

Evaluation of Lenticulostriate Arteries Changes by 7 T Magnetic Resonance Angiography in Type 2 Diabetes

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Aim: Progress in neuroimaging techniques allows us to investigate the microvasculature characteristics including lenticulostriate arteries (LSA), which are closely associated with lacunar infarction. Because ischemic stroke is a more critical health problem in East Asian than in other populations, in order to clarify pathological changes underlying cerebral small vessel disease (SVD), we projected an imaging analysis of LSA using high-resolution brain magnetic resonance imaging (MRI) in middle-aged Japanese subjects with type 2 diabetes.

Methods: Twenty-five subjects with type 2 diabetes and 25 non-diabetic control subjects underwent 7 Tesla (7 T) brain MRI. The prevalences of SVD and LSA structural changes were determined in each group.

Results: SVD prevalence did not differ significantly between the type 2 diabetes and control groups. The average numbers of stems, as well as numbers of branches, of LSA were significantly smaller in diabetic subjects than non-diabetic control subjects. The signal intensity of LSA was markedly decreased, indicating reduced blood flow in type 2 diabetes.

Conclusion: In spite of the prevalence of SVD being similar, structural changes and decreased signal intensity of LSA were highly detected in diabetic subjects compared with non-diabetic controls, suggesting that 7 T MRA enables us to determine LSA impairment prior to the development of SVD. Early detection of LSA impairment allows us earlier interventions aimed at the prevention of atherosclerotic events.

Key words: Diabetes, Small vessel disease, Neuroimaging, Lenticulostriate arteries

Introduction

Type 2 diabetes is a major risk factor for ischemic stroke, resulting in physical impairment and cognitive dysfunction¹. In the Japanese population, the risk of cerebral infarction after adjustment for multiple factors is 3.2-fold higher in those with type 2 diabetes than in subjects with normal glucose tolerance². The major subtypes of ischemic stroke in type 2 diabetes patients include not only large-artery occlusive infarction³ but also, even more commonly, cerebral small vessel disease (SVD)⁴, which is thought to arise from impairments of the perforating cerebral arteries, capillaries, and venules⁵. The major risks for SVD were

reported to be aging, genetic factors, and hypertension⁶. Unexpectedly, according to several epidemiological surveillance, the association of diabetes with the development of SVD, including white matter hyperintensities (WMH)^{7, 8}, lacunar infarctions⁹, and microbleeds, is yet to be confirmed and thus remains controversial¹⁰. Therefore, to clarify the impact of diabetes on cerebral vascular disease, detailed investigation of the microvasculature is required.

The lenticulostriate arteries (LSA) are the major microvasculature branching from the middle cerebral arteries and supplying blood to the basal ganglia, which are particularly susceptible to ischemic stroke¹¹. Impairment of the blood supply from LSA is closely

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associated with lacunar infarction and cerebral hemorrhage¹²⁻¹⁴). Therefore, imaging of the LSA may have important clinical implications and provide insights into the mechanisms underlying the development of cerebral microvascular disease.

Ultra-high-field 7.0 Tesla (7 T) magnetic resonance imaging (MRI) provides an increased signal-to-noise ratio (SNR) of the inflow signal at a high spatial resolution, enabling us to investigate the microvasculature characteristics under several pathological conditions^{15, 16}). Progress in neuroimaging techniques, including magnetic resonance angiography (MRA), now allows LSA branches to be clearly visualized^{17, 18}). The associations between structural deformities of LSA and hypertension¹⁹) or cerebral infarction involving the basal ganglia²⁰) were demonstrated using 7 T MRA imaging in previous studies. However, the characteristics of LSA in diabetic subjects remain unknown. Thus, visual analysis of LSA is urgently needed to enhance our understanding of diabetic cerebrovascular complications.

Aim

Because ischemic stroke is a more critical health problem than coronary heart disease in East Asian populations, in order to clarify pathological changes underlying cerebral SVD, we projected this imaging analysis of LSA using high-resolution brain MRA in middle-aged Japanese subjects with type 2 diabetes.

