

# Dynamic Scheimpflug Ocular Biomechanical Parameters in Untreated Primary Open Angle Glaucoma Eyes

Atsuya Miki,<sup>1</sup> Yuichi Yasukura,<sup>1,2</sup> Robert N. Weinreb,<sup>3</sup> Naoyuki Maeda,<sup>1</sup> Tomomi Yamada,<sup>4</sup> Shizuka Koh,<sup>1,5</sup> Tomoko Asai,<sup>1,6</sup> Yasushi Ikuno,<sup>1,7</sup> and Kohji Nishida<sup>1,8</sup>

<sup>1</sup>Department of Ophthalmology, Osaka University Graduate School of Medicine, Osaka, Japan

<sup>2</sup>Department of Ophthalmology, Yodogawa Christian Hospital, Osaka, Japan

<sup>3</sup>Hamilton Glaucoma Center, Viterbi Family Department of Ophthalmology and Shiley Eye Institute, University of California, San Diego, La Jolla, California, United States

<sup>4</sup>Data Coordinating Center, Department of Medical Innovation, Osaka University Hospital, Osaka, Japan

<sup>5</sup>Department of Innovative Visual Science, Osaka University Graduate School of Medicine, Osaka, Japan

<sup>6</sup>Asai Eye Clinic, Hyogo, Japan

<sup>7</sup>Ikuno Eye Center, Osaka, Japan

<sup>8</sup>Integrated Frontier Research for Medical Science Division, Institute for Open and Transdisciplinary Research Initiatives (OTRI), Osaka University, Osaka, Japan

Correspondence: Atsuya Miki, Department of Ophthalmology, Osaka University Graduate School of Medicine, 2-2 Yamada-Oka, Suita, Osaka, Japan 565-0871; [amiki@ophthal.med.osaka-u.ac.jp](mailto:amiki@ophthal.med.osaka-u.ac.jp)

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**PURPOSE.** To characterize the corneal biomechanical properties of glaucoma eyes by comparing the dynamic Scheimpflug biomechanical parameters between untreated glaucoma and control eyes.

**METHODS.** Cross-sectional observational data of dynamic Scheimpflug analyzer (Corvis ST) examinations were retrospectively collected from 35 eyes of 35 consecutive patients with untreated normal tension glaucoma and 35 eyes of 35 healthy patients matched on age and IOP. Ten biomechanical parameters were compared between the two groups using multivariable models adjusting for IOP, central corneal thickness, age, and axial length. The Benjamini-Hochberg method was used to correct for multiple comparison.

**RESULTS.** In multivariable models, glaucoma was associated with smaller applanation 1 time ( $P < 0.001$ , coefficient =  $-0.5865$ ), applanation 2 time ( $P = 0.012$ , coefficient =  $-0.1702$ ), radius ( $P = 0.006$ , coefficient =  $-0.5447$ ), larger peak distance ( $P = 0.011$ , coefficient =  $0.1023$ ), deformation amplitude ratio at 1 mm ( $P < 0.001$ , coefficient =  $0.072$ ), and integrated radius ( $P < 0.001$ , coefficient =  $1.094$ ). These associations consistently indicate greater compliance of the cornea in glaucoma eyes.

**CONCLUSIONS.** Untreated normal tension glaucoma eyes were more compliant than healthy eyes. The greater compliance (smaller stiffness) of normal tension glaucoma eyes may increase the risk of optic nerve damage. These results suggest the relevance of measuring biomechanical properties of glaucoma eyes.

**Keywords:** corneal biomechanics, Scheimpflug photography, glaucoma, glaucoma anterior segment

Alterations in corneal tissue properties such as corneal thinning have been associated with the risk of developing glaucoma.<sup>1,2</sup> Recent reports have suggested that corneal hysteresis (CH) was more strongly correlated with glaucoma than corneal thickness.<sup>3,4</sup> CH is a corneal biomechanical parameter measured by the ocular response analyzer (Reichert Ophthalmic Instruments, Buffalo, NY).<sup>5,6</sup> Low CH has been associated with the development,<sup>7-10</sup> severity,<sup>11</sup> and progression of glaucoma.<sup>3,4,12</sup> These studies support the possibility of biomechanical alterations in glaucoma eyes. A more detailed characterization of the biomechanical changes associated with glaucoma could contribute to the development of new diagnostic and predictive biomarkers. However, it is impossible to calculate the corneal stiffness of the individual eye from CH; instead, it is an estimate of the pressure difference between inward and outward applanation.

