·Clinical Research·

Comparison of corneal biomechanical properties in normal tension glaucoma patients with different visual field progression speed

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Abstract

• AIM: To compare the corneal biomechanical properties difference by ocular response analyzer (ORA) in normal tension glaucoma (NTG) patients with different visual field (VF) progression speed.

• METHODS: NTG patients with well-controlled Goldmann applanation tonometer (GAT) who routinely consulted Kitasato University Hospital Glaucoma Department between January 2010 and February 2014 were enrolled. GAT and ORA parameters including corneal compensated intraocular pressure (IOPcc), Goldmann estimated intraocular pressure (IOPg), corneal hysteresis (CH), corneal resistance factor (CRF) were recorded. VF was tested by Swedish interactive threshold algorithm (SITA)-standard 30-2 fields. All patients underwent VF measurement regularly and GAT did not exceed 15 mm Hg at any time during the 3y follow up. Patients were divided into four groups according to VF change over 3y, and ORA findings were compared between the upper 25th percentile group (slow progression group) and the lower 25th percentile group (rapid progression group).

• RESULTS: Eighty-two eyes of 56 patients were studied. There were 21 eyes (21 patients) each in rapid and slow progression groups respectively. GAT, IOPcc, IOPg, CH, CRF were 12.1±1.4 mm Hg, 15.8±1.8 mm Hg, 12.8±2.0 mm Hg, 8.4±1.1 mm Hg, 7.9±1.3 mm Hg respectively in rapid progression group and 11.5±1.3 mm Hg, 13.5±2.1 mm Hg, 11.2±1.6 mm Hg, 9.3±1.1 mm Hg, 8.2±0.9 mm Hg respectively in slow progression group (P=0.214, <0.001, 0.007, 0.017, 0.413, respectively). In bivariate correlation analysis, IOPcc, IOPcc-GAT and CH were significant correlated with m△MD (r=-0.292, -0.312, 0.228 respectively, P=0.008, 0.004, 0.039 respectively).

• CONCLUSION: Relatively rapid VF progression occurred in NTG patients whose IOPcc are rather high, CH are rather low and the difference between IOPcc and GAT are relatively large. Higher IOPcc and lower CH are associated with VF progression in NTG patients. This study suggests that GAT measures might underestimate the IOP in such patients.

• KEYWORDS: ocular response analyzer; intraocular pressure; corneal biochemical properties; visual field; normal tension glaucoma
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INTRODUCTION

The prevalence of primary open angle glaucoma (POAG) in Japan is 3.9% with 92% of POAG patients whose intraocular pressure (IOP) did not exceed 21 mm Hg, which is defined as normal-tension glaucoma (NTG)[1]. In some patients with well-controlled IOP, the visual field (VF) remains stable or progresses very slowly, while in others the condition is quite different: IOP is well controlled but VF progresses rapidly [2]. There have been a number of studies focusing on the pressure-independent pathway of glaucoma[3-7], but the accuracy of IOP measurement may play an important role in such cases.

Goldmann applanation tonometer (GAT) is currently the gold standard for IOP measurement, but these values (GAT-IOP) may be affected by central corneal thickness (CCT), corneal curvature, corneal astigmatism and other

corneal biomechanical properties [8-11]. Therefore, it is very important to find a new method to determine the true IOP.

Ocular response analyzer (ORA) (Reichert ©; Reichert Technologies, Buffalo, NY, USA) is a new device that is described as a non-contact tonometer. ORA can measure corneal hysteresis (CH), corneal resistance factor (CRF) and determine a specific corneal compensated intraocular pressure (IOPcc) which is less influenced by corneal viscoelasticity. There have been studies discussing the relationship between ORA measurements and structural or functional changes in glaucoma patients, but most of them have focused on patients with POAG or suspected glaucoma[2,12-15].

There are limited data on ORA measurements in NTG patients. Moreover, the relationship between corneal viscoelasticity, corneal thickness and VF progression in NTG patients remains unclear. In the current study, we obtained ORA parameters including IOPcc, Goldmann estimated intraocular pressure (IOPg), GAT, CH and CRF in NTG patients with well-controlled GAT-IOP. We compare ORA data in patients with different VF progression speed to see relatively rapid VF progression might occur in what kind of NTG patients.

SUBJECTS AND METHODS

This retrospective study was approved by the Kitasato University Hospital Review Board and followed the tenets of the Declaration of Helsinki. Informed consent was obtained from all patients included in this study. Patients routinely consulted Kitasato University Hospital glaucoma department between January 2010 and February 2014 and were usually seen at intervals of 3-6mo.

