Impact of Myopia on Corneal Biomechanics in Glaucoma and Nonglaucoma Patients

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PURPOSE. We evaluated the impact of myopia on corneal biomechanical properties in primary open-angle glaucoma (POAG) and nonglaucoma patients, and the effect of modification of glaucoma on myopic eyes.

METHODS. This cross-sectional study included 66 POAG eyes (33 myopia, 33 nonmyopia) and 66 normal eyes (33 myopia, 33 nonmyopia). Seven corneal biomechanical parameters were measured by ultra-high-speed Scheimpflug imaging, including corneal deformation amplitude (CDA), inward/outward corneal applanation length (ICA, OCA), inward/outward corneal velocity (ICV, OCV), radius, and peak distance (PD).

RESULTS. Mean age (SD) of the 65 male (49%) and 67 female (51%) patients was 59 (9.82) years. Myopia was associated with significantly higher CDA (adjusted effect = 0.104, P = 0.001) and lower OCV (adjusted effect = −0.105, P < 0.001) in the POAG group. Within the nonglaucoma group, myopic eyes had a significantly lower OCV (adjusted effect = −0.086, P < 0.001) and higher CDA (adjusted effect = 0.079, P = 0.001). All parameters except PD suggested that glaucoma modified the effect of myopia on corneal biomechanics. Percentage differences in the adjusted myopic effect between POAG and nonglaucoma patients was 31.65, 27.27, 31.65, 50.00, 22.09, and 60.49 for CDA, ICA, OCA, ICV, OCV, and radius, respectively.

CONCLUSIONS. Myopia had a significant impact on corneal biomechanical properties in the POAG and nonglaucoma groups. The differences in corneal biomechanical parameters suggest that myopia is correlated with significantly lower ocular rigidity. POAG may enhance the effects of myopia on most of these parameters.

Keywords: corneal biomechanics, myopia, glaucoma

Glaucoma is one of the leading causes of irreversible blindness worldwide, and primary open-angle glaucoma (POAG) is the most common type of glaucoma.1–2 Many studies have found that myopia has been associated with POAG.1,3 This association is notably higher in moderate to high myopia with axial length more than 26 mm.1,2 However, the pathogenesis for why myopia increases the susceptibility for and progression of glaucoma remains controversial.1–3 Numerous theories focus on the deformation of the lamina cribrosa. Jonas et al.4–6 found that stretching of the globe in the long-axial-length myopic eye made the optic nerve head enlarged, and the lamina cribrosa stretched and thinned. All of these factors may contribute to the increase in nerve fiber susceptibility to higher IOP.5,7

In myopia, the globe usually is elongated and scleral thickness and scleral rigidity are reduced. The viscoelastic properties of the cornea also are altered. Since the cornea, sclera, peripapillary ring, and lamina cribrosa are formed primarily by the same extracellular matrix constituents, corneal biomechanical properties can represent the elasticity of collagen fibers in the eyeball as a whole.8,9

Corneal biomechanical properties can be measured by many techniques. The Ocular Response Analyzer (ORA) was the first instrument launched and is extensively used to measure corneal biomechanical properties in terms of corneal hysteresis (CH) and corneal resistance factor (CRF).10–14 The ultra-high speed Scheimpflug camera (Corvis ST) is a new device with precise, repeatable, and reproducible measurements of corneal biomechanical properties. The device provides quantitative information, including the magnitude and direction of the displacement of the corneal apex. Published data have shown that the device has excellent reproducibility.15,16

Most of the available studies on corneal biomechanics have been conducted using the ORA.10,11 High myopes were reported to have significantly lower CH.10,12 However, the data obtained from the ORA denote only the rate-dependent viscoelastic properties of the cornea, which only represent a portion of the currently available measures of corneal biomechanical properties. The Corvis ST provides the advantage of dynamic cross-sectional imaging during the deformation, which may give additional information about the biomechanical status of the cornea. Currently, only a few studies have been done.
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using the Corvis ST to evaluate the corneal biomechanical properties.15,16

Since myopia is one of the significant risk factors for glaucoma and could alter the biomechanical properties of the eye, the understanding of these properties in relation to myopia and glaucoma can be useful in detection and understanding of the pathophysiology. We evaluated the impact of myopia on corneal biomechanical properties in POAG and nonglaucoma patients and the effect modification of glaucoma on these myopic effects.

