

# Major risk factors for the appearance of white-matter lesions on MRI in hypertensive patients with controlled blood pressure

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**Purpose:** Blood pressure (BP), age, and reduced renal function are major risk factors for white-matter lesions (WMLs) in the general population. However, it remains unclear whether or not the BP itself or other parameters related to the BP are associated with WMLs in hypertensive patients with well-controlled BP. We investigated the relationships of the presence of WMLs with the central systolic BP (cSBP) and estimated glomerular filtration rate (eGFR) in treated hypertensive patients.

**Method:** We studied 185 hypertensive patients with median duration of hypertension, 10.0 years, whose BP is controlled to SBP and diastolic BP (DBP) of  $139 \pm 17$  and  $79 \pm 10$  mmHg, respectively. We measured cSBP and brain magnetic resonance imaging (MRI) was examined within 2 weeks after last BP and biological measurements.

**Results:** Patients with higher-grade WMLs, as assessed by the presence of Scheltens deep white-matter hyperintensity (SDWMH) in the frontal (grade 0–2 vs 3–6) and parietal areas (grade 0–2 vs 3–6) where small arteries are affected at earlier stage of hypertension, as well as that of Fazekas deep white-matter hyperintensity (FDWMH) (grade 2–3 vs 0–1) and Fazekas periventricular hyperintensity (FPVH) (grade 1–3 vs 0) were older, had higher serum creatinine levels, a longer duration of hypertension, and lower eGFR values. The grade of the WMLs was not associated with either the cSBP or the brachial SBP. In logistic regression analyses after adjustment for age, sex, cSBP, and hypertension duration, showed significant association between eGFR and WMLs. The patients with lower eGFR ( $<60$  mL/minute/1.73 m<sup>2</sup>) tended to have higher grade WMLs. The odds ratio was 2.87 for FDWMH ( $P = 0.017$ ), 1.99 for FPVH ( $P = 0.131$ ), and 2.33 for SDWMH in the parietal area ( $P = 0.045$ ).

**Conclusion:** Presence of WMLs was associated with eGFR, but not with either the brachial SBP or cSBP in hypertensive patients with well-controlled BP.

**Keywords:** white-matter lesions, central systolic blood pressure, estimated glomerular filtration rate

## Introduction

White-matter lesions (WMLs) are frequently observed on cerebral magnetic resonance imaging (MRI) of elderly patients without apparent neurological symptoms. In addition to age, hypertension has also been consistently reported to be a common risk factor for the development of cerebral WMLs.<sup>1–3</sup> The association between hypertension and the development of WMLs has been established in cross-sectional<sup>4</sup> as well as longitudinal studies.<sup>1</sup> Several studies have examined the prevalence of WMLs in hypertensive and high-normotensive subjects.<sup>5,6</sup> White-matter hyperintensities (WMHs) seen on MRI scans are associated with degenerative changes in the arterioles that are related to

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atherosclerosis, suggesting that cerebral arteriosclerosis of the penetrating vessels is a major factor in the pathogenesis of ischemic WMLs.<sup>4</sup>

Recently, several noninvasive parameters have been described for the assessment of vascular stiffness. Central systolic blood pressure (cSBP) and the augmentation index (AI) are parameters that can be estimated noninvasively from the central arterial waveforms through radial arterial pulse wave analysis.<sup>7-9</sup> AI and cSBP are reported to be closely related to several risk factors for atherosclerosis and future cardiovascular events.<sup>9-11</sup>

A recent study showed that the cSBP was more strongly correlated with the presence of WMLs than the brachial systolic blood pressure (brachial SBP).<sup>12</sup>

Recently, the relationship between chronic kidney disease (CKD) and cardiovascular disease has also been highlighted. Furthermore, recent studies have reported the existence of an association between CKD (lower estimated glomerular filtration rates [eGFR]) and the presence of WMLs.<sup>13,14</sup> Renal dysfunction may be related to cerebral small vessel disease, for example WMLs.

Therefore, this study chose cSBP and eGFR as variables of interest. The association of WMLs with cSBP and eGFR in treated hypertensive patients has not yet been studied. Correlations between the presence of subcortical WMLs and clinical parameters have also not been studied yet.

In this study, we investigated the relationships of the presence of WMLs with the cSBP and eGFR in treated hypertensive patients.

