

# Association of Myopia with Peripapillary Retinal Nerve Fiber Layer Thickness in Diabetic Patients Without Diabetic Retinopathy

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**PURPOSE.** To investigate the association between myopia and peripapillary retinal nerve fiber layer (pRNFL) thickness in diabetic patients without diabetic retinopathy (DR).

**METHODS.** A total of 271 eyes of 271 participants were included. They were divided into four groups according to the presence of myopia ( $\leq -3$  diopters [D]) and diabetes without DR: (1) control group ( $n = 76$ ), (2) myopia group ( $n = 57$ ), (3) diabetes group ( $n = 82$ ), and (4) diabetes + myopia group ( $n = 56$ ). The peripapillary average and sector RNFL thicknesses were measured and compared among the four groups to determine the effects of myopia and diabetes. Covariates were adjusted using analyses of covariance. Linear regression analyses were fitted to evaluate the factors associated with pRNFL.

**RESULTS.** Spherical equivalents were  $0.12 \pm 1.31$  D in the control group,  $-4.00 \pm 1.47$  D in the myopia group,  $0.00 \pm 1.05$  D in the diabetes group, and  $-4.33 \pm 1.70$  D in the diabetes + myopia group ( $P < 0.001$ ). The respective axial lengths (ALs) were  $23.91 \pm 0.99$  mm,  $25.16 \pm 0.94$  mm,  $23.68 \pm 0.77$  mm, and  $25.34 \pm 1.33$  mm ( $P < 0.001$ ). The average pRNFL showed a progressive decrease from the control group ( $97.16 \pm 8.73$   $\mu\text{m}$ ) to the myopia group ( $94.04 \pm 9.13$   $\mu\text{m}$ ) to the diabetes group ( $93.33 \pm 9.07$   $\mu\text{m}$ ) to the diabetes + myopia group ( $91.25 \pm 9.72$   $\mu\text{m}$ ) ( $P = 0.009$ ). Age, diabetes, hypertension, and AL were significantly correlated with the pRNFL. The rate of reduction of pRNFL with increasing age was higher in the diabetes + myopia group than in the other groups, and pRNFL in the diabetes groups decreased more steeply with increasing AL compared to the non-diabetic groups.

**CONCLUSIONS.** Myopia and diabetes are important factors affecting pRNFL thickness, and the simultaneous presence of diabetes and myopia results in greater pRNFL damage than observed with either pathology alone.

Keywords: diabetic mellitus, diabetic retinopathy, peripapillary retinal nerve fiber layer, myopia

Myopia, also known as short-sightedness, is a major public health problem.<sup>1,2</sup> Its prevalence has increased significantly globally, and a recent meta-analysis suggested that half of the world's population may be myopic by 2050.<sup>3</sup> A particularly high prevalence has been reported in the developed countries of eastern and southeastern Asia,<sup>4</sup> and myopia has even been found in 96.5% of the 19-year-old population in Korea.<sup>5</sup>

Myopia, particularly high myopia, increases the risk for pathological ocular conditions, such as glaucoma, cataract, macular degeneration, and retinal detachment.<sup>6</sup> Our group recently found that the peripapillary retinal nerve fiber layer (pRNFL) is significantly thinner in patients with high myopia but without glaucoma compared to normal controls.<sup>7</sup> Diabetic retinopathy (DR) is the most common complication of diabetes, and the conventional clinical perspective of DR has focused on retinal vascular abnormal-

ities. However, emerging evidence of structural and functional deficits supports the presence of retinal degeneration before DR, which is referred to as diabetic retinal neurodegeneration (DRN).<sup>8</sup> The most important characteristics of DRN involve reactive gliosis and neuronal apoptosis, which may predominantly affect the inner retinal layer.<sup>9</sup> Several studies have reported inner retinal injury associated with DRN,<sup>8,10-12</sup> and we also reported progressive pRNFL thinning in diabetic patients with or without DR.<sup>13</sup>

Because the prevalence of diabetes and myopia is increasing worldwide,<sup>3,14</sup> the number of diabetic patients with myopia is expected to increase in the future. Myopia causes pRNFL reduction, which may accelerate pRNFL loss in diabetic patients, but the effects of myopia on pRNFL thickness in diabetic patients have not been definitively evaluated. Several studies, including cross-sectional and large population studies, have reported a negative correlation

between myopia and DR, suggesting that myopia may have a protective effect on the development of DR.<sup>15–18</sup> In contrast, one study reported no association between myopia and DR.<sup>19</sup> We therefore designed this cross-sectional study to determine pRNFL thicknesses in myopic and/or diabetic patients without DR to identify the effects of myopia and diabetes on the pRNFL.

