Normal-tension glaucoma in high myopia is associated with the presence of posterior staphyloma and subfoveal scleral thinning.

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J. H. Park

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ABSTRACT

Normal-Tension Glaucoma in High Myopia is Associated with the Presence of Posterior Staphyloma and Subfoveal Scleral Thinning.

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Purpose: To evaluate the ocular biometry in patients with normal-tension glaucoma (NTG) and highly myopic eyes and to identify the ocular parameters significantly associated with the biomechanical changes of high myopia and glaucomatous optic neuropathy.

Materials and Methods: The study included 45 patients with NTG and 38 controls with highly myopic eyes (≤ -6 diopters (D) or axial length ≥ 26.0 mm). The subfoveal retinal, choroidal, scleral thickness and the posterior staphyloma heights were examined from enhanced depth imaging spectral-domain optical coherence tomography (EDI-OCT). Scleral thickness and posterior staphyloma height in patients with highly myopic NTG was compared with those in highly myopic, non-glaucomatous eyes. A Pearson correlation was calculated to assess the relationships of scleral thickness and posterior staphyloma height with ocular parameters. Multiple regression analysis was performed to identify the ocular parameters significantly associated with the changes

of scleral thickness and posterior staphyloma height.

Results: Subfoveal scleral thickness could be measured in 32(71.1%) and 24(63.2%) of highly myopic NTG and highly myopic eyes, respectively. Highly myopic NTG eyes had thinner subfoveal scleral thickness (473.03 ± 43.75 versus(vs). 579.46 ± 75.87 ㎛, *P* < .001) and higher posterior staphyloma (97.80 ± 70.19 vs. 62.83 ± 32.01 ㎛, *P* = .027) than highly myopic, non-glaucomatous eyes. Subfoveal scleral thickness was significantly correlated with age (r = -0.453, *P* =.014), axial length (r = -0.343, *P*=.040), corneal hysteresis (CH) (r = 0.460, *P* = .010), and the posterior staphyloma height of superior quadrant (r = -0.538, *P* = .003), nasal quadrant (r = -0.519, *P* = .004) and the sum of four quadrants (r = -0.424, *P* = .022) in highly myopic NTG eyes. Corneal hysteresis (B = 2.694, *P* = .015), corneal resistance factor (B=-2.916, *P* = .010) and the posterior staphyloma height of nasal quadrant (B = -0.463, *P* = .017) were most significantly associated with the subfoveal scleral thickness in highly myopic NTG eyes.

Conclusion: Subfoveal scleral thinning and ununiform posterior staphyloma formation were closely related in highly myopic NTG eyes. CH may be a clinically useful parameter to demonstrate the biomechanical material properties such as scleral stiffness.

Key words : corneal hysteresis, high myopia, normal tension glaucoma, posterior staphyloma, scleral thickness

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I. INTRODUCTION

High myopia is one of the leading causes of visual disturbance in the world. Asian countries have higher prevalence of severe myopia(≤ -6 D), reported to be 5.5% in Japan, 3.6% in Singapore, 2.8% in China, and 2.3% in Korea, but it is estimated that 1% of the global population exhibits high myopia.[1-5] High myopia is associated with an axial elongation of the globe, leading to the stretching and thinning of the posterior ocular tissues and further pathological changes.[6] Pathological studies show that highly myopic eyes have a significantly thinner retina, choroid and sclera than age-matched controls without myopia.[7] The structural changes of posterior ocular tissues is considered to be the theoretical background of the visual impairments and the glaucomatous changes in the optic nerve head in eyes with high myopia.

Recents studies have demonstrated the importance of the posterior ocular structures such as lamina cribrosa and sclera in the pathogenesis of glaucoma.[8-10] The mechanical influence of the peripapillary sclera to the lamina cribrosa is considered to be important in that scleral deformations make an effect to the stiffness and thickness of the sclera and affect the optic nerve head biomechanics by aggravating the strain and stress.[11] The increased risk for glaucoma in myopic

eyes may be related in part to the sclera's biomechanical material properties. There have been some hypotheses for scleral remodeling mechanisms, for instance, a narrowing and dissociation of the collagen fibers, or a downregulation of certain extracellular matrix components constituting the sclera.[12,13] However, to date few studies investigated the association between the scleral mechanical changes and the increased risk for glaucoma in highly myopic eyes.