The inclusion criteria were as follows: NTG was defined by the presence of glaucomatous optic neuropathy [16] associated with reproducible VF abnormalities. GAT-IOP did not exceed 15 mm Hg including diurnal variation during the recent 3y, because NTG patients whose IOP exceed 16 mm Hg in the daytime are likely to have an IOP that exceeds 21 mm Hg at night[17].

The ocular examination included visual acuity, corneal parameters such as corneal curvature and corneal refractive power, GAT, ORA parameters including IOPcc, IOPg, CH, CRF and CCT. VF was examined by SITA-Standard 30-2 fields (Carl Zeiss Meditec, Inc., Dublin, CA, USA). The parameters of VF using for the current study were the mean deviation (MD) and the pattern standard deviation (PSD). The minimum criterion for a VF abnormality was a glaucoma hemifield test outside normal limits or a PSD result $<5\%$ on 2 consecutive reliable examinations. All enrolled patients underwent at least 5 VF tests to analyze VF progression statistically. We analyzed VF change by global trend analysis by MD slope. The MD slope, MD change per year (dB/y) was obtained from linear regression analysis of the HFA II glaucoma progression analysis software. MD change was calculated by MD slope multiply 3 because the follow-up period was 3y. And the PSD change was the difference between the VF results at last follow-up and the baseline ones.

All eyes had best corrected visual acuity $\geqslant$20/30. Refractive error of the patients was between -8.0 diopters and 8.0 diopters spherical equivalent and corneal astigmatism between -3.0 diopters and 3.0 diopters.

We excluded patients with an insufficient number of VF results because we could not analyze whether VF had progressed in such cases. Patients with other diseases that may affect the VF test and/or ORA test were also excluded. Patients who had undergone any type of intraocular surgery within the past 3mo before the participation in this study were also excluded [13]. Patients underwent VF test first and then IOP measurements were obtained in a random sequence in order to minimize the potential for a statistical effect of applanation on lowering IOP.

Corneal biomechanical properties were measured with ORA once at the patient's study visit. All patients were tested by one experienced doctor. The device obtains 2 measurements of the corneal response to the air pulse. The major outcomes are CH, CRF and IOPcc (mm Hg). The difference between the 2 pressures is CH (mm Hg). CRF is thought to be one of the indices of corneal elasticity based on CH, IOPg is the average of P1 and P2. IOPcc is a pressure measurement based on CH, which is thought little to be affected by corneal biomechanical properties. ORA can also provide CCT results[9,11,18]. A good quality reading was defined as one with symmetrical height of force-in and force-out waveform peaks and a waveform score >7 on a software-generated scale of 0 to 10[18-19].

Statistical Analysis Data were analyzed by statistical software (SPSS version 20.0 SPSS Inc., Chicago, IL, USA). Categorical data were compared by χ^2 tests. Continuous variables were tested for normal distribution. Variables with normal distribution are presented as mean ±SD and were compared by independent Student's t-test. Variables with skewed distribution are presented as median with interquartile range (IR) and were compared by Mann-Whitney U test. Bivariate correlation analysis was constructed to determine variables associated with VF damage. A two-tailed $P<0.05$ was considered significant.

RESULTS

There were 142 NTG patients with good follow-up during the study period, but only 82 eyes of 56 patients met the inclusion criterion of GAT-IOP (GATmax) not exceeding 15 mm Hg during the 3y. Therefore, 82 eyes of 56 patients were enrolled in this study. These 26 males and 30 females had an average age of 62.6y (range from 37-84y). One eye of 30 patients and both eyes of 26 patients were included. All patients were Asian. The included eyes underwent a

Table 1 Antiglaucoma eye drops of the patients

Treatment	Number (eyes)	Percentage (%)
None	16	19.5
PG	31	37.8
β-Blocker	11	13.4
CAI	1	1.2
PG+β-Blocker	11	13.4
PG+CAI	6	7.3
PG+β-Blocker+CAI	6	7.3

PG: Prostaglandin; CAI: Carbonic anhydrase inhibitor.

median of 7.1 (range from 5-12) VF tests during follow-up. There were 16 eyes (19.5%) without any kind of antiglaucoma eye drops, 43 eyes (52.4%) receiving one kind of eye drops, 17 eyes (20.7%) receiving 2 kinds of eye drops and 6 eyes (7.3%) receiving 3 kinds of eye drops. Details are showed in Table 1.