Nor is it possible to know the elasticity or viscosity of the cornea from measured CH values because CH represents a combined effect of component biomechanical properties.<sup>13</sup> More quantitative measurements of the shape and dimensions of the deformation are needed to characterize the biomechanical properties of glaucoma eyes.

The dynamic Scheimpflug analyzer (Corvis ST, Oculus Optikgeräte GmbH, Wetzlar, Germany) captures ultra-high-speed dynamic images of the cornea during air-puff-induced deformation.<sup>14,15</sup> One of the advantages of the dynamic Scheimpflug analyzer is that it can provide quantitative biomechanical parameters such as the shape (radius) and dimensions (amplitude, length, and area) of the corneal deformation. Also, it can subdivide the posterior movement of the corneal apex into the pure corneal deformation and the posterior movement of the eye ball by quantifying the

latter, which can be affected by a variety of baseline factors and thus can be a source of bias.<sup>16</sup> Several previous studies showed differences in the dynamic Scheimpflug biomechanical parameters between healthy and glaucoma eyes.<sup>17–21</sup> However, these results are conflicting with respect to the biomechanical changes associated with glaucoma.<sup>17–21</sup> Part of the discrepancy may be explained by the confounding effects of baseline factors such as age, IOP, type of disease, and axial length.<sup>16,22</sup> For example, most prior studies included glaucoma patients with high baseline<sup>18,19</sup> or relatively high treated IOP.<sup>16,17,22</sup> In a previous study, we demonstrated the greater compliance of glaucoma eyes compared with healthy eyes after controlling for these confounding effects.<sup>23</sup> However, because most previous studies, including ours, enrolled glaucoma patients under medical treatment, the question remains unanswered as to whether biomechanical alterations in glaucoma eyes were caused by glaucoma per se, medications for glaucoma, or both.

In this study, we investigated the difference in biomechanical parameters measured with the dynamic Scheimpflug analyzer between untreated (treatment-naïve) eyes with POAG and matched control patients.

## METHODS

### Participants and Design

This retrospective case-control study was designed to evaluate the changes in ocular biomechanical parameters caused by glaucoma. A patient list of Corvis ST was reviewed for selecting glaucoma patients and healthy control patients who were examined from June 2012 to December 2018. Then we reviewed the charts of the possible participants to determine the eligibility for the study. POAG was defined by the optic disc appearance (presence of neuroretinal rim thinning, excavation, notching, or characteristic retinal nerve fiber layer defect) based on fundus photography, corresponding visual field abnormality, gonioscopically open angle, and absence of secondary cause of IOP elevation. Visual field abnormality in standard automated perimetry was based on Anderson and Patella criteria<sup>24</sup> of one or more of the following: a cluster of three or more non-edge points with a *P* value of less than 5%, including 1 point or more with a *P* value of less than 1%, on the pattern deviation map in at least one hemifield; a pattern SD with a *P* value of less than 5%; or glaucoma hemifield test results outside the normal limits. The healthy control group consisted of patients with suspected cataract, myopia, or those who had ophthalmologic examinations that were within normal limits. Patients with other intraocular diseases except for cataract, best-corrected visual acuity worse than 0.5, the use of IOP-lowering medication, or low quality score of Corvis ST measurement were excluded. The quality score is an indicator of the examination reliability determined by the device software based on edge detection, alignment, and pressure property. Exclusion criteria for healthy control patients included an IOP 22 mm Hg or greater or a history of elevated IOP; any type of glaucoma in either eye; evidence of vitreoretinal disease; or evidence of optic nerve abnormality in either eye.

Control participants were matched on age and Corvis IOP with cases using the matching function of the statistical programming language R (The R Foundation for Statistical Computing, Vienna, Austria).

This study was conducted as a part of an ongoing anterior segment imaging study. The study protocol adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of Osaka University Hospital. The Institutional Review Board waived the need for written informed consent because of the noninvasive and retrospective nature of the study. The protocol, the nature, and possible consequence of the study is published on the department's website (<http://www.med.osaka-u.ac.jp/pub/ophthal/www/attend/research/index.html>), and each participant gave oral consent before the initiation of the examination.

### Examinations

Baseline demographic data such as age and sex, and ocular data such as refractive error, axial length, and lens status were collected from the medical charts. All of these ocular examinations were performed within 3 months of the Corvis measurement. The axial length was measured by laser interferometry (IOLMaster, Carl Zeiss Meditec, Jena, Germany).