Posterior staphyloma is a protrusion of the posterior shell of the globe, which is considered to be a hallmark of high myopia. The scleral shell of highly myopic eyes has increased elasticity and a tendency to expand.[14] Recent reports showed that there is a significant difference of the subfoveal scleral thickness depending on the presence of posterior staphyloma, and the sclera at the posterior pole stretches ununiformly in highly myopic eyes.[15] Especially the mechanical stretching nasally and superiorly around the fovea most significantly influences the subfoveal scleral thinning, and the staphyloma in this area may be associated with axial elongation.[16] Thus, the posterior staphyloma formation is recognized as an important risk factor to cause high myopia related diseases.

Herein we measured the thicknesses of posterior segments of eyes and the posterior staphyloma heights based on the images obtained by EDI-OCT in highly myopic NTG patients and controls with high myopia. And the relationships between the scleral thicknesses, the posterior staphyloma heights, and other ocular parameters were evaluated.

II. MATERIALS AND METHODS

1. Participants

This retrospective study was approved by the Institutional Review Board (IRB) of Ewha Womans University Mokdong Hospital, Seoul, Korea, and was

conducted in accordance with the tenets of the Declaration of Helsinki. This study investigated 45 adults with normal tension glaucoma and high myopia and 38 controls with high myopia. Participants were recruited from Ewha Womans University Mokdong Hospital between October 2013 and March 2014. Informed consent was obtained from all participants.

A. Inclusion Criteria

The inclusion criteria were (1) phakic highly myopic eyes, defined as a spherical equivalent refractive error less than -6.0 D or an axial length longer than 26.0 mm; (2) no posterior abnormalities such as choroidal neovascularization, foveoschisis, macular hole, or whitish round atrophy at the fovea; (3) best corrected visual acuity (BCVA) better than 20/40; and (4) both SD-OCT (Spectralis; Heidelberg Instruments, Inc., Heidelberg, Germany) data and axial length measured by an inferometer (IOL Master; Carl Zeiss Meditec, Inc.).

B. Exclusion criteria

The exclusion criteria were (1) eyes with media opacities such as dense cataracts preventing detailed fundus observation; (2) aphakic or pseudophakic eyes; (3) eyes with axial lengths longer than 30.0 mm; and (4) eyes undergoing refractive surgery. Subjects with any abnormalities (including a large parapapillary atrophy) in the circumpapillary region that affected the scan ring where the OCT RNFL thickness measurements were obtained were excluded from this study. After ophthalmic evaluation, the right eye was randomly selected for inclusion in cases in which both eyes of the patient were eligible for the study.

C. Definition of normal-tension glaucoma

NTG was defined as the presence of an abnormal glaucomatous optic disc (diffuse or localized neuroretinal rim loss, excavation, and retinal nerve fiber layer (RNFL) defects); an abnormal glaucomatous visual field (VF); and an intraocular pressure (IOP) ≤ 21 mmHg (without topical medical treatment). The control group was defined as those having IOP ≤ 21 mmHg, with no history of increased IOP, the absence of glaucomatous disc appearance, no identifiable RNFL defect according to OCT RNFL scans, and normal VF results.

2. Examinations

The clinical examinations included measurement of BCVA, slit-lamp biomicroscopy with or without contact lens, Goldmann applanation tonometry, refractive error by an autorefractometer (Topcon, Tokyo, Japan), axial length by partial coherence interferometry (IOL Master; Carl Zeiss Meditec, Inc.), dilated fundoscopic examination using a 90-diopter lens, automated perimetry using the 30-2 Swedish Interactive Threshold Algorithm standard program (Humphrey Visual Field Analyzer; Carl Zeiss Meditec, Dublin, CA), and Spectralis SD-OCT (Heidelberg Instruments, Inc., Heidelberg, Germany). The refraction was further refined subjectively by experienced ophthalmologists. Refraction data were converted to spherical equivalents, which was calculated by adding the spherical refractive error (in dioptres [D]) to one-half the cylindrical refractive power. Central corneal thickness (CCT) and corneal biomechanical properties such as CH or corneal resistance factor (CRF) were measured using ultrasound pachymetry (Tomey, Nagoya, Japan) and the Ocular Response Analyzer (ORA; Reichert Ophthalmic Instruments Inc., Depew, NY).

