Article

Association Between Ocular Biomechanics Measured With Corvis ST and Glaucoma Severity in Patients With Untreated Primary Open Angle Glaucoma

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Purpose: To compare the ocular biomechanical differences between normal controls and patients with untreated primary open angle glaucoma, including normal-tension glaucoma (NTG) and high-tension glaucoma (HTG), and to investigate the association between ocular biomechanics and glaucoma severity in each group.

Methods: One hundred fifty-three eyes of 153 subjects, including 51 controls, 47 NTG, and 55 HTG cases, were enrolled in this cross-sectional study. Each participant underwent biomechanical measurements by using the Corneal Visualization Scheimpflug Technology. Glaucoma severity was evaluated by mean deviation (MD), pattern standard deviation (PSD), ganglion cell complex (GCC), and retinal nerve fiber layer (RNFL) thickness.

Results: Deformation amplitude ($P = 0.001$) significantly increased, whereas first applanation time ($P < 0.0001$), highest concavity time ($P = 0.001$), stiffness parameter at first applanation ($P = 0.009$), and time of whole eye movement (WEM, $P = 0.008$) decreased significantly in NTG eyes compared with controls. Besides, NTG had the highest first applanation velocity than controls ($P < 0.0001$) and HTG ($P = 0.044$). Shorter time of WEM was independently correlated with worse MD ($P = 0.02$) and higher values of PSD ($P = 0.03$) in NTG. Axial length was positively related to PSD ($P = 0.02$) and negatively related to GCC ($P < 0.0001$) and RNFL ($P < 0.0001$) thickness in HTG.

Conclusions: NTG corneas are more deformable than healthy ones and HTG. Time of WEM, which relates to orbital compliance, is significantly associated with glaucomatous visual field defect in NTG, whereas axial length is correlated with glaucoma severity in HTG.

Translational Relevance: Ocular biomechanics may partly account for the differences of pathogenic mechanisms between NTG and HTG.

Introduction

Glaucoma is a leading cause of irreversible visual impairment and blindness worldwide.[1] It is accompanied by retinal nerve fibers loss and optic disc excavation, eventually leading to visual field (VF) defects. Intraocular pressure (IOP) is the most significant risk factor for glaucoma development and progression.[2,3]

Corneal biomechanical properties are of increasing interest in glaucoma because of their influences on corneal resistance to applanation and therefore IOP measurement obtained by Goldmann Applanation Tonometry.[4,5] In addition, it has been reported that corneal biomechanics is associated with optic nerve surface compliance during transient IOP elevation.[6] Corneal hysteresis (CH), measured with the ocular response analyzer, is a corneal biomechanical

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parameter related to viscoelastic dampening.[7] CH is found to be lower in glaucomatous compared to healthy eyes[8] and is a risk factor for VF progression.[9,10]

Most of the available studies about the relationship between corneal biomechanics and glaucoma severity were conducted using the ocular response analyzer. CH is reported to be positively correlated with both of visual field index and mean deviation (MD) in primary open angle glaucoma (POAG) patients.[11,12] In addition, lower CH is associated with worse VF eyes in asymmetric POAG patients, which is independent of its effect on IOP measurements.[7] However, Hirneiss et al.[13] reported there was no difference of corneal biomechanics in both eyes of patients with unilateral POAG when CH was corrected for IOP. These results indicate that the relationship between corneal biomechanics and glaucoma severity is controversial and needs to be studied further.

The Corneal Visualization Scheimpflug Technology (Corvis ST) is another non-contact device that has the advantage of dynamic cross-sectional imaging during the corneal deformation, which give additional information about corneal biomechanics.[14] Only a few studies reported the relationship between corneal biomechanics measured by Corvis ST and glaucoma severity.[15,16] However, these studies did not exclude the influence of antiglaucomatous medications on corneal biomechanics, which has been demonstrated by several studies.[17–19]

Normal-tension glaucoma (NTG) and high-tension glaucoma (HTG) are two subtypes of POAG. IOP always remains within normal range in NTG, whereas elevated IOP is presented in HTG. Different pathogeneses may exist between NTG and HTG.[20] Previous literature had reported there were differences in ocular biomechanics between NTG and HTG. The corneas were significantly softer and more deformable in medically controlled NTG patients than those in HTG.[16,21] However, whether ocular biomechanics contribute differently to glaucomatous damage between NTG and HTG are still unknown. Therefore the aim of the current study was to investigate the correlation between Corvis ST measured ocular biomechanics and glaucoma severity in untreated NTG and HTG patients and in normal controls. The differences of biomechanical factors were compared among the groups as well.

Materials and Methods

Subjects

Newly diagnosed NTG and HTG patients were consecutively recruited in Eye & ENT Hospital, Fudan University. Normal controls were enrolled from those who visited our hospital for regular eye checkups. Written informed consent was obtained from all participants before the enrollment. This study was approved by the hospital's Ethics Committee and was conducted in accordance with the tenets of the Declaration of Helsinki.

