Effect of Systemic Hypertension on Peripapillary RNFL Thickness in Patients With Diabetes Without Diabetic Retinopathy

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Type 2 diabetes mellitus (T2DM) and hypertension (HTN) are both relatively common systemic diseases and cause damage to the retina, such as inner retina reduction and microvascular impairment. The purpose of this study was to identify peripapillary retinal nerve fiber layer (pRNFL) damage by diabetic neurodegeneration and the effects of HTN on the pRNFL thickness in patients with T2DM without clinical diabetic retinopathy. Subjects were divided into three groups: healthy control subjects (group 1), patients with T2DM (group 2), and patients with both diabetes and HTN (group 3). The pRNFL thickness was measured using optical coherence tomography and compared among each group. Linear regression analyses were performed to identify factors associated with pRNFL thickness. A total of 325 eyes were included: 143 eyes in the group 1, 126 eyes in group 2, and 56 eyes in group 3. The mean pRNFL thicknesses of each group were 96.1 ± 7.7, 94.4 ± 8.6, and 91.6 ± 9.6 μm, respectively ($P = 0.003$). In multivariate linear analyses, diabetes duration ($\beta = -0.236$; $P = 0.018$) and HTN ($\beta = -3.766$; $P = 0.008$) were significant factors affecting the pRNFL thickness in groups 2 and 3. Additionally, the HTN duration was significantly correlated with pRNFL thickness in group 3 ($R^2 = 0.121$; $P = 0.008$). In conclusion, patients with T2DM with HTN showed thinner pRNFL thickness than those with T2DM only. Additionally, the duration of HTN was significantly correlated with pRNFL thickness in patients with both diabetes and HTN.

Patients with type 2 diabetes mellitus (T2DM) could show various impairments in visual function, including decreased hue discrimination, decreased contrast sensitivity, delayed dark adaptation, reduced visual field sensitivity, and reduced visual acuity, although they do not have clinical diabetic retinopathy (DR) (1–4). Such impairment of visual function is related to diabetic neurodegeneration (DRN). Previous studies reported that the DRN preceded the microvascular abnormalities associated with DR progression, showing accelerated peripapillary retinal nerve fiber layer (pRNFL) and ganglion cell-inner plexiform layer reductions over time (5–8). Therefore, inner retinal changes should not be overlooked in patients with T2DM without clinical DR.

Hypertension (HTN) is another significant systemic disease causing visual impairment, and it is a risk factor for various ophthalmic diseases, including retinal vascular occlusion, retinal macroaneurysm, ischemic optic neuropathy, and glaucoma. Uncontrolled HTN can cause hypertensive retinopathy, with retinal hemorrhage, hard exudates, cotton wool spots, optic disc edema, and macular edema (9). Additionally, chronic HTN without HTN retinopathy can also result in retinal damage. Previous studies reported inner retinal damage in patients with HTN under conditions of well-controlled blood pressure without a history of HTN retinopathy (10,11).

Both T2DM and HTN can cause inner retinal damage and reduction over time. However, there have been no reports regarding how the two diseases interact with regard to pRNFL thickness. This study was performed to assess the pRNFL damage caused by DRN and the effects of HTN on the pRNFL thickness in patients with T2DM without clinical DR.

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RESEARCH DESIGN AND METHODS

Patients

This retrospective, cross-sectional study was performed in accordance with the tenets of the Declaration of Helsinki and approved by the Institutional Review Board of Chungnam National University Hospital (Daejeon, Republic of Korea). Patients with T2DM without clinical DR who visited the retina clinic of Chungnam National University Hospital for a checkup for retinal abnormalities between March 2017 and December 2020 were enrolled. The control group included patients without any systemic disease, including T2DM and HTN, and diagnosed with a unilateral epiretinal membrane, macular hole, or intraocular lens dislocation—all of the fellow eyes without any ophthalmic disease. Patients with HTN were initially diagnosed with HTN and follow-up at the Department of Internal Medicine of Chungnam National University Hospital. The diagnosis of HTN was made according to the Korean HTN treatment guideline (12). The blood pressure of all patients with HTN was well controlled. The requirement for informed consent was waived due to the retrospective nature of the study. Subjects were divided into three groups: control group (group 1), patients with T2DM (group 2), and patients with both T2DM and HTN (group 3). Patients with a history of any systemic disease other than T2DM and HTN, blood pressure >140/90 after treatment, any ophthalmic disease, intraocular pressure ≥21 mmHg, optic disc abnormalities, any history of intraocular surgery other than cataract extraction, and axial length ≥26 mm were excluded. Patients with any evidence of DR or any changes associated with hypertensive retinopathy, such as retinal hemorrhage, microaneurysm, arteriovenous nicking, cotton wool spots, or optic disc edema, were also excluded. If both eyes met the inclusion criteria in one person, one eye was randomly selected for the study to avoid statistical bias.

