Relationship between corneal deformation amplitude and optic nerve head structure in primary open-angle glaucoma

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Abstract
The purpose of the study was to investigate the relationship between corneal deformation amplitude (DA), which is the amount of corneal displacement at highest degree of concavity measured by Corvis Scheimpflug Technology (ST), and various optic nerve head parameters in patients with primary open-angle glaucoma (POAG).

Fifty-eight POAG patients were included in this observational study. For each patient, DA with Corvis ST, color optic disc photography, and optic nerve head imaging by enhanced depth imaging with a Heidelberg spectralis optical coherence tomography (OCT), Cirrus OCT, and Heidelberg retina tomograph (HRT) were obtained. Pearson correlation was used to analyze the relationship between DA and optic nerve head parameters before and after adjusting for age, intraocular pressure, central corneal thickness, and axial length.

Corneal DA was negatively associated with lamina cribrosa (LC) depth ($r = -0.390, P = .003$) after adjusting for confounders. It showed positive relationship with parapapillary atrophy (PPA) area ($r = 0.321, P = .046$). In addition, the corneal DA was negatively correlated with cup volume ($r = -0.351, P = .017$) and mean cup depth ($r = -0.409, P = .005$) measured by HRT.

Corneal DA is related with optic nerve head parameters in patients with POAG. Patients with lower corneal DA showed greater LC depth, greater cup area, deeper cup, and smaller PPA than those with higher corneal DA.

Abbreviations: CDR = cup-to-disc ratio, DA = deformation amplitude, EDI = enhanced depth imaging, HC = highest concavity, HRT = Heidelberg retina tomograph, IOP = intraocular pressure, LC = lamina cribrosa, OCT = optical coherence tomography, POAG = primary open-angle glaucoma, PPA = parapapillary atrophy, RNFL = retinal nerve fiber layer, SD OCT = spectral-domain optical coherence tomography.

Keywords: corneal biomechanical property, deformation amplitude, glaucoma, optic nerve head

1. Introduction
Studying the morphometric changes of the optic nerve head is important to understanding the pathophysiology of glaucomatous damage. The advent of imaging devices such as spectral-domain optical coherence tomography (SD OCT) has enabled the clinical assessment of the optic nerve head structures, including the lamina cribrosa (LC). Previous studies have demonstrated posterior displacement of the optic nerve head and thinner LC in glaucoma.\textsuperscript{[1–3]} These structural changes are determined by various factors including the biomechanical environment surrounding the lamina. Different biomechanical environments may affect how optic nerve configuration is altered in glaucoma, but the biomechanical properties of the optic nerve head cannot be measured clinically in vivo.\textsuperscript{[4–6]} The biomechanical properties of the cornea, however, can be examined in vivo using various devices including Corvis ST (Oculus Optikgeräte GmbH, Germany) and the ocular response analyzer (ORA; Reichert Corp., New York).\textsuperscript{[7–9]} Corvis ST measures various biomechanical properties of the cornea including the corneal deformation amplitude which is the amount of corneal displacement at highest degree of concavity (HC). We have previously described the relationship between the corneal deformation amplitude using the Corvis ST and the posterior pole profiles in primary open-angle glaucoma and suggested that it may reflect the biomechanical property of the posterior pole.\textsuperscript{[10]} Bartolomé et al\textsuperscript{[11]} examined the relationship between corneal biomechanics measured by ORA and the optic disc and reported that corneal resistance showed significant correlation with LC thickness. To our knowledge, relationship between corneal deformation amplitude measured by Corvis ST and optic nerve head parameters has not been reported.

The aim of the present study was to investigate the relationship between corneal biomechanical property measured by corneal deformation amplitude and the optic nerve head parameters measured by SD OCT and Heidelberg retina tomograph (HRT) in patients with primary open-angle glaucoma.
2. Methods

This study enrolled patients with primary open-angle glaucoma who visited the Seoul St. Mary’s Hospital, College of Medicine, the Catholic University of Korea in March 2017. The medical charts were reviewed retrospectively including best-corrected visual acuity, intraocular pressure (IOP) measured by Goldmann applanation tonometry, refraction (RK-5; Canon, Tokyo, Japan), gonioscopy, corneal deformation amplitude measured by Corvis ST, (software ver. 1.2r1092; Oculus Optikgeräte GmbH), optic nerve head evaluation after dilation, color and red-free optic disc photography (Nonmyd 7; Kowa Optimed, Tokyo, Japan), axial length using ocular biometry (IOL Master, Carl Zeiss Meditec, Inc, Dublin, CA), central corneal thickness using ultrasound pachymeter (Tomey Corporation, Nagoya, Japan), achronistic standard automated perimetry 24-2 using the Swedish Interactive Threshold Algorithm (Humphrey Visual Field Analyzer, Carl Zeiss Meditec, Inc), enhanced depth imaging (EDI) with a Heidelberg Spectralis OCT (Spectralis; Heidelberg Engineering, Heidelberg, Germany) imaging, OCT imaging (Cirrus OCT; Carl Zeiss Meditec, Inc), and confocal scanning laser ophthalmoscopy with the HRT (Heidelberg Engineering).

