

# Impacts of Systemic Hypertension on the Macular Microvasculature in Diabetic Patients Without Clinical Diabetic Retinopathy

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**PURPOSE.** To identify the impact of hypertension (HTN) on macular microvasculature in type 2 diabetes (T2DM) patients without clinical diabetic retinopathy.

**METHODS.** In this retrospective cross-sectional study, subjects were divided into three groups: controls (control group), patients with T2DM (DM group), and patients with both T2DM and HTN (DM + HTN group). The vessel length density (VD) was compared among the groups. Linear regression analyses were performed to identify factors associated with VD.

**RESULTS.** The VD in the control, DM, and DM + HTN groups was  $20.43 \pm 1.16$ ,  $19.50 \pm 1.45$ , and  $18.19 \pm 2.06 \text{ mm}^{-1}$ , respectively ( $P < 0.001$ ). The best-corrected visual acuity ( $B = -9.30$ ;  $P = 0.002$ ), duration of T2DM ( $B = -0.04$ ;  $P = 0.020$ ), HTN ( $B = -0.51$ ;  $P = 0.016$ ), signal strength ( $B = 1.12$ ;  $P < 0.001$ ), and ganglion cell-inner plexiform layer thickness ( $B = 0.06$ ;  $P < 0.001$ ) were significant factors affecting VD in patients with T2DM. Additionally, the hemoglobin A1c (HbA1c) ( $B = -0.49$ ;  $P = 0.016$ ) was significantly associated with VD in patients with both T2DM and HTN.

**CONCLUSIONS.** Patients with T2DM had impaired macular microvasculature, and patients with T2DM with HTN exhibited greater impairment of the microvasculature than did patients with T2DM only. Additionally, physicians should be aware that the macular microvasculature would be more vulnerable to hyperglycemic damage under ischemic conditions by HTN.

Keywords: hypertension, type 2 diabetes, OCTA

Diabetic retinopathy (DR) is the leading cause of preventable visual impairment in patients with type 2 diabetes mellitus (T2DM).<sup>1</sup> DR can cause diabetic macular edema, tractional retinal detachment, and neovascular glaucoma, which would result in permanent visual loss without appropriate management. Therefore, patients showing DR changes, such as retinal hemorrhage, hard exudates, and cotton wool spots, require careful observation for various DR-related complications. Meanwhile, anatomical and functional impairments of the retina have been reported recently in diabetic patients without clinical DR. Diabetic retinal neurodegeneration (DRN), which causes accelerated inner retinal reduction over time, is a representative type of retinal damage preceding DR.<sup>2-6</sup> Additionally, as detailed observation of microvasculature at high resolution has become possible using optical coherence tomography angiography (OCTA), impairments of peripapillary and macular microvasculature have been reported in diabetic patients without DR.<sup>7,8</sup>

Hypertension (HTN), a major risk factor for cardiovascular disease and mortality, is another systemic disease associated with visual impairment.<sup>9</sup> Chronic sustained HTN can cause hypertensive retinopathy, which is characterized by retinal hemorrhage, hard exudates, cotton wool spots, optic disc edema, and macular edema.<sup>10,11</sup> Additionally, inner retinal damage, such as peripapillary retinal nerve fiber layer (pRNFL) and ganglion cell-inner plexiform layer (GC-IPL) reduction similar to that seen in DRN, has been reported in patients with chronic HTN, even with well-controlled blood pressure.<sup>12,13</sup> After inner retinal thinning, the impairment of macular microvasculature causing low vessel density (VD) and perfusion density (PD) has also been reported.<sup>10,14</sup>

Diabetes and HTN are both relatively common systemic diseases that cause similar damage to the retina, such as inner retina reduction and microvascular impairment.<sup>3,15-18</sup> Therefore, HTN in patients with T2DM may cause more severe damage to the retina. However, few studies have reported retinal damage in patients with both diseases. In

this study, we evaluated the macular microvasculature in patients with T2DM and HTN to identify the impact of HTN on the retinal microvasculature of patients with T2DM.