METHODS

This study followed the tenets of the Declaration of Helsinki and was approved by the institutional review ethics committee of the Faculty of Medicine, Chulalongkorn University. This cross-sectional study was conducted at the general ophthalmology clinic and the glaucoma clinic, King Chulalongkorn Memorial Hospital, Bangkok, Thailand, between September 2015 and July 2016. Written informed consent was obtained from each subject.

Participants

Subjects were classified into 4 groups (myopia with POAG, nonmyopia with POAG, myopia without glaucoma, nonmyopia without glaucoma). Inclusion criteria were age over 40 years and willingness to participate in the study. Exclusion criteria were any of the following: (1) presence of corneal and other ocular pathology (except for nonvisually significant cataract and normal age-related posterior vitreous detachment), (2) history of corneal surgery, (3) pregnancy, (4) history of cataract surgery, (5) presence or history of underlying connective tissue disease, (6) inability to communicate and give consent, or (7) inability to perform the test, which required maintaining posture in the upright position for a few minutes.

POAG was defined as patients those who had gonioscopically open anterior chamber angles and met the glaucoma criteria based on the International Society of Geographical and Epidemiological Ophthalmology (ISGEO) guidelines.17 Category 1, a visual field (VF) defect that is consistent with glaucomatous optic neuropathy, and either a vertical cup-to-disc ratio (C/D) $\geq 0.7$ (97.5th percentile) or C/D asymmetry between both eyes $\geq 0.2$ (97.5th percentile); Category 2, VF results are not definitive or are unattainable due to patient inability to perform an adequate quality test, and optic disc has a C/D $\geq 0.9$ (99.5th percentile) or C/D asymmetry between both eyes $\geq 0.3$ (99.5th percentile); or Category 3, VF testing and optic disc examination are not possible in the subject, and visual acuity (VA) is less than 20/400 (for any ophthalmic pathology) and IOP $> 21$ mm Hg (99.5th percentile).

In conjunction with ISGEO criteria, subjects in whom C/D assessment was difficult and all subjects belonging to categories 2 (4 in the nonmyopia group) and 3 (1 in the myopia and 2 in the nonmyopia groups) were further evaluated with optical coherence tomography (OCT) of the retinal nerve fiber layer, optic nerve head, and ganglion cell layer, and optic disc photography. Clinical assessment and interpretation of all data of the Corvis ST for the central corneal thickness (CCT). The Corvis ST can measure optical pachymetry and IOP. We used pachymetry parameters used in this study were: (1) corneal deformation amplitude (CDA): the distance of the maximum corneal deformation amplitude measured from its resting state to highest concavity at the corneal apex; (2) inward corneal applanation (ICA) length: the length of the flattened cornea at the first applanation moment; (3) outward corneal applanation (OCA) length: length of the flattened cornea at the second applanation moment; (4) inward corneal velocity (ICV): corneal velocity during the second applanation moment; (5) outward corneal velocity (OCV): corneal velocity during the second applanation moment; (6) peak distance (PD): distance between two bending points of the cornea at the highest concavity; and (7) radius: the radius of the circle that best fits the corneal curve at the highest concavity. A diagram illustrating these parameters is shown in the Figure. The Corvis ST also can measure optical pachymetry and IOP. We used pachymetry data of the Corvis ST for the central corneal thickness (CCT).

All images were taken by a single operator (RP). After each scan, the video output was checked for any artifacts and the corneal boundary lines were reviewed for their accuracy. The scan was repeated if the quality score (QS) bar did not show “OK” the video revealed the presence of artifact, or boundary lines were in wrong positions. If a qualified image could not be obtained by the third attempted scan, the subject was not included in the study.

Interobserver reproducibility of studied parameters was calculated from 10 eyes of 10 normal subjects with 2 sets of
scans. Each scan was performed separately by 2 operators—an investigator (RP) and a trained technician—with 5-minute intervals between each scan. The sequence of operators was randomized.