The study followed all the guidelines required and was approved by the Institutional Review Board of the Seoul St. Mary’s Hospital, College of Medicine, The Catholic University of Korea, which waived the written informed consent due to its retrospective design. It was also carried out in accordance with the Declaration of Helsinki.

To be included in the study, the following criteria were required: a best-corrected visual acuity of at least 20/40 and at least 3 standard automated perimetry with at least 2 years of follow-up. Patients with a history of any previous or current corneal disease, history of contact lens wearing during 6 months prior, a history of intraocular surgery other than simple cataract surgery or refractive laser surgery were excluded.

To be included in the study, primary open-angle glaucoma was defined as open-angle on gonioscopy, glaucomatous optic neuropathy, and corresponding glaucomatous visual field defect confirmed by more than 2 reliable standard automated perimetry. A glaucomatous optic neuropathy was defined as the presence of notching, diffuse, or focal neuroretinal rim thinning, and/or retinal nerve fiber layer (RNFL) defect. Glaucomatous visual field defect was defined as the following:

1. outside normal limits on glaucoma hemifield test;
2. 3 or more nonedge points with a probability of <5% and with one of these points having a probability of <1% on a pattern deviation plot; or
3. a pattern standard deviation of <5%.

A reliable visual field examination required less than 20% of fixation loss and less than 15% false-positive or-negative errors.

2.1. Corvis ST measurements

The corneal deformation amplitude was measured using Corvis ST (software ver. 1.2r1092; Oculus Optikgeräte GmbH). First, the patient’s chin and forehead were rested in front of the device. When the cornea was centered and forehead were rested in front of the device. The device; average RNFL thickness, disc area, rim area, average cup-to-disc ratio (CDR), vertical CDR, and cup volume.

2.2. Evaluation of optic nerve head structure

2.2.1. EDI OCT. The EDI OCT image was captured using the Heidelberg Spectralis OCT which has been described in detail. Briefly, the EDI OCT B-scans were obtained in 15° x 10° rectangle B-scans around the optic nerve head (Fig. 1). A total of 512 A-scans were obtained spanning 6-mm horizontally at approximately 30-μm intervals. The device uses a real-time averaging algorithm, which allows the retinal infrared fundus image to be “frozen.” Then, the OCT optimizes the scan centering, adjusts the number of frames to be averaged, and enhances the quality of image for each scan by moving within the stabilized optic disc image. In the EDI OCT mode, for each cross-sectional B-scan, an average of 35 frames was produced with speckle noise reduction. Only images with quality score greater than 15, clear optic disc imaging, and continuous scan pattern with no missing or blank areas were included.

Only scans including the LC region were included in the study. For each frame, after drawing a reference line connecting the Bruch’s membrane opening, the LC depth and LC thickness were measured perpendicular from the reference line at the center and 100 μm both nasally and temporally. LC depth was measured from the reference line to the anterior border of the LC, which is the highly reflective region, and LC thickness was measured from the anterior border to the posterior border of the LC (Fig. 2A) The average of 3 measurements from all frames was defined as the average LC depth and LC thickness for each patient.

A focal LC defect was defined as a discontinued anterior lamina surface contour that expands more than 100 μm in diameter and 30 μm in depth. The defect must be present in at least 2 neighboring frames to avoid false positives (Fig. 1B).

The beta zone parapapillary atrophy (PPA) area was measured using color optic disc photographs in a previously described method. After manually tracing the disc and PPA margin defined as the inner crescent of chorioretinal atrophy with visible sclera and choroidal vessels using ImageJ (ver. 1.48; http://imagej.nih.gov/ij/download.html, National Institutes of Health, Bethesda, MD), the area was calculated automatically in pixels within the program.

