyes (study group). Sixteen cases (16.5%) were newly diagnosed of CRVO. There were 112 controls. All subjects were Asian. Mean age was higher in the study group than controls, $59.7 \pm 10.3$ (range 32-78) vs. $46.4 \pm 5.8$ years (range 35-62) ($p < 0.001$). Males were more prevalent in the study group than among the controls, 47.4% vs. 25% ($p = 0.001$). Self-reported systemic status are as follows: diabetes (32 cases, 33%), hypertension (57 cases, 58.8%), ischemic heart disease (4 cases, 4.1%), dyslipidemia (16 cases, 16.5%), smoking (9 cases, 9.3%), and aspirin taking (6 cases, 6.2%). Pseudophakia, diabetic retinopathy, and panretinal photocoagulation were found in four (4.1%), four (4.1%), and two cases (2.1%), respectively. Pseudoexfoliation syndrome (PEX) was detected in one eye (1.0%) of the study group (Table 1).

Mean spherical equivalence and axial length were not different between groups. Twenty-one patients (21.6%) were diagnosed as having glaucoma. Two patients (2.1%) were OHT, and one was a glaucoma suspect. Mean highest-recorded IOP was not significantly different, $15.8 \pm 4.91$ vs. $15.32 \pm 2.85$ mmHg ($p = 0.339$). However, mean IOP correction by Ehlers’ regression formula\(^{25}\), $5$ mmHg for $70$ μm CCT, was $16.97 \pm 5.12$ vs. $15.44 \pm 3.34$ mmHg ($p = 0.01$), respectively. Mean cup-to-disc ratio was $0.46 \pm 0.21$ vs. $0.37 \pm 0.15$ ($p < 0.001$). Mean number of glaucoma medications in the study group was $0.10 \pm 0.39$ (Table 2).

Mean CCT in the study group was thinner than controls, $529.2 \pm 30.3$ (range 465.7-618) vs. $543.3 \pm 31.8$ μm (range 464.7-623.7), ($p = 0.001$) (Table 3). It was not significantly different between male (n = 74) and female (n = 135), $534.4 \pm 34.3$ vs. $538.0 \pm 30.5$ μm ($p = 0.437$). It was weakly correlated to axial length ($r = 0.128$, $p = 0.045$). Central corneal thickness was decreased with age, $\beta$ coefficient was $-5.6$ μm ($p = 0.007$) per decade. Multiple linear regression models adjusted for age, sex, diabetes, hypertension, spherical equivalence, cup-to-disc ratio, IOP, and axial length revealed that CCT of the study group was 16.9 μm thinner than controls ($p = 0.016$), (Table 4).

With regard to the study group analysis, the mean CCT of subjects with and without diabetes, hypertension, and glaucoma, was not significantly different ($p > 0.05$), (Table 5).

**Discussion**

Corneal thickness in CRVO-fellow eye was 16.9 μm thinner than controls. CCT in the present control group was found to be similar to the meta-analysis study by Doughtry and Zaman, 543 vs. 544 μm\(^{26}\). CCT decline rate is varied from unchanged overtime\(^{26}\) to 5 μm per decade\(^{24}\). In the present study, CCT decreased 5.6 μm per decade. Mean CCT difference was still significant after the authors adjusted the age of the groups.