Optical Coherence Tomography Measurements

We performed spectral-domain optical coherence tomography (OCT) (Cirrus HD OCT 5000, version 10.0; Carl Zeiss Meditec, Dublin, CA), which has an axial resolution of 5 μm and lateral resolution of 15 μm and generates a high-definition scan at a depth of 2.0 mm. The pRNFL thickness was measured using a 200 × 200 optic disc cube scanning protocol. We excluded scans with a signal strength <7, obvious decentration, or segmentation errors.

Statistical Analyses

Demographics and OCT measurements were compared by an ANOVA followed by a Bonferroni post hoc test. The χ^2 test was used for the comparison of categorical data. An ANCOVA was performed to control for the effects of covariate values. Linear regression analyses were performed to identify the factors affecting pRNFL thickness. After applying the Shapiro-Wilk test of normality, correlations between pRNFL thickness and T2DM duration or HTN duration were evaluated in groups 2 and 3. All statistical analyses were performed using SPSS software (version 18.0; IBM Corp., Armonk, NY).

Data and Resource Availability

The data sets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

RESULTS

Demographics

A total of 365 eyes were initially enrolled. Of these, 40 eyes were excluded from the study: 28 eyes due to retinal hemorrhage or cotton wool spots, 5 eyes due to epiretinal membrane, 4 eyes due to RNFL defect and glaucomatous disc, and 3 eyes due to low signal strength. As a result, a total of 325 eyes were included: 143 eyes in group 1, 126 eyes in group 2, and 56 eyes in group 3 (Table 1). T2DM duration and HbA_{1c} were not significantly different between group 2 and group 3 ($P = 0.276$ and $P = 0.158$). The HTN duration of group 3 was 9.6 ± 6.1 years.

The pRNFL Thickness of Each Group

The mean pRNFL thicknesses of groups 1, 2, and 3 were 96.1 ± 7.7, 94.4 ± 8.6, and 91.6 ± 9.6 μm, respectively ($P = 0.003$) (Table 2). In post hoc analyses, the pRNFL was thinner in group 3 than in group 2 ($P = 0.002$) and in group 2 than in group 1 ($P = 0.031$). The thicknesses of the superior, temporal, and inferior sectors showed similar trends to the mean pRNFL thickness.

Factors Associated With pRNFL Thickness in Patients With T2DM

In univariate analyses, age ($\beta = -0.164$; $P = 0.014$), T2DM duration ($\beta = -0.258$, $P = 0.011$), HbA_{1c} level ($\beta = -1.522$; $P = 0.049$), and HTN ($\beta = -4.035$; $P = 0.005$) were significant factors affecting the pRNFL thickness in group 2 and group 3 (Table 3). In multivariate analyses, T2DM duration ($\beta = -0.236$; $P = 0.018$) and HTN ($\beta = -3.766$; $P = 0.008$) showed significant results.

Association of the Duration of T2DM and HTN With pRNFL Thickness

In group 2, the duration of T2DM showed a significant negative correlation with pRNFL thickness ($R^2 = 0.125$; $P < 0.001$) (Fig. 1). In group 3, the T2DM duration also showed a negative correlation with pRNFL thickness, but it was not statistically significant ($R^2 = 0.052$; $P = 0.092$). The HTN duration was significantly correlated with pRNFL thickness in group 3 ($R^2 = 0.121$; $P = 0.008$).