All participants underwent corneal deformation response measurements using the Corvis ST. The high-speed Scheimpflug camera obtains 140 images in the horizontal section of the cornea and anterior chamber up to 8.5 mm in diameter with a resolution of 640 × 480 pixels and a speed of 4330 frames per second. This imaging system allows visualization of the corneal response to an air impulse.

The new analysis software (version 1.3r1538) of the dynamic Scheimpflug analyzer provides 38 parameters, including IOP, central corneal thickness (CCT), and 36 parameters that show the deformation responses. The dynamic Scheimpflug biomechanical parameters were calculated in three defined states during deformation: inward appplanation or appplanation 1 (A1), outward appplanation or appplanation 2 (A2), and highest concavity (HC). The appplanation phase was defined as the transition from a convex to a concave shape (A1) or from a concave to a convex shape (A2). The HC is the time at which the cornea is maximally displaced. Ten relevant parameters were selected a priori before analysis, including eight parameters investigated in our previous study<sup>23</sup> and two additional newly developed parameters based on reliability.<sup>25</sup> The parameters in our previous study<sup>23</sup> included A1 time (A1T, the time of the first appplanation), A1 velocity (the speed of the corneal apex at the first appplanation), A2 time (A2T, the time of the second appplanation), A2 velocity (A2V, the speed of the corneal apex at the second appplanation), deflection amplitude (DeflA, the motion of the cornea, calculated by subtracting whole eye motion from corneal apex displacement, at the HC), peak distance (PD, the distance between the two bending peaks created in the cornea at the HC), and radius of curvature at HC (radius, radius of the central cornea at the HC based on a parabolic fit). The whole eye movement (WEM) is a motion in the posterior direction of the whole eye during the air-puff tonometry.<sup>26</sup> We selected DeflA as a parameter showing the vertical movement of the cornea,<sup>26</sup> instead of deformation amplitude (DA); DA is the sum of DeflA and WEM. In addition, two other parameters were selected that showed good reproducibility and good correlation to keratoconus in recent studies.<sup>27,28</sup> The inverse concave radius (Iradius) is plotted over the duration of the air pulse and the integrated sum is calculated between the first and second appplanation events. DA ratio at 1 mm (DAR1) describes the ratio between the DA at the apex and the average DA measured at 1 mm

TABLE 1. Biomechanical Parameters

| Condition | Property   | Abbreviation | Name                                  | Description  |
|-----------|------------|--------------|---------------------------------------|--|
| A1        | Time       | A1T          | A1 Time (ms)                          | Time of the first applanation  |
| A1        | Velocity   | A1V          | A1 Velocity (m/s)                     | Velocity of the corneal apex at the first applanation  |
| A2        | Time       | A2T          | A2 Time (ms)                          | Time of the second applanation   |
| A2        | Velocity   | A2V          | A2 Velocity (m/s)                     | Velocity of the corneal apex at the second applanation   |
| HC        | Vertical   | HCDefla      | HC Deflection Amp. (mm)               | Deflection amplitude of the HC   |
| HC        | Horizontal | PD           | Peak Dist. (mm)                       | Distance between both nondeformed peaks  |
| HC        | Flatness   | Radius       | Radius (mm)                           | Radius of curvature at maximum deformation   |
| HC        | Steepness  | DAR1         | DA.Ratio 1 mm                         | The ratio between the deformation amplitude of the apex and the average of two points located 1 mm on either side of the apex. |
| HC        | Steepness  | Iradius1     | Integrated Radius (mm <sup>-1</sup> ) | The reciprocal of radius during the concave state of the cornea  |
| Other     | Vertical   | WEM          | Whole Eye Movement Max (mm)           | Maximum whole eye movement   |