## Methods

### Study population

Study participants were recruited from hypertensive patients under treatment with antihypertensive medications. They were outpatients of the Jingumae Clinic from June 2010 to February 2011. All study participants were aged over 60 years. The exclusion criteria included inability to apply the tonometric system for evaluation, such as in patients with atrial fibrillation, and inability to perform MRI, as in patients with pacemakers and other implants. Informed consent was obtained from all participants prior to study enrollment. The present study was performed under approval of the clinical research protocol by the institutional ethics committee of Nara medical university, and in compliance with the Helsinki Declaration of 1975. Among the 200 participants who agreed with the study objectives and protocols of the study and provided written consent to undergo all the procedures, 15 were excluded due to the aforementioned MRI contraindications

or because they had atrial fibrillation, which made use of the tonometric system impossible.

### MRI examinations

MRI was performed at one of two centers with a 1.5-T clinical MR unit (Magnetom Avanto; Siemens AG, Erlangen, Germany) equipped with an 8-channel phased array coil, or with a 1.5-T clinical MR unit (GE Signa HDx; General Electric, Harvey, USA) equipped with a 12-channel phased array coil. All examinations included axial sections of conventional spin-echo T1-weighted (TR = 560 to 2100 ms, TE = 8.8 to 12 ms), spin-echo T2-weighted (TR = 3934 to 4000 ms, TE = 94 to 110 ms), and fluid-attenuated inversion recovery (FLAIR; TR = 8400 to 10,000 ms, TI = 2100 to 2600 ms, TE = 110 to 125 ms) sequences. The slice orientation was the axial plane perpendicular to the posterior margin of the pons, and the slice thickness was 5 mm with a 1 or 2 mm gap. Images were obtained using a 256 × 256 matrix or 352 × 352 matrix and a 230 mm field of view.

### Assessment of deep white-matter hyperintensities and periventricular hyperintensities

WMLs consist of deep white-matter hyperintensities (DWMH) and periventricular hyperintensities (PVH). DWMH assessment was performed centrally by a single rater blinded to the clinical data of the study participants. The severity of the WMHs was rated visually on axial FLAIR images using the Fazekas scale<sup>15</sup> (absent, grade 0; punctuate, grade 1; early-confluent, grade 2; confluent, grade 3) and Scheltens rating scale<sup>16</sup> (range, 0 to 30), in which scores 0 to 6 are given for four subcortical white-matter regions (frontal, parietal, temporal, occipital), and scores from 0 to 2 for 3 periventricular regions (frontal caps, occipital caps, bands). Basal ganglia and infratentorial hyperintensities were not rated for this study.

PVHs were graded as 0 = absence, 1 = 'caps' or pencil-thin lining, 2 = smooth 'halo', 3 = irregular PVH extending into the deep white matter using the Fazekas scale<sup>15</sup>, and scored from 0 to 2 for three periventricular lesions using the Scheltens rating scale.<sup>16</sup>

Grade 2 or 3 DWMHs classified according to the Fazekas scale are progressive and likely malignant, whereas grades 0 to 1 are not progressive.<sup>17,18</sup> Grade 0 to 1 DWMHs as classified by the Fazekas scale are equivalent in severity to grades 0, 1, and 2 as classified by Scheltens rating scale.<sup>16</sup> Therefore, we divided patients with DWMHs into two clinical groups according the lesion grade.

Grade 0 PVH represents the normal condition, whereas grades 1, 2, 3 PVHs are abnormal. Therefore, we also divided patients with PVHs into two groups according to the severity grade of the lesions.