## METHODS

This was a retrospective, cross-sectional study. The study protocol was approved by the Institutional Review Board of Chungnam National University Hospital, Daejeon, Republic of Korea, and adhered to the tenets of the Declaration of Helsinki.

### Study Population

This study included patients with or without diabetes who visited the Retina and Vitreous Clinic of Chungnam National University Hospital for a checkup for retinal abnormality and who were enrolled consecutively between January 2015 and June 2019. The enrolled patients were not included in other studies. All diabetic patients were initially diagnosed with type 2 diabetes at the Department of Internal Medicine of Chungnam National University Hospital, and the diagnosis of diabetes was made according to the criteria of the American Diabetes Association.<sup>20</sup> For study purposes, we defined a lack of myopia as a refractive error within  $\pm 3$  diopters (D) and myopia as a refractive error with a spherical equivalent of  $-3$  D or more. The patients were divided into two groups according to the presence of diabetes and were then divided into four groups according to the presence of myopia: control group, myopia group, diabetes group, and diabetes + myopia group. All patients exhibited a best-corrected visual acuity (BCVA) of 20/25 or better. The exclusion criteria included a history of systemic disease other than diabetes mellitus (DM) and hypertension, glaucoma, or optic nerve disorder; intraocular pressure (IOP)  $> 21$  mm Hg; optic disc abnormalities; history or evidence of ocular surgery including refractive and cataract surgery; prior laser, retinal, or choroidal trauma; or any other optic nerve or retinal dysfunction. If both eyes met the inclusion criteria, one eye was randomly selected.

All patients initially underwent a comprehensive ophthalmic examination, including a review of their medical history, BCVA, slit-lamp examination, IOP measurement, dilated fundus examination, photography, axial length (AL) measurement using the IOLMaster (Carl Zeiss Meditec, Jena, Germany) and spectral-domain optical coherence tomography (SD-OCT; Carl Zeiss Meditec). All diabetic patients also underwent fluorescein angiography with the Spectralis HRA (Heidelberg Engineering, Heidelberg, Germany), and patients who were diagnosed with retinal abnormalities such as retinal hemorrhage or microaneurysm were excluded from the study.

Among subjects who visited our clinic for various reasons (e.g., health screening checkup, routine check for ocular disease such as cataract or peripheral vitreous floater), those who met eligibility criteria and had glucose level records (fasting plasma glucose  $< 100$  mg/dL or hemoglobin A1C [HbA1c]  $< 5.7\%$ ) within 1 year of the date of ophthalmic examination were enrolled in the non-diabetic groups involving the control group and myopia group. These

subjects had no ocular disease or prior intraocular surgery, including refractive or cataract surgery; normal anterior segment and fundus; BCVA  $\geq 20/25$ ; and an IOP in the normal range.

### Optical Coherence Tomography

SD-OCT was performed with a Cirrus HD-OCT (Carl Zeiss Meditec) using a  $512 \times 128$  macular cube combination scan and a  $200 \times 200$  optic disc cube scan. The central macular thickness (CMT) was measured using a  $512 \times 128$  macular cube combination scan. A  $200 \times 200$  scan mode optic disc cube was used to image the optic disc and the pRNFL over a  $6 \times 6$ -mm optic nerve head. Then, the pRNFL thicknesses of the four quadrant sectors (superior, inferior, nasal, and temporal) were measured. Two scans were performed for all participants by an experienced examiner, and we selected the best scan among those showing a signal strength  $\geq 7$ . We excluded scans with a signal strength less than 7 and scans with other image quality problems, such as motion or being off-centered, as well as those missing data due to floaters, vignetting, or cataract on the OCT scan.