DISCUSSION

This study shows that patients with T2DM had a thinner pRNFL than control subjects, and patients with T2DM with HTN had a thinner pRNFL than those with T2DM

Table 1—Demographics and clinical characteristics

	Group 1 (n = 143)	Group 2 (n = 126)	Group 3 (n = 56)	P value
Age, years	59.3 ± 9.0	58.3 ± 10.3	64.8 ± 7.8	**<0.001**
Sex (male), %	60 (42.0)	55 (43.7)	33 (64.3)	0.091
Laterality (right), %	72 (50.4)	61 (48.4)	28 (50.0)	0.992
BCVA, logMAR	−0.019 ± 0.060	−0.002 ± 0.061	0.003 ± 0.053	**0.018**
SE, diopters	−0.28 ± 1.76	−0.37 ± 1.78	−0.07 ± 1.55	0.565
IOP, mmHg	14.5 ± 2.8	15.6 ± 2.9	14.8 ± 2.7	0.081
Axial length, mm	23.7 ± 1.0	23.7 ± 0.8	23.9 ± 1.0	0.577
Diabetes duration, years	N/A	7.3 ± 5.9	8.5 ± 7.8	0.276
HbA_{1c}, %	N/A	6.85 ± 0.87	7.05 ± 0.85	0.158
SBP, mmHg	117.8 ± 8.9	118.7 ± 7.9	122.7 ± 8.0	0.201
DBP, mmHg	73.7 ± 8.0	74.1 ± 7.5	73.9 ± 8.7	0.723
Rim area, mm^2	1.33 ± 0.11	1.29 ± 0.23	1.20 ± 0.23	**0.037**
Disc area, mm^2	1.76 ± 0.27	1.99 ± 0.39	1.90 ± 0.36	0.167
Cup-disc ratio	0.46 ± 0.11	0.55 ± 0.16	0.56 ± 0.16	0.274
CMT, μm	251.9 ± 18.2	247.2 ± 17.9	253.4 ± 20.5	0.081
GC-IPL thickness, μm	83.8 ± 5.5	82.5 ± 6.1	79.2 ± 7.5	**<0.001**

Data are mean ± SD unless otherwise indicated. Group 1, control subjects; group 2, patients with T2DM; group 3, patients with both T2DM and HTN. P values in boldface are statistically significant ($P < 0.05$). BCVA, best-corrected visual acuity; CMT, central macular thickness; DBP, diastolic blood pressure; GC-IPL, ganglion cell-inner plexiform layer; IOP, intraocular pressure; N/A, not applicable; SBP, systolic blood pressure; SE, spherical equivalent.

only. T2DM duration and HTN were significant factors associated with pRNFL thickness in multivariate analyses in patients with T2DM. Additionally, the HTN duration was significantly correlated with pRNFL thickness in patients with T2DM with HTN.

Lim et al. (6) reported that diabetes was associated with accelerated pRNFL loss, regardless of whether DR progressed. Other studies also showed that the pRNFL thickness was thinner in patients with T2DM, consistent with the current study (7,8,13). Such a pRNFL reduction in patients with T2DM is related to DRN. DRN, which could develop before any definite microvascular changes, would cause the apoptosis of retinal ganglion cells, and such cell loss would result in a reduction in pRNFL thickness (14). Therefore, physicians should be aware of these reductions in pRNFL thickness in patients with T2DM and consider this when interpreting changes in pRNFL thickness in patients with T2DM with other diseases that cause damage to the pRNFL, such as glaucoma.

Table 2—pRNFL thickness in each group

	Group 1	Group 2	Group 3	P value*
Mean	96.1 ± 7.7	94.4 ± 8.6	91.6 ± 9.6	**0.005**
Sector				
Superior	120.8 ± 20.2	118.1 ± 18.1	113.3 ± 21.0	0.088
Temporal	72.7 ± 10.4	71.1 ± 12.0	67.4 ± 14.8	**0.026**
Inferior	124.7 ± 14.9	123.9 ± 18.7	114.9 ± 20.3	**0.003**
Nasal	68.4 ± 8.8	68.7 ± 12.6	71.6 ± 14.6	0.258

Data are expressed as the mean ± SD (μm). Group 1, control subjects; group 2, patients with T2DM; group 3, patients with both T2DM and HTN. P values in boldface are statistically significant ($P < 0.05$). *P value after adjusting for covariates including age and best-corrected visual acuity.