<table>
<thead>
<tr>
<th>Data</th>
<th>CRVO-fellow eye (n = 97) (%)</th>
<th>Control (n = 112) (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>$59.7 \pm 10.3$</td>
<td>$46.4 \pm 5.8$</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex: male</td>
<td>46 (47.4)</td>
<td>28 (25)</td>
<td>0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>32 (33)</td>
<td>0 (0)</td>
<td>&lt;0.001</td>
</tr>
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<td>Hypertension</td>
<td>57 (58.8)</td>
<td>6 (5.4)</td>
<td>&lt;0.001</td>
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<tr>
<td>Ischemic heart</td>
<td>4 (4.1)</td>
<td>0 (0)</td>
<td>0.030</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>16 (16.5)</td>
<td>2 (1.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking</td>
<td>9 (9.3)</td>
<td>0 (0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Aspirin taking</td>
<td>6 (6.2)</td>
<td>1 (0.9)</td>
<td>0.034</td>
</tr>
<tr>
<td>Family history of glaucoma</td>
<td>0 (0)</td>
<td>1 (0.9)</td>
<td>0.351</td>
</tr>
<tr>
<td>Pseudophakia</td>
<td>4 (4.1)</td>
<td>0 (0)</td>
<td>0.030</td>
</tr>
<tr>
<td>Diabetic retinopathy</td>
<td>4 (4.1)</td>
<td>0 (0)</td>
<td>0.030</td>
</tr>
<tr>
<td>Panretinal photocoagulation</td>
<td>2 (2.1)</td>
<td>0 (0)</td>
<td>0.127</td>
</tr>
<tr>
<td>Pseudoexfoliation syndrome</td>
<td>1 (1.0)</td>
<td>0 (0)</td>
<td>0.281</td>
</tr>
</tbody>
</table>

CRVO-fellow eye = central retinal vein occlusion-fellow eye
Mean CCT of diabetes patients was 531 μm, and it was thinner than controls. This finding conflicts with previous studies. Busted et al reported that diabetes patients have thicker CCT than non-diabetes patients\(^{(27)}\). In OHTS and EGPS, diabetes patients have thicker CCT than non-diabetes\(^{(2,3)}\). In the population-based study of Singapore Malay Eye Study, mean CCT of diabetes was thicker than the average of all participants, 547 vs. 541 μm\(^{(24)}\). The population was in the same region of south-east Asia as the present study. The CCT difference of diabetes from the present study to that study was 16 μm. Mean CCT of those having hypertension was also thinner than in the controls. The reason for the thinner cornea in the risk groups of CRVO is unknown.
Glaucoma was frequent in CRVO-fellow eyes (21%). Primary angle-closure glaucoma and primary open-angle glaucoma were almost equally present. The authors are aware that glaucoma is a possible confounding factor of thin CCT in CRVO-fellow eyes. The mean CCT of glaucoma patients was quite thin, 522 μm, but did not reach statistical significance. IOP in CRVO-fellow eyes appears to be underestimated, and mean IOP correction by CCT was significantly higher in CRVO-fellow eyes than in the controls. This higher IOP correction relates to larger cup-to-disc ratio, and possibly increases the risk of CRVO(19). However, no standard formula is thus far accepted for IOP correction. PEX is associated with CRVO in previous reports(28,29), but it was not common in the fellow eyes of the present study (1%).

According to previous reports, inter-eye CCT difference is small(2,8). Thin cornea in CRVO-fellow eyes appears to be an independent factor of CRVO. The mechanism of CCT in association with CRVO is discussed below.

LC is a part of the corneoscleral shell, and LC rigidity is possibly relevant to the biomechanical properties of the thin cornea. Posterior bowing of LC (or optic disc cupping) inversely correlates to LC rigidity, as an equation of displacement; \( D = \frac{P}{4\pi k} \), when \( D = \) LC displacement, \( P = \) IOP, \( A = \) disc area, and \( k = \) LC rigidity(30). LC displacement, presenting as mean cup depth obtained with Heidelberg retina tomograph, was studied with regard to the corneal thickness by Lesk et al(31). After 35% IOP reduction for glaucoma and OHT, the thinner cornea group (mean CCT, 518 μm) demonstrated the greater anterior mobility of LC than the thicker one (mean CCT, 587 μm). This finding indicates that the corneal structure relates to the biomechanics of the ONH: the thinner the CCT, the less LC rigidity. Thin cornea relates to low corneal hysteresis (CH), and low CH relates to glaucoma damage(32,33). In addition, the corrected IOP in the CRVO-fellow eyes appears to be higher than the controls, in the present study. In such a thin corneal eye, LC is more susceptible to changes because of that higher IOP(34,35). Subsequently, the retinal vein will be compressed, leading to CRVO development(20,22). However, CH device is not available in Rajavithi Hospital.