3. Measurement of thicknesses of the posterior ocular tissues

Retinal, choroidal, and scleral thicknesses were measured at the fovea. Two independent observers (JHP, SYK) using the caliper function of the built-in software of the OCT measured in a blind fashion. Retinal thickness was defined as the vertical distance from the RPE (the outermost hyperreflective line at the retina-choroidal interface) to the retinal surface. Choroidal thickness was defined as the vertical distance from the RPE line to the hyperreflective line behind the large vessel layers of the choroid, presumed to be the choroid-sclera interface. Scleral thickness was defined as the distance from the choroid-sclera interface to the outer scleral border and measured in eyes whose outer scleral border could be clearly distinguished from the fat tissues in the retro-ocular structures. Subfoveal scleral thickness was defined as the average of 3 measurements – from the subfoveal point and 1000㎛ temporal and 1000㎛ nasal from the subfoveal point. All measurements were performed perpendicular to the RPE line.

4. Measurement of the posterior staphyloma height

Selection of the posterior staphyloma was performed in eyes with type I and/or II staphyloma (classification by Curtin[17]), which are the most prominent type and involve the macular region, and eyes that, in EDI-OCT images, the curvature of the inner scleral surface was symmetrically centered on the fovea. OCT images of staphyloma were excluded that the fovea was not situated at the bottom of the curvature and the contour of the inner scleral surface was irregular or curved posteriorly with the curvature asymmetrical around the central fovea. The posterior staphyloma height or depth was defined as the distance from the RPE line beneath the fovea to the nasal and temporal edge of the horizontal scan and superior and inferior vertical scan including the fovea. Specifically, each posterior staphyloma height was measured as the horizontal distance between the subfoveal

RPE and the peripheral RPE 2 mm from the fovea in the four quadrants. The sum of these four measurements was used as posterior staphyloma height in this study.

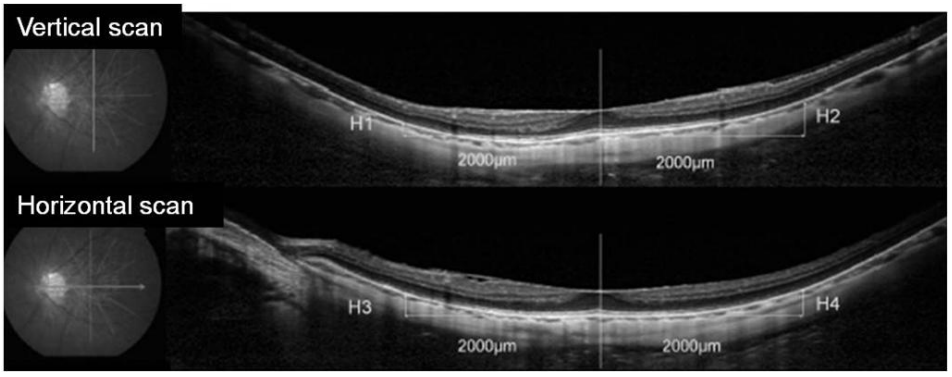

Figure 1. The posterior staphyloma height or depth was defined as the distance from the RPE line beneath the fovea to the nasal and temporal edge of the horizontal scan and superior and inferior vertical scan including the fovea. Specifically, each posterior staphyloma height was measured as the horizontal distance between the subfoveal RPE and the peripheral RPE 2 mm from the fovea in the four quadrants. The sum of these four measurements was used as posterior staphyloma height.

5. Measurement Reproducibility

In this study, the points of the chorioscleral border and the outer scleral border were decided manually by two masked observers. The intraobserver reproducibility was evaluated with the intraclass correlation coefficient (ICC) from a 2-way mixed-effect model. The interobserver reproducibility was evaluated with the averaged ICC values calculated by the Spearman-Brown prophecy formula.

6. Statistical Analysis

Differences for continuous variables including age, refraction error, axial length, corneal hysteresis, and scleral thickness were compared between the controls and the eyes with NTG by Student's *t*- test. Differences for categorical data including gender and the prevalence of a posterior staphyloma were compared using the χ^2 test. The correlation between the subfoveal scleral and choroidal thicknesses and the various ocular parameters was analyzed using Pearson tests for rank correlation coefficients. Multivariate linear regression model was created to investigate the association between the subfoveal scleral thickness and the patient's age and measured continuous variables. Statistical significance was defined at P less than 0.05. Statistical analyses were performed using the SPSS software (version 21.0; SPSS Inc., Chicago, IL).

III. RESULTS

EDI-OCT images of 45 patients with NTG and 38 controls were obtained. Of these 83 eyes, 32 (71.1%) of the patients with NTG and 24 (63.2%) of the controls were satisfied with two criteria that the curvature of the inner scleral surface is symmetrically centered on the fovea and the outer scleral border is clear and identifiable. In the end, these qualified eyes were considered for the measurement and analysis of posterior ocular parameters. Intraobserver and interobserver reproducibility showed excellent measurement reproducibility, with an ICC between 0.970 and 0.996, and the mean ICC of 0.959 (0.926-0.977) for the subfoveal scleral thickness.