## METHODS

### Patients

This retrospective, cross-sectional study was performed in accordance with the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of Chungnam National University Hospital, Daejeon, Republic of Korea (number: 2021-03-089). The study enrolled patients with T2DM who visited the retina clinic of Chungnam National University Hospital for DR checkups between March 2017 and December 2020. All patients were diagnosed with T2DM and HTN at the Department of Internal Medicine of Chungnam National University Hospital. The diagnosis of T2DM (fasting plasma glucose of  $\geq 126$  mg/dL or 2-hour plasma glucose of  $\geq 200$  mg/dL or hemoglobin A1c [HbA1c] of  $\geq 6.5\%$ ) and HTN (clinic blood pressure,  $\geq 140/90$  mm Hg; home blood pressure,  $\geq 135/85$  mm Hg) was made according to the criteria of the American Diabetes Association and the Korean HTN treatment guideline.<sup>19,20</sup> The blood pressure of all patients with HTN was well-controlled. The control group included subjects with no known ocular or systemic disease. The requirement for obtaining informed consent was waived owing to the retrospective nature of the study. We recorded detailed histories and measurements of best-corrected visual acuity (BCVA), intraocular pressure, spherical equivalent, and axial length. Subjects were divided into three groups: controls (control group), patients with T2DM (DM group), and patients with both T2DM and HTN (DM + HTN group). The exclusion criteria were a history of systemic disease other than T2DM and HTN, any other retinal disease, glaucoma, optic nerve disorder, intraocular pressure of 21 mm Hg or higher, axial length of 26 mm or more, and any prior intraocular surgery other than cataract extraction. We also excluded patients with clinical evidence of DR such as retinal hemorrhage or microaneurysm, and any changes associated with HTN retinopathy, such as arteriovenous nicking, cotton wool spots, or optic disc edema. If both eyes met the inclusion criteria, one eye was selected at random for the study.

### OCT and OCTA Measurements

Spectral domain OCT examinations were performed using a Cirrus HD-OCT 5000 (Carl Zeiss Meditec, Dublin, CA) with a  $512 \times 128$  macular cube scanning protocol, and we analyzed GC-IPL thickness based on an algorithm using the Ganglion Cell Analysis module. The algorithm automatically measured the GC-IPL by identifying the outer boundaries of the retinal nerve fiber layer and inner plexiform layer using three-dimensional information from the macular cube. The GC-IPL thickness was measured within an annulus with inner vertical and horizontal diameters of 1.0 and 1.2 mm, respectively, and outer vertical and horizontal diameters of 4.0 and 4.8 mm, respectively.

OCTA examinations were performed using a Cirrus HD-OCT 5000 with AngioPlex software (Carl Zeiss Meditec), with a wavelength of 840 nm and taking 68,000 A-scans per second. The device ensures sensitivity and accuracy by incorporating the optical microangiography algorithm and retinal tracking technology. We measured patterns in a foveal

centered scan area of  $3 \times 3$  mm, and all scans were analyzed using en face OCTA images generated automatically by the optical microangiography algorithm in AngioPlex software. The  $3 \times 3$  mm scan was composed of a 1 mm center and four-quadrant sectors that were identical to the inner circles used in the Early Treatment of Diabetic Retinopathy Study (Fig. 1). The central area was a central circle 1 mm in diameter, the inner area was the sum of our quadrant sectors, and the full area was the 3-mm inner circle defined in the Early Treatment of Diabetic Retinopathy Study. The VD (the total length of perfused vasculature per unit area) and PD (the total area of perfused vasculature per unit area) were measured automatically by the software. All images were reviewed individually by two investigators (L.M.W., K.H.M.) for quality evaluation and images with loss of fixation or foveal centration, segmentation errors, motion artifacts, and a signal strength of less than 8 were excluded.

### Statistical Analysis

Baseline demographics and OCT measurements were compared using one-way ANOVA, followed by a post hoc test (Bonferroni test). The  $\chi^2$  test was used for comparisons of categorical data. For the comparison of OCTA measurements, analysis of covariance was performed to control for the effects of covarying values. Univariate and multivariate linear regression analyses were performed to identify the factors affecting the VD of the full area. All statistical analyses were performed using SPSS software (version 18.0; IBM Corp., Armonk, NY).