Methods

Study Subjects

The study subjects were 25 type 2 diabetes patients admitted to Iwate Medical University Hospital during the period from November 2014 to September 2016. Type 2 diabetes was defined as taking glucose-lowering medication or hemoglobin A1c $\geq 6.5\%$ or fasting blood glucose ≥ 126 mg/dL, on the basis of the diagnostic criteria proposed by the Japan Diabetes Society²¹). Their diabetic retinopathy grades were determined by an ophthalmologist, using the Davis classification, and simple, pre-proliferative, and proliferative diabetic retinopathy were collectively defined as having diabetic retinopathy. Diabetic nephropathy was classified according to Japan Diabetes Society classification²²). Twenty-five normoglycemic 25 subjects with asymptomatic cerebral aneurysm were enrolled as age-matched non-diabetic controls. It was confirmed by previous 3T MRI that these subjects had no apparent abnormalities involving the brain and large vessels except for a solitary aneurysm. Most had undergone brain MRI screening for neurological

symptoms, for headache in eight subjects, for vertigo in two, numbness in one, and faintness in one. In addition, three cases were willing to be examined for their family histories of subarachnoid hemorrhage. Other three cases were detected by health screening. One was examined after a traffic accident, the other for increased carotid intima-media thickness (IMT) over time. The exclusion criteria applied for identifying “non-diabetic” status were past history of either hyperglycemia or diabetes treatment and casual blood glucose levels ≥ 140 mg/dL the day after admission. None of the study subjects had any history of either coronary heart disease or ischemic cerebrovascular disease. In addition, subjects were excluded if they had severe metabolic disorders, such as diabetic ketoacidosis and hyperosmolar hyperglycemic syndrome, end-stage renal disease, or an infectious disorder. Written informed consent was obtained from all study participants. This study was approved by the Institutional Review Board of Iwate Medical University (Approval number: H26-104).

MR Protocols

We used a 7 T MRI scanner (Discovery MR950; GE Healthcare, Milwaukee, WI, USA) with quadrature transmission and 32-channel receive head coil. High-resolution time-of-flight MRA was acquired using a three-dimensional spoiled gradient recalled echo sequence with the following scanning parameters: repetition time (TR) 12 ms, echo time (TE) 2.4 ms, flip angle (FA) 12° , field of view (FOV) 240 mm, acquisition matrix size 768×384 , reconstructed matrix size 1024×1024 , slice thickness 0.3 mm (after zero-fill interpolation), number of slices 180, and acquisition time 10 min 26 s. The maximum intensity projection (MIP) images, including the anterior and middle cerebral arteries focused on LSA, were reconstructed at the oblique coronal planes parallel to the LSA (thickness, 20 mm; interval, 1.0 mm; partitions, 40) with a 90 mm FOV, and at the axial (thickness, 2 mm; interval, 0.5 mm; partitions, 92) and bilateral sagittal (thickness, 20 mm; interval, 0.6 mm; partitions, 35) planes with a 100 mm FOV²³). Conventional brain MRI images of T1-weighted, T2-weighted, T2*-weighted, and fluid-attenuated inversion recovery (FLAIR) images were also obtained with the following scanning parameters: T1-weighted images, TR 8.8 ms, TE 2.7 ms, FA 15° , number of slices 50, and acquisition time 5 min 6 s; T2-weighted images, TR 2000 ms, TE 60 ms, number of slices 20, and acquisition time 4 min 32 s; T2*-weighted images, TR 30 ms, TE 15 ms, FA 20° , number of slices 50, and acquisition time 6 min 47 s; FLAIR images, TR 7000 ms, TE 103 ms, number of slices 50,

and acquisition time 12 min 32 s. Other scanning parameters of these images were as follows: FOV 220 mm, acquisition matrix size 512×224–256, reconstructed matrix size 512×512, slice thickness 3 mm.

Data Analysis

Conventional brain MRI images were examined to evaluate WMH in Fazekas grade II or III, lacunar infarctions, and microbleeds. Subjects with one or more of these findings were defined as having SVD.

MIP reconstructions were performed by one of the authors (H. K.) using a commercially available workstation (Advantage Workstation 4.5; GE Medical Systems, Milwaukee, WI, USA). To delineate LSA distributions, we overlaid line tracings based on the three-dimensional LSA images onto the conventional two-dimensional MIP images. By using these images, the morphological characteristics of LSA, including stems, branches, length, and tortuosity, for comparison between diabetic subjects and non-diabetic controls were analyzed. Stems were defined as the portion of the LSA that originated directly from the middle cerebral artery or anterior cerebral artery. Branches were defined as daughter vessels originating from a parent LSA. Only the blood vessels pointing toward the anterior perforated substances were counted. The length of each LSA was measured in 2D MIP images using Vox-base II (J-MAC SYSTEM, Inc., Japan). We also calculated the tortuosity of LSA, defined as the ratio of the actual path length over the linear distance¹⁹.