**Statistical Analysis**

Sample size was calculated based on 2-tailed testing, an effect size of $d = 0.05$, 80% power and $\alpha$ error probability of 0.05. This calculation suggested a total sample size of at least 31 participants per group. Data were analyzed as means and standard deviations for continuous variables and counts, and percentages for categorical variables. Inferential analysis was conducted using general linear modeling to obtain unadjusted (bivariate) and adjusted (multivariate) effects for each of the seven outcomes. Along with the study predictor (myopia) the effects of age, sex, VA, and CCT were assessed for the glaucoma and nonglaucoma groups to gauge whether they were either confounders or independent risk factors. Additional clinical parameters, including C/D ratio and mean deviation (MD) on the VF were considered for the glaucoma group only. Covariate selection in the adjusted models was based on statistical significance and/or a confounding effect, with covariates resulting in a more than a 20% change in the unadjusted myopia effect included in the multivariate model as confounders. Once the final models were determined, adjusted effects and model-based means of each group (estimated marginal means) were generated. Estimated marginal mean was the calculated mean that corrected for the baseline differences and adjusted for other potential confounding variables in the model. As we considered seven different outcomes, there was a potential multiplicity problem (inflation of type I error). Consequently, we used Bonferroni correction to control family-wise type 1 error ($G_{FW} = 0.05/7 = 0.007$). Finally, given the potential effect modification phenomenon of POAG and myopia, a stratified analysis was conducted. Impact of myopia on outcomes was analyzed separately in each group; then, percentage difference in adjusted myopic effect between POAG and nonglaucoma patients was calculated for evaluating

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**FIGURE.** Diagram illustrates each state of corneal deformation during Corvis ST measurement, and the parameters: Top: First flattened state or the first applanation point. Middle: Maximum deformation state or point of highest concavity. Bottom: Second flattened state or second applanation point.
RESULTS

We recruited 66 POAG eyes (33 myopia, 33 nonmyopia) and 66 normal eyes (33 myopia, 33 nonmyopia). Among the POAG subjects, 2 in the myopia group and 3 in the nonmyopia group had normal-tension glaucoma. Table 1 shows the demographics and clinical characteristics for all groups in the study population. The mean age (SD) of the 65 male (49%) and 67 female (51%) patients studied was 59 (9.8) years. Mean (SD) spherical equivalent was $-7.78 (3.37)$ D in the myopia and $-7.09 (3.22, 0.15–23)$ D in the nonmyopia groups. Mean (SD, range) IOP was $14.56 (3.22, 8–23)$ in POAG and $13.78 (2.88, 8–20)$ in the nonglaucoma groups.

Of the patients with POAG, the mean (SD) C/D ratio was 0.73 (0.10) in the myopia and 0.71 (0.29) in the nonmyopia groups ($P < 0.10$). Mean (SD) visual field mean deviation was $-7.57 (8.68)$ dB, respectively ($P < 0.05$).

The estimated marginal means along with the effect size are shown in Table 2. The clinical parameters that resulted in changing the unadjusted effect of myopia more than 20% were used for calculating the adjusted effect.

### Table 2. Estimated Marginal Means Along With Effect Size (and 95% CI) for Myopia and Nonmyopia Patients by Glaucoma Status

| CDA (EMM) | ICA (EMM) | OCA (EMM) | ICV (EMM) | OCV (EMM) | PD (EMM) | Radius (MM) |
|-----------|-----------|-----------|-----------|-----------|----------|-------------|
| **POAG**  |           |           |           |           |          |             |
| Myopia    | 1.14      | 1.76      | 1.60      | 0.14      | -0.46    | 3.14        | 6.51        |
| Nonmyopia | 1.05      | 1.73      | 1.79      | 0.13      | -0.35    | 2.53        | 6.04        |
| Unadjusted effect | 0.104* | 0.028 | -0.183* | 0.009 | -0.105† | 0.610* | -0.134 |
| Adjusted effect | 0.001 | 0.35 | 0.03 | 0.07 | <0.001 | 0.03 | 0.7 |
| **95% CI (adjusted effect)** | 0.04, 0.17 | -0.03, 0.09 | -0.35, -0.01 | -0.001, 0.02 | -0.15, -0.06 | 0.06, 1.17 | -0.84, 0.58 |