### Statistical Analyses

All statistical analyses were performed using SPSS Statistics 21.0 (IBM, Armonk, NY, USA) and RStudio, version 1.1.453 (R Foundation for Statistical Computing, Vienna, Austria). Snellen BCVA results were converted into the logarithm of the minimum angle of resolution (logMAR). Continuous variables are presented as the mean  $\pm$  SD. Differences were considered significant at  $P < 0.05$ . Baseline demographics and OCT measurements, including CMT and pRNFL thickness, were compared using one-way ANOVA, followed by a post hoc test (Bonferroni test). The  $\chi^2$  test was used to compare categorical data. Analyses of covariance (ANCOVA) were also used to control the effects of covariate values such as spherical equivalent and AL. Univariate and multivariate linear regression analyses were performed to evaluate the factors affecting pRNFL thickness. These parameters were first fitted to a univariate model, and then variables significant at  $P < 0.05$  were included in multivariate analyses to determine the independence of the effects. In addition, correlations between pRNFL and age or AL were also evaluated.

## RESULTS

### Patient Demographics

This study recruited a total of 271 participants, including 76 subjects in the control group, 57 patients in the myopia group, 82 patients in the diabetes group, and 56 patients in the diabetes + myopia group. The mean ages of the four groups were  $52.37 \pm 12.96$ ,  $49.49 \pm 10.11$ ,  $52.60 \pm 8.04$ , and  $50.23 \pm 13.42$  years, respectively ( $P = 0.289$ ) (Table 1). The myopic groups (myopia group and diabetes + myopia group) had a lower spherical equivalent ( $P < 0.001$ ) and longer AL ( $P < 0.001$ ) than the other groups. There were no significant differences among the four groups in any other baseline characteristic, such as sex, hypertension, duration of diabetes, HbA1c, BCVA, IOP, CMT, or the cup/disc ratio. DM and HbA1c also showed no significant difference between the diabetes and the diabetes + myopia groups.

TABLE 1. Demographics and Clinical Characteristics of the Participants

Demographic	Group				P	Post Hoc
	Control (n = 76)	Myopia (n = 57)	Diabetes (n = 82)	Diabetes + Myopia (n = 56)		
Age (y), mean ± SD	52.37 ± 12.96	49.49 ± 10.11	52.60 ± 8.04	50.23 ± 13.42	0.289*	
Sex (male/female), n	34/42	23/34	27/55	30/26	0.105†	
Hypertension, n (%)	12 (15.8)	8 (14.0)	21 (24.4)	16 (28.6)	0.141†	
Duration of diabetes (y), mean ± SD	n/a	n/a	3.62 ± 4.06	8.13 ± 5.66	0.296‡	
HbA1c (%), mean ± SD	n/a	n/a	7.04 ± 0.98	7.24 ± 0.97	0.107‡	
BCVA (logMAR), mean ± SD	-0.02 ± 0.11	-0.02 ± 0.10	-0.01 ± 0.05	-0.01 ± 0.08	0.152*	
Spherical equivalent (D), mean ± SD	0.12 ± 1.31	-4.00 ± 1.47	0.00 ± 1.05	-4.33 ± 1.70	<b>&lt;0.001*</b>	Control, diabetes > myopia, diabetes + myopia
Intraocular pressure (mm Hg), mean ± SD	15.84 ± 2.96	16.07 ± 2.46	16.40 ± 2.73	16.71 ± 3.01	0.202*	
Axial length (mm), mean ± SD	23.91 ± 0.99	25.16 ± 0.94	23.68 ± 0.77	25.34 ± 1.33	<b>&lt;0.001*</b>	Control, diabetes > myopia, diabetes + myopia
Central macular thickness (µm), mean ± SD	248.95 ± 24.45	256.91 ± 18.50	246.96 ± 19.92	250.45 ± 21.22	0.067*	
Cup/disc ratio, mean ± SD	0.48 ± 0.11	0.41 ± 0.16	0.47 ± 0.14	0.45 ± 0.15	0.205*	

Boldface values indicate statistically significant differences at  $P < 0.05$ .

\* One-way ANOVA followed by the post hoc Bonferroni correction.

†  $\chi^2$  test.

‡ Student's  $t$ -test (diabetes vs. diabetes + myopia group).