Patient general information, their ORA parameters and VF change over the 3y are listed in Table 2. In brief, the GAT on the day ORA obtained was 12.0 mm Hg, as the same as the median GAT (GATavg, 12 mm Hg) over the 3y. Both of such measurements were approximately 3 mm Hg lower than IOPcc (15.0 mm Hg). The average CH was 8.9 mm Hg and CRF was 8.1 mm Hg, which were both below normal limits [18,20]. The median MD change (m△MD) was -0.8 dB over the 3y, indicating approximately 0.3 dB VF loss per year.

Patients were divided into four groups according to the m△MD over 3y (Figure 1). The median, P25 and P75 value of the m△MD in the four groups are -2.1 (-3.2, -1.9) dB; -1.1 (-1.3, -0.9) dB; -0.5 (-0.6, -0.3) dB and 0.4 (0.1, 0.8) dB respectively. The data-box plots of CH, CRF, IOPcc and IOPg for 4 groups were shown in Figure 2. And findings were compared between the upper 25th percentile group (slow progression group, 21 eyes in total) and the lower 25th percentile group (rapid progression group, 21 eyes in total). Patient age, gender and the numbers of antiglaucoma eyedrops did not significantly differ between the two groups (P=0.484, 1.000, 0.396 respectively). There were no statistically significant differences of the parameters that may affect ORA results such as corneal curvature or corneal refractive power between the two groups (P=0.106, 0.101, respectively). And there were no significant differences in GAT, GATmax or GATavg between two groups (P=0.142, 0.890, 0.966, respectively).

ORA results showed that the average IOPcc in the rapid progression group was 15.8 mm Hg, significantly higher than that in the slow group (13.5 mm Hg) (P<0.001). The average IOPg in the rapid group was 12.8 mm Hg, significantly higher than that in the slow group (11.2 mm Hg) (P=0.006). The difference between IOPcc and IOPg was 3.0 mm Hg in the rapid group, significantly higher than 2.3 mm Hg in the slow group (P=0.035). The difference between IOPcc and GAT was 3.8 mm Hg in the rapid group, significantly higher than 1.9 mm Hg in the slow group (P=0.004).

The average CH in the rapid group was 8.4 mm Hg, significantly lower than 9.3 mm Hg in the slow group (P=

Table 2 General and clinical characteristics of the patients

Characteristics	$\bar{x} \pm s$ (median)	Range
Age	62.6±11.8	37-84
Gender (M/F)	26/30	
Eyedrops	1.2±0.8	0-3
Corneal curvature	7.73±0.23	7.27-8.49
Corneal refractive power	43.7±1.3	39.75-46.50
GAT (mm Hg)	12.0±1.5	9-15
GATmax	14 (14, 15)	10-15
GATavg	12 (12, 13)	9-14
IOPcc (mm Hg)	15.0±2.5	9.3-20.1
IOPg (mm Hg)	12.3±2.2	7.4-17.7
IOPcc-IOPg (mm Hg)	2.6±1.4	-0.9-5.6
IOPcc-GAT (mm Hg)	2.9±2.2	-2.0-9.1
CRF (mm Hg)	8.1±1.2	5.6-11.5
CH (mm Hg)	8.9±1.3	6.1-11.7
CCT (μm)	520.0±26.8	474-580
MD (dB)	-5.2 (-9.6, -2.5)	-27.86-1.91
PSD (dB)	9.3±4.4	1.66-18.34
Baseline MD (dB)	-4.9 (-7.8, -1.3)	-28.15-1.48
Baseline PSD (dB)	8.5 (3.7, 12.5)	1.72-18.31
△MD (dB)	-0.8 (-1.8, -0.1)	-5.58-1.58
△PSD (dB)	0.9 (-0.2, 1.8)	-2.75-6.67

GAT: Goldmann applanation tonometer; IOP: Intraocular pressure; IOPcc: Corneal compensated intraocular pressure; IOPg: Goldmann estimated intraocular pressure; CRF: Corneal resistance factor; CH: Corneal hysteresis; CCT: Central corneal thickness; MD: Mean deviation; PSD: Pattern standard deviation. Data are skewed distribution and presented as median (IR).