## Measurement of the CBP and AIx@75

Measurements of the CBP and AI corrected to a heart rate of 75 bpm (AIx@75) were performed as described previously.<sup>19</sup> The pulse pressure waveform of the radial artery was recorded using an automated tonometry system (HEM-9000AI; Omron Healthcare, Kyoto, Japan) with the patient in the sitting position after having rested for at least 5 minutes. The waveform was automatically calibrated using the built-in oscillometric brachial sphygmomanometer, and the peak and trough of the radial pressure wave were adjusted for the brachial SBP and diastolic blood pressure (DBP), respectively. The second peak (late systolic inflection) was automatically detected by an algorithm programmed into the HEM-9000AI system using the second maxima of the fourth derivative of the radial pressure waveform to determine the radial AI, as well as the late or second SBP (SBP2). This algorithm is described in greater detail elsewhere.<sup>20</sup> The height of the second peak corresponds to the SBP2 value obtained using HEM-9000AI. The value of SBP2 is very similar to that of aortic CBP recorded using invasive techniques,<sup>21</sup> and thus, SBP2 was used as an estimate of CBP. CBP determined using HEM9000-AI is comparable to that determined using a generalized aorta–radial transfer function.<sup>22,23</sup> The AI was calculated using the following formula:  $(\text{SBP2} - \text{DBP}) / (\text{the first peak SBP} - \text{DBP}) \times 100$ . Because the AI is influenced by the heart rate, AI was normalized for a heart rate of 75 bpm (AIx@75), as proposed by Wilkinson et al.<sup>24</sup> In this study, these measurements were performed by a single highly experienced investigator.

## Statistical analyses

We presented categorical variables as numbers and percentages and assessed the differences in the categorical variables according to the MRI scores using the chi-square test, while describing continuous variables as mean values  $\pm$  standard deviations, unless otherwise indicated. Based on their distribution, we estimated the differences in the continuous variables according to the MRI scores by Student's *t*-test or the Wilcoxon's rank sum test. We used logistic regression analyses to assess the association between high MRI scores and low eGFR ( $<60$  mL/minute/1.73 m<sup>2</sup>) adjusted for age ( $\geq 70$  years), sex, cSBP ( $\geq 140$  mmHg) and the quartile of hypertension duration. We performed all

statistical analyses using JMP software (v. 9.0; SAS Institute Inc, Cary, NC) and STATA (v. 10; Stata Corporation, College Station, TX). Differences at *P* values of less than 0.05 were considered to be statistically significant.

## Results

The patient characteristics are shown in Table 1. In total, 185 patients were included in this study, of which 84 (45%) were male. The mean ( $\pm$  standard deviation) age of the patients was 70 ( $\pm 7$ ) years. 3 (2%) had a history of myocardial infarction, 16 (9%) had a history of angina pectoris, 1 (0.5%) had a history of aortic disease, 1 (0.5%) had a history of peripheral arterial disease, and 8 (4%) had a history of heart failure. As for risk factors other than hypertension, 56 patients (30%) smoked habitually, 38 (21%) had diabetes mellitus, and 101 (55%) were dyslipidemic. Calcium-channel blockers, angiotensin-receptor blockers, angiotensin-converting enzyme, and  $\beta$ -blockers were used by 58%, 69%, 24%, and 2% of the study participants, respectively.

The mean ( $\pm$  standard deviation) SBP was 139 ( $\pm 17$  mmHg), that of the cSBP was 143 ( $\pm 20$ ) mmHg, and that of AIx@75 was 83% ( $\pm 13$ )%.

The MRI study results are shown in Table 2. The WMLs were rated in severity visually on axial FLAIR images using the Fazekas scale;<sup>18</sup> 84% had grade 1 or 2 FDWMHs, and 91% had grade 0 or 1 FPVHs. Using the Scheltens rating scale,<sup>19</sup> 85% had grade 0 lesions in the temporal region, whereas 89% had grade 1–6 lesions in the parietal region.

Comparison of the clinical parameters between WMLs with low and high Fazekas scores are shown in Table 3. The patients with higher-grade WMLs, (for both FDWMH [grade 2–3 versus 0–1] and FPVH [grade 1–3 versus 0]) were older, and had a higher serum creatinine level, a longer duration of hypertension, and a lower eGFR. The WML grade was not associated with either the cSBP or brachial SBP. Comparison of the clinical parameters between patients with WMLs assigned low and high Scheltens scores are shown in Table 4. The patients with higher-grade WMLs (both frontal SDWMH [grade 0–2 versus 3–6] and parietal SDWMH [grade 0–2 versus 3–6]) were older, and had a higher serum creatinine level, a longer duration of hypertension, and a lower eGFR. The WML grade was not associated with either the cSBP or the brachial SBP.