TABLE 2. Comparison of Peripapillary Retinal Nerve Fiber Layer Thicknesses Among the Four Groups

	Group				P	Post Hoc
	Control (n = 76)	Myopia (n = 57)	Diabetes (n = 82)	Diabetes + Myopia (n = 56)		
Average	97.16 ± 8.73	94.04 ± 9.13	93.33 ± 9.07	91.25 ± 9.72	<b>0.009</b>	Control > diabetes + myopia
Superior	119.82 ± 16.49	117.66 ± 17.96	118.75 ± 12.81	113.00 ± 18.42	0.190	
Temporal	72.82 ± 12.70	76.30 ± 16.64	63.54 ± 8.85	75.19 ± 15.66	<b>0.001</b>	Control, myopia, diabetes + myopia > diabetes
Inferior	126.00 ± 17.06	118.32 ± 17.02	120.00 ± 13.59	111.85 ± 17.27	<b>&lt;0.001</b>	Control > diabetes + myopia
Nasal	67.87 ± 8.83	62.81 ± 9.18	66.61 ± 7.68	62.38 ± 8.10	<b>0.001</b>	Control > myopia, diabetes + myopia

Boldface values indicate statistically significant differences at  $P < 0.05$ .

\* One-way ANOVA followed by post hoc Bonferroni correction.

### Comparison of pRNFL Thicknesses

Average pRNFL thicknesses in the control, myopia, diabetes, and diabetes + myopia groups were  $97.16 \pm 8.73$ ,  $94.04 \pm 9.13$ ,  $93.33 \pm 9.07$ , and  $91.25 \pm 9.72$  µm ( $P = 0.009$ ) (Table 2), and a significant difference was found only

between the control and diabetes + myopia groups in post hoc analyses ( $P = 0.005$ ). In analyses of sectoral pRNFL thicknesses, the temporal (control, myopia, diabetes + myopia > diabetes,  $P = 0.001$ ), inferior (control > diabetes + myopia,  $P < 0.001$ ), and nasal (control > myopia, diabetes + myopia,  $P = 0.001$ ) segments showed significant

**TABLE 3.** Estimated Average Peripapillary Retinal Nerve Fiber Layer Thicknesses After Adjusting for Covariants

Model	Nerve Fiber Layer Thickness ( $\mu\text{m}$ ), Group*				<i>P</i> †	Post Hoc
	Control (n = 76)	Myopia (n = 52)	Diabetes (n = 82)	Diabetes + Myopia (n = 56)		
1	96.63 ± 1.35 (94.27–99.59)	94.32 ± 1.61 (91.15–97.49)	93.12 ± 1.29 (90.58–95.65)	91.58 ± 1.71 (88.21–94.95)	0.055	
2	96.74 ± 1.13 (94.51–98.97)	94.72 ± 1.35 (92.07–97.37)	92.71 ± 1.13 (90.48–94.94)	92.03 ± 1.38 (89.32–94.74)	<b>0.012</b>	Control > diabetes, diabetes + myopia

Model 1, adjustment for spherical equivalent; model 2, adjustment for axial length. Boldface values indicate statistically significant differences at  $P < 0.05$ .

\* Mean ± standard error (95% confidence interval).

† ANCOVA using post hoc Bonferroni correction.

**TABLE 4.** Univariate and Multivariate Linear Regression Analyses Among Various Clinical Factors and Peripapillary Retinal Nerve Fiber Layer Thicknesses

Variable	Univariate Regression		Multivariate Regression	
	$\beta \pm \text{SE}$	<i>P</i>	$\beta \pm \text{SE}$	<i>P</i>
Age	-0.256 ± 0.051	<b>&lt;0.001</b>	-0.255 ± 0.058	<b>&lt;0.001</b>
Sex (0 = male, 1 = female)	-0.471 ± 1.203	0.696		
Diabetes mellitus	-3.334 ± 1.171	<b>0.005</b>	-3.370 ± 1.209	<b>0.006</b>
Duration of diabetes	-0.599 ± 0.127	<b>&lt;0.001</b>		
HbA1c	-2.257 ± 0.809	<b>0.006</b>	-0.912 ± 0.684	0.184
Hypertension	-7.199 ± 1.400	<b>&lt;0.001</b>	-4.087 ± 1.413	<b>0.004</b>
BCVA	-18.046 ± 6.883	<b>0.009</b>	-8.902 ± 7.035	0.207
Intraocular pressure	-0.271 ± 0.103	0.102		
Spherical equivalent	0.481 ± 0.237	<b>0.043</b>		
Axial length	-1.345 ± 0.466	<b>0.004</b>	-2.029 ± 0.436	<b>&lt;0.001</b>
Central foveal thickness	-0.007 ± 0.027	0.787		
Cup/disc ratio	-13.082 ± 4.350	<b>0.003</b>	-7.106 ± 4.070	0.082

Boldface numbers indicate statistically significant differences at  $P < 0.05$ . Duration of diabetes and spherical equivalent were not included in the multivariate regression model because of the interaction between diabetes mellitus and axial length. SE, standard error.

differences, whereas there were no differences in the superior segment ( $P = 0.190$ ).