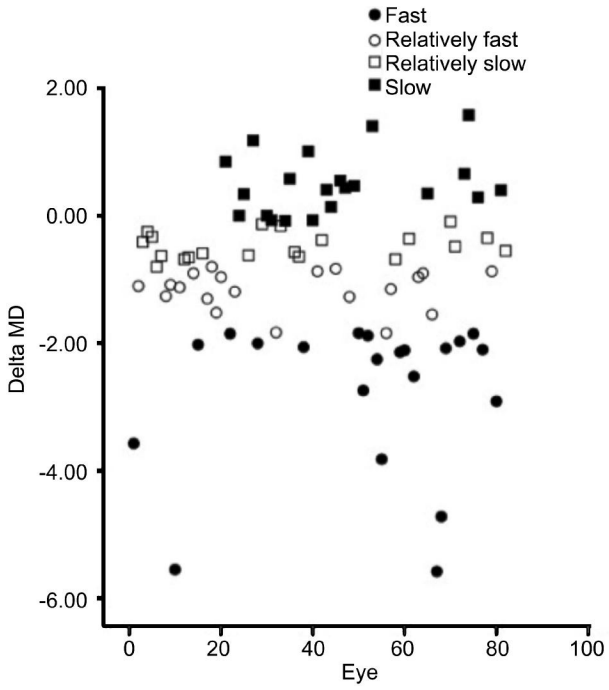

Figure 1 Delta MD of all patients over 3y.

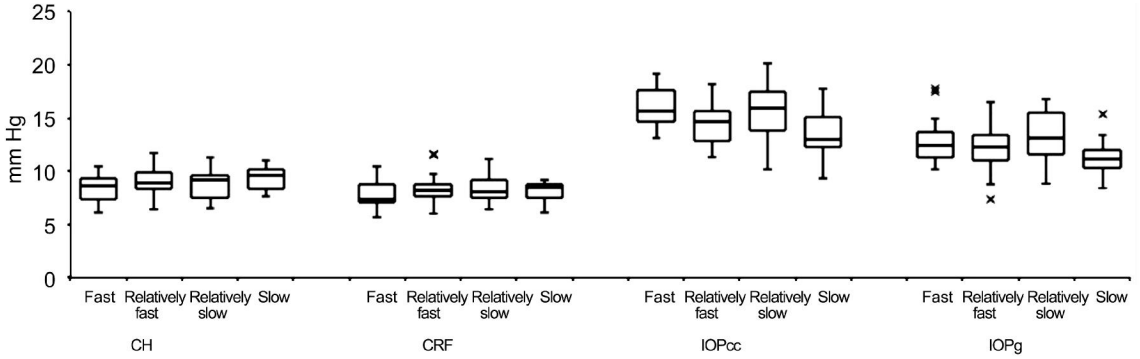

Figure 2 The data-box plots of CH, CRF, IOPcc and IOPg for 4 groups.

0.009). The average CRF in the rapid group was 7.9 mm Hg, which was lower than 8.2 mm Hg in the slow group, but the difference did not reach significance (P=0.310). There was no significant difference in CCT between the two groups (P=0.849).

At baseline, MD did not significantly differ between the rapid and slow group (P=0.134) but PSD significantly differ between the two groups (P=0.037). After 3y, there was a significant difference. MD and PSD were -8.8 dB and 10.4 dB in the rapid group, but -2.1 dB and 6.4 dB in the slow group (P=0.001, 0.002, respectively). Therefore, the VF change was also significantly different between the two groups, m△MD and m△PSD were -2.1 dB and 1.9 dB in the rapid group, but 0.4 dB and -1 dB in the slow group (P<0.001, 0.036 respectively) (Table 3).

In bivariate correlation analysis, the Pearson correlation coefficient of CH, CRF *etc.* were listed in Table 4. Briefly, IOPcc, IOPcc-GAT and CH were significant correlated with m△MD (r=-0.292, -0.312, 0.228 respectively and P= 0.008, 0.004 and 0.039 respectively).