2.2.2. Optical coherence tomography. The optic nerve head was imaged with the Cirrus OCT after pharmacological dilation of the pupil. Cirrus OCT generates an optic disc cube from 200 cross-sectional B-scans, each from 200 1-dimensional A-scans. Images with a signal strength ≥2, misalignment of the surface detection algorithm on <15% of cumulative A-scans or <20% of cumulative A-scans, and no decentration of the measurement circle location were included in the analysis. The following optic nerve head parameters were analyzed automatically within the device; average RNFL thickness, disc area, rim area, average cup-to-disc ratio (CDR), vertical CDR, and cup volume.

2.2.3. Confocal scanning laser ophthalmoscopy. Confocal scanning laser ophthalmoscopy imaging was performed using an HRT III. The interscan standard deviation was required to be <30 μm. Scans that were well-centered and focused with an overall quality score of acceptable or better as defined by HRT III.
were included in the analysis. The following parameters were included in the analysis; disc area, rim area, cup area, cup-to-disc area ratio, cup volume, rim volume, mean cup depth, maximum cup depth, cup shape measure, mean RNFL thickness, and rim steepness.

2.3. Statistical analysis

Pearson correlation was performed to evaluate the relationship between the corneal deformation amplitude and optic nerve head parameters. Partial Pearson correlation coefficients were calculated and adjusted for age, IOP, central corneal thickness, and axial length. For all statistical analyses, the Statistical Package for the Social Sciences for Windows (v. 17.0; SPSS Inc., Chicago, IL) was used, and \( p < .05 \) was considered statistically significant.

3. Results

This study included 58 eyes from 58 patients with primary open-angle glaucoma. The age was \( 55.89 \pm 14.73 \) years and visual field mean deviation was \(-7.85 \pm 8.64\) dB (Table 1). The corneal deformation amplitude was \( 1.08 \pm 0.12 \) mm. Table 2 shows the optic nerve head parameters as measured by Heidelberg EDI OCT, Cirrus OCT, and HRT.

Table 3 shows the relationship between the corneal deformation amplitude and various optic nerve head parameters. The corneal deformation amplitude was positively correlated with PPA area \( (r=0.385, P=.014) \) and negatively correlated with LC depth \( (r=-0.369, P=.005) \), whereas it was not significantly related with LC thickness \( (r=-0.223, P=.095) \). There was no difference in corneal deformation amplitude between patients with focal lamina defects \( (1.09 \pm 0.08 \text{ mm}) \) and those without \( (1.07 \pm 0.15 \text{ mm}, P=.447) \). In addition, the corneal deformation amplitude was negatively correlated with cup area \( (r=-0.395, P=.003), \) cup volume \( (r=-0.324, P=.019), \) mean cup depth \( (r=-0.443, P=.001), \) and maximum cup depth \( (r=-0.456, P<.001) \) measured by HRT (Table 3). It was negatively correlated with cup volume \( (r=-0.263, P=.052) \) measured by Cirrus OCT which fell just short of statistical significance. After adjusting for age, IOP, central corneal thickness, and axial length, the corneal deformation amplitude positively correlated with PPA area \( (r=0.321, P=.046), \) and negatively with LC depth \( (r=-0.390, P=.003), \) cup volume \( (r=-0.351, P=.017), \) and mean cup depth \( (r=-0.409, P=.005) \).

Figure 2 shows representative cases of 2 patients with low (A) versus high (B) deformation amplitude. In Figure 2A, a 56-year-old female with deformation amplitude of 1.02 mm shows greater LC depth, greater cup volume, cup area, mean cup depth, and cup shape measure than a 53-year-old male with deformation amplitude of 1.21 mm with similar degree of visual field mean deviation as shown in Figure 2B.

4. Discussion

The relationship between corneal biomechanical viscoelastic property and optic nerve head structure has been studied
previously by other researchers. Although performed with a different device on a different group of subjects, Bartolome et al. reported that corneal resistance factor measured by ORA was related with LC thickness in normal subjects. Vu et al. also investigated the relationship between biomechanical parameters and structural markers in glaucoma and reported that corneal hysteresis measured by ORA was related with visual field mean deviation but not with structural markers as measured by OCT. However, Corvis ST and ORA parameters measure different biomechanical properties which show only weak to moderate relationships, and Tejwani et al. reported that Corvis ST may be more useful in assessing true biomechanical properties than ORA. To the best of our knowledge, relationship between deformation amplitude measured by Corvis ST and optic nerve head parameters has not been reported.