Healthy controls were defined as those with no history of eye diseases, IOP $\leq$ 21 mm Hg, open anterior chamber angles, normal appearances of the optic nerve head, and normal VF. A normal VF test result was defined as one with MD and pattern standard deviation (PSD) within 95% confidence limits of normal reference and glaucoma hemifield test within normal limits.

POAG was diagnosed as typical glaucomatous disc cupping and compatible VF defects in at least one eye and with the presence of open angles with Shaffer grading >2 on gonioscopy. In addition, patients were diagnosed with HTG when they had at least one measurement of IOP > 21 mm Hg with a Goldmann applanation tonometer taken at three different time points before treatment. On the contrary, patients were diagnosed as NTG when they had IOP $\leq$ 21 mm Hg at all time points in a 24-hour IOP test. Exclusion criteria included histories of intraocular surgery, laser, trauma, secondary glaucoma and corneal abnormalities. Patients with any VF loss caused by nonglaucomatous diseases were also excluded from this study. Subjects with concurrent or prior use of antiglaucoma medications were excluded as well.

All subjects underwent a comprehensive ophthalmologic examination, including visual acuity, best corrected visual acuity, slit-lamp biomicroscopy, fundus evaluation of the optic disc with a 90-diopter lens, IOP measurement using the Goldmann applanation tonometer and gonioscopy examination by an experienced glaucoma specialist. The VF tests were performed by the 30-2 SITA Standard program of the Humphrey Field Analyzer (Carl Zeiss Meditec, Dublin, CA, USA) to obtain MD and PSD. Only reliable VF measurements, which was defined as fixation loss rate less than 20%, false-positive and -negative rates less than 15%, were used for analysis. The retinal nerve fiber layer (RNFL) and ganglion cell complex (GCC) thickness were measured by spectral domain optical coherence tomography (SD-OCT; RTVue OCT; Optovue Inc., Fremont, CA, USA). VF and SD-OCT tests were conducted within one month before the Corvis ST measurements. Glaucoma severity was evaluated by the VF indexes (MD and PSD) and the structural parameters of optic disc and macular features (RNFL and GCC thickness). Axial length was measured by IOL Master (Zeiss, Oberkochen, Germany).
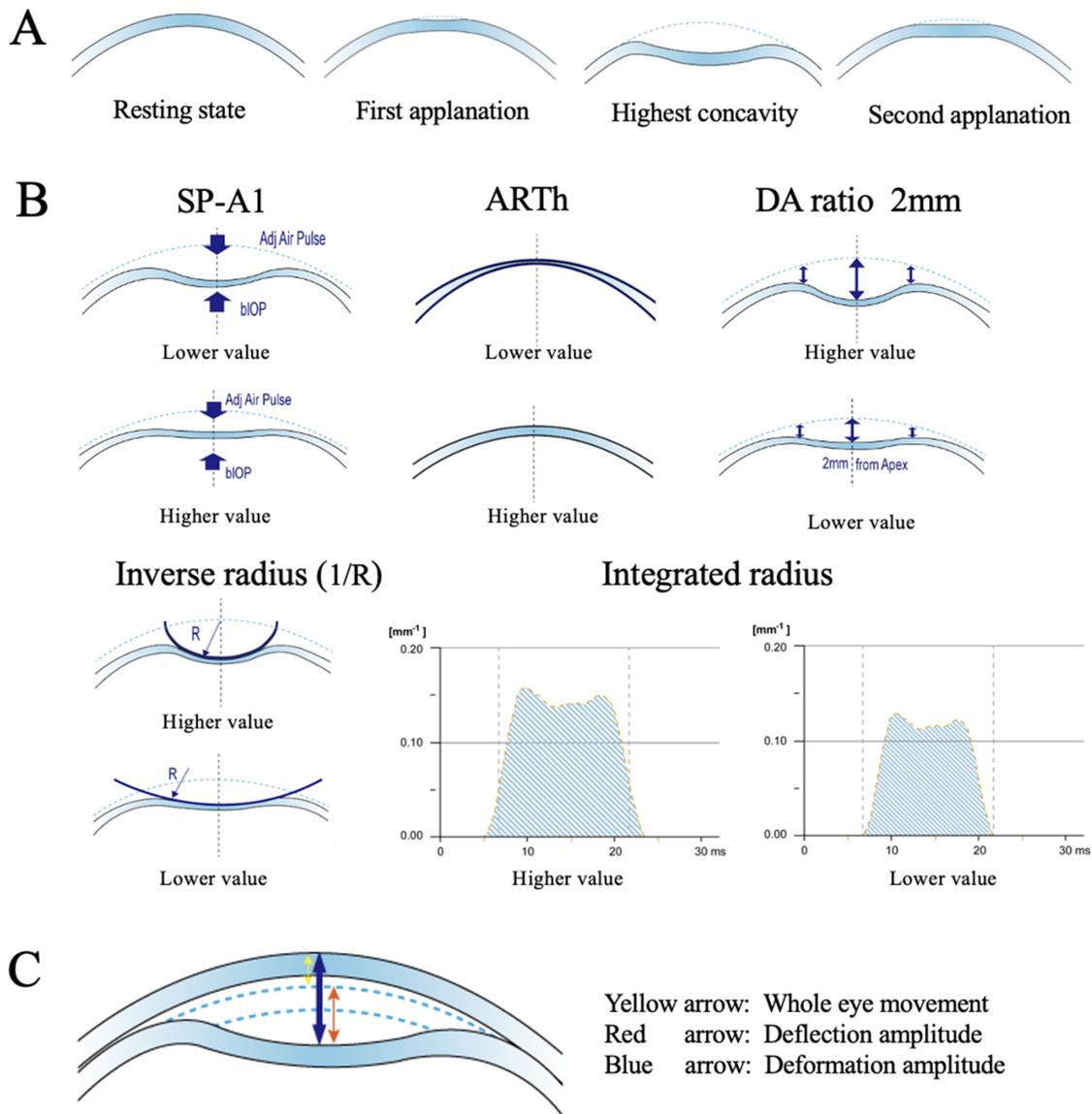
Figure 1. Schematic diagrams of the ocular biomechanical parameters provided by Corvis ST. (A) Cornea deformation during the Corvis ST measurement. From left to right: resting state before the measurement; first applanation; highest concavity; second applanation. (B) Graphs illustrating SP-A1, ARTh, DA ratio 2 mm, inverse radius and integrated radius. Lower values of SP-A1 and ARTh indicate a more deformable cornea, whereas higher values of DA ratio 2 mm, inverse radius and integrated radius indicate a more deformable cornea. (C) Correlation between deformation amplitude and whole eye movement. Deformation amplitude is a sum of whole eye movement and pure corneal deformation named deflection amplitude. *Yellow arrow*: whole eye movement; *Red arrow*: deflection amplitude; *Blue arrow*: deformation amplitude.