Logistic regression analyses were conducted to assess the association of the MRI scores with the eGFR after adjustment for age, sex, cSBP, and history of hypertension. The patients with lower eGFR values ( $<60$  mL/minute/1.73 m<sup>2</sup>) tended

to have higher-grade WMLs. The odds ratio for FDWMH (grade 2–3 versus 0–1) was 2.87 ( $P = 0.017$ ), that for FPVH (grade 1–3 versus 0) was 1.99 ( $P = 0.131$ ), and that for SDWMH in the parietal (grade 3–6 versus 0–2) area was 2.38 ( $P = 0.045$ ).

**Table 1** Patient characteristics

Number of patients	185
Age year [Mean (SD)]	70 (7)
Male n (%)	84 (45)
Height cm [Mean (SD)]	157 (9)
Weight kg [Mean (SD)]	60 (11)
BMI kg/m <sup>2</sup> [Mean (SD)]	24.3 (3.7)
Waist circumference cm [Mean (SD)]	88 (10)
Duration of hypertension [Median (Q1–Q4)]	10.0 (5.0–20.0)
Current smoking or past smoking n (%)	56 (30)
Current smoking n (%)	21 (11)
Regular alcohol drinkers n (%)	50 (27)
Hyperlipidemia n (%)	101 (55)
Diabetes mellitus n (%)	38 (21)
Hyperuricemia n (%)	18 (10)
Proteinuria n (%)	6 (3)
<b>Laboratory data</b>	
T-cho mg/dL [Mean (SD)]	202 (30)
TG mg/dL [Mean (SD)]	154 (89)
HDL-cho mg/dL [Mean (SD)]	55 (15)
LDL-cho (direct method) mg/dL [Mean (SD)]	117 (25)
LDL-cho (indirect method) mg/dL [Mean (SD)]	116 (28)
Serum creatinine mg/dL [Mean (SD)]	0.8 (0.2)
eGFR mL/min/1.73 m <sup>2</sup> [Mean (SD)]	69.7 (14.7)
<b>Past medical history</b>	
Cardiac infarction n (%)	3 (2)
Angina pectoris n (%)	16 (9)
Aortic disease n (%)	1 (0.5)
Peripheral artery disease n (%)	1 (0.5)
Heart failure n (%)	8 (4)
<b>Blood pressure, heart rate, rAIx</b>	
SBP mmHg [Mean (SD)]	139 (17)
DBP mmHg [Mean (SD)]	79 (10)
PP mmHg [Mean (SD)]	60 (13)
HR/min [Mean (SD)]	72 (11)
SBP2 mmHg [Mean (SD)]	139 (18)
CSBP mmHg [Mean (SD)]	143 (20)
CPP mmHg [Mean (SD)]	64 (16)
rAIx% [Mean (SD)]	84 (15)
rAIx@75% [Mean (SD)]	83 (13)
<b>Current medication</b>	
CCBs n (%)	107 (58)
β-blockers n (%)	4 (2)
ACE-Is n (%)	44 (24)
ARBs n (%)	128 (69)

**Abbreviations:** BMI, body mass index; Q1, ≤5 years; Q2, 5–10 years; Q3, 10–20 years; Q4, >20 years; T-cho, total lipoprotein cholesterol; TG, triglyceride; HDL-cho, high-density lipoprotein cholesterol; LDL-cho, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; SBP, brachial systolic blood pressure; DBP, brachial diastolic blood pressure; PP, brachial pulse pressure; HR, heart rate; SBP2, secondary systolic pressure; CSBP, central systolic blood pressure; CPP, central pulse pressure; rAIx, radial augmentation index; rAIx@75, radial augmentation index normalized for a heart rate of 75/minute; CCB, calcium channel blockers; ACE-Is, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers.

## Discussion

Among the major factors associated with the development of WMLs is high blood pressure. It was recently reported that the cSBP is correlated more strongly with WMLs than the brachial SBP, and that the cSBP is a better predictor of WMLs than the brachial SBP in relatively early stages of WMLs.<sup>12</sup> Another study found that the cSBP was significantly associated with the presence of intracerebral small vessel disease in an apparently healthy general population.<sup>25</sup> Both were cross-sectional observational studies of the general population.

However, more than 50% of the subjects in these studies had normal blood pressure, and most were not receiving treatment with antihypertensive drugs. Our study involved only hypertensive patients, and all were receiving antihypertensive drugs. To the best of our knowledge, there have been no prior studies of the relationship between the cSBP and WMLs in hypertensive patients under treatment with antihypertensive agents. Under such conditions, WMLs are not affected by either the cSBP or brachial SBP. The lesions were associated with age, history of hypertension, and eGFR.