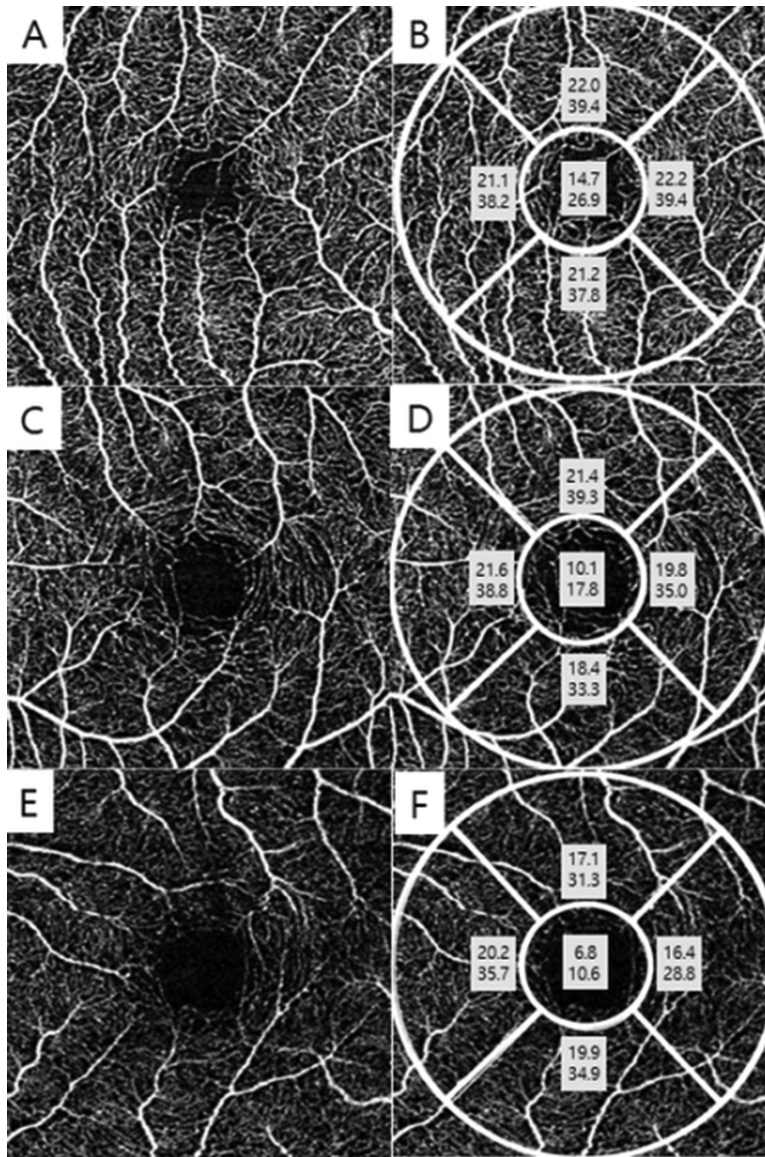
## RESULTS

### Demographics

A total of 280 eyes were enrolled; 95 eyes in the control group, 94 eyes in the DM group, and 91 eyes in the DM + HTN group (Table 1). The average ages of the control, DM, and DM + HTN groups were  $63.7 \pm 4.3$ ,  $59.3 \pm 10.1$ , and  $62.5 \pm 9.7$  years, respectively ( $P = 0.001$ ). In post hoc analyses, the control group versus the DM group, and the DM group versus the DM + HTN group showed a significantly different age ( $P = 0.001$  and  $P = 0.027$ , respectively). The average BCVA was significantly different among groups ( $P = 0.001$ ), which showed a significant difference in the control group versus the DM group ( $P = 0.029$ ), and the control group versus the DM + HTN group ( $P < 0.001$ ) in post hoc analyses. Sex, laterality, the spherical equivalent, intraocular pressure, and axial length were not significantly different among the three groups. Regarding OCT parameters, GC-IPL and pRNFL thicknesses were significantly different among the three groups (both  $P < 0.001$ ).

### OCTA Parameters of Each Group

The VDs of the full area in the control, DM, and DM + HTN groups were  $20.43 \pm 1.16$ ,  $19.50 \pm 1.45$ , and  $18.19 \pm 2.06$  mm<sup>-1</sup>, respectively ( $P < 0.001$ ) (Table 2). In the post hoc analyses, VD was significantly lower in the DM group than in the control group ( $P < 0.001$ ), and in the DM + HTN than in the DM group ( $P < 0.001$ ). After adjustment for age, BCVA, and signal strength, the VD of the full area remained different among the groups ( $P < 0.001$ ). The inner diameter and VD in each group showed similar results to the full area of VD in each group, but the VD of the central area was



**FIGURE 1.** A representative 3 × 3 mm OCTA image and image overlaid with an Early Treatment of Diabetic Retinopathy Study grid showing VD (*upper row*) and PD (*lower row*) of the control group (A, B), DM group (C, D), and DM + HTN group (E, F).

not significantly different after adjustment for covariates ( $P = 0.357$ ) (Fig. 2).