1. Baseline characteristics

Age, gender, logMAR visual acuity, refractive error, and axial length were similar in the control and NTG groups. With regard to the corneal parameters, mean K value, CCT, CH, and CRF showed significant differences between the control and NTG groups (P = .005, P = .018, P = .039, P = .033, respectively). (Table 1.)

Table 1. Baseline characteristics of patients with normal-tension glaucoma and controls with myopia

	Control (n=38)	NTG (n=45)	*P*
Age (year)	44.75 ± 10.71	49.44 ± 11.15	0.065
Gender, female (%)	19 (50.0%)	15 (33.3%)	0.179
logMAR visual acuity	0.01 ± 0.02	0.02 ± 0.05	0.150
Spherical equivalent (diopter)	-7.98 ± 1.44	-7.36 ± 2.28	0.137
Axial length (mm)	26.59 ± 0.91	27.11 ± 1.11	0.055
Mean K (diopter)	43.94 ± 0.59	43.22 ± 1.11	0.005
Central corneal thickness (㎛)	571.72 ± 36.61	549.01 ± 36.33	0.018
CH (mmHg)	10.97 ± 1.76	10.43 ± 1.70	0.039
CRF (mmHg)	11.43 ± 1.89	10.37 ± 1.81	0.033
Intraocular pressure (mmHg)	13.95 ± 2.55	13.11 ± 2.95	0.061
Average RNFL thickness (㎛)	84.11 ± 8.83	69.84 ± 13.78	<0.001
Mean deviation of perimetry (dB)	-1.14 ± 1.11	-5.64 ± 4.48	<0.001
Posterior staphyloma, Number of eyes (%)	24 (63.2%)	32 (71.1%)	0.487

Values are presented as mean ± standard deviation.

CH, corneal hysteresis; CRF, corneal resistance factor; dB, decibel; RNFL, retinal nerve fiber layer.

2. Thicknesses of the posterior ocular parameters

The mean ± standard deviation (SD) thicknesses of the subfoveal retina were 227.21 ± 15.78 ㎛ in the control group and 217.75 ± 20.91 ㎛ in the NTG group. (P = .408) The subfoveal choroidal thicknesses were 192.83 ± 66.98 ㎛ in the control group and 148.25 ± 72.85 ㎛ in the NTG group. (P = .104) The subfoveal scleral thicknesses were 579.46 ± 75.87 ㎛ in the control group and 473.03 ± 43.75 ㎛ in the NTG group. (P < .001)

The posterior staphyloma heights of the sum of four directions were 62.83 ± 32.01 ㎛ in the control group and 97.80 ± 70.10 ㎛ in the NTG group. The posterior staphyloma heights of the superior scan were 96.38 ± 82.01 ㎛ in the control group and 161.78 ± 159.35 ㎛ in the NTG group. The posterior staphyloma heights of the nasal scan were 41.63 ± 55.17 ㎛ in the control group and 89.31 ± 121.82 ㎛ in the NTG group. All of these differences were significant (P = .027, P = .044, P = .037, respectively). The posterior staphyloma heights of the inferior and temporal scans were not significantly different in the control and NTG groups.

Table 2. Posterior ocular parameters of patients with normal-tension glaucoma and controls with myopia

	Control (n=24)	NTG (n=32)	*P*
Subfoveal retinal thickness (㎛)	227.21 ± 15.78	217.75 ± 20.91	0.408
Subfoveal choroidal thickness (㎛)	192.83 ± 66.98	148.25 ± 72.85	0.104
Subfoveal scleral thickness (㎛)	579.46 ± 75.87	473.03 ± 43.75	<0.001
Posterior staphyloma height (㎛)	62.83 ± 32.01	97.80 ± 70.10	0.027
Superior	96.38 ± 82.01	161.78 ± 159.35	0.044
Inferior	27.71 ± 59.81	29.97 ± 97.63	0.921
Nasal	41.63 ± 55.17	89.31 ± 121.82	0.037
Temporal	85.50 ± 59.05	110.03 ± 84.53	0.230

Values are presented as mean ± standard deviation.