A board-certified senior radiologist (M. S. with over 20 years of experience), blinded to the clinical status of the patients, visually evaluated all images twice each for the presence of any abnormalities. This radiologist concurrently determined narrowing or interruption of the LSA, as indicated by a decrease in signal intensity because of reduced blood flow, which was collectively referred to as “impaired LSA visualization.”

Measurements of ABI, baPWV, Carotid Artery IMT, and Abdominal CT

The ankle brachial pressure index (ABI) and brachial ankle pulse wave velocity (baPWV) were measured using an automatic waveform analyzer (BP-203RPE; Colin Co., Komaki, Japan). The IMT of the carotid arteries was measured using ultrasound diagnostic equipment (LOGIQ 500, GE Yokogawa Medical Systems Corp., Hino, Tokyo, Japan), and the max IMT, that is, the thickest portion detected in the scanned regions, was determined as described previously²⁴. The abdominal fat volume, divided into the visceral fat area and the subcutaneous fat area, was

obtained from CT images scanned at the level of the fourth lumbar vertebra²⁵.

Laboratory Data Analysis

Laboratory values were measured employing routine techniques on blood and urine samples obtained after a 12 h overnight fast in type 2 diabetes patients. Polyunsaturated fatty acids, including eicosapentaenoic acid, docosahexaenoic acid, and arachidonic acid were measured by SRL, Inc. (Tokyo, Japan).

Statistical Analysis

Quantitative data are presented as means ± standard deviation (SD) or as medians with interquartile range (IQR) when the data showed a non-normal distribution. The level of significance was set at $P < 0.05$. Comparisons between the subject groups were performed employing the Student *t* test and the chi-square test or, when the data showed a non-normal distribution, the Mann–Whitney *U*-test. All statistical analyses were carried out using SPSS version 21 (SPSS Japan Inc., Tokyo, Japan).

Results

The clinical characteristics of the enrolled subjects, both the type 2 diabetes and the control group, are shown in **Table 1**. The average of hemoglobin A1c was 9.2%, and the duration of diabetes was 9.0 years in the type 2 diabetes group. The proportion of females, body weight, body mass index, serum γ -glutamyltranspeptidase, and the uric acid level were significantly higher in the type 2 diabetes group than in the controls. There were no significant differences in other parameters, including mean age, blood pressure, hypertension, dyslipidemia, and medications prescribed for hypertension and dyslipidemia.

First, we investigated apparent brain damage and large vessel abnormalities, using scout images with 7 T MRI. We found no major abnormalities in the type 2 diabetes or the non-diabetic subjects, except for the previously diagnosed cerebral aneurysms in the latter.

The results of the high-resolution brain MRI analysis are shown in **Table 2**. Contrary to our expectations, the overall prevalence of WMH, lacunar infarctions, and microbleeds, collectively called SVD, did not reach statistical significance between the type 2 diabetes and control groups (type 2 diabetes, 60.0% vs. control, 44.0%, $p = 0.26$).

Representative MRA images are shown in **Fig. 1**. High-resolution MRA clearly visualized bilateral LSA in diabetic subjects (**Fig. 1B, D**) as well as non-diabetic subjects (**Fig. 1A, C**). Interestingly, detailed investigation revealed that the average numbers of