TABLE 2. Baseline Characteristics

|                     | Glaucoma                   | Healthy Control         | Total                   | P Value |
|---------------------|----------------------------|-------------------------|-------------------------|---------|
| Patients (n)        | 35                         | 35                      | 70                      |         |
| Age (years)         | 52.7 ± 14.6 (22.3–85.9)    | 56.4 ± 13.2 (30.0–79.6) | 54.6 ± 14.0 (22.3–85.9) | .2695   |
| Corvis IOP (mm Hg)  | 16.4 ± 1.9 (12–19)         | 15.8 ± 1.3 (12–18)      | 16.1 ± 1.6 (12–19)      | .174    |
| GAT IOP (mm Hg)     | 15.6 ± 2.8 (11–21)         | NA                      | NA                      |         |
| bIOP (mm Hg)        | 15.3 ± 2.0 (10.1–19.4)     | 14.4 ± 1.3 (10.9–17.2)  | 14.8 ± 1.7 (10.1–19.4)  | .037    |
| CCT (µm)            | 546.1 ± 33.2 (457–615)     | 557.5 ± 27.9 (501–612)  | 551.8 ± 31.0 (457–615)  | .123    |
| Axial length (mm)   | 25.8 ± 1.6 (23.2–29.1)     | 25.9 ± 2.3 (22.6–29.9)  | 25.8 ± 2.0 (22.6–29.9)  | .7948   |
| Mean deviation (dB) | -7.77 ± 7.64 (-28.45–1.14) | NA                      | NA                      |         |

bIOP, biomechanical IOP; GAT, Goldmann applanation tonometry; NA, not applicable. Values are mean ± SD (range).

from the center. The 10 relevant parameters evaluated in this study are detailed in Table 1.

### Statistical Analysis

Descriptive statistics such as the mean, SD, and range were computed for the baseline clinical factors and Corvis parameters. Baseline characteristics were compared between the glaucoma and the control group with Student's *t* test.

Differences in biomechanical parameters between glaucoma and normal eyes were evaluated using multivariable linear regression analyses. For each biomechanical parameter, multivariable models were fit with type (glaucoma vs healthy), IOP, CCT, age, and axial length as covariates. We used uncorrected Corvis IOP as IOP values, and CCT values measured with Corvis ST as CCT values, in the multivariable models. *P* values were adjusted with the Benjamini-Hochberg method to obtain *q* values to control for the effect of multiple comparison.<sup>29</sup> *Q* values of less than 0.05 were considered significant in this study.

For the biomechanical parameters that showed significant difference (*P* < .05) in multivariable models, receiver operating characteristic (ROC) analyses were performed. Area under the curve was calculated to assess the ability of biomechanical parameters in discriminating glaucoma eyes from healthy control eyes. The point on the ROC curve closest to the top left corner was used to determine the best cutoff value for each parameter.<sup>30</sup>

In addition, we performed an additional multivariable analysis with only type, CCT, age, and axial length as covariates (without IOP) using all the control patients' data (with-

out matching) to minimize the possibility of collider bias.<sup>31</sup> All statistical analyses were performed using the statistical programming language R.

## RESULTS

### Descriptive Statistics

Thirty-five eyes from 35 patients with POAG were enrolled. Chart review revealed that all the POAG patients who fulfilled the inclusion criteria in this study had IOP at or less than 21 mm Hg with both Goldmann applanation tonometry and Corvis IOP. Therefore, all the patients included in this study were classified as having NTG. Thirty-five patients were matched on age and IOP from 63 potentially eligible healthy control patients. There was no significant difference in age, IOP, CCT, or axial length between the glaucoma and the control group. Baseline characteristics of enrolled patients are summarized in Table 2. Baseline characteristics of all the eligible patients (before matching) are shown in Supplementary Table S1.

### Biomechanical Parameters in Glaucomatous Versus Control Eyes

The values of the biomechanical parameters in glaucoma and control patients are shown in Table 3. Those values for all the eligible patients (before matching) are shown in Supplementary Table S2. Raw *P* values obtained with multivariable linear regression analyses controlling for IOP, CCT, age, and axial length, and *q* values after adjustment with the Benjamini-Hochberg method for controlling multi-