In this study, patients with T2DM with HTN had a thinner pRNFL than control subjects and patients with T2DM only. HTN could cause inner retinal damage similar to T2DM. Previous studies reported accelerated pRNFL loss and reduced pRNFL thickness in patients with HTN (10,15). This reduction would be related to the impairment of retinal microvasculature by HTN. Previous studies reported the reduced vessel density of the retina using OCT angiography in patients with HTN without hypertensive retinopathy, and such microvascular impairment may affect the reduction of the inner retina, which is linked to each other by neurovascular unit (16–18). Meanwhile, Sohn et al. (8) reported that neural apoptosis, glial cell reactivity, and numerous aberrant biochemical pathways associated with DRN seemed to be independent of vascular changes, indicating that DRN is not ischemic in origin. Therefore, two different mechanisms, DRN and ischemic damage caused by HTN, would result in more severe inner retinal damage, leading to accelerated pRNFL reduction.

The duration of T2DM was a significant factor associated with pRNFL thickness in patients with T2DM, which was consistent with previous studies (6,8). It is noteworthy that such inner retinal damage by DRN was found to occur consistently under conditions of relatively good glycemic control in these studies. Once DRN begins, neural apoptosis, glial dysfunction, and several pathological

Table 3—Univariate and multivariate linear regression analyses determining the factors associated with pRNFL thickness in patients with T2DM

	Univariate		Multivariate	
	β (95% CI)	*P* value	β (95% CI)	*P* value
Age	−0.164 (−0.295 to −0.033)	**0.014**	−0.083 (−0.227 to 0.061)	0.258
Sex	0.974 (−1.679 to 3.627)	0.470		
Laterality	−1.079 (−3.730 to 1.573)	0.423		
BCVA	−11.161 (−33.988 to 11.666)	0.336		
IOP	−0.363 (−0.826 to 0.11)	0.124		
SE	−0.485 (−1.256 to 0.286)	0.216		
AXL	0.403 (−1.123 to 1.928)	0.603		
Diabetes duration	−0.258 (−0.456 to −0.060)	**0.011**	−0.236 (−0.432 to −0.041)	**0.018**
HbA_{1c}	−1.522 (−3.039 to −0.005)	**0.049**	−1.001 (−2.514 to 0.512)	0.193
HTN	−4.035 (−6.832 to −1.239)	**0.005**	−3.766 (−6.535 to −0.997)	**0.008**
SBP	−0.188 (−0.402 to 0.032)	0.100		
DBP	−0.079 (−0.352 to 0.239)	0.766		

P values in boldface are statistically significant ($P < 0.05$). AXL, axial length; BCVA, best-corrected visual acuity; DBP, diastolic blood pressure; IOP, intraocular pressure; SBP, systolic blood pressure; SE, spherical equivalent.

pathways may persist even under good glycemic control, causing consistent pRNFL reduction over time. Therefore, physicians should not conclude that the retina of patients with T2DM is stable, even if it does not show any DR changes under conditions of good glycemic control.

In patients with T2DM with HTN, diabetes duration was negatively correlated with pRNFL thickness, but the correlation was not statistically significant ($P = 0.092$). In contrast, HTN duration showed a significant correlation with pRNFL thickness ($P = 0.008$). Ischemic damage, which may be associated with the impairment of microvasculature caused by HTN, could accumulate over time. Neural cell damage due to DRN could impair the function of the retinal neurovascular unit, which plays a key role in the regulation of the blood supply to the inner retina, and the inner retinal layer may be more vulnerable to the accumulated ischemic damage under such conditions (7,8,19). That is, the ischemic damage that accumulates over time could have one of the greatest effects on the inner retinal layer with impaired function of the neurovascular unit by DRN. Additional studies are needed to confirm this hypothesis.