The full area PDs in the control, DM, and DM + HTN groups were  $36.8 \pm 1.9$ ,  $35.3 \pm 2.4$ , and  $33.6 \pm 4.2\%$ , respectively ( $P < 0.001$ ). In the post hoc analyses, PD was significantly lower in the DM + HTN group than in the DM group ( $P = 0.001$ ), and in the DM group than in the control group ( $P < 0.001$ ). The full area of PD was significantly different among groups after adjustment of age, BCVA, and signal strength ( $P < 0.001$ ). Trends in the PD of the inner and central areas across groups were similar to those for the PD of the full area, but the PD of the central area was not significantly different among groups ( $P = 0.484$ ). The signal strength in each group was  $9.6 \pm 0.5$ ,  $9.5 \pm 0.7$ , and  $9.4 \pm 0.8$ , respectively ( $P = 0.080$ ).

### Factors Associated With VD in Patients With T2DM

In univariate analyses, age ( $B = -0.04$ ;  $P = 0.004$ ), the BCVA ( $B = -8.12$ ;  $P < 0.001$ ), duration of T2DM ( $B = -0.10$ ;  $P < 0.001$ ), HbA1c level ( $B = -0.35$ ;  $P = 0.040$ ), HTN status ( $B = -1.31$ ;  $P < 0.001$ ), signal strength ( $B = 1.39$ ;  $P < 0.001$ ), GC-IPL thickness ( $B = 0.10$ ;  $P < 0.001$ ), and pRNFL thickness ( $B = 0.05$ ;  $P < 0.001$ ) were associated significantly with the VD of the full area in patients with T2DM (Table 3). In multivariate analyses, the BCVA ( $B = -9.30$ ;  $P = 0.002$ ), duration of T2DM ( $B = -0.04$ ;  $P = 0.020$ ), HTN status ( $B = -0.51$ ;  $P = 0.016$ ), signal strength ( $B = 1.12$ ;  $P < 0.001$ ), and GC-IPL thickness ( $B = 0.06$ ;  $P < 0.001$ ) showed significant results.

TABLE 1. Demographics and Clinical Characteristics

Characteristics	Control Group (n = 95)	DM Group (n = 94)	DM + HTN Group (n = 91)	P Value
Age (mean ± SD, years)	63.7 ± 4.3	59.3 ± 10.1	62.5 ± 9.7	<b>0.001</b>
Sex (male, %)	44 (46.3)	48 (51.1)	41 (45.1)	0.781
Laterality (right, %)	55 (57.9)	50 (53.2)	49 (53.8)	0.780
BCVA (mean ± SD, logMAR)	-0.019 ± 0.060	0.008 ± 0.079	0.022 ± 0.083	<b>0.001</b>
SE (mean ± SD, diopters)	-0.65 ± 1.12	-0.27 ± 1.62	-0.41 ± 1.75	0.465
IOP (mean ± SD, mm Hg)	15.7 ± 2.7	15.5 ± 3.1	16.2 ± 2.9	0.078
Axial length (mean ± SD, mm)	23.6 ± 0.7	23.7 ± 0.8	23.5 ± 0.9	0.502
DM duration (mean ± SD, years)	N/A	9.2 ± 6.8	10.6 ± 5.7	0.067
HbA1C (mean ± SD, %)	N/A	6.9 ± 0.8	7.1 ± 0.8	0.069
HTN duration	N/A	N/A	7.9 ± 6.4	N/A
CMT (mean ± SD, μm)	250.6 ± 19.6	247.1 ± 17.8	252.8 ± 20.1	0.196
GC-IPL thickness (mean ± SD, μm)	84.9 ± 8.8	83.5 ± 5.8	78.7 ± 8.7	< <b>0.001</b>
pRNFL thickness (mean ± SD, μm)	97.0 ± 8.5	94.7 ± 7.4	89.9 ± 12.8	< <b>0.001</b>

CMT, central macular thickness; DM, diabetes mellitus; IOP, intraocular pressure; pRNFL, peripapillary nerve fiber layer; SD, standard deviation; SE, spherical equivalent.

Values in boldface are statistically significant (*P* < 0.05).