3. Relationships of ocular parameters and subfoveal scleral thickness

Before regression analysis, univariate analysis using Pearson correlation test was performed to determine the correlation between subfoveal scleral thickness and ocular variables. In the control group, there were no significant relationships between subfoveal scleral thickness and variable ocular parameters including age, BCVA, axial length, CCT, CH, CRF, MD of perimetry, and the posterior staphyloma heights. In the NTG group, the subfoveal scleral thickness showed a significant negative correlation with age (r = -0.452, P = .014), axial length (r = -0.343, P = .040) and the superior, nasal, and the sum of posterior staphyloma heights (r = -0.424, P = .022; r = -0.538, P = .003; r = -0.519, P = .004; respectively). On the other hand, the subfoveal scleral thickness had a significant positive correlation with corneal hysteresis (r = 0.460, P = .010). The subfoveal

scleral thickness was not significantly associated with BCVA, CCT, CRF, MD of perimetry, and average RNFL thickness in the NTG group.

Stepwise multiple regression analysis in the NTG group showed 3 significant factors most associated with the subfoveal scleral thickness: corneal hysteresis (B = 2.694, *P* = .015), corneal resistance factor (B=-2.916, *P* = .010) and the posterior staphyloma height of nasal quadrant (B = -0.463, *P* = .017).

Table 3. Relationship of scleral thickness with age, axial length, central corneal thickness, corneal hysteresis, corneal resistance factor, mean deviation of visual field, and posterior staphyloma height in patients with normal-tension glaucoma and myopia

	Control		NTG	
	R	*P*	R	*P*
Subfoveal scleral thickness				
Age	-0.237	0.157	-0.453	**0.014**
Axial length	-0.101	0.591	-0.343	**0.040**
Central corneal thickness	0.192	0.381	-0.141	0.443
Corneal hysteresis	-0.082	0.718	0.460	**0.010**
Corneal resistance factor	-0.045	0.842	0.220	0.242
RNFL thickness	-0.458	**0.024**	0.020	0.916
Posterior staphyloma height	0.235	0.268	-0.424	**0.022**
PSH, superior	0.019	0.928	-0.538	**0.003**
PSH, inferior	0.407	0.054	-0.093	0.571
PSH, nasal	0.333	0.112	-0.519	**0.004**
PSH, temporal	-0.110	0.610	0.160	0.330

MD, mean deviation; PSH, posterior staphyloma height; RNFL, retinal nerve fiber layer.

The bold values indicate associations that were statistically significant ($p<0.05$).

Table 4. Relationship of posterior staphyloma heights with age, axial length, refractive error, central corneal thickness, corneal hysteresis, retinal thickness and choroidal thickness in patients with normal-tension glaucoma and myopia

	PSH, sum		PSH, nasal		PSH, superior	
	R	P	R	P	R	P
Age	0.527	**0.003**	0.398	**0.032**	0.386	**0.039**
Axial length	0.836	**<0.001**	0.778	**<0.001**	0.799	**<0.001**
Spherical equivalent	-0.576	**0.001**	-0.643	**<0.001**	-0.521	**0.004**
Central corneal thickness	-0.350	0.111	-0.040	0.861	-0.360	0.100
Corneal hysteresis	-0.523	**0.010**	-0.338	0.115	-0.571	**0.004**
Average RNFL thickness	-0.371	**0.047**	-0.471	**0.010**	-0.318	0.093
Subfoveal retinal thickness	-0.218	0.256	-0.084	0.664	-0.186	0.334
Subfoveal choroidal thickness	-0.777	**<0.001**	-0.571	**0.001**	-0.628	**<0.001**

PSH, posterior staphyloma height; RNFL, retinal nerve fiber layer.

The bold values indicate associations that were statistically significant (p<0.05).

Table 5. Multiple linear regression analyses with scleral thickness in patients with normal-tension glaucoma and myopia

	Univariate model		Multivariate model	
Variable	Coefficient	*P*	Coefficient	*P*
Age	-0.663	0.090		
Spherical equivalent	-0.454	0.142		
Axial length	-0.674	0.105		
Central corneal thickness	-0.517	0.337		
Corneal hysteresis	2.181	0.016	2.694	0.015
Corneal resistance factor	-2.045	0.011	-2.916	0.010
MD of perimetry	0.344	0.276		
Average RNFL thickness	0.110	0.746		
PSH, sum	-0.302	0.112		
PSH, superior	-0.066	0.732		
PSH, inferior	0.111	0.566		
PSH, nasal	-0.482	0.008	-0.463	0.017
PSH, temporal	-0.046	0.812		

CI, confidence interval; MD, mean deviation; OR, odds ratio; PSH, posterior staphyloma height; RNFL, retinal nerve fiber layer.