ANCOVA was performed after adjusting for the spherical equivalent (model 1) or AL (model 2) among the four groups. The estimated average pRNFL thicknesses in the four groups after adjusting for AL (model 2) were 96.74, 94.72, 92.71, and 92.03  $\mu\text{m}$ , respectively ( $P = 0.012$ ) (Table 3). Post hoc analyses showed that the values were significantly lower in the diabetes ( $P = 0.027$ ) and diabetes + myopia ( $P = 0.025$ ) groups than in controls; however, the estimated average RNFL thickness in model 1 did not differ significantly among groups ( $P = 0.055$ ).

### Determination of Factors Associated with Average pRNFL Thicknesses

Univariate regression analyses showed that age ( $P < 0.001$ ), DM ( $P = 0.005$ ), duration of diabetes ( $P < 0.001$ ), HbA1c ( $P = 0.006$ ), hypertension ( $P < 0.001$ ), BCVA ( $P = 0.009$ ), spherical equivalent ( $P = 0.043$ ), AL ( $P = 0.004$ ), and cup/disc ratio ( $P = 0.003$ ) were associated with average pRNFL thickness (Table 4). Multivariate regression analyses included seven variables from the univariate regression analyses; duration of diabetes and spherical equivalent were excluded because their interaction showed that age ( $\beta = -0.255 \pm 0.058$ ,  $P < 0.001$ ), DM ( $\beta = -3.370 \pm 1.209$ ,  $P = 0.006$ ), hypertension ( $\beta = -4.087 \pm 1.413$ ,  $P = 0.004$ ), and AL ( $\beta = -2.029 \pm 0.436$ ,  $P < 0.001$ ) were significant factors.

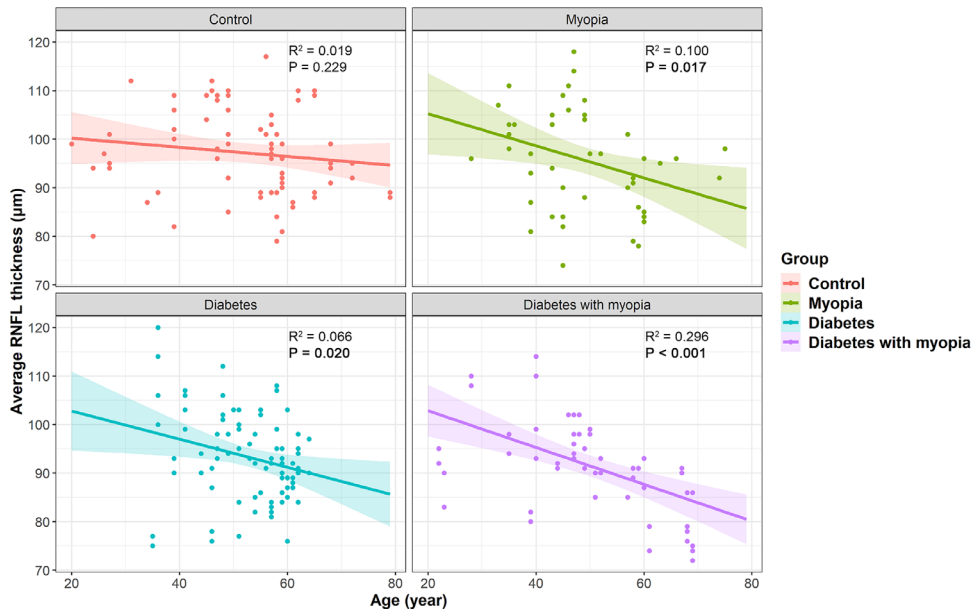
### Association of Average pRNFL Thicknesses with Age and AL

We performed correlation analyses between average pRNFL thickness and age for the four groups. There was no significant association in the control group, whereas the other three groups showed negative correlations (Fig. 1). Notably, the relationship between pRNFL and age in the diabetes + myopia group was more significant than in the other two groups (myopia group,  $P = 0.021$ ; diabetes group,  $P = 0.011$ ). The subjects were divided into two groups: non-DM and DM. In the DM group the pRNFL thickness tended to decrease as the AL increased, whereas in the non-DM group the correlation was not statistically significant (Fig. 2).