TABLE 3. Biomechanical Parameter Values in the Glaucoma and Control Groups

|         | Glaucoma Group |      |         |         | Control Group |      |         |         | Coefficient | Raw P Value | Q Value |
|---------|----------------|------|---------|---------|---------------|------|---------|---------|-------------|-------------|---------|
|         | Average        | SD   | Minimum | Maximum | Average       | SD   | Minimum | Maximum |             |             |         |
| A1T     | 7.35           | 0.24 | 6.83    | 7.79    | 7.86          | 0.2  | 7.31    | 8.26    | -0.586      | <.001       | <.001*  |
| A1V     | 0.15           | 0.02 | 0.11    | 0.19    | 0.15          | 0.02 | 0.12    | 0.18    | 0.001       | 0.828       | 0.828   |
| A2T     | 21.9           | 0.35 | 21.08   | 22.52   | 22.1          | 0.38 | 21.31   | 22.94   | -0.170      | 0.012       | 0.021*  |
| A2V     | -0.26          | 0.02 | -0.3    | -0.18   | -0.27         | 0.03 | -0.33   | -0.22   | 0.005       | 0.434       | 0.482   |
| PD      | 5.02           | 0.29 | 4.42    | 5.7     | 4.98          | 0.24 | 4.4     | 5.38    | 0.102       | 0.011       | 0.022*  |
| Radius  | 6.92           | 0.82 | 5.57    | 9.45    | 7.52          | 0.73 | 6.3     | 9.32    | -0.545      | 0.006       | 0.015*  |
| HCDeflA | 0.9            | 0.1  | 0.74    | 1.13    | 0.91          | 0.09 | 0.73    | 1.1     | 0.018       | 0.198       | 0.248   |
| DAR1    | 1.6            | 0.05 | 1.51    | 1.74    | 1.52          | 0.04 | 1.45    | 0.159   | 0.072       | <.001       | <.001*  |
| Iradius | 8.75           | 1.01 | 7.08    | 12.27   | 7.61          | 0.69 | 5.92    | 8.79    | 1.094       | <.001       | <.001*  |
| WEM     | 0.27           | 0.09 | 0.14    | 0.43    | 0.33          | 0.08 | 0.21    | 0.51    | -0.046      | 0.018       | 0.025*  |

DAR, DA ratio; T, time; V, velocity. \*:  $P < 0.05$

TABLE 4. Summary of the Multivariable Analyses

| Condition | Property   | Parameter | Type (Glaucoma) |         | IOP     |         | CCT     |         | Age     |         | Axial Length |         | P Value | R2    |
|-----------|------------|-----------|-----------------|---------|---------|---------|---------|---------|---------|---------|--------------|---------|---------|-------|
|           |            |           | $\beta$         | P Value | $\beta$ | P Value | $\beta$ | P Value | $\beta$ | P Value | $\beta$      | P Value |         |       |
| A1        | Time       | A1T       | -0.587          | <.001*  | 0.136   | <.001*  | 0.000   | .820    | 0.000   | .289    | 0.004        | .145    | <.001*  | 0.987 |
| A1        | Velocity   | A1V       | 0.001           | .828    | -0.008  | <.001*  | 0.000   | .227    | -0.000  | .001*   | 0.001        | .393    | <.001*  | 0.683 |
| A2        | Time       | A2T       | -0.170          | .013*   | -0.138  | <.001*  | 0.002   | .137    | -0.008  | .002*   | -0.024       | .148    | <.001*  | 0.682 |
| A2        | Velocity   | A2V       | 0.005           | .434    | 0.008   | <.001*  | 0.000   | .794    | -0.000  | .452    | -0.005       | .002*   | <.001*  | 0.662 |
| HC        | Vertical   | HCDeflA   | 0.018           | .198    | -0.040  | <.001*  | 0.000   | .423    | 0.000   | .485    | 0.027        | <.001*  | <.001*  | 0.138 |
| HC        | Horizontal | PD        | 0.102           | .011*   | -0.105  | <.001*  | 0.000   | .563    | -0.001  | .634    | 0.071        | <.001*  | <.001*  | 0.644 |
| HC        | Flatness   | Radius    | -0.545          | .006*   | 0.033   | .581    | 0.006   | .061    | 0.003   | .652    | 0.015        | .756    | .012    | 0.518 |
| HC        | Steepness  | DAR1      | 0.072           | <.001*  | -0.013  | <.001*  | -0.001  | <.001*  | -0.000  | .507    | 0.001        | .616    | <.001*  | 0.286 |
| HC        | Steepness  | Iradius   | 1.094           | <.001*  | -0.249  | <.001*  | -0.011  | <.001*  | -0.011  | .063    | -0.019       | .629    | <.001*  | 0.233 |
| Other     | Vertical   | WEM       | -0.047          | .018*   | -0.009  | .122    | -0.000  | .645    | 0.002   | .005*   | -0.011       | .026*   | .001    | 0.630 |

DAR, DA ratio; T, time; V, velocity. \*:  $P < 0.05$

ple comparison are also shown in Table 3. Results of the multivariable regression analyses are summarized in Table 4. Detailed information such as P values and R2 values for each parameter of the original analyses are listed in Supplementary Table S3, and those of the additional analyses are listed in Supplementary Table S4.

