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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.[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.[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).[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.[10] Bartolomé et al[7] 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), achromatic 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 perimetries 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 perimetries. 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 error.

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 appropriately, an air impulse was automatically emitted at a pressure of 25 kPa from 11 mm away. An ultra-high-speed Scheimpflug camera recorded the response of the central 8.5 mm of the cornea. It took 140 digital frames in 30 ms with a resolution of 640 × 480 pixels. In response to the air impulse, the cornea moved inward passing a concavity phase until reaching the HC. At HC, the deformation amplitude, defined as the amount of corneal displacement at HC, was obtained by the device. For each eye, an average of 3 measurements was used for analysis.

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.[11–13] Briefly, the EDI OCT B-scans were obtained in 15° × 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 50 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).[14,15]

The beta zone parapapillary atrophy (PPA) area was measured using color optic disc photographs in a previously described method.[10] 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 ≥6, misalignment of the surface detection algorithm on <15% of consecutive 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
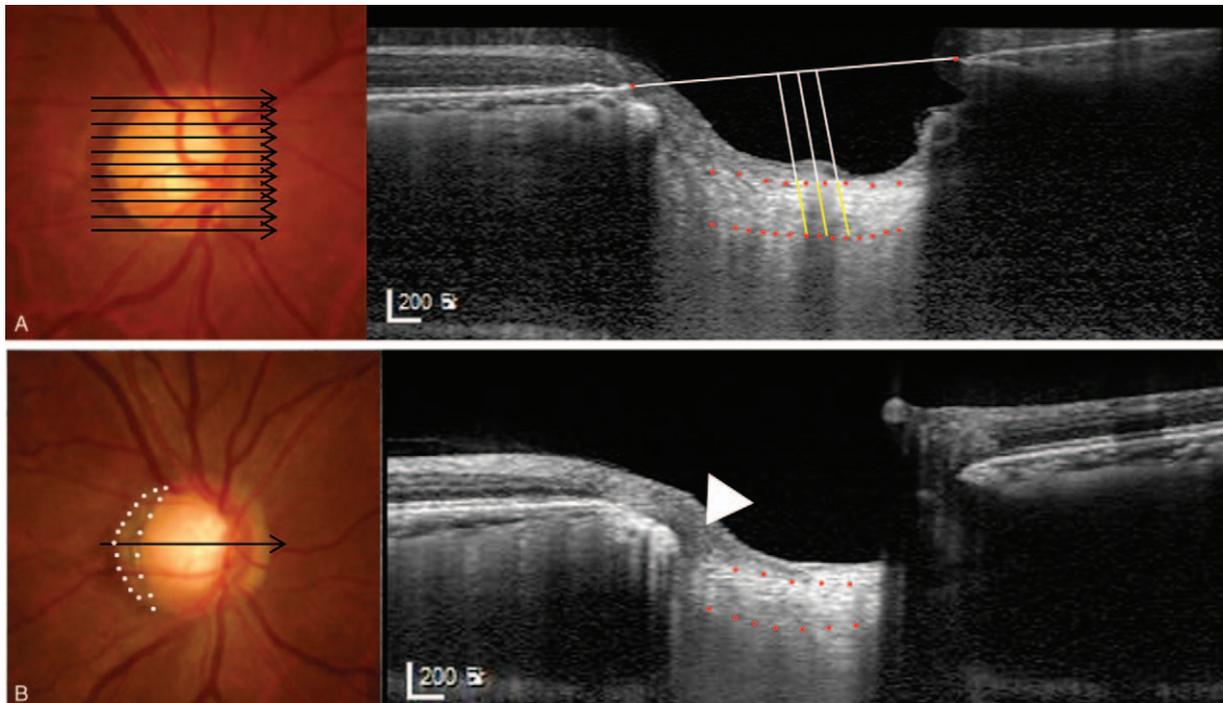
Figure 1. Measurement of LC depth, LC thickness (A), focal lamina defect and parapapillary atrophy area (B). After drawing a reference line connecting the Bruch's membrane opening, the LC depth and LC thickness were measured perpendicular from the reference line at the center and 100 μm both nasally and temporally. LC depth was measured from the reference line to the anterior border of the LC, and LC thickness was measured from the anterior border to the posterior border of the LC (A). 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 (B, white arrow). The defect must be present in at least 2 neighboring frames to avoid false positives. The beta zone PPA was by manually tracing the disc and PPA margin defined as the inner crescent of chorioretinal atrophy with visible sclera and choroidal vessels using ImageJ, which was calculated automatically in pixels within the program (B). LC = lamina cribrosa, PPA = parapapillary atrophy.