Table 1. Clinical Characteristics of Subjects

	Non-diabetic control (n = 25)	Type 2 diabetes (n = 25)	P-value
Age (years)	60.1 ± 7.9	57.2 ± 8.7	n.s.
Male sex (%)	8 (32)	15 (60)	< 0.05
Body weight (kg)	56.0 ± 2.5	68.8 ± 3.3	< 0.01
Body mass index (kg/m ²)	21.9 ± 3.1	25.3 ± 5.3	< 0.05
Systolic blood pressure (mmHg)	134.3 ± 16.1	128.2 ± 16.6	n.s.
Diastolic blood pressure (mmHg)	81.3 ± 10.5	79.8 ± 10.9	n.s.
Serum creatinine (mg/dL)	0.66 (0.57-0.71)	0.70 (0.56-0.94)	n.s.
T2DM duration (years)		9.0 (1-14)	
HbA1c (%)		9.4 (8.5-13.5)	
Casual blood glucose (mg/dL)	105 ± 12	149 (126-205)	< 0.01
AST (IU/mL)	22 (20-29)	23 (15-31)	n.s.
ALT (IU/mL)	22 (18-28)	32 (15-44)	n.s.
γ-GTP (IU/mL)	25 (18-28)	39 (30-67)	< 0.01
Uric acid (mg/dL)	4.9 ± 0.9	5.9 ± 1.7	< 0.01
Hypertension (%)	12 (48)	12 (48)	n.s.
Dyslipidemia (%)	8 (32)	7 (28)	n.s.
ARB or ACEi use (%)	10 (35)	9 (36)	n.s.
CCB use (%)	7 (30)	7 (28)	n.s.
Statin use (%)	6 (24)	6 (24)	n.s.

values are Mean ± SD, Median (IQR),

AST: aspartate Aminotransferase, ALT: alanine aminotransferase, γ-GTP: γ-glutamyltranspeptidase

ARB : Angiotensin II Receptor Blocker, ACEi : Angiotensin Converting Enzyme Inhibitor,

CCB : calcium channel blocker

Table 2. Prevalence of SVD findings

	Non-diabetic control (n = 25)	Type2 diabetes (n = 25)	statistical significance
WMH	4/25 (16.0%)	5/25 (20.0%)	n.s.
Lacunar infarction	7/25 (28.0%)	7/25 (28.0%)	n.s.
Microbleeds	2/25 (8.0%)	4/25 (16.0%)	n.s.
Total SVD	11/25 (44.0%)	15/25 (60.0%)	n.s.

analyzed by χ -square test

total SVD indicates the number of subjects who had more than one finding of SVD

stems of LSA were significantly smaller in diabetic than in non-diabetic control subjects (4.6 ± 1.6 vs. 5.7 ± 2.0 , $p < 0.05$, **Table 3**). In addition, the average numbers of LSA branches in diabetic subjects were about 63% of those in the control group (2.4 ± 2.3 vs. 4.2 ± 2.3 , $p < 0.01$, **Table 3**). The average length and tortuosity of LSA were similar in two groups (**Table 3**). Next, the LSA images were examined by a trained neuroradiologist in order to determine the decrease in signal intensity visualized as the narrowing or interruption of LSA, indicative of blood flow reduction. Intriguingly, prevalence of this impaired LSA visualization was markedly increased in type 2 diabetes as compared with control subjects (type 2 diabetes,

68.0% vs. control, 16.0%, $p < 0.05$) as shown in **Table 4**.

Next, to identify the variables affecting the structural characteristics of LSA in type 2 diabetes, we compared clinical parameters between subgroups divided according to the median values of LSA branches (**Table 5**). The numbers of LSA branches ranged widely from 0 to 7 in each of the diabetic subjects, and the diabetic subjects were thereby divided into two groups, 0 or 1 group and more than 2 LSA branches group. Interestingly, this analysis revealed the glomerular filtration rate (GFR) to be significantly lower in the subjects with few LSA branches. Furthermore, GFR showed a strong correlation with the