Six parameters showed significant differences between groups in multivariable models after Benjamini-Hochberg adjustment. Of these, three parameters (PD, DAR1, and Iradius) showed a positive association with glaucoma ( $P = 0.011$ , coefficient = 0.1023,  $P < 0.001$ , coefficient = 0.072, and  $P < 0.001$ , coefficient = 1.094, respectively), whereas three parameters (A1T, A2T, and Radius) showed a negative association with glaucoma ( $P < 0.001$ , coefficient = -0.5865,  $P = 0.012$ , coefficient = -0.1702, and  $P = 0.006$ , coefficient = -0.5447, respectively). Glaucoma eyes exhibited smaller A1T value (slower applanation) than control eyes. The PD was larger in glaucoma eyes, suggesting greater deformation in glaucoma eyes. The radius was smaller and DAR1 and Iradius were greater in glaucomatous eyes than healthy control eyes, all of which mean steeper corneal deformation in glaucomatous eyes. Earlier applanation and wider and steeper corneal deformation in glaucoma eyes mean larger deformability (smaller stiffness) in those eyes.<sup>32</sup> Results of the additional multivariable analyses (without matching, without IOP) were similar in that most of the Corvis parameters (except PD) that were significant

in the original model also showed significant correlation in the same direction in the additional analyses (Supplementary Table S2, S4).

### Other Factors Associated With Biomechanical Parameters

IOP showed a positive association with two parameters (A1T, A2V) and a negative association with six parameters (A1V, A2T, HCDeflA, PD, DAR1, and Iradius). CCT showed negative association with two parameters (DAR1 and Iradius). Age showed positive association with WEM, and negative association with two parameters (A1V and A2T). Axial length showed positive association with two parameters (HCDeflA and PD) and a negative association with A2V.

### ROC Analysis

For the six parameters that showed significant difference between groups in the multivariable models, ROC analyses were performed to evaluate the potential discriminative ability. Area under the curve values, threshold values, and sensitivity and specificity at the threshold values are shown in Table 5. A1T, DAR1, and Iradius showed excellent discriminative performance.<sup>33</sup>

TABLE 5. Results of the ROC Analyses

| Parameter | AREA Under the Curve | 95% CI        | Threshold | Sensitivity | Specificity |
|-----------|----------------------|---------------|-----------|-------------|-------------|
| A1T       | 0.9518               | 0.9045–0.9991 | 7.6545    | 0.9429      | 0.8857      |
| A2T       | 0.6588               | 0.5306–0.7869 | 22.0535   | 0.6571      | 0.5714      |
| PD        | 0.4776               | 0.3401–0.615  | 5.044     | 0.5143      | 0.5143      |
| Radius    | 0.7216               | 0.6017–0.8416 | 7.3265    | 0.7143      | 0.6286      |
| DAR1      | 0.8686               | 0.7882–0.9489 | 1.54858   | 0.8286      | 0.8         |
| Iradius   | 0.8286               | 0.7348–0.9223 | 7.99      | 0.7714      | 0.7143      |

## DISCUSSION

In this study, we evaluated dynamic Scheimpflug biomechanical parameters in eyes with untreated (treatment-naïve) POAG and matched control eyes. All the patients who fulfilled the inclusion criteria had IOP within normal range, probably because of the very high frequency (92% of POAG) of NTG in Japan.<sup>34</sup> Multivariable analyses controlling for IOP, CCT, age, and axial length showed earlier applanation and steeper corneal deformation in glaucoma eyes, both of which suggest greater compliance of the cornea in eyes with NTG.<sup>32</sup> These results are similar to the results of our previous study.<sup>23</sup> In addition, ROC analyses suggest the potential discriminative capability of some of the biomechanical parameters. The results of the current study give insight into the biomechanical aspects of glaucoma, and could contribute to the future development of new diagnostic and treatment strategies for the disease, possibly by combining the best performing biomechanical parameters into a simple combined index.