Corvis ST Measurements

The Corvis ST (Oculus, GmbH, Wetzlar, Germany) was used to measure IOP, biomechanically corrected IOP, central corneal thickness (CCT), as well as ocular biomechanical parameters. Corvis ST monitors cornea's dynamic reaction to an air impulse with a high-speed Scheimpflug camera, which captures 4330 images per second.[22] Under the pressure, the cornea bends inward from the resting state to the first applanation point and continues to move until it reaches the maximum deformation state, namely highest concavity (HC). When the pressure decreases, the cornea moves outward and passes the second applanation point before reaching to its resting state.[14,23] After each measurement, corneal biomechanical parameters are produced as follows (Fig. 1A): time from start to the first and second applanations (AT1 and AT2, respectively), velocity during the first and second applanations (AV1 and AV2, respectively), time and maximum deformation amplitude (DA) from resting state to HC, peak distance (PD) between corneal

bending points and radius of HC. In addition, several new biomechanical parameters measured by the latest Corvis ST software (v. 1.3r1538) were included in our study (Figs. 1B, 1C):

Stiffness parameter at first applanation (SP-A1): the difference between the strength of the air puff at the corneal surface and biomechanically corrected IOP divided by deflection amplitude at the first applanation.[24,25]

Ambrosio relational thickness to the horizontal profile (ARTh): the quotient of corneal thickness at the thinnest point of the horizontal meridian and the thickness increase toward the periphery.[25]

DA ratio 2 mm: the ratio of deformation amplitude at corneal apex to that at 2 mm.[25,26]

Integrated radius: the integrated area under the radius of the inversed curvature (Fig. 1B) during the concave phase.[26]

Whole eye movement length (WEM length): the length of the linear anterior-posterior movement of the whole eye after maximum displacement of the cornea.[25,27,28]

WEM time: the time taken for the linear anterior-posterior movement of the whole eye after maximum displacement of the cornea.[25,27,28]

Statistical Analysis

Only data of one eye for each subject was included for statistical analysis. The left eye was selected if both eyes had eligible Corvis ST measurements. Data were presented as mean ± standard deviation (SD) or as median interquartile range. Analysis of variance or Kruskal Wallis rank sum tests were used to assess the differences of demographic and ocular parameters among the normal control, NTG and HTG groups. Biomechanical differences among the three groups were analyzed by general linear model. Furthermore,

the Bonferroni post hoc tests were used for pairwise comparisons. Spearman rank correlation tests were employed to identify the possible correlated factors of glaucoma severity indices since at least one variable in each group did not obey the normal distribution. Multivariate linear regression tests were performed to evaluate the association between glaucoma severity parameters with the demographic and ocular variables in each group. In this study, significant P value was set at <0.05 (two tailed), and SPSS version 23.0 program was used for the whole analysis.