In addition, examination of the lesions by site demonstrated that only WMLs in the temporal region<sup>26</sup> with less prominent sclerotic changes of the medullary arteries showed no correlation with the eGFR, while correlations were evident for WMLs in regions with prominent sclerotic changes of the medullary arteries.

Despite being influenced by age, the eGFR showed a correlation with the presence of WMLs, even after adjustment for age and history of hypertension (by multivariate analysis).

The presence of WMLs is significantly related to the risk of stroke, cognitive decline and dementia.<sup>27–29</sup> The Northern Manhattan Study demonstrated that the WML volume is associated with moderate-to-severe CKD, which was estimated using the serum creatinine and the Cockcroft–Gault formula, with eGFR values between 15 and 59 mL/min.<sup>13</sup> Wada et al demonstrated that subjects with lower eGFR tended to have a larger number of lacunar infarcts and higher-grade WMLs; moreover, the mean grade of WMLs and the mean number of lacunar infarcts in subjects with albuminuria were greater than those in subjects without albuminuria.<sup>14</sup> Our study also showed higher grades of WMLs in patients with lower eGFR values than in those with a higher eGFR. Furthermore, Wada et al also reported the existence of an association between urinary albumin levels and cerebral small vessel disease, independently of traditional cerebrovascular risk factors, in community-based elderly persons.<sup>30</sup> In our study, the urinary protein excretion rate of our patients was very low,

**Table 2** Distribution of MRI findings in white-matter lesions

MRI findings	Number of cases (%)						
	0	1	2	3	4	5	6
<b>Fazekas scale</b>							
DWMH	14 (8)		96 (52)		60 (32)		15 (8)
PVH	83 (45)		86 (46)		15 (8)		1 (1)
<b>Scheltens scale</b>							
DWMH							
Frontal	81 (44)	76 (41)	7 (4)	18 (10)	2 (1)	1 (1)	0 (0)
Parietal	21 (11)	64 (35)	27 (15)	31 (47)	23 (11)	8 (4)	13 (7)
Occipital	103 (56)	54 (29)	8 (4)	16 (9)	1 (1)	2 (1)	1 (1)
Temporal	157 (85)	23 (12)	1 (1)	4 (3)	0 (0)	0 (0)	0 (0)
PVH caps							
Frontal	83 (45)	92 (50)	10 (5)	–	–	–	–
Occipital	90 (49)	67 (36)	28 (15)	–	–	–	–
Lat ventricular bands	170 (94)	10 (5)	2 (1)	–	–	–	–

**Abbreviations:** DWMH, deep white-matter hyperintensities; PVH, periventricular hyperintensities.

and urinary albumin was not determined. Similarly, Ikram et al investigated the relationship between kidney function as evaluated by the eGFR, and the occurrence of cerebral small-vessel disease by MRI analysis. They clearly showed that decreased eGFR was related to subclinical markers of cerebral small-vessel disease, such as deep white-matter volume and WMLs independently of cardiovascular risk factors such as age, sex, blood pressure, and diabetes.<sup>31</sup> In our study as well, patients with lower eGFR values had higher-grade

WMLs, even after adjustments for these risk factors, than those with a higher eGFR. Takahashi et al<sup>32</sup> reported that mild renal dysfunction may be associated with an increase in the occurrence of cerebral small-vessel disease, independent of the presence of hypertension.

In our study also, lower eGFR was associated with higher grades of WMLs, independent of hypertension.