In this study, untreated glaucoma eyes showed earlier A1T, A2T, and radius, and larger PD, DAR1, and Iradius than matched control eyes. Because the air pressure increases with time in the inward indentation (loading) phase,<sup>35</sup> a smaller A1T in glaucoma eyes means less pressure is necessary to applanate the cornea in those eyes. This finding suggests that glaucoma eyes were more compliant than healthy control eyes. The radius of the curvature is proportional to the flexural rigidity, because the moment–curvature equation shows that the curvature (reciprocal of the radius of curvature) is inversely proportional to the flexural rigidity (or bending stiffness).<sup>36</sup> Therefore, smaller values of radius mean smaller rigidity in glaucoma eyes. Larger DAR1 and PD also mean greater curvature at HC, and thus greater compliance. Larger PD means larger deformation at the HC, which also suggest larger deformability of glaucoma eyes. In summary, all of the significant correlations between biomechanical parameters and NTG suggests greater compliance of NTG eyes.

ROC analyses showed excellent area under the curve values of A1T, DAR1, and Iradius. These results suggest the potential of the biomechanical parameters as new diagnostic biomarkers for glaucoma. It should be emphasized, however, that the use of these parameters as single biomarkers for diagnosing glaucoma in clinical practice is not recommended. Because biomechanical parameters are deeply influenced by various factors such as age, IOP, and axial length,<sup>16</sup> the optimal cutoff values of biomechanical parameters shown in this study cannot be directly applied into a real-world clinical practice where glaucoma patients and healthy patients are not matched on such confounding factors. Nevertheless, the results of the ROC analyses demonstrated the possibility that biomechanical parameters may contribute to better glaucoma diagnosis. A combination

of the single parameters may be developed as a potential biomarker for NTG.

This study clarified that eyes with NTG were more compliant than matched healthy eyes, but it remains unclear what caused the difference. One possible explanation is that glaucoma eyes are less stiff in nature, making those eyes more susceptible to IOP-induced injury and increasing the risk of developing optic neuropathy. Previous studies reporting that stiffer eyes exhibited smaller retinal ganglion cell damage support this hypothesis.<sup>37,38</sup> Further longitudinal study is necessary to answer this question.

Biomechanical parameters showed significant correlations with other baseline factors. Higher IOP associated with greater resistance to deformation (larger A1T, A2V and smaller A1V, A2T), smaller (smaller HCDeflA and PD) and flatter (smaller DAR1 and Iradius1) deformation of the cornea. A thicker CCT showed flatter deformation of the cornea as suggested by smaller DAR1 and Iradius. Older age associated with greater resistance to deformation (smaller A1V and A2T) and larger WEM. Longer axial length was associated with greater compliance (smaller A2V, larger HCDeflA and PD). These significant associations confirmed the necessity of adjustment for these demographic and ocular confounding factors whenever studying the biomechanical parameters in ocular diseases.

The results of this study agreed with our previous study that showed greater compliance of medially treated glaucoma eyes.<sup>23</sup> A comparison of parameter values between our previous study and the current study revealed that corneal deformability of medically treated glaucoma eyes were larger than that of untreated glaucoma eyes. This finding raises the possibility that medical treatment makes glaucoma eyes even more deformable. Longitudinal study is necessary to clarify the effect of glaucoma medication on corneal biomechanical properties.

The current study does not agree with some previous studies that showed slower applanation or smaller deformation at HC.<sup>17–19</sup> Besides the difference in participant population, statistical methods, and medication status, differences in IOP might contribute to the discrepancies. All of these previous studies included glaucoma eyes with high baseline IOP, whereas all of our participants were NTG patients. It has been suggested that the tissue remodeling in response to pressure may vary depending on the cumulative level of the pressure-induced stress.<sup>39,40</sup> Therefore, biomechanical study of untreated glaucoma with high pressure is necessary to determine whether there is a difference in ocular biomechanical properties between NTG and POAG with a higher IOP.

In clinical practice, the true IOP is not known, and measured IOP and biomechanical parameters are correlated. In vivo studies on biomechanical parameters should therefore be performed in a way that minimize the bias caused by this limitation. With this factor in mind, we performed multi-

variable analyses in two ways: in matched patients controlling for IOP and in unmatched patients not controlling for IOP.<sup>31</sup> We confirmed that the results of these two analyses were basically similar.

In conclusion, eyes with untreated NTG demonstrated larger deformability of the cornea compared with healthy eyes. This factor may influence the susceptibility to glaucoma through biomechanical vulnerability of the eyeball. ROC analyses suggested the possible role of biomechanical parameters for improving the diagnosis of glaucoma. Further investigation of ocular biomechanical parameters could contribute to the development of new diagnostic and treatment strategies for glaucoma, through improved understanding of underlying pathophysiologic events in the disease.

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