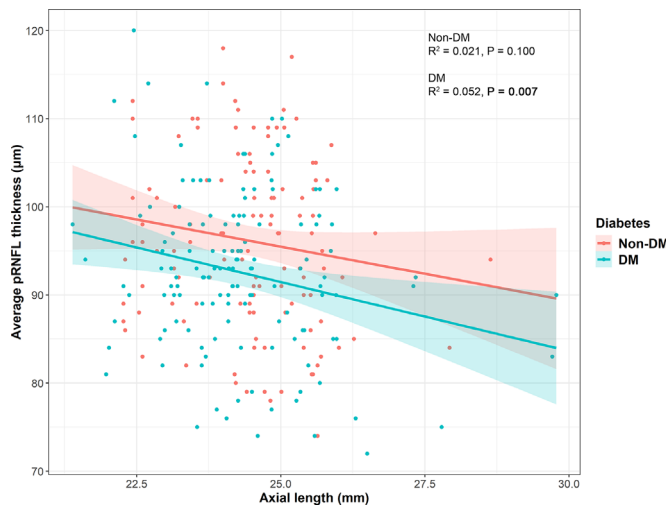
### DISCUSSION

The pRNFL thicknesses of myopic and/or diabetic patients were evaluated using SD-OCT. Analyses of 271 participants showed that diabetes and myopia were significant factors affecting pRNFL, and the simultaneous presence of diabetes and myopia resulted in more pRNFL damage than in the individual myopia and diabetes groups. Because the DM and myopia population is currently on the rise globally, particularly in eastern and southeastern Asia, the role of diabetes and myopia in pRNFL analyses will continue to grow in importance.

The pathophysiology of DR has been a substantial area of research for decades. In diabetic patients,



**FIGURE 1.** Scatterplot and results of linear regression analyses showing correlations between the average pRNFL thickness and age for the control (*top left*), myopia (*top right*), diabetes (*bottom left*), and diabetes + myopia (*bottom right*) groups. Significant negative correlations were found in the myopia ( $R^2 = 0.100, P = 0.017$ ), diabetes ( $R^2 = 0.068, P = 0.020$ ), and diabetes + myopia groups ( $R^2 = 0.296, P < 0.001$ ) but not in controls ( $R^2 = 0.019, P = 0.229$ ).



**FIGURE 2.** Scatterplot and results of linear regression analyses showing associations between average pRNFL thickness and AL in the non-diabetes mellitus (DM) groups (control and myopia groups) and the DM group (diabetes and diabetes + myopia groups). There was a significant negative correlation only in the DM group ( $R^2 = 0.052, P = 0.007$ ).

hyperglycemia triggers metabolic pathways, such as the polyol and hexosamine pathways, resulting in the production of free radicals and advanced glycation end products, along with inflammation and ischemia.<sup>21,22</sup> The activation of these pathways causes abnormalities in the neural retina, resulting in retinal neurodegeneration and retinal microangiopathy in the capillary bed. These processes can cause a reduction in pRNFL thickness, which can be detected by OCT.

Recent studies have suggested that DRN occurs prior to vascular abnormalities in diabetic patients and is involved in the development of early microvascular changes. Breakdown of the blood–retina barrier (BRB),<sup>23,24</sup>

vasoregression,<sup>25</sup> and impairment of neurovascular coupling<sup>26,27</sup> cause neurodegeneration. In addition, glutamate accumulation induced by DRN increases the secretion of vascular endothelial growth factor, which leads to damage to the BRB.<sup>28</sup> Considering these mechanisms, DRN is a crucial factor in the development of DR, and it could explain the findings of the present and a previous study<sup>13</sup> of significant pRNFL loss in patients without DR.

Myopia is also an important factor affecting pRNFL thickness. With the progression of myopia, globe elongation mechanically stretches retinal tissue, resulting in thinning of the retina.<sup>29–31</sup> In addition, peripapillary and choroidal perfusion in myopic eyes may be decreased, which could be

associated with reduced oxygen demand because of retinal thinning in myopic eyes. There have been reports that vascular endothelial growth factor (VEGF) levels are decreased in myopia,<sup>32,33</sup> which might also be associated with a decrease in retinal perfusion.