Table 3 The comparison of the worst and best 25th percentile group

Characteristics	Rapid (n=21)	Slow (n=21)	P
Age	60.9±12.2	62.2±12.9	0.484
Gender (M/F)	10/11	11/10	1.000
Eyedrops	1.4±0.9	1.2±0.9	0.396
Corneal curvature	7.73±0.23	7.65±0.16	0.106
Corneal refractive power	43.67±1.29	44.13±0.91	0.101
GAT (mm Hg)	12.1±1.4	11.5±1.3	0.142
GATmax	14 (14, 14.5)	14 (13.5, 14)	0.890
GATavg	12 (12, 12)	12 (11.5, 12.5)	0.966
IOPcc (mm Hg)	15.8±1.8	13.5±2.1	<0.001
IOPg (mm Hg)	12.8±2.0	11.2±1.6	0.006
IOPcc-IOPg (mm Hg)	3.0±1.3	2.3±1.1	0.035
IOPcc-GAT (mm Hg)	3.8±2.1	1.9±1.8	0.004
CRF (mm Hg)	7.9±1.3	8.2±0.9	0.310
CH (mm Hg)	8.4±1.1	9.3±1.1	0.009
CCT (μm)	516.1±28.2	515.3±25.0	0.849
MD (dB)	-8.8 (-11.4, -3.4)	-2.1 (-5.5, 0.1)	0.001
PSD (dB)	10.4±4.6	6.4±3.7	0.002
Baseline MD (dB)	-5.4 (-9.3, -1.1)	-2.9 (-5.7, -0.6)	0.134
Baseline PSD (dB)	8.9±5.2	6.1±3.8	0.037
△MD (dB)	-2.1 (-3.2, -1.9)	0.4 (0.1, 0.8)	<0.001
△PSD (dB)	1.9 (0.3, 2.6)	-1 (-0.7, 1.4)	0.036

Data are skewed distribution and presented as median (IR).

Table 4 The Pearson correlation coefficient of bivariate correlation analysis

Characteristics	r	P
Age	-0.044	0.693
Corneal curvature	-0.058	0.606
Corneal refractive power	0.056	0.619
GAT (mm Hg)	-0.020	0.860
GATmax	0.006	0.960
GATavg	0.109	0.330
IOPcc (mm Hg)	-0.292	0.008
IOPg (mm Hg)	-0.206	0.063
IOPcc-IOPg (mm Hg)	-0.191	0.085
IOPcc-GAT (mm Hg)	-0.312	0.004
CRF (mm Hg)	0.106	0.344
CH (mm Hg)	0.228	0.039
CCT (μm)	-0.042	0.709

DISCUSSION

The current study investigated whether there was difference of corneal biomechanical properties in NTG patients with different VF progression speed. The results demonstrated that in NTG patients whose GAT-IOP did not exceed the mid-teens during the recent 3y, relatively rapid VF progression occurred in patients with rather high IOPcc, rather low CH and relatively large difference between IOPcc and GAT. IOPcc and CH were significantly correlated with VF progression. These findings indicated that IOPcc and CH might be associated with VF progression in NTG patients.

Recently, there have been some studies focusing on corneal biomechanical properties, the accuracy of IOP measurement and VF progression. The study by Congdon *et al*[13] in 2006 included 230 subjects (POAG, suspected POAG and ocular hypertension) and showed that neither CCT nor CH was related to VF progression. However, other studies suggested that there was relationship between corneal biomechanical properties and VF progression [2,12,14-15]. Anand *et al*[12] compared CH and VF asymmetry in open angle glaucoma. Their findings demonstrated that CH, CRF and IOPcc were risk factors for worse VF. Mansouri *et al*[14] compared corneal biomechanical properties and VF between glaucoma

Table 5 Summary of recent similar researches

Authors	Eye/Patient	Diagnosis	MD (dB)	PSD (dB)	GAT (mm Hg)	CH (mm Hg)	CRF	IOPcc (mm Hg)	Associated with worse VF
Congdon *et al*[13]	N/A/230	POAG; POAG suspect; OH	N/A	N/A	N/A	N/A	N/A	N/A	Neither nor CH
Anand *et al*[12]	234/117	POAG with asymmetric VF	Worse eye -11.2±6.4 Better eye -2.1±2.5	Worse eye 9.6±3.2 Better eye 3.2±2.3	14	Worse eye 8.2±1.9 Better eye 8.9±1.9	Worse eye 8.6±2.0 Better eye 8.8±2.1	Worse eye 17.4 Better eye 16.9	CH; CRF; IOPcc
Mansouri *et al*[14]	299/191	Glaucoma; glaucoma suspect	Glaucoma -3.3±3.3 Suspect -0.38±1.6	Glaucoma 4.0±3.0 Suspect 1.6±0.9	Glaucoma 15.0±5.6 Suspect 16.6±4.5 (IOPg)	Glaucoma 9.4±1.7 Suspect 10.4±1.7	Glaucoma 9.4±2.0 Suspect 10.7±2.1	Glaucoma 16.6±5.4 Suspect 6.9±4.1	CH; CRF
De Moraes *et al*[2]	153/153	POAG; NTG; XFG; ACG; JOAG; PG	Progress -5.3±4.1 Non-prog -6.5±6.8	Progress 4.7±3.0 Non-prog 5.4±4.3	Progress 15.3±3.7 Non-prog 14.7±3.9	Progress 7.5±1.4 Non-prog 9.0±1.8	Progress 7.6±1.3 Non-prog 8.9±2.0	Progress 18.0±5.3 Non-prog 16.5±5.0	CH
Medeiros *et al*[15]	114/68	POAG	Baseline -2.45±3.22	Baseline 3.32±2.84	Baseline 16.1±3.8	Baseline 9.5±1.7	N/A	N/A	Baseline; CH; baseline GAT