TABLE 2. VD and PD in Each Group

Characteristics	Control Group	DM Group	DM + HTN Group	P Value*
VD (mm <sup>-1</sup> )				
Full area	20.43 ± 1.16	19.50 ± 1.45	18.19 ± 2.06	< <b>0.001</b>
Inner area	21.81 ± 1.15	20.84 ± 1.45	19.24 ± 2.79	< <b>0.001</b>
Central area	9.54 ± 2.63	8.94 ± 2.84	8.43 ± 2.77	0.357
PD (%)				
Full area	36.8 ± 1.9	35.3 ± 2.4	33.6 ± 4.2	< <b>0.001</b>
Inner area	39.3 ± 1.8	37.8 ± 2.4	35.4 ± 4.3	< <b>0.001</b>
Central area	16.6 ± 5.6	15.6 ± 5.0	15.5 ± 6.0	0.484

All values are expressed as the mean ± standard deviation (μm).

\* Analysis of covariance after adjustment of age, BCVA, and signal strength.

Values in boldface are statistically significant (*P* < 0.05).

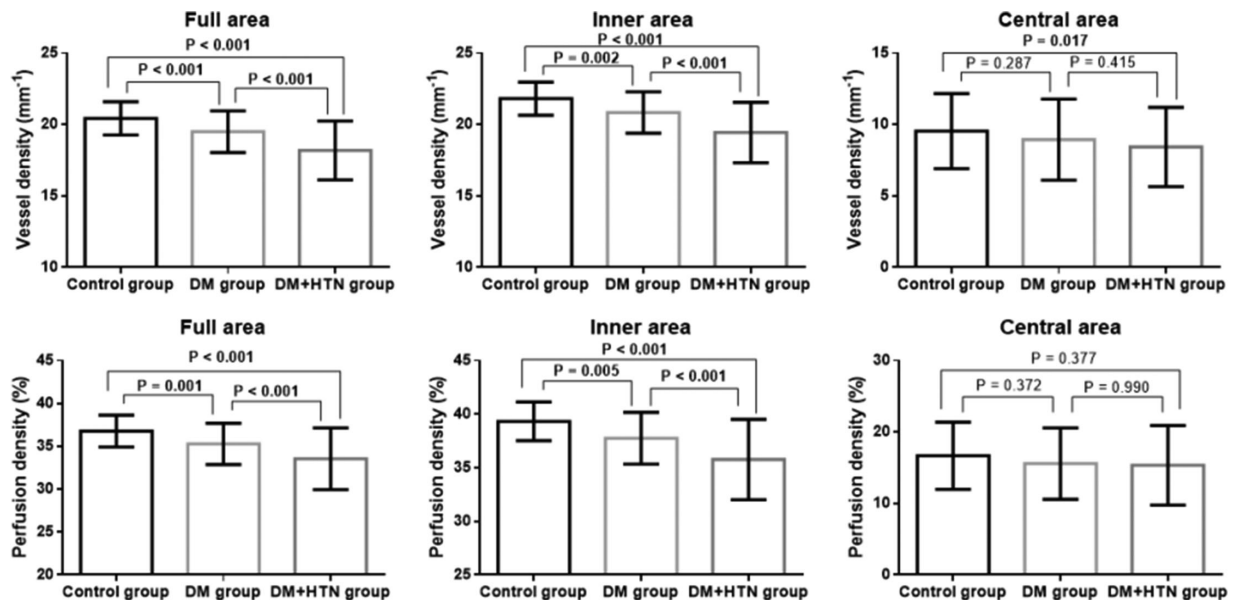


FIGURE 2. The mean VD and PD in each group. Error bars indicate standard deviations.

**TABLE 3.** Univariate and Multivariate Linear Regression Analyses to Identify Factors Associated With VD in Patients With T2DM