IV. DISCUSSION

The goal of this study was to investigate the characteristics of the posterior segments of eyes with high myopia and NTG and specifically identify which ocular parameters were most associated with scleral thinning and posterior staphyloma formation. This information is valuable for understanding the structural and biological mechanism of high myopia and glaucomatous optic neuropathy and may provide insight into the relationship between the material properties and the pathogenesis of myopia and glaucoma.

A major result of this study was that the subfoveal scleral thickness was thinner in the highly myopic NTG eyes compared to the myopic controls. According to previous studies, a thinner sclera was found in highly myopic eyes than eyes without axial elongation.[15] Other studies have observed the scleral thinning in glaucoma by computational modeling studies using the finite element method[10,18] and investigations on the nonlinear properties of the sclera[19,20], and have demonstrated that the scleral deformations have significant effects on the biomechanical environment of the optic nerve head (ONH) complex. Modeling studies have indicated that several properties, such as the scleral geometry, thickness, and the material properties, are all influential factors to determine the ONH biomechanics by IOP-related stress and strain.[9,10,18] Quigley and associates reported that mice with a mutation in the collagen gene, the main component of sclera, may respond differently to IOP elevation. Elevated IOP caused the scleral remodeling and alterations in the composition of the sclera extracellular matrix.[11] Most existing studies have focused on the scleral thickness, because the measurement of other scleral parameters in human eyes in vivo in not possible. Many researchers have pointed out the exclusive measurement of the scleral thickness as a limitation of their investigations. In fact, the stiffness of the sclera was the most influential factor in several studies.[21,22] It is possible that there is a compensatory mechanism whereby individuals with thinner sclera have tissue that

is stiffer, resulting in similar biomechanical behavior to a thicker, weaker tissue.[23] Recently published models have underlined that the ocular connective tissues have nonlinear material properties of viscoelasticity, as well as the mechanical properties based on Laplace's law.[24,25] The increased risk for glaucoma in myopic eyes may be related to these sclera's material properties.

The outermost structures of the eye, consisting of the cornea, sclera, and lamina cribrosa, originate in neural crest-derived mesenchymal cells.[26] Recent reports have shown that the ONH and peripapillary sclera behave as a complete system, and scleral changes may result in the stretching and distortion of the optic nerve fibers and the optic disc changes, such as disc tilting, disc torsion, and peripapillary atrophy, leading to damage of the axons of the retinal ganglion cells.[27,28] The cornea and sclera also have a common histologic properties in that the corneal stroma consists of interwoven collagen fibrils continuing to the sclera. The number, arrangement, and types of collagen fibrils are considered to determine the mechanical strength of the outer coat of the eye.[29] CH is a physical property related to the ability of connective tissues to dampen pressure changes, and is tied to the extracellular matrix constituents of the cornea that may be related to those of the posterior ocular tissues.[30] Wells et al[31] showed that CH was associated with increased deformation of the optic nerve surface during transient IOP elevations, and demonstrated that CH may be a surrogate measure of lamina cribrosa backward bowing/optic disc compliance in the pathogenesis of glaucoma. This is supported by Kotecha's study finding that CH tended to decrease with high IOP, possibly due to a remodeling response of the cornea to IOP elevations.[32] In our study, CH and the subfoveal scleral thickness were significantly lower in highly myopic NTG eyes than myopic controls, and the subfoveal scleral thickness had a significant positive correlation with CH in highly myopic NTG eyes not in myopic controls. CH was one of the significant factors most associated with the subfoveal scleral thickness in myopic NTG eyes by stepwise multiple regression model. These findings suggest that CH can be the material property to reflect the

viscoelasticity of not only the cornea but the outer coat of ocular tissues including cornea, sclera, and ONH complex. Furthermore, CH may be a parameter to determine the structural susceptibility of the posterior ocular tissues. From this viewpoint, the thinner sclera in the myopic NTG eyes is related to the lower CH, which may imply the increased stiffness of sclera, and these hypotheses can explain the increased risk for glaucoma in myopic eyes. More research is needed to speculate the relationship of the scleral thickness and stiffness.