patients and suspected glaucoma patients and found worse CH, CRF and CCT values in the glaucoma group. De Moraes *et al* [2] categorized different types of glaucoma patients based on whether VF progressed and concluded that CH and CCT are associated with VF progression. Most recently, a prospective longitudinal study by Medeiros *et al*[15] claimed that baseline CH and baseline GAT were associated with the risk of glaucoma progression. A summary of recent research is presented in Table 5. Our study differed from the previous studies are all of the patients included in the current study were Asian and NTG patients. A group comprised of a single race might demonstrate fewer anatomic differences than a group comprised of different races[21].

The findings of the current study concurred with recent articles suggesting that corneal biomechanical properties were associated with VF change [2,12,14-15]. This difference between IOPcc and GAT was similar to what was found in other studies [2,12]. The VF loss of approximately 0.3 dB per year which did not reach the progression standard of 1 dB per year[22], indicating that the patients included in the current study were relatively well controlled. These results of the comparison of rapid progression group and slow progression group indicate that patients showing rapid progression had rather high IOPcc, rather low CH which along with relatively large difference between IOPcc and GAT. This finding suggests that the IOP values obtained of such patients during follow up were underestimated. In such cases, the optic nerve might be chronically exposed to relatively high IOP resulting in obvious progression of VF.

There are lots of experimental and clinical evidence that the biomechanical properties of the eyeball may be related to those of the optic nerve complex [23-27]. Scleral stiffness and collagen fiber organization influence IOP-induced deformation of the optic nerve head in a computer model[27]. Downs *et al* [24] reported a change in the viscoelastic properties of peripapillary sclera on exposure to chronic IOP elevations in monkey eyes with glaucoma. Another study reported that monkey eyes with stiff or thick sclera seemed to be less prone to biomechanical changes in response to chronic IOP elevation [26]. Another experimental study found an association between higher CH and greater optic nerve deformation when IOP was artificially elevated in glaucoma eyes[25]. We think the biomechanical properties of the eyeball in NTG patients may also be related to those of the optic nerve complex. So it may explain why the VF progress rapidly of NTG patients with rather high IOPcc and rather low CH. But it remains unclear whether there is a causal relationship between CH and VF progression or not [2,12-15]. It may be that the corneal biomechanical properties change first, then compliance of the eyeball to IOP decreases and pressure on the optic nerve head increases, finally causing retina nerve fiber layer defects (RNFLD) and glaucomatous VF change. Another possibility is that lower CH presents as a result of chronic IOP elevation, similar to optic disc cupping and RNFLD. A third possibility is that these are simultaneous but independent changes. Further research is needed to clarify the nature of the association.

As far as was concerned, unlike ocular hypertension treatment study [28], we did not find was associated with VF progression in our study. This may be because the patients in their study had hypertension, while our study investigated NTG. And other studies did not find any relationship between and VF progression too[12-13,15,25,29].

There are several limitations in current study. First, it is a small sample study. It is because the inclusion criteria were very strict. Although this choice reduced the number of patients, it increased the homogeneity and reduced the influence of other confounding factors. Second, both eyes of some patients were included in this study, but only one eye of each patient was compared in the two groups. Third,

because of the retrospective nature of the study, the baseline corneal biomechanical properties of the patients were not available.

The current study demonstrated that relatively rapid VF progression occurred in NTG patients with rather high IOPcc, rather low CH and relatively large difference between IOPcc and GAT. These findings indicated that IOPcc and CH were associated with VF progression in NTG patients.

Since treatment to decrease IOP is the only therapy confirmed by evidence-based medicine for controlling the progression of VF in NTG patients, the "target" IOP should take corneal biomechanical properties into consideration. IOPcc is significantly higher than GAT in those who appear to progress faster. So IOPcc may be a better method of monitoring IOP in NTG patients and patients with low CH should undergo more thorough investigation and careful monitoring.

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