Characteristics	Univariate		Multivariate	
	B (95% CI)	P Values	B (Standardized Coefficients, 95% CI)	P Values
Age	-0.04 (-0.07 to -0.01)	<b>0.004</b>	0.01 (0.01, -0.02 to 0.02)	0.932
Sex	-0.09 (-0.63 to 0.45)	0.737		
Laterality	-0.43 (-0.97 to 0.12)	0.126		
BCVA	-8.12 (-11.30 to -4.95)	<b>&lt;0.001</b>	-9.30 (-0.17, -6.35 to -1.52)	<b>0.002</b>
IOP	0.01 (-0.09 to 0.10)	0.888		
SE	-0.05 (-0.21 to 0.12)	0.589		
AXL	0.14 (-0.17 to 0.45)	0.384		
DM duration	-0.10 (-0.14 to -0.06)	<b>&lt;0.001</b>	-0.04 (-0.13, -0.07 to -0.01)	<b>0.020</b>
HbA1c	-0.35 (-0.69 to -0.02)	<b>0.040</b>	-0.15 (-0.06, -0.39 to 0.10)	0.237
HTN	-1.31 (-1.82 to -0.79)	<b>&lt;0.001</b>	-0.51 (-0.14, -0.92 to -0.10)	<b>0.016</b>
Signal strength	1.39 (1.13 to 1.65)	<b>&lt;0.001</b>	1.12 (0.49, 0.88 to 1.36)	<b>&lt;0.001</b>
CMT	0.01 (-0.01 to 0.02)	0.199		
GC-IPL	0.10 (0.06 to 0.13)	<b>&lt;0.001</b>	0.06 (0.24, 0.03 to 0.09)	<b>&lt;0.001</b>
pRNFL	0.05 (0.03 to 0.08)	<b>&lt;0.001</b>	0.01 (0.06, -0.01 to 0.03)	0.415

AXL, axial length; CMT, central macular thickness; DM, diabetes; IOP, intraocular pressure; pRNFL, peripapillary nerve fiber layer; SE, spherical equivalent; Values in boldface are statistically significant ( $P < 0.05$ ).

**TABLE 4.** Univariate and Multivariate Linear Regression Analyses to Identify Factors Associated With VD in Patients With Both T2DM and HTN

Characteristics	Univariate		Multivariate	
	B (95% CI)	P Values	B (Standardized Coefficients, 95% CI)	P Values
Age	-0.01 (-0.05 to 0.04)	0.898		
Sex	0.31 (-0.55 to 1.18)	0.472		
Laterality	-0.59 (-1.45 to 0.26)	0.173		
BCVA	-9.19 (-14.00 to -4.36)	<b>&lt;0.001</b>	-5.24 (-0.21, -8.81 to -1.68)	<b>0.004</b>
IOP	-0.03 (-0.18 to 0.12)	0.727		
SE	-0.23 (-0.27 to 0.23)	0.854		
AXL	-0.04 (-0.50 to 0.42)	0.866		
DM duration	-0.07 (-0.15 to 0.01)	0.057	-0.01 (-0.02, -0.06 to 0.05)	0.133
HbA1c	-0.58 (-1.13 to -0.05)	<b>0.014</b>	-0.49 (-0.19, -0.89 to -0.10)	<b>0.016</b>
HTN duration	-0.02 (-0.09 to 0.04)	0.495		
SBP	0.01 (-0.05 to 0.05)	0.902		
DBP	-0.02 (-0.06 to 0.03)	0.433		
Signal strength	1.46 (1.08 to 1.84)	<b>&lt;0.001</b>	1.31 (0.56, 0.98 to 1.64)	<b>&lt;0.001</b>
CMT	0.02 (0.01 to 0.03)	<b>0.026</b>	0.01 (0.11, -0.01 to 0.02)	0.124
GC-IPL	0.10 (0.06 to 0.15)	<b>&lt;0.001</b>	0.07 (0.28, 0.03 to 0.10)	<b>0.001</b>
pRNFL	0.04 (0.01 to 0.08)	<b>0.008</b>	-0.02 (-0.15, -0.06 to 0.01)	0.143

AXL, axial length; CMT, central macular thickness; DBP, diastolic blood pressure; DM, diabetes; IOP, intraocular pressure; SBP, systolic blood pressure; SE, spherical equivalent.

Values in boldface are statistically significant ( $P < 0.05$ ).

### Factors Associated With VD in Patients With Both T2DM and HTN

In univariate analyses, the BCVA ( $B = -9.19$ ;  $P < 0.001$ ), HbA1c level ( $B = -0.58$ ;  $P = 0.014$ ), signal strength ( $B = 1.46$ ;  $P < 0.001$ ), central macular thickness ( $B = 0.02$ ;  $P = 0.026$ ), GC-IPL thickness ( $B = 0.10$ ;  $P < 0.001$ ), and pRNFL thickness ( $B = 0.04$ ;  $P = 0.008$ ) were significant factors affecting the VD of the full area in patients with both T2DM and HTN (Table 4). In multivariate analyses, the BCVA ( $B = -5.24$ ;  $P = 0.004$ ), HbA1c level ( $B = -0.49$ ;  $P = 0.016$ ), signal strength ( $B = 1.31$ ;  $P < 0.001$ ), and GC-IPL thickness ( $B = 0.07$ ;  $P = 0.001$ ) were significant factors (Fig. 3).