Several studies have demonstrated that posterior staphyloma formation is related to posterior retinal diseases, especially high myopia-specific diseases, including macular retinoschisis, macular holes, and choroidal neovascularization.[33,34] This connection is probably because the posterior shell of highly myopic eyes has increased elasticity and expandable tendency and deeper posterior staphyloma contributes to greater inward vector force to detach or spilt neural retina.[29] In the present study, together with the scleral thinning, the increased posterior staphyloma heights of the nasal, superior quadrant, and the sum of four quadrants were significant in highly myopic NTG eyes than myopic controls. This indicates that the posterior staphyloma expansion seems to be asymmetrical. And the posterior staphyloma heights of these regions had a significant negative correlation with the subfoveal scleral thickness and positive correlation with axial length in highly myopic NTG eyes. Maruko et al[15] reported that the sclera at the posterior pole in highly myopic eyes stretches nonuniformly. Hayashi et al[16] reported that the nasal and superior posterior staphyloma heights were significantly associated with subfoveal scleral thickness, which is consistent with our results. The mechanical stretching nasally and superiorly around the fovea by an extension of a staphyloma may have a more direct effect on the subfoveal scleral thinning, and the staphyloma in this area may be associated with axial elongation and the presence of myopic glaucomatous lesions. In addition, our stepwise regression models showed that the nasal posterior staphyloma height was one of the significant factor most associated with the subfoveal scleral thickness in

myopic NTG eyes. This indicates that there may be a geomorphological directivity for the posterior staphyloma formation and the characteristic shape of the staphyloma around the fovea may influence the scleral thickness at the fovea in myopic NTG eyes.

Some studies on pathologic myopia have demonstrated that the posterior staphyloma not only deepens but also its morphologic features change as the patients ages, even though the axial length does not change significantly.[29] Ohno-Matsui and associates[29] reported that the type IX staphylomas develop secondarily by the formation of a ridge-like protrusion temporal to the optic disc in eyes originally with the most prominent type II staphyloma as the patient ages, and an increased mechanical tension caused by an increased depth of posterior staphyloma may facilitate the development and progression of myopic retinal degeneration and aggravation of visual field defects. Our results showed that the posterior staphyloma heights had a significant positive correlation with age in highly myopic NTG eyes, which indicates there may be an aging effect on the morphologic changes of the posterior staphyloma in our study groups. However the precise morphologic classification was not performed in this study, because our selection of posterior staphyloma was restricted to EDI-OCT images that the inner scleral borders were symmetrically centered on the fovea, which probably represented the type I or II staphyloma. And the compound staphylomas including the type IX staphyloma were at risk of being omitted. Further research is necessary to investigate the reason why the morphologic features of posterior staphyloma worsen with increasing age.

Another interesting point is that, the posterior staphyloma heights had correlations with choroidal thickness, scleral thickness, axial length, refractive error, age, and RNFL thickness only in highly myopic NTG eyes, whereas there were no relationships between the posterior staphyloma heights and these parameters except for choroidal thickness in myopic controls. From this analysis, we can assume that the posterior staphyloma formation or deepening is probably

due to not only the myopic mechanism of an axial elongation, which increases tension by mechanical stretching effect, but also another mechanism related with glaucomatous changes onto the posterior fundus or combination effects of glaucoma and/or myopia. After all these findings, there may be a biomechanical link between high myopia and glaucoma, in which the higher degree of myopia is associated with the more axial elongation, the larger mechanical tension, the decreased scleral thickness, the increased scleral stiffness, the deeper posterior staphyloma, the lower corneal hysteresis, and eventually the deterioration of VF defects.

This study has the significance in that to the best of our knowledge, this is the first study to demonstrate the relationship between the material properties of posterior ocular tissues and the pathogenesis of high myopia and myopia-related glaucomatous optic neuropathy. Several properties of the sclera, especially scleral stiffness, should have considered when evaluating the structural changes of high myopia related diseases. The scleral factor of previous studies has been restricted to the scleral thickness. However this study adopted CH, the factor compatible with scleral stiffness, that reflects the viscoelasticity and the material property of the outermost ocular structures and suggested the association of low CH, scleral thinning and the increased posterior staphyloma in highly myopic NTG eyes.

However, there are a few limitations in this study. There were limitations in interpreting the ocular parameters measured from OCT imaging techniques. First, the measured scleral thickness has not been confirmed by histology, and they may not be valid when we want to know the actual thickness of the tissue in vivo. Second, the staphyloma height was measured at 2 mm from the fovea, but the staphyloma can have different shapes because the posterior sclera expands in a nonuniform fashion and the contour of the inner scleral surface has different patterns, such as inclining toward the optic disc, symmetrical on the fovea centered, asymmetrical and irregular curve. Although this study selected the posterior staphyloma whose pattern was symmetrical centered on the fovea, the

selection was only based upon the EDI-OCT images, not on the B-scans or magnetic resonance imaging (MRI) findings. Thus there is a potential for unintentional omission of the compound staphylomas. Further investigations measuring the scleral inner/outer borders more clearly from more deeply penetrating OCT devices, such as swept-source OCT, and evaluating the posterior staphyloma by adjusting different patterns would overcome these limitations. Another limitation is that the subjects of the study were identified in a referral clinic-based practice, rather than through population-based screening. Thus, they may represent a subgroup of highly myopic NTG patients in Korea that may not represent the characteristics of similar patients in other populations. This was also a cross-sectional study, and a future longitudinal study will be required to confirm the cause-effect relationships.