Results

A total of 51 normal controls and 102 untreated POAG patients, including 47 NTG and 55 HTG patients were enrolled in the study. The demographic and ocular characteristics of the participants were shown in Table 1. Gender, age, IOP, and all glaucoma severity parameters (MD, PSD, GCC and RNFL) showed statistically significant differences among the groups of control, NTG and HTG (all $P < 0.01$), whereas axial length and CCT revealed no significant differences ($P = 0.143$ and 0.155, respectively).

The differences of biomechanical parameters among the three groups were compared by the general linear model with adjustment for gender, age, axial length, IOP and CCT. There were statistically significant differences in several parameters between the controls and untreated glaucoma groups (Table 2). DA was significantly higher whereas AT1 and HC time were significantly lower in NTG (DA = 1.01 ± 0.01 mm, P = 0.001; AT1 = 7.62 ± 0.02 ms, $P <$ 0.0001; HC time = 16.91 ± 0.10 ms, P = 0.001) and HTG eyes (DA = 1.02 ± 0.01 mm, P = 0.002; AT1 = 7.64 ± 0.03 ms, $P < 0.0001$; HC time = 16.77 ± 0.10 ms, P = 0.0002) than in controls (DA = 0.95 ± 0.01 mm; AT1 = 7.82 ± 0.02 ms; HC time = 17.41 ± 0.01

Table 1. Demographic and Ocular Characteristics of Normal Control and Glaucoma Participants

	Mean ± SD/Median (P25, P75)			
Variables	Normal Control (n = 51)	NTG (n = 47)	HTG (n = 55)	*P*
Gender (Male/Female)	22/29	19/28	42/13	<0.0001
Age, years	37.00 (32.00, 40.00)	44.00 (36.00, 51.50)	37.50 (32.50, 46.00)	0.0012
Axial length, mm	24.87 (24.07, 26.77)	25.78 (23.77, 27.01)	26.08 (24.75, 27.13)	0.143
IOP, mmHg	16.50 (15.25, 18.75)	17.00 (15.75, 18.25)	20.75 (18.19, 23.31)	<0.0001
CCT, μm	546.74 ± 31.72	547.10 ± 33.73	557.45 ± 31.27	0.155
MD, dB	−2.01 (−2.81, −0.77)	−5.33 (−8.98, −2.43)	−4.17 (−9.73, −2.92)	<0.0001
PSD, dB	1.69 (1.52, 2.05)	5.33 (2.82, 10.72)	4.90 (2.21, 11.12)	<0.0001
GCC, μm	96.90 ± 5.62	77.77 ± 9.42	76.57 ± 10.99	<0.0001
RNFL, μm	100.43 ± 8.32	82.23 ± 12.96	78.38 ± 13.41	<0.0001

Table 2. Adjusted Ocular Biomechanical Parameters and Comparative Analysis Among Groups of Normal Control, NTG and HTG

Variables	Normal Control	NTG	HTG	*P*	P1	P2	P3
DA, mm	0.95 ± 0.01	1.01 ± 0.01	1.02 ± 0.01	**<0.0001**	**0.001**	**0.002**	1.000
AT1, ms	7.82 ± 0.02	7.62 ± 0.02	7.64 ± 0.03	**<0.0001**	**<0.0001**	**<0.0001**	1.000
AV1, m/s	0.12 ± 0.01	0.14 ± 0.01	0.13 ± 0.01	**<0.0001**	**<0.0001**	0.096	**0.044**
AT2, ms	21.83 ± 0.10	21.62 ± 0.10	21.49 ± 0.11	0.057	0.356	0.062	1.000
AV2, m/s	−0.24 ± 0.01	−0.25 ± 0.01	−0.24 ± 0.01	0.497	0.719	1.000	1.000
HC time, ms	17.41 ± 0.01	16.91 ± 0.10	16.77 ± 0.10	**<0.0001**	**0.001**	**0.0002**	1.000
HC PD, mm	4.74 ± 0.04	4.80 ± 0.04	4.80 ± 0.04	0.539	0.925	1.000	1.000
HC radius, mm	7.32 ± 0.50	6.97 ± 0.53	7.97 ± 0.57	0.472	1.000	1.000	0.672
SP-A1, mm Hg/mm	132.85 ± 3.02	119.55 ± 3.19	126.09 ± 3.41	**0.012**	**0.009**	0.477	0.554
Integrated radius, mm^{-1}	7.98 ± 0.14	8.42 ± 0.14	8.17 ± 0.15	0.089	0.084	1.000	0.881
ARTh, μm	418.52 ± 10.51	449.16 ± 11.16	451.72 ± 11.88	0.065	0.144	0.142	1.000
DA ratio 2 mm	4.44 ± 0.10	4.32 ± 0.12	4.19 ± 0.12	0.349	1.000	0.444	1.000
WEM length, mm	0.29 ± 0.01	0.28 ± 0.01	0.32 ± 0.01	0.130	1.000	0.357	0.152
WEM time, ms	22.86 ± 0.17	22.12 ± 0.18	22.34 ± 0.19	**0.008**	**0.008**	0.147	1.000