This study had limitations. First, hypertensive patients under treatment with various antihypertensive medications

**Table 3** Comparison of clinical parameters between low and high Fazekas scores

Score grade		FDWMH			FPVH		
		0–1	2–3	P value	0	1–3	P value
Number of patients		110	75		83	102	
Age (years)	Mean (SD)	67 (5)	74 (6)	<0.0001	67 (5)	72 (7)	<0.0001
BMI (kg/m <sup>2</sup> )	Mean (SD)	24.1 (3.6)	24.6 (3.9)	0.38	23.7 (3.3)	24.9 (4.0)	0.03
Male	n (%)	49 (45)	35 (47)	0.78	39 (47)	45 (44)	0.7
Current or past smoking	n (%)	34 (31)	22 (29)	0.82	29 (35)	27 (26)	0.21
Hyperlipidemia	n (%)	60 (55)	41 (55)	0.99	49 (59)	52 (51)	0.27
Diabetes mellitus	n (%)	23 (21)	15 (20)	0.88	18 (22)	20 (20)	0.73
SBP (mmHg)	Mean (SD)	139 (17)	139 (16)	0.78	138 (16)	140 (17)	0.28
DBP (mmHg)	Mean (SD)	79 (10)	78 (11)	0.58	79 (9)	79 (11)	0.67
PP (mmHg)	Mean (SD)	60 (13)	61 (13)	0.77	58 (12)	62 (13)	0.059
CPP (mmHg)	Mean (SD)	64 (16)	64 (15)	0.85	62 (16)	66 (16)	0.17
SBP2 (mmHg)	Mean (SD)	129 (19)	131 (18)	0.6	128 (18)	132 (19)	0.17
CSBP (mmHg)	Mean (SD)	144 (20)	142 (20)	0.66	142 (20)	144 (21)	0.4
rAlx (%)	Mean (SD)	85 (16)	84 (12)	0.63	84 (15)	84 (14)	0.88
rAlx@75 (%)	Mean (SD)	83 (13)	83 (12)	0.95	82 (13)	84 (13)	0.45
HR/min	Mean (SD)	71 (12)	73 (10)	0.14	71 (12)	73 (10)	0.14
Serum creatinine (mg/dL)	Mean (SD)	0.71 (0.16)	0.83 (0.24)	<0.0001	0.71 (0.16)	0.80 (0.23)	0.007
eGFR (mL/min/1.73 m <sup>2</sup> )	Mean (SD)	74.1 (13.2)	63.2 (14.5)	<0.0001	74.3 (12.4)	65.9 (15.4)	<0.0001
Duration of hypertension (years)	Median (interquartile range)	10 (5–15)	15 (8–20)	0.0002	10 (5–15)	12 (5.75–20)	0.0059

**Abbreviation:** FDWMH, deep white-matter hyperintensities of Fazekas scale; FPVH, periventricular hyperintensities of Fazekas scale; BMI, body mass index; SBP, brachial systolic blood pressure; DBP, brachial diastolic blood pressure; PP, brachial pulse pressure; CPP, central pulse pressure; SBP2, secondary systolic blood pressure; CSBP, central systolic blood pressure; rAlx, radial augmentation index; rAlx@75, radial augmentation index normalized for a heart rate of 75/min; HR, heart rate; eGFR, estimated glomerular filtration rate.