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 ± 14.73 years and visual field mean deviation was -7.85 ± 8.64 dB (Table 1). The corneal deformation amplitude was 1.08 ± 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 ± 0.08 mm) and those without (1.07 ± 0.15 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
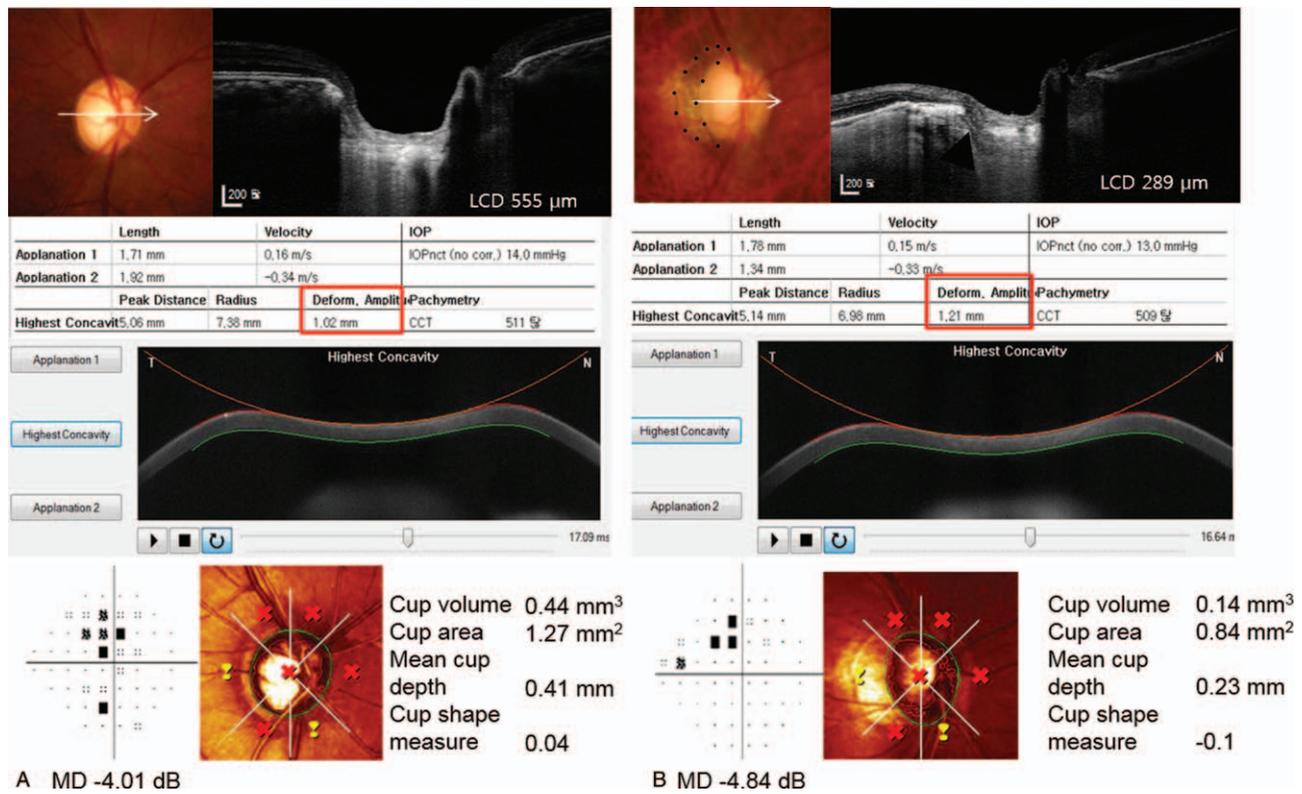
Figure 2. Representative cases of patients with low (A) versus high (B) deformation amplitude. A 56-year-old female with deformation amplitude of 1.02 mm shows greater lamina cribrosa depth, greater cup volume, cup area, mean cup depth, and cup shape measure (A) than a 53-year-old male with deformation amplitude of 1.21 mm with similar degree of visual field mean deviation (B).

previously by other researchers.[7,9] Although performed with a different device on a different group of subjects, Bartolome et al[7] reported that corneal resistance factor measured by ORA was related with LC thickness in normal subjects. Vu et al[9] 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,[16] and Tejwani et al[17] 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

Values are presented as means ± standard deviation.