P, *P* values of the general linear model with adjustment for gender, age, axial length, IOP and CCT;
P1: *P* values by Bonferroni post hoc tests between control and NTG;
P2: *P* values by Bonferroni post hoc tests between control and HTG;
P3: *P* values by Bonferroni post hoc tests between NTG and HTG.
Bold *P* values are <0.05 with statistical significances.

ms). In addition, NTG showed the highest AV1 (0.14 ± 0.01 m/s) compared with controls (0.12 ± 0.01 m/s, *P* < 0.0001) and HTG (0.13 ± 0.01 m/s, *P* = 0.044). SP-A1 and time of WEM decreased statistically significantly in NTG eyes (SP-A1 = 119.55 ± 3.19 mm Hg/mm; WEM = 22.12 ± 0.18 ms) than in controls (SP-A1 = 132.85 ± 3.02 mm Hg/mm, *P* = 0.009; WEM = 22.86 ± 0.17 ms, *P* = 0.008). The ocular biomechanical differences between the POAG patients (composed of NTG and HTG) and healthy controls were also analyzed by the general linear model and the results were shown in Supplementary Table S1. DA (1.02 ± 0.01 vs. 0.95 ± 0.01 mm, *P* < 0.0001), AV1 (0.13 ± 0.01 vs. 0.12 ± 0.01 m/s, *P* < 0.0001), integrated radius (8.35 ± 0.09 vs. 7.97 ± 0.14 mm^{-1}, *P* = 0.028) and ARTh (449.65 ± 7.11 vs. 420.84 ± 10.44 μm, *P* = 0.031) were significantly higher, whereas AT1 (7.62 ± 0.02 vs. 7.82 ± 0.02 ms, *P* < 0.0001), AT2 (21.57 ± 0.06 vs. 21.82 ± 0.09 ms, *P* = 0.035), HC time (16.87 ± 0.06 vs. 17.40 ± 0.09 ms, *P* < 0.0001), SP-A1 (121.97 ± 2.05 vs. 132.82 ± 3.01 mm Hg/mm, *P* = 0.005) and time of WEM (22.20 ± 0.11 vs. 22.85 ± 0.17 ms, *P* = 0.002) were significantly lower in POAG eyes compared to those in normal controls.

In further analyses on the associated factors of glaucoma severity, we found a number of demographic and ocular variables were significantly associated with both of VF and SD-OCT indices by Spearman rank correlation (Supplementary Tables S2 and S3). The biomechanical parameters which showed statistically significant differences in the univariate analysis in each group as well as gender, age, axial length, CCT and IOP, were entered into the multivariate linear regression models. In normal controls (Supplementary Table S4), there was a significant negative correlation between DA ratio 2mm and MD (β = −0.43, 95% confidence interval [CI], −0.75 to −0.10, *P* = 0.01). CCT was significantly associated with PSD (β = −0.01, 95% CI, −0.01 to 0.01, *P* = 0.03). Longer axial length was associated with decreased thickness of GCC (β = −1.28, 95% CI, −2.38 to −0.19, *P* = 0.02) and RNFL (β = −2.65, 95% CI, −4.22 to −1.08, *P* = 0.0007). In addition, healthy females showed reduced GCC thickness compared with males (β = −3.72, 95% CI, −7.04 to −0.40, *P* = 0.03). No statistically significant variables were detected in POAG subjects except axial length showed a positive relationship with PSD (β = 0.64, 95% CI, 0.08 to 1.20, *P* = 0.03, Supplementary Table S4).

Interestingly, when NTG and HTG were analyzed separately, shorter time of WEM was significantly associated with worse MD (β = 1.57, 95% CI, 0.21 to 2.94, *P* = 0.02) and higher values of PSD (β = −1.55, 95% CI, −2.98 to −0.12, *P* = 0.03) in NTG (Table 3). However, only axial length revealed a positive correlation with PSD (β = 0.95, 95% CI, 0.15 to 1.75, *P* =

Table 3. Association Between Demographic and Ocular Variables With Glaucoma Severity Parameters by Multivariate Linear Regression Analysis in NTG and HTG Groups