Some investigators have hypothesized that myopia has a protective effect against DR.<sup>15–18,34</sup> First, with eyeball elongation, there is narrowing of retinal vessels, which leads to a decrease in retinal blood flow that results in lower capillary hydrostatic pressure, thus reducing the likelihood of capillary leakage and rupture of retinal vessels in diabetic patients.<sup>35,36</sup> A second hypothesis is that myopic eyes have a thin retina, which results in decreased metabolic demand. It can reduce the hypoxic response.<sup>34</sup> Finally, decreased VEGF levels might also be associated with the protective effect.

In the present study, pRNFL thickness tended to decrease gradually to 97.16, 94.04, 93.33, and 91.25  $\mu\text{m}$  in the control, myopia, diabetes, and diabetes + myopia groups, respectively, with the lowest thickness in the diabetes + myopia group. Comparisons of differences in the pRNFL thicknesses among the four groups were difficult, but the pRNFL reduction in the diabetes + myopia group was similar to the sum of the pRNFL reductions in the myopia and diabetes groups. No noticeable protective effect was identified. The reason for this finding is not clear, but considering that the estimated pRNFL thickness after adjusting for AL in the diabetes + myopia group was similar to that of the diabetes group (92.71  $\mu\text{m}$  vs. 92.03  $\mu\text{m}$ ; Table 3), axial elongation was a major factor affecting the pRNFL, and the other factors such as decreased retinal perfusion were minimal.

Many factors can affect pRNFL thickness. In the present study, using multivariate linear regression, we found that age, duration of diabetes, hypertension, and AL were associated with pRNFL. This is consistent with previous studies.<sup>13,29,37,38</sup> We further analyzed the association with age and found that the rate of RNFL reduction with age was higher in the diabetes + myopia, diabetes, and myopia groups than in the control group, particularly in the diabetes + myopia group. We previously reported longitudinal changes in pRNFL thickness in patients with high myopia and confirmed that older patients with high myopia were more sensitive to these changes than normal subjects.<sup>7</sup> Considering the effect from diabetes and myopia, it is assumed that the reduction in the diabetes + myopia group was steeper than in the other groups; however, there was no significant decrease in pRNFL with increasing AL in the non-DM group (Fig. 2). It is generally accepted that, as AL increases, the pRNFL thickness decreases. The reasons for these results are not definitively known. Presumably, fewer patients with high myopia (myopia group, six patients; diabetes + myopia group, five patients) were included in our study, and the distribution of the AL was narrow, which is thought to be related to our results. Further research is needed to clarify these findings.

This study had some limitations. First, it had a retrospective design, which might have involved selection bias and might not represent the general population. Second, we did not perform OCT angiography scans, so the effects of peripapillary perfusion could not be determined. Third, ophthalmic examination and blood tests for diabetes in non-diabetes groups (myopia and control groups) were not performed at the same time, having a gap of up to 1 year. Thus, although unlikely, it is possible that a patient who did not have diabetes at the time of the blood test had diabetes at the time of the ophthalmic examination. Fourth,

several highly myopic patients were included in the study, and their pRNFL measurements may be less reliable. Finally, although we carefully checked for glaucomatous findings, such as pRNFL defects and a glaucomatous optic disc based on OCT findings, a visual field test was not performed, and a glaucoma specialist was not involved in this study; thus, it is possible that we enrolled patients with pre-perimetric glaucoma. Despite these limitations, the present study establishes the effects of myopia and diabetes on pRNFL thickness and confirms that these factors could be confounding factors in analyses of pRNFL thickness. These results could be helpful to physicians. Additional well-designed longitudinal studies are needed.

In conclusion, pRNFL thicknesses were thinner in the myopia, diabetes, and diabetes + myopia groups than in the control group, and the simultaneous presence of diabetes and myopia resulted in greater pRNFL damage than was observed with either pathology alone. The myopia, diabetes, and diabetes + myopia groups tended to have decreased pRNFL thicknesses with increasing age, particularly in the diabetes + myopia group. In addition, myopia did not show a protective effect on RNFL thickness reduction in diabetic patients. Our results increased our understanding of the pathophysiology of pRNFL changes in diabetic patients and should be valuable in the analyses of pRNFL thicknesses in patients with various ocular diseases, such as glaucoma and neuroretinal disease.

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