| Nonglaucoma |          |           |           |           |          |             |
| Myopia      | 1.15      | 1.75      | 1.63      | 0.14      | -0.45    | 3.15        | 6.53        |
| Nonmyopia   | 1.05      | 1.73      | 1.77      | 0.13      | -0.36    | 2.52        | 6.02        |
| Unadjusted effect | 0.041 | -0.0005 | -0.042 | -0.002 | -0.054 | 0.155 | -0.199 |
| Adjusted effect | 0.079* | 0.022 | -0.159 | 0.006 | -0.086† | 0.621* | -0.081 |
| **95% CI (adjusted effect)** | 0.03, 0.13 | -0.04, 0.08 | -0.30, 0.03 | -0.004, 0.02 | -0.13, -0.05 | 0.04, 1.20 | -0.79, 0.62 |

Percentage difference in adjusted myopic effect between POAG and nonglaucoma patients

31.65% 27.27% 31.65% 50.00% 22.09% 1.77% 60.49%

*Statistically significant values with Bonferroni correction ($P < 0.007$) are indicated in bold.

† $P < 0.05$.

P values for the cornea biomechanical parameters are not provided in Table 1 as a more formal and appropriate analysis of these outcomes are provided in Table 2. SE, spherical equivalence.

* Indicates $P$ values that are from Pearson $\chi^2$. Other $P$ values are from independent $t$-test.
In the POAG group, CDA did not need to be adjusted (there was no confounder change in myopia effect >20% in our confounder adjusting model). No adjustments were needed for ICV, OCV, and PD. However, ICA needed adjustment for age, VA, C/D, CCT; and MD; OCA required adjustment for MD; and Radius required adjustment for age, IOP, and CCT.

In the nonglaucoma group, CDA required adjustments for VA and IOP; ICA required adjustments for sex, age, VA, IOP, and CCT; OCA required adjustments for IOP; ICV required adjustment for age, VA, and IOP; OCV required adjustment for VA and IOP; PD required adjustments for VA and IOP; and Radius required adjustment for VA and IOP to achieve an appropriate comparison between myopia and nonmyopia.

For POAG patients, there were significantly higher values for CDA (adjusted effect = 0.104, \( P = 0.001 \)) and significantly lower values for OCV (adjusted effect = -0.105, \( P < 0.001 \)) associated with myopia. For the nonglaucoma group, myopia also had significantly higher CDA (adjusted effect = 0.079, \( P = 0.001 \)) and significantly lower OCV (adjusted effect = -0.086, \( P < 0.001 \)). It should be noted that the minus symbol of OCV indicates the outward direction of the velocity; thus, the greater magnitude of the absolute value in eyes with myopia is associated with a greater amount of velocity for the OCV.

Further analysis was performed to gauge whether POAG was an effect modifier of myopia. POAG substantially modified the effect of myopia on all corneal biomechanical parameters with the exception of PD. Among POAG patients, the impact of myopia was 31.65%, 27.27%, 31.65%, 50.00%, 22.09%, and 60.49% higher on CDA, ICA, OCA, ICV, OCV, and radius, respectively.

General linear models were created to evaluate the effects of sex, age, VA, IOP, CCT, and severity of glaucoma on each parameter in the POAG and nonglaucoma groups. The data are shown in Supplementary Tables 1 and 2.

For interobserver analysis, the ICCs (95% confidence interval [CI]) of CDA, ICA, OCA, ICV, OCV, and radius were 0.82 (0.80–0.85), 0.77 (0.73–0.80), 0.71 (0.68–0.74), 0.75 (0.72–0.79), 0.91 (0.86–0.95), 0.77 (0.70–0.84), and 0.87 (0.84–0.90), respectively.

**Discussion**

We evaluated corneal biomechanical properties between myopia and nonmyopia in POAG patients and controls using Corvis ST imaging. The results showed that myopia was associated with significantly increased CDA and decreased OCV among POAG subjects. Increased CDA and decreased OCV were correlated with myopia in the nonglaucoma group. Furthermore, our data suggested that POAG modifies the effect of myopia in all parameters except PD. There was a moderate to excellent reproducibility of the Corvis ST parameters.