	MD		PSD		GCC		RNFL	
	β (95% CI)	P	β (95% CI)	P	β (95% CI)	P	β (95% CI)	P
NTG								
Gender	0.55 (−2.28 to 3.39)	0.70	0.57 (−2.17 to 3.32)	0.67	6.62 (−0.08 to 13.32)	0.05	3.63 (−5.03 to 12.29)	0.40
Age	−0.09 (−0.19 to 0.01)	0.08	0.05 (−0.05 to 0.15)	0.28	0.01 (−0.24 to 0.25)	0.95	−0.25 (−0.58 to 0.08)	0.13
Axial length	0.12 (−0.63 to 0.88)	0.74	−0.04 (−0.82 to 0.74)	0.92	0.59 (−1.09 to 2.27)	0.48	−0.47 (−2.72 to 1.79)	0.68
IOP	−0.08 (−0.62 to 0.47)	0.78	0.30 (−0.29 to 0.89)	0.31	−0.34 (−1.83 to 1.15)	0.65	0.21 (−1.62 to 2.05)	0.81
CCT	−0.01 (−0.05 to 0.03)	0.49	0.00 (−0.04 to 0.04)	0.93	−0.02 (−0.11 to 0.08)	0.73	−0.09 (−0.21 to 0.03)	0.15
WEM time	1.57 (0.21–2.94)	**0.02**	−1.55 (−2.98 to −0.12)	**0.03**	—	—	—	—
WEM length	17.88 (−1.15 to 36.91)	0.06	−19.61 (−39.24 to 0.02)	0.05	—	—	—	—
ARTh	−0.01 (−0.02 to 0.01)	0.21	—	—	—	—	—	—
AT2	—	—	−0.17 (−2.07 to 1.72)	0.85	—	—	—	—
HTG								
Gender	0.75 (−2.54 to 4.03)	0.65	−1.69 (−4.57 to 1.19)	0.24	−1.15 (−7.90 to 5.60)	0.73	−0.18 (−6.85 to 6.49)	0.96
Age	−0.02 (−0.16 to 0.11)	0.73	0.01 (−0.10 to 0.13)	0.82	−0.02 (−0.32 to 0.27)	0.88	−0.04 (−0.34 to 0.25)	0.77
Axial length	−0.72 (−1.73 to 0.28)	0.16	0.95 (0.15–1.75)	**0.02**	−3.21 (−5.02 to −1.40)	**<0.0001**	−3.12 (−4.95 to −1.29)	**<0.0001**
IOP	−0.31 (−0.65 to 0.03)	0.08	0.13 (−0.17 to 0.44)	0.38	−0.49 (−1.22 to 0.24)	0.19	−0.59 (−1.32 to 0.13)	0.11
CCT	0.05 (0.00–0.10)	0.07	−0.02 (−0.06 to 0.02)	0.38	0.09 (−0.01 to 0.20)	0.09	0.09 (−0.02 to 0.20)	0.10
DA ratio 2mm	0.72 (−0.54 to 1.98)	0.26	—	—	—	—	—	—
WEM time	—	—	—	—	1.83 (−0.80 to 4.47)	0.17	—	—

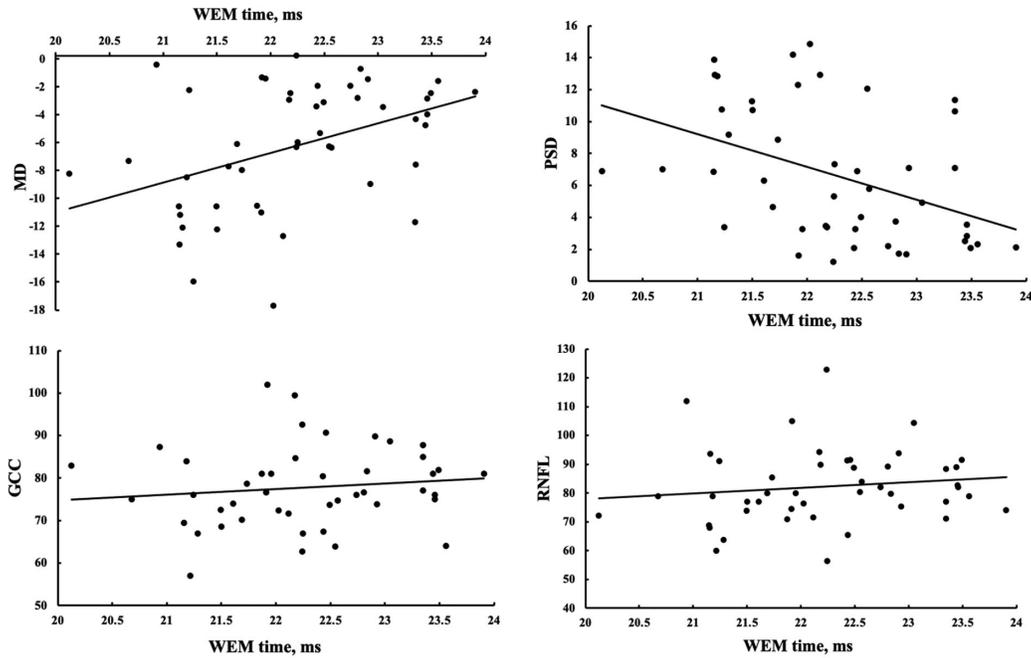Bold *P* values are <0.05 with statistical significances.