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%)
Clrrus OCT	
Average RNFL thickness, μm	73.96 ± 14.96
Rim area, mm^2	0.78 ± 0.25
Disc area, mm^2	2.02 ± 0.35
Average C/D ratio	0.75 ± 0.13
Vertical C/D ratio	0.74 ± 0.13
Cup volume, mm^3	0.58 ± 0.35
HRT	
Disc area, mm^2	2.16 ± 0.40
Rim area, mm^2	1.04 ± 0.44
Cup area, mm^2	1.11 ± 0.58
Cup volume, mm^3	0.38 ± 0.29
Rim volume, mm^3	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

C/D = cup to disc, EDI = enhanced depth imaging, HRT = Heidelberg retinal tomograph, LC = lamina cribrosa, OCT = optical coherence tomography, RNFL = retinal nerve fiber layer thickness.

Table 3

Relationship between deformation amplitude and optic nerve head parameters.

Optic nerve head parameters	Pearson coefficient	P-value	Partial Pearson coefficient[†]	P-value
Visual Field mean deviation	−0.176	.198	−0.170	.218
Parapapillary atrophy area	0.385	.014[*]	0.321	.046[*]
Heidelberg EDI OCT				
LC depth, μm	−0.369	.005[*]	−0.390	.003[*]
LC thickness, μm	−0.223	.095	−0.215	.114
Cirrus OCT				
Average RNFL thickness, μm	−0.162	.236	−0.160	.248
Rim area, mm^2	0.043	.753	0.052	.707
Disc area, mm^2	−0.052	.707	−0.060	.668
Average C/D ratio	−0.048	.729	−0.068	.627
Vertical C/D ratio	−0.143	.296	−0.168	.225
Cup volume, mm^3	−0.263	.052	−0.267	.051
HRT				
Disc area, mm^2	−0.122	.375	−0.135	.329
Rim area, mm^2	0.047	.740	0.206	.169
Cup area, mm^2	−0.395	.003[*]	−0.264	.076
Cup volume, mm^3	−0.324	.019[*]	−0.351	.017[*]
Rim volume, mm^3	0.126	.361	0.130	.390
Mean cup depth, mm	−0.443	.001[*]	−0.409	.005[*]
Maximum cup depth, mm	−0.456	<.001[*]	−0.375	.010[*]
Cup-to disc area ratio	−0.130	.354	−0.293	.307
Cup shape measure	−0.161	.245	−0.142	.345
Mean RNFL thickness, mm	−0.067	.629	0.118	.436
Rim steepness	0.141	.313	0.110	.468

C/D = cup to disc, EDI = enhanced depth imaging, HRT = Heidelberg retinal tomograph, LC = lamina cribrosa, OCT = optical coherence tomography, RNFL = retinal nerve fiber layer thickness.
[*] $P < .05$.
[†] Partial Pearson correlation coefficient adjusted for age, intraocular pressure, central corneal thickness, and axial length.

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.[5,6,18–20] 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[2] 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.[21,22]

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

Conceptualization: Younhea Jung, Hae-Young Lopilly Park, Chan Kee Park.
Data curation: Younhea Jung.
Formal analysis: Younhea Jung.
Investigation: Younhea Jung.
Methodology: Younhea Jung.
Supervision: Hae-Young Lopilly Park, Chan Kee Park.
Validation: Hae-Young Lopilly Park, Chan Kee Park.
Writing – original draft: Younhea Jung.
Writing – review & editing: Hae-Young Lopilly Park, Chan Kee Park.

References

[1] Agoumi Y, Sharpe GP, Hutchison DM, et al. Laminar and prelaminar tissue displacement during intraocular pressure elevation in glaucoma patients and healthy controls. Ophthalmology 2011;118:52–9.

[2] Wu Z, Xu G, Weinreb RN, et al. Optic nerve head deformation in glaucoma: a prospective analysis of optic nerve head surface and lamina cribrosa surface displacement. Ophthalmology 2015;122:1317–29.