Axial length was not different between groups in the present study. The role of axial length in CRVO is not clear. Shorter axial length may indicate crowded posterior segment and may be a predisposing factor of CRVO. There are reports which show a shorter axial length in CRVO than in normal subjects(36-38), but other reports do not confirm this finding(39). Longer axial length is not associated with thinner cornea(40). In the present study, axial length was weakly correlated to mean CCT.

Limitations of the present study include the fact that the study group was CRVO-fellow eye, not CRVO. Inter-eye CCT difference in this asymmetrical disease may be more or less than previous reports indicate. The finding reveals only an extra-luminous cause of CRVO. Intra-luminous obstruction, such as coagulation, was not investigated in the present study. Mean age difference of 15 years may be a confounding factor. Age-matched subjects should be conducted to elucidate this finding. Males were more frequent in the study group than in control. The number of diabetes, hypertension, and glaucoma patients is possibly biased for mean CCT analysis. However, the presented sample size was the strength of the present study. Multiple regression analysis should reduce the effect of the confounders. A cohort study of the risk patient is needed to verify whether thin CCT is, or is not, a risk factor of CRVO.

In conclusion, CRVO is a multi-factor disorder. Thin cornea is a variable, which has never been previously reported in CRVO. The association of the thin cornea and pathophysiology of CRVO is unclear, but may be related to less LC rigidity and LC displacement from IOP. This preliminary study demonstrates that in patients who have underlying diseases, such as diabetes and hypertension, thin cornea could be an additional risk of pathogenesis of CRVO.

References

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ความหนาของกระจกตาในตาอีกข้างหนึ่งของผู้ที่เป็นโรคหลอดเลือดดำในจอประสาทตาอุดตัน

บุญส่ง ววิชณุสรร, วิภาวดี ลงพูลสุข, สุเมธ วาณิชวรานนท์, กิติพงษ์ หาญเจริญ

วัตถุประสงค์: เพื่อศึกษาความหนาของกระจกตาเปรียบเทียบระหว่าง ตาอีกข้างหนึ่งของผู้ที่เป็นโรคหลอดเลือดดำในจอประสาทตาอุดตันกับคนปกติ

วัสดุและวิธีการ: เป็นการศึกษาแบบภาคตัดขวาง ใช้การวัดความหนาของกระจกตาแบบเสียงคลื่นความถี่สูง 3 ครั้งแล้วหาค่าเฉลี่ยโดยมีผู้ที่เป็นโรค 97 ราย และคนปกติ 112 ราย

ผลการศึกษา: ความหนาของกลุ่มที่เป็นโรคสูงกว่ากลุ่มปกติ 59.7 ± 10.3 และ 46.4 ± 5.8 ปี (p < 0.001) กลุ่มที่เป็นโรคเป็นผู้ชายมากกว่า มีโรคประจำตัวมากกว่า และมีผู้ที่เป็นต้อหินมากกว่ากลุ่มปกติ ค่าเฉลี่ยความหนาของกระจกตาผู้ที่เป็นโรคอยู่ที่ 529.2 ± 30.3 ไมครอน ที่เปรียบกับกลุ่มปกติอยู่ที่ 543.3 ± 31.8 ไมครอน (p = .001) เมื่อทำการวิเคราะห์แบบถดถอยพบว่า กระจกตาบางกว่า 16.9 ไมครอน

สรุป: กระจกตาในตาอีกข้างหนึ่งของผู้ที่เป็นโรคหลอดเลือดดำในจอประสาทตาอุดตัน บางกว่ากลุ่มปกติ ความสัมพันธ์ของการเกิดโรค จากการศึกษาที่ก่อนหน้านี้ อาจเกิดจากการที่กระจกตาบางนั้น พร้อมกับความบางของขั้วประสาทตาที่รอง จึงเป็นปัจจัยเสี่ยงในการเกิดโรคหลอดเลือดดำในจอประสาทตาอุดตัน