Table 1
Baseline characteristics.

| Baseline characteristic | Mean ± standard deviation (n = 58) |
|-------------------------|----------------------------------|
| Age, yr                 | 55.89 ± 14.73                    |
| Gender (male/female)    | 24/34                            |
| Intraocular pressure, mm Hg | 14.52 ± 2.81                  |
| Spherical equivalent, Diopter | −1.66 ± 3.34                |
| Axial length, mm        | 24.62 ± 1.37                     |
| Central corneal thickness, μm | 529.00 ± 27.32            |
| Visual field mean deviation, dB | −7.85 ± 8.64            |
| Deformation amplitude, mm | 1.08 ± 0.12                     |

Table 2
Optic nerve head parameters.

| Optic nerve head parameters | Mean ± standard deviation |
|-----------------------------|---------------------------|
| Parapapillary atrophy area (pixels) | 13215.53 ± 20099.17 |
| Heidelberg EDI OCT          |                           |
| LC depth, μm                | 447.52 ± 111.38           |
| LC thickness, μm            | 253.50 ± 45.10            |
| Focal lamina defect         | 25 (43.1%)                 |
| Cirrus OCT                  |                           |
| Average RNFL thickness, μm  | 73.96 ± 14.96             |
| Rim area, mm²               | 0.78 ± 0.25               |
| Disc area, mm²              | 2.02 ± 0.35               |
| Average CD ratio            | 0.75 ± 0.13               |
| Vertical CD ratio           | 0.74 ± 0.13               |
| Cup volume, mm³             | 0.58 ± 0.35               |
| HRT                         |                           |
| Disc area, mm²              | 2.16 ± 0.40               |
| Rim area, mm²               | 1.04 ± 0.44               |
| Cup area, mm²               | 1.11 ± 0.58               |
| Cup volume, mm³             | 0.38 ± 0.29               |
| Rim volume, mm³             | 0.25 ± 0.15               |
| Mean cup depth, mm          | 0.34 ± 0.14               |
| Maximum cup depth, mm       | 0.74 ± 0.23               |
| Cup-to-disc area ratio      | 0.71 ± 0.23               |
| Cup shape measure           | −0.06 ± 0.09              |
| Mean RNFL thickness, mm     | 0.21 ± 0.09               |
| Rim steepness               | −0.42 ± 0.44              |

CD = cup to disc, EDI = enhanced depth imaging, HRT = Heidelberg retinal tomograph, LC = lamina cribrosa, OCT = optical coherence tomography, RNFL = retinal nerve fiber layer thickness.
The purpose of our study was to analyze the relationship between biomechanical property as measured by corneal deformation amplitude and optic nerve head structure in patients with primary open-angle glaucoma. We found that corneal deformation amplitude showed significant negative relationship with LC depth, but no significant relationship with LC thickness or focal lamina defect. It was positively correlated with PPA area and negatively correlated with cup-related measures including cup area, cup volume, and cup depth. In addition, patients with low corneal deformation amplitude showed greater LC depth, larger cup area and cup volume than those with high corneal deformation amplitude when both groups showed similar visual field mean deviation.

The results of our study support the hypothesis proposed by many previous experimental reports which described the effect of IOP on the lamina and peripapillary sclera as a mechanical system. In stiff sclera, represented by smaller deformation amplitude, the lamina is directly pushed posteriorly by the IOP, resulting in larger cup volume. On the other hand, in compliant sclera, represented by greater deformation amplitude, the indirect tangential force of the IOP deforms the sclera, which then pulls the lamina taut, resulting in larger PPA area and smaller LC depth. Wu et al. reported that among glaucoma patients who showed LC changes during the follow-up period of 5.3 years, LC not only deepened but also became shallower in a significant portion and concluded that the direction of LC deformation is influenced by biomechanical properties of the LC and the surrounding sclera. In our study, low and high deformation amplitude groups showed similar glaucoma severity as measured by visual field mean deviation, but the underlying pathophysiology of retinal ganglion cell degeneration may have been different.

Our study has some limitations. First, it was a retrospective study. It would also be interesting to conduct a prospective study to further explore the effect of biomechanical properties on the change of optic nerve head structures in glaucoma. Second, we were unable to include the potential influence of antiglaucoma treatment in the analyses. It has been shown that topical prostaglandin analogs induce changes in corneal biomechanical properties in patients with glaucoma, therefore, the use of topical antiglaucoma treatment may have some impact on corneal deformation amplitude.

In conclusion, patients with lower corneal deformation amplitude showed greater LC depth, larger cup area and volume, and smaller PPA area than those with higher corneal deformation amplitude. Different ocular biomechanics may result in different structural changes of the optic nerve head in patients with primary open-angle glaucoma. Further in vivo studies are needed to address the potential role of ocular biomechanics in structural changes in glaucoma.

Author contributions
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