[3] Lee EJ, Kim TW, Kim M, et al. Influence of lamina cribrosa thickness and depth on the rate of progressive retinal nerve fiber layer thinning. Ophthalmology 2015;122:721–9.

[4] Nguyen TD, Ethier CR. Biomechanical assessment in models of glaucomatous optic neuropathy. Exp Eye Res 2015;141:125–38.

[5] Burgoyne CF, Downs JC, Bellezza AJ, et al. The optic nerve head as a biomechanical structure: a new paradigm for understanding the role of IOP-related stress and strain in the pathophysiology of glaucomatous optic nerve head damage. Prog Retin Eye Res 2005;24:39–73.

[6] Sigal IA, Ethier CR. Biomechanics of the optic nerve head. Exp Eye Res 2009;88:799–807.

[7] Bartolome FP, Martinez de la Casa JM, Bosca IC, et al. Correlating corneal biomechanics and ocular biometric properties with lamina cribrosa measurements in healthy subjects. Semin Ophthalmol 2018; 33:223–30.

[8] Wells AP, Garway-Heath DF, Poostchi A, et al. Corneal hysteresis but not corneal thickness correlates with optic nerve surface compliance in glaucoma patients. Invest Ophthalmol Vis Sci 2008;49:3262–8.

[9] Vu DM, Silva FQ, Haseltine SJ, et al. Relationship between corneal hysteresis and optic nerve parameters measured with spectral domain optical coherence tomography. Graefes Arch Clin Exp Ophthalmol 2013;251:1777–83.

[10] Jung Y, Park HY, Park CK. Association between corneal deformation amplitude and posterior pole profiles in primary open-angle glaucoma. Ophthalmology 2016;123:959–64.

[11] Park H-YL, Jeon SH, Park CK. Enhanced depth imaging detects lamina cribrosa thickness differences in normal tension glaucoma and primary open-angle glaucoma. Ophthalmology 2012;119:10–20.

[12] Park HY, Park CK. Diagnostic capability of lamina cribrosa thickness by enhanced depth imaging and factors affecting thickness in patients with glaucoma. Ophthalmology 2013;120:745–52.

[13] Jung YH, Park HY, Jung KI, et al. Comparison of prelaminar thickness between primary open angle glaucoma and normal tension glaucoma patients. PLoS One 2015;10:e0120634.

[14] Kiumehr S, Park SC, Syril D, et al. In vivo evaluation of focal lamina cribrosa defects in glaucoma. Arch Ophthalmol 2012;130:552–9.

[15] Tatham AJ, Miki A, Weinreb RN, et al. Defects of the lamina cribrosa in eyes with localized retinal nerve fiber layer loss. Ophthalmology 2014;121:110–8.

[16] Matsuura M, Hirasawa K, Murata H, et al. The relationship between corvis ST tonometry and ocular response analyzer measurements in eyes with glaucoma. PLoS One 2016;11:e0161742.

[17] Tejwani S, Shetty R, Kurien M, et al. Biomechanics of the cornea evaluated by spectral analysis of waveforms from ocular response analyzer and Corvis-ST. PLoS One 2014;9:e97591.

[18] Yang H, Downs JC, Sigal IA, et al. Deformation of the normal monkey optic nerve head connective tissue after acute IOP elevation within 3-D histomorphometric reconstructions. Invest Ophthalmol Vis Sci 2009;50:5785–99.

[19] Sigal IA, Flanagan JG, Tertinegg I, et al. Finite element modeling of optic nerve head biomechanics. Invest Ophthalmol Vis Sci 2004;45:4378–87.

[20] Crawford Downs J, Roberts MD, Sigal IA. Glaucomatous cupping of the lamina cribrosa: a review of the evidence for active progressive remodeling as a mechanism. Exp Eye Res 2011;93:133–40.

[21] Meda R, Wang Q, Paoloni D, et al. The impact of chronic use of prostaglandin analogues on the biomechanical properties of the cornea in patients with primary open-angle glaucoma. Br J Ophthalmol 2017;101:120–5.

[22] Schrems WA, Schrems-Hoesl LM, Mardin CY, et al. The effect of long-term antiglaucomatous drug administration on central corneal thickness. J Glaucoma 2016;25:274–80.