### DISCUSSION

The results of the present study indicate that the macular microvasculature was impaired in patients with T2DM

compared with healthy individuals, and patients with T2DM with HTN exhibited more severe microvascular impairment than did patients with T2DM only. The BCVA, duration of T2DM, HTN, signal strength of OCTA, and GC-IPL thickness were significant factors affecting the macular microvasculature in patients with T2DM. Additionally, the HbA1c level was significantly associated with the microvasculature in patients with T2DM with HTN.

Previous studies reported that the parafoveal VD in both superficial and deep capillary plexi was decreased in the eyes of DM patients without DR compared with healthy controls, which was consistent with our study.<sup>16,21</sup> Indeed, the mean circulation time, which was investigated using video fluorescein angiography, decreased and the oxygen saturation status in major peripapillary arteries and veins, as assessed using retinal oximetry, showed maldistribution in patients with T2DM without DR.<sup>22,23</sup> This decreased macular microcirculation may be related to the impairment of retinal

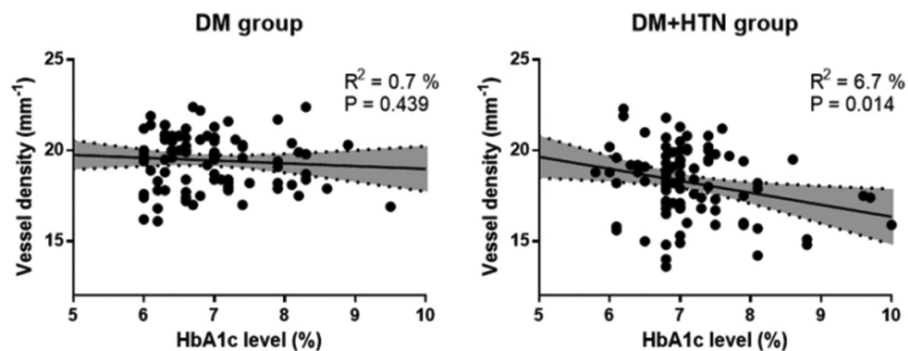


FIGURE 3. Scatterplots showing the results of linear regression analyses between the HbA1c level and VD in patients with diabetes only and patients with both diabetes and HTN.

neurovascular autoregulation in DRN.<sup>4</sup> An autoregulatory response of the neurovascular unit to complex circulatory and neural cues is essential to regulate blood flow through the inner retina owing to the lack of autonomic innervation of the intraretinal vasculature, so disruption of the neurovascular unit by DRN would affect the impaired macular microcirculation.<sup>3,4,7,24</sup> Therefore, even in the absence of signs related to DR, such as microaneurysm or retinal hemorrhage, patients with T2DM would have impaired macular microcirculation and microvasculature.

Patients with T2DM with HTN exhibited more marked decreases in macular VD and PD than did patients with T2DM only. Additionally, HTN was a significant factor affecting the macular VD in patients with T2DM. Previous studies reported the impairment of retinal microvasculature in patients with HTN.<sup>15,18</sup> Sustained vasospasms of the retinal arterioles, which reflect vasoconstriction as an autoregulatory response to HTN, could cause compression of the venules and lead to decreased macular VD.<sup>25</sup> Microvascular damage such as atherosclerosis, increased resistance, and rigidity caused by HTN may also be related to impaired macular microvasculature. In this ischemic condition induced by hypertensive microvascular pathogenesis, the impairment of neurovascular unit function in T2DM may accelerate the damage to the microvasculature, which would result in a more severe decrease in macular VD. Although these two diseases are very common and often coexist, a more severe microvascular impairment that could occur when both diseases are present has not been reported yet. Therefore, physicians should consider this factor when interpreting changes of retinal microvasculature in patients with T2DM with HTN.