The HbA_{1c} level was also significant only in univariate analyses, and previous studies have reported less impact of HbA_{1c} on inner retinal layer changes caused by DRN (1,6). This result may come from the enrolled patients of the study, who showed an HbA_{1c} level of ∼7.0% (53 mmol/mol). In patients with relatively good glycemic control, other factors may be more important. However, long-term hyperglycemia could induce impairment of retinal structures and neural function by retinal hypoxia and inflammation, and HbA_{1c} is known to affect microvasculopathy in patients with diabetes, which may result in more severe inner retina impairment with ischemic damage to the retinal microvasculature caused by HTN

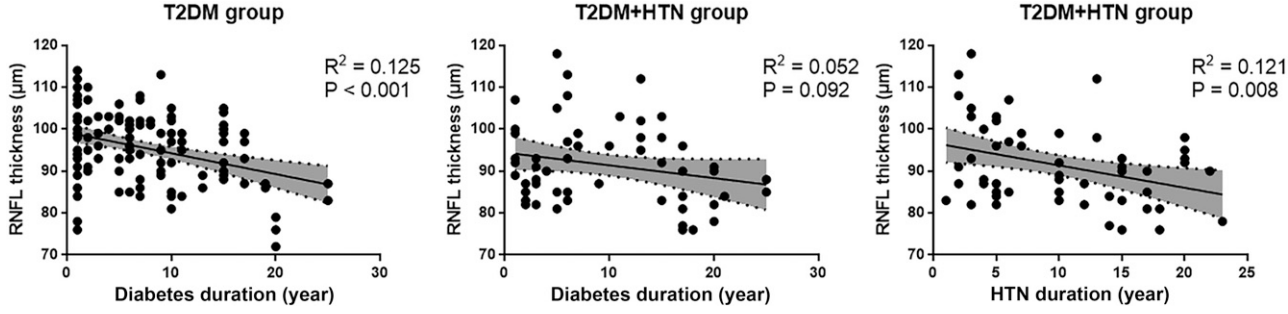

Figure 1—Scatter plot and results of linear regression analyses showing correlations between the mean pRNFL thickness and duration of T2DM and HTN.

(20–22). Therefore, the importance of glycemic control for the inner retinal layer should not be overlooked, especially in patients with T2DM with HTN.

This study has several limitations. First, the retrospective nature of the study inevitably introduced some selection bias. Second, although glaucoma specialists were consulted and excluded patients with pRNFL defects, a glaucomatous optic disc, and history of intraocular pressure ≥21 mmHg, a visual field test was not performed, so we cannot totally rule out the possibility that patients with preperimetric glaucoma were included in the analysis. Third, we cannot also exclude the possibility that the study population included patients with HTN who had a previous occurrence and subsequent regression of HTN retinopathy. Additionally, further studies with a larger number of cases are needed, including histories of HTN medication to identify the exact mechanism of pRNFL reduction in patients with HTN.

In conclusion, patients with T2DM had a thinner pRNFL than healthy individuals, and patients with T2DM with HTN showed a much thinner pRNFL than patients with T2DM only. This result may come from two different mechanisms; DRN and ischemic microvascular damage caused by HTN on the reduction of the inner retinal layer. Additionally, diabetes duration was a significant factor associated with pRNFL thickness in patients with T2DM, and HTN duration significantly affected the pRNFL thickness in patients with both T2DM and HTN. These results indicate that the inner retina is more vulnerable to accumulated ischemic damage under conditions of impaired neurovascular unit function caused by DRN. Physicians should consider these findings when interpreting changes of pRNFL thickness in patients with T2DM with HTN.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. M.-W.L. and J.-Y.K. were responsible for the design and conduct of the study. M.-W.L., G.-S.P., M.-S.K., and J.-Y.K. were responsible for collection of data. M.-W.L., G.-S.P., H.-B.L., and J.-Y.K. performed analysis and interpretation of data. M.-W.L., G.-S.P., and J.-Y.K. were responsible for writing the article. M.-W.L., G.-S.P., H.-B.L., W.-H.L., Y.-H.L., and J.-Y.K. performed critical revision of the article. M.-W.L., G.-S.P., H.-B.L., W.-H.L., M.-S.K., Y.-H.L., and J.-Y.K. gave final approval of the article. J.-Y.K. is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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