Figure 2. Scatterplots of the correlation between time of WEM and glaucoma severity parameters in NTG patients.

0.02) and negative correlation with GCC ($\beta = -3.21$, 95% CI, -5.02 to -1.40, $P < 0.0001$) and RNFL ($\beta = -3.12$, 95% CI, -4.95 to -1.29, $P < 0.0001$) thickness in HTG (Table 3). Scatterplots showing the relationship between these ocular parameters and glaucoma severity indexes were presented in Figures 2 and 3.
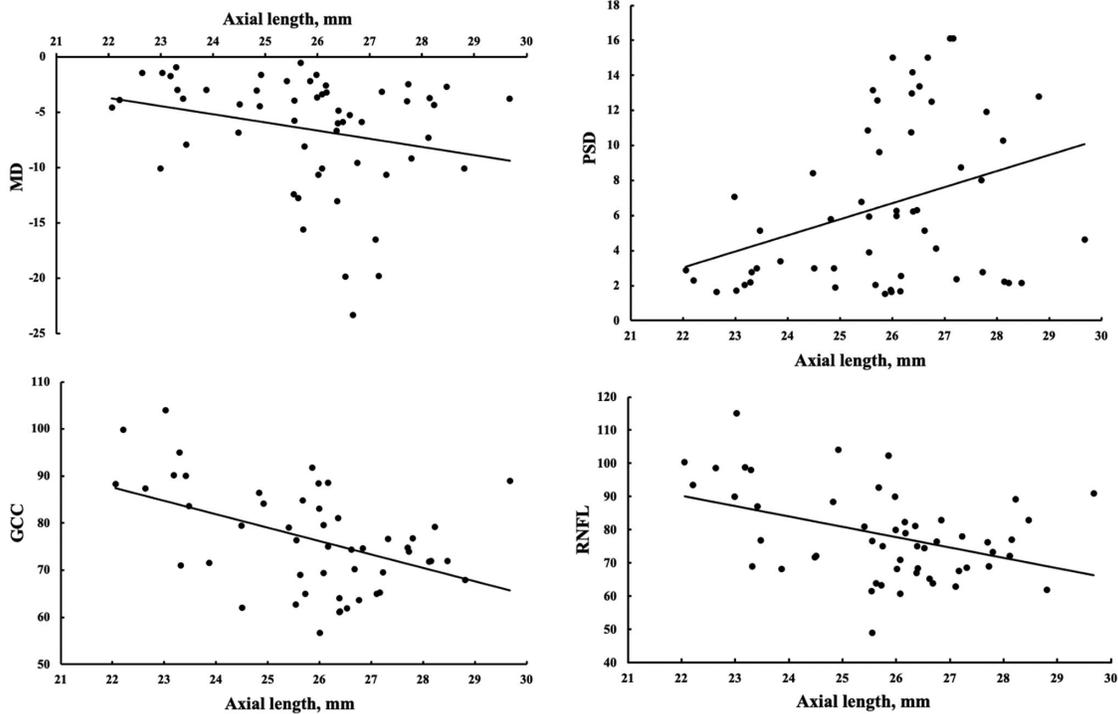

Figure 3. Scatterplots of the correlation between axial length and glaucoma severity parameters in HTG patients.

Discussion

Corneal biomechanical properties are gaining increasingly research attention and have been demonstrated differences across various ocular situations. Our results found that the ocular biomechanics were significantly different between untreated POAG (including NTG and HTG separately) patients and normal controls. More interestingly, our findings revealed shorter time of WEM was independently associated with more severe visual field defect in NTG, whereas longer axial length was related to glaucoma damage in HTG, suggesting different involvement of biomechanics in glaucoma severity between NTG and HTG.

Comparative analysis by the general linear model suggested that the corneal deformability is higher in untreated POAG patients than normal controls as indicated by increased values of DA, AV1, integrated radius, and decreased values of AT1, HC time and SP-A1 (Supplementary Table S1). Different results were obtained about the corneal biomechanical differences between POAG and normal controls in previous studies. Some reported corneas of POAG were less deformable compared to controls,[17,29] whereas others reported that no biomechanical differences were found between the two groups.[30,31] The possible reasons for this disagreement could be due to the influences of antiglaucoma medications on corneal biomechanics, differences in sample size and variables used for adjustment. When NTG and HTG were analyzed separately and compared with controls (Table 2), DA, AT1 and HC time showed similar changes in the two glaucoma groups. Additionally, SP-A1 decreased and AV1 increased significantly in NTG than in controls. This finding revealed that NTG corneas were more deformable than healthy ones and HTG, which were in agreement with previous studies.[16,21,32,33] More deformable corneas were more likely to show glaucomatous visual field defect.[9,16] It has been reported that in untreated NTG patients with asymmetric visual field damage, the worse eyes were the ones with a larger degree of corneal deformability compared to the better eyes.[34] More compliant corneas may reflect higher deformability in sclera and lamina cribrosa to some extent since they are in structural continuum with the cornea, thus making the optic nerve head more vulnerable to glaucomatous damage.[9,35,36]