The macular VD was significantly associated with the BCVA in patients with T2DM and patients with both DM and HTN. Previous studies showed similar results that peripapillary and macular VD were significantly related to the BCVA in patients with T2DM without DR.<sup>7,26</sup> A significant association between VD and visual function has also been reported in other diseases, including nonarteritic anterior ischemic optic neuropathy and glaucoma.<sup>27,28</sup> Therefore, the impairment of visual function, including decreased hue discrimination and contrast sensitivity, delayed dark adaptation, and decreased visual field sensitivity, in patients with T2DM may be related to such macular microvasculature impairment.<sup>29–31</sup> Hence, patients with T2DM with HTN with more severe macular microvasculature damage may exhibit greater impairment of visual function. Differences in BCVA between groups may have come from significant differences

in VD and PD in our study. Therefore, even though clinical DR is not observed, it should not be concluded that the retina of patients with T2DM is under stable status, and the retinal microvasculature, which would be related to visual function directly, should be observed closely especially when coexisting HTN.

The GC-IPL thickness was associated significantly with the macular VD in patients with T2DM and patients with DM and HTN. Our previous study showed that the GC-IPL thickness was correlated significantly with the macular VD in patients with a prolonged duration of T2DM.<sup>7</sup> Lim et al.<sup>10</sup> also reported significant correlations between the inner retinal layer thickness and microvascular metrics using OCTA in patients with HTN. The impairment of autoregulation owing to neurovascular unit damage, which resulted from DRN and hypertensive ischemic damage, can lead to decreased macular microvasculature, and such impairment of the macular microvasculature may reversely cause the acceleration in inner retina decrease in a positive feedback manner. Although the precise temporal relationship could not be determined in this study, the inner retina and macular microvasculature interact closely and reflect the status of each other.

Previous studies reported a significant relationship between the retinal microvasculature and duration of T2DM in patients with T2DM, which was consistent with this study.<sup>7,21</sup> Other studies found a significant relationship between inner retina reduction by DRN and the duration of DM in patients with T2DM.<sup>2,5</sup> Because the inner retinal layer and macular microvasculature are closely related to each other via the neurovascular unit, both would show similar trends for the duration of T2DM. Meanwhile, the HbA1c level was not significant in multivariate analyses of patients with T2DM, which is consistent with previous studies.<sup>2,7,16</sup> Whereas the HbA1c level significantly affected the macular VD in patients with T2DM with HTN. The HbA1c level is an indicator of blood glucose control over a period of approximately 3 months, and long-term hyperglycemia can cause retinal hypoxia and inflammation, thus impairing retinal structures and neural function.<sup>32–34</sup> Therefore, glycemic control should be further emphasized when there is coexisting HTN, which could make the retinal microvasculature more vulnerable to damage in hyperglycemia.

The signal strength is well-known as an important factor when interpreting the OCTA parameters in normal individuals and patients with various retinal diseases.<sup>35,36</sup> This study showed that the signal strength was also associated significantly with macular VD in patients with T2DM and patients

with T2DM with HTN. Because the OCTA parameters of the macular microvasculature are strongly influenced by the signal strength, physicians should be aware that the comparison of such parameters would be inaccurate if the signal strength is low or different between two tests when analyzing OCTA data for patients with T2DM.

This study had several limitations. First, the retrospective nature of the study inevitably introduced some selection bias. Second, we could not exclude the possibility that our study population included patients with HTN who had a previous occurrence and subsequent regression of HTN retinopathy that might have affected the macular microvasculature. Third, we could not determine the relationship between an impaired macular microvasculature and various aspects of visual function owing to the lack of various visual function tests. Fourth, although there was no difference in axial length among the groups, we did not perform the correction of the image scale according to the axial length, which may be a slight image scale difference in each individual. The strength of our study was that we included OCTA images with relatively high signal strength, which was more than 9 in average values and could result in accurate analyses. Additionally, few studies have reported the impact of HTN on macular microvasculature in patients with T2DM.

In conclusion, patients with T2DM had impaired macular microvasculature, and patients with T2DM with HTN exhibited greater microvasculature impairment than did patients with T2DM only. The ischemic condition owing to hypertensive microvascular pathogenesis would make the macular microvasculature more sensitive to damage to the impaired neurovascular unit by DM. Additionally, the BCVA, duration of DM, signal strength, and GC-IPL thickness were significantly associated with the macular VD in patients with T2DM, and the HbA1c was significantly associated with the macular VD in patients with T2DM with HTN. Physicians should be aware that the macular microvasculature would be more vulnerable to hyperglycemic damage under ischemic conditions caused by HTN.

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