V. CONCLUSION

Both subfoveal scleral thickness and CH showed a significant difference in highly myopic NTG eyes compared to the myopic controls and they had a positive correlation only in highly myopic NTG eyes. These results may suggest the increased stiffness of sclera and be eligible to explain the increased risk for glaucoma in myopic eyes. And the posterior staphyloma heights were significantly higher in highly myopic NTG eyes and negatively correlated with the subfoveal scleral thickness. Of various ocular parameters, CH and the nasal posterior staphyloma height were most significantly associated with the scleral thickness. Posterior staphyloma formation and subfoveal scleral thinning were closely related in highly myopic NTG eyes, and CH may be a clinically useful parameter to reflect the material's property of posterior ocular tissues and act as a bridge to explain the biomechanical association between high myopia and glaucoma.

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ABSTRACT(IN KOREAN)

고도근시에서 정상안압녹내장은 후포도종 형성 및 황반하 공막두께 감소와 연관이 있다.

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목적 : 정상안압녹내장과 고도근시안 환자의 안구생체계측을 평가하고, 고도근시 및 녹내장성 시신경병증의 생체역학적 변화와 관련된 안인자를 알아보고자 한다.

방법 : 본 연구는 45명 45안의 정상안압녹내장 환자와 38명 38안의 고도근시안 (굴절오차 -6.0 디옵터 이하 또는 안축장 26.0mm 이상)을 대상으로 하였다. 스펙트럼 영역 빛간섭단층촬영에서 Enhanced Depth Imaging(EDI) 방법을 이용하여 황반하 망막, 맥락막, 공막의 두께와 후포도종높이를 측정하였다. 고도근시를 동반한 정상안압녹내장 환자의 공막두께와 후포도종높이를 비녹내장성 고도근시안과 비교하였다. 피어슨상관분석을 통하여 공막두께 및 후포도종높이와 다른 안인자와의 관계를 평가하였고, 다중회귀분석을 이용하여 공막두께 및 후포도종높이의 변화와 가장 연관 있는 안인자를 확인하였다.

결과 : 황반하 공막두께는 고도근시를 동반한 정상안압녹내장 안과 비녹내장성 고도근시안에서 각각 71.1%와 63.2%로 측정되었다. 고도근시를 동반한 정상안압녹내장 안은 비녹내장성 고도근시안에 비해 얇은 황반하 공막두께(473.03 ± 43.75 versus(vs). 579.46 ± 75.87 ㎛, *P* < .001)와 높은 후포도종높이(97.80 ± 70.19 vs. 62.83 ± 32.01 ㎛, *P* = .027)를 보였다. 고도근시를 동반한 정상안압녹내장에서 황반하 공막두께는 나이(r = -0.453, *P* =.014), 안축장길이(r = -0.343, *P*=.040), 각막히스테리시스(r = 0.460, *P* = .010), 그리고 상측사분면(r = -0.538, *P* = .003)과 비측사분면(r = -0.519, *P* = .004)의 후포도종높이 및 각 사분면의 후포도종높이의 합(r = -0.424, *P* = .022)과 통계적으로 유의한 상관성을 보였다. 단계적 다중회귀분석 결과 황반하 공막두께와 가장 연관성이 있는 안인자는 각막히스테리시스(B = 2.694, *P* = .015), 각막저항인자(B=-2.916, *P* = .010) 그리고 비측사분면의 후포도종높이(B = -0.463, *P* = .017)였다.

결론 : 고도근시를 동반한 정상안압녹내장에서 황반하 공막두께 감소와 비균등한 후포도종 형성이 관련이 있었다. 각막히스테리시스는 공막경성도와 같은 생체역학적 물성을 반영하는 인자로서 임상적으로 유용하게 적용될 수 있을 것이다.

핵심되는 말 : 각막히스테리시스, 고도근시, 정상안압녹내장, 후포도종, 공막두께