**Table 4** Comparison of clinical parameters between low and high Scheltens scores

Score grade	SDWMH frontal			SDWMH parietal			SDWMH occipital			SDWMH temporal		
	0-2	3-6	P value	0-2	3-6	P value	0-2	3-6	P value	0-2	3-6	P value
Number of patients	164	21		112	73		165	20		181	4	
Age (years)	Mean (SD) 69 (6)	74 (7)	0.005	68 (5)	73 (7)	<0.0001	70 (7)	73 (5)	0.03	70 (7)	66 (3)	0.2
BMI (kg/m <sup>2</sup> )	24.4 (3.8)	24.0 (3.2)	0.7	24.1 (3.5)	24.7 (4.1)	0.28	24.4 (3.7)	23.6 (4.1)	0.33	24.3 (3.8)	24.2 (2.5)	0.95
Male	n (%) 71 (43)	13 (62)	0.11	53 (47)	31 (42)	0.52	72 (43)	12 (60)	0.7	81 (45)	3 (75)	0.23
Current or past smoking	n (%) 48 (29)	8 (38)	0.41	35 (31)	21 (29)	0.72	50 (30)	6 (30)	0.21	54 (30)	2 (50)	0.39
Hyperlipidemia	n (%) 92 (56)	9 (43)	0.25	61 (54)	40 (55)	0.96	91 (55)	10 (50)	0.27	97 (54)	4 (100)	0.07
Diabetes mellitus	n (%) 34 (21)	4 (19)	0.86	26 (23)	12 (16)	0.26	34 (21)	4 (20)	0.73	38 (21)	0 (0)	0.3
SBP (mmHg)	Mean (SD) 139 (17)	136 (15)	0.34	139 (17)	140 (17)	0.75	139 (17)	138 (14)	0.28	139 (17)	141 (15)	0.81
DBP (mmHg)	Mean (SD) 79 (10)	79 (11)	0.96	79 (10)	79 (11)	0.99	79 (10)	81 (11)	0.67	79 (10)	89 (9)	0.06
PP (mmHg)	Mean (SD) 61 (13)	58 (13)	0.43	60 (12)	61 (14)	0.54	61 (13)	57 (11)	0.059	60 (13)	53 (9)	0.23
CPP (mmHg)	Mean (SD) 65 (16)	61 (14)	0.3	64 (16)	65 (16)	0.63	64 (16)	63 (14)	0.17	64 (16)	55 (14)	0.25
SBP2 (mmHg)	Mean (SD) 130 (19)	129 (17)	0.79	129 (18)	132 (19)	0.31	129 (19)	134 (16)	0.17	130 (18)	132 (19)	0.75
CSBP (mmHg)	Mean (SD) 144 (20)	140 (17)	0.43	143 (20)	144 (20)	0.71	143 (20)	144 (18)	0.4	143 (20)	144 (20)	0.95
rAlx (%)	Mean (SD) 85 (15)	81 (14)	0.28	84 (16)	84 (13)	0.96	84 (15)	87 (10)	0.88	84 (15)	78 (16)	0.36
rAlx@75 (%)	Mean (SD) 83 (13)	81 (13)	0.54	83 (13)	83 (12)	0.66	82 (13)	86 (11)	0.45	83 (13)	79 (12)	0.54
HR (/min)	Mean (SD) 71 (11)	75 (11)	0.12	71 (11)	73 (10)	0.18	72 (11)	73 (8)	0.14	72 (11)	78 (12)	0.29
Serum creatinine (mg/dL)	Mean (SD) 0.75 (0.20)	0.84 (0.16)	0.051	0.73 (0.17)	0.81 (0.24)	0.006	0.76 (0.21)	0.79 (0.18)	0.48	0.76 (0.20)	0.89 (0.12)	0.21
eGFR (mL/minute/1.73 m <sup>2</sup> )	Mean (SD) 70.5 (20)	63.2 (12.2)	0.03	73.3 (13.7)	64.2 (14.5)	<0.001	69.9 (14.8)	68.1 (13.7)	0.6	69.9 (14.8)	62.5 (4.4)	0.32
Duration of hypertension (years) (interquartile range)	Median 10 (5-19.5)	15 (10-25)	0.009	10 (5-15)	15 (9-20)	0.0014	10 (5-20)	13.5 (6.5-19.25)	0.48	10 (5-20)	12.5 (2.75-34.25)	0.91

**Abbreviations:** SDWMH, deep white-matter hyperintensities of Scheltens scale; BMI, body mass index; SBP, brachial systolic blood pressure; DBP, brachial diastolic blood pressure; PP, brachial pulse pressure; CPP, central blood pressure; SBP2, secondary systolic blood pressure; CSBP, central systolic blood pressure; rAlx, radial augmentation index; rAlx@75, radial augmentation index normalized for a heart rate of 75/minute; HR, heart rate; eGFR, estimated glomerular filtration rate.

were recruited. Calcium channel blockers were used by 58%, angiotensin-receptor blockers by 69%, and angiotensin-converting enzyme inhibitors by 24% of the study participants. The effects of medications on untreated hypertensive patients were not evaluated. Second, in our study, the methodology of WML assessment was performed using visual rating scale which was poorly substantiated and poorly undertaken. To evaluate of WML with precision, we should have used volumetric analysis that has been shown to be a superior method.

In conclusion, WMLs in patients with well-controlled BP were not found to be associated with either the central aortic blood pressure or the brachial blood pressure. Patients with lower eGFR values showed more marked progression of the WMLs than those with a higher eGFR. As to the sites of the WMLs, lesions in the frontal and parietal areas with prominent sclerotic changes of the medullary arteries were more advanced in the patients with lower eGFR values than in those with higher eGFR.

## Disclosure

The authors have no conflicts of interest to declare in association with this work.

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