After the air impulse applying on the cornea, the kinetic energy of the puff is absorbed by the cornea as well as extraocular tissues such as fat and orbital muscles.[37] When the cornea reaches its maximum displacement, the whole eye displays a slow linear motion in the anterior-posterior direction,[25] namely WEM, which reflects orbital compliance,[38] and the pure corneal deformation is called deflection amplitude. As shown in Figure 1C, WEM is a part of DA (deformation amplitude). Our study showed that the time of WEM was significantly decreased in NTG patients compared with controls (Table 2), which was in line with a previous study.[32] Decreased WEM indicated decreased orbital compliance[28,39] in these patients. Unlike other corneal biomechanical parameters, only a few literatures studied WEM, and its clinical relevance need to be fully established in future.

Furthermore, we evaluated the potential contribution of ocular biomechanics to glaucoma severity in each group. In total POAG patients, only axial length showed a significantly positive correlation with PSD (Supplementary Table S4). To our knowledge, studies about the relationship between ocular biomechanics measured by Corvis ST and glaucoma severity were very few. Hirasawa et al reported that eyes with fast AV1 and shorter AT2 were related to more severe VF damage in POAG patients.[15] Vinciguerra et al.[16] found there was a significant negative correlation between MD and DA ratio in addition to its positive correlation with SP-A1 in POAG patients. The most possible reason for this inconsistency could be that these two studies did not exclude patients under usage of hypotensive eye drops. IOP lowering medications, particularly the prostaglandin analogues, have been shown to influence corneal biomechanics significantly.[17–19] Our results were in agreement with the study from Bolivar et al.,[40] which found that the initial Corvis ST biomechanical parameters (DA, AT1, AV1, AT2, AV2, HC time, HC PD, HC radius) had no significant correlation with MD in treatment naïve POAG eyes.

Interestingly, when analyzed separately, shorter time of WEM was demonstrated to be associated with worse glaucoma damage in NTG, but not in HTG (Table 3). Decreased WEM in NTG patients indicated decreased orbital compliance, perhaps suggesting the buffering ability of the orbit tissues to the whole eyeball was reduced. That made the optic nerve head more vulnerable to forces, finally leading to increased susceptibility to glaucomatous damage. More studies should be conducted on the significant relevance of WEM in clinical setting. Regarding HTG, only axial length was associated with glaucoma severity in our study. The possible reason for the association between longer axial length and more severe glaucoma damage may be partly due to increased deformability of the eyeball with axial elongation. Eyeball elongation is often accompanied by a reduction of sclera collagen fiber bundles, and thus a thinner sclera[41] and laminar cribrosa,[42] leading to scleral rigidity decreased

and greater compliance of the eyeball.[43] Different involvement of biomechanics in glaucoma severity between NTG and HTG further suggested different pathogenic mechanisms existing between these two glaucoma subtypes. Our results added more biomechanical evidence for the underlying mechanism differences between NTG and HTG.

IOP and age have been demonstrated as important risk factors for visual field progression in glaucoma.[44] However, neither showed statistically significant association with glaucoma severity in our study. Several previous studies reported the lack of association between IOP and MD in untreated POAG patients as well.[40,45] Also, there was a study that observed that age was not correlated with glaucoma severity in POAG patients.[15] The lack of association between IOP and age with glaucoma severity in our study may be explained by the cross-sectional design and small sample size. Another possible reason for the nonsignificant association between age and glaucoma damage could be due to relatively young age of glaucoma patients in our study, in which the median age of NTG and HTG was 44 and 37.5 years, respectively.

Our study has several limitations. First, the sample size was small, and the participants were recruited from a single tertiary hospital, which may not necessarily represent for a more general normal and POAG population. In addition, the cross-sectional nature of the study made it only assess association but not causality. Longitudinal studies are necessary to further explore the relationship between baseline ocular biomechanics and glaucoma progression.

In conclusion, our study demonstrated NTG corneas were more deformable than those of normal controls and HTG. More importantly, our results showed glaucoma severity was correlated with different factors between NTG and HTG. Shorter time of WEM was independently associated with more severe visual field defect in NTG, whereas longer axial length was associated with glaucoma damage in HTG. Our findings may have implications for understanding the etiological differences between NTG and HTG. In future, more studies should be conducted on the biomechanical relevance of WEM in glaucoma.

Acknowledgments

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