Results from population-based studies have indicated a strong link between myopia and POAG. In the Blue Mountains Eye Study, compared to emmetropic eyes, high and low myopia had odds ratios of 3.3 and 2.3, respectively, in developing POAG. Likewise, the Beaver Dam Eye Study showed that the risk of glaucoma was increased by 60% in patients compared with those without myopia. The data suggested that myopia was an independent risk factor for POAG. In the Singapore Malay Eye Study, the investigators found an association between longer axial length and POAG. This finding led to the presumption that axial myopia might be the main biomechanistic constituent that underlies the risk for POAG.

Several theories have been proposed to explain the link between myopia and glaucoma. Most have focused on the scleral change in myopia. Myopic eyes are associated with longer axial length, which is associated with changes in the sclera and contiguous lamina cribrosa. Fong et al. proposed that the elongated myopic eye causes deformability of the lamina cribrosa. The stretching and thinning of this nerve-supporting structure may increase the susceptibility to IOP.

There is increasing evidence of changes in the biomechanical properties of myopic eyes. Studies in animal models have demonstrated a significant reduction in scleral collagen fibrils and decrease in the rate of proteoglycan synthesis in the sclera of myopic eyes. This change could lead to weakening of scleral mechanical properties. Similar changes appear to occur in the cornea with the development of myopia. According to Kotecha et al., myopic eyes are associated with increased CDA and decreased OCV among POAG subjects. Increased CDA and decreased OCV were correlated with myopia in the nonglaucoma group. Furthermore, our data suggested that POAG modifies the effect of myopia in all parameters except PD. There was a moderate to excellent reproducibility of the Corvis ST parameters.

Myopic eyes had significantly higher CDA than emmetropic eyes in POAG and nonglaucoma subjects. CDA represents the maximum deformation amplitude, which is measured at the corneal apex from the start to the highest concavity. It denotes the flexibility of the eye in response to a certain amount of pressure. Our study showed that myopic eyes could deform farther and deeper than emmetropic eyes. Low ocular rigidity in myopia may be responsible for this finding. Several studies have investigated the association of myopia and corneal rigidity as representative of overall global rigidity. They used the ORA to measure the biomechanics of the cornea and found that myopia had significantly lower corneal hysteresis, indicating possibly softer and more flexible eyes. With the Corvis ST technology, we had the opportunity to study the rigidity of the eye with more quantitative parameters, including the magnitude of the displacement. Our findings affirmed the relative “flaccidity” of the eye in myopia.

OCV or the velocity at the second appplanation represents how fast the deformed cornea goes back to its neutral position. We found significantly faster OCV in myopic eyes in POAG and nonglaucoma subjects. Myopic eyes tend to recoil backward more rapidly. We speculated that the emmetropic eye has the rigidity to dampen the force applied to the eye, while the myopic eye has a poorer ability to dampen this force.

We found that CDA and OCV differ between myopia and nonmyopia. The characteristics of these differences are similar to what has been described as the differences between glaucoma and nonglaucomatous eyes in previous studies. Lee et al. compared Corvis ST parameters between POAG and normal subjects. The study recruited only myopic eyes (refractive error less than -3.0 D), and found significantly higher CDA and faster OCV in glaucomatous eyes compared to normal eyes. There was no significant difference in ICA, ICV, and radius. These outcomes are similar to what we found in myopic eyes compared to emmetropic eyes, suggesting common ocular biomechanical changes in glaucoma and myopia.

The percentage difference in adjusted myopic effect between POAG and nonglaucoma patients shows the impact of POAG in modifying the myopia effect on each parameter. This percentage difference should be interpreted based on clinical judgement. From our results, the relative change in CDA, ICA, OCA, ICV, OCV, and Radius suggested that POAG had a major impact in modifying the effect of myopia. However, given that myopia did not show a statistically significant effect for ICA, ICV, and Radius in the POAG and nonglaucoma groups, the effect of glaucoma on these parameters was likely to be independent of the myopic condition. Interestingly, the myopic effect on PD was not modified by glaucoma (adjusted effect was 0.61 and was 0.62...
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