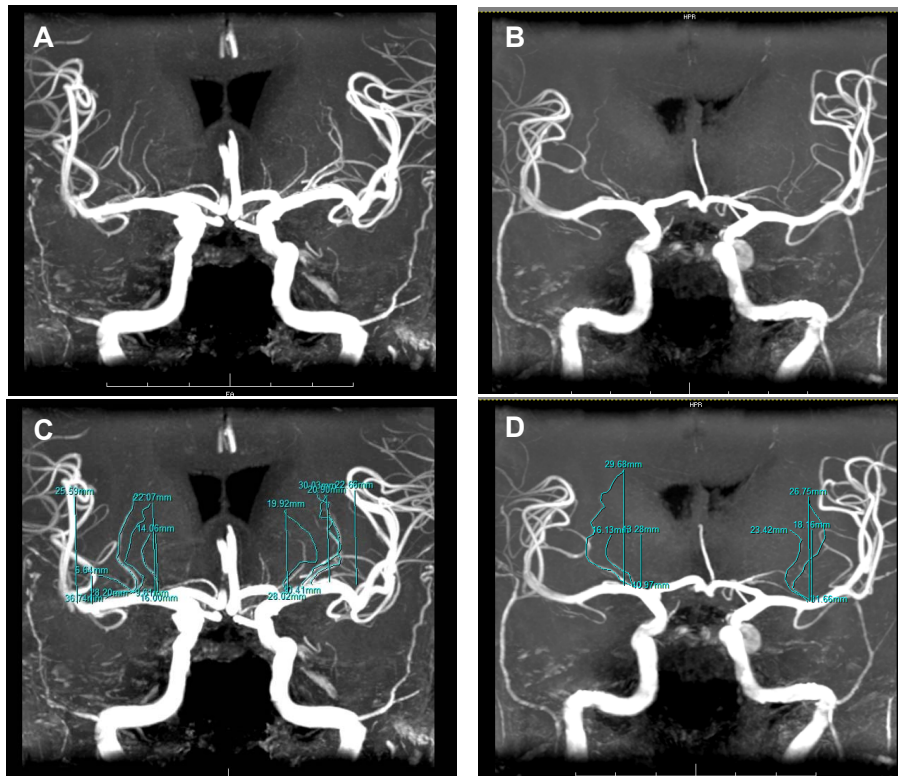


Fig. 1.

Representative 7 T MRA images of the LSA in non-diabetic controls (A) and subjects with type 2 diabetes (B). Line tracings of the LSA of non-diabetic controls (C) and subjects with type 2 diabetes (D), which correspond to the original images shown in A and B, respectively. The numbers indicate the lengths of each LSA, respectively.

Table 3. Comparison of LSA characteristics

	Non-diabetic control (n = 25)	Type2 diabetes (n = 25)	p value
stems (number)	5.7 ± 2.0	4.6 ± 1.6	< 0.05
branches (number)	4.2 ± 2.3	2.4 ± 2.3	< 0.01
length (mm)	25.9 ± 5.5	26.0 ± 6.3	n.s.
tortuosity	1.5 ± 0.49	1.4 ± 0.2	n.s.

analyzed by student *t*-test

Table 4. Prevalence of LSA impairment

	Non-diabetic control (n = 25)	Type 2 diabetes (n = 25)	p < 0.01
Slab-MIP MRA (p < 0.01)	4/25 (16.00%)	17/25 (68.00%)	

number of LSA branches ($r=0.62$, $p<0.001$). This result suggests an association of chronic kidney disease (CKD) with early structural changes in of the cerebral microvasculature.

Discussion

This study is the first, to our knowledge, to demonstrate changes in LSA visualization. Such changes probably contribute to the development of cerebral SVD, in subjects with type 2 diabetes. In this study,

Table 5. Comparison of clinical characteristics between subgroups based on numbers of LSA branches in type2 diabetes

	number of LSA branches,		<i>p</i> value
	0 or 1 (<i>n</i> = 12)	≥ 2 (<i>n</i> = 13)	
Age (years)	60.4 ± 9.8	55.0 ± 6.4	0.19
Body mass index (kg/m ²)	24.6 ± 4.8	26.0 ± 5.7	0.51
Systolic blood pressure (mmHg)	127 (119-130)	132 (120-146)	0.13
Diastolic blood pressure (mmHg)	82 (72-88)	80 (73-84)	0.47
Diabetes duration (years)	8 (1-17)	13 (1-14)	0.27
Fasting plasma glucose (mg/dL)	149 (118-163)	136 (126-205)	0.89
HbA1c (%)	8.8 (8.4-12.4)	9.4 (8.8-11.5)	0.72
Fasting IRI (μU/mL)	4.5 (1.7-11.3)	5.5 (3.5-8.7)	0.88
Total Cholesterol (mg/dL)	204.7 ± 81.6	184.8 ± 50.5	0.48
Triglycerides (mg/dL)	154.9 ± 82.3	143.4 ± 69.2	0.71
HDL-Cholesterol (mg/dL)	43.8 ± 10.4	43.6 ± 17.7	0.97
LDL-Cholesterol (mg/dL)	130.5 ± 64.1	111.7 ± 43.3	0.40
24 hrs. Creatinine clearance (mL/min)	60.8 ± 27.7	97.4 ± 27.2	0.003
baPWV (cm/s)	1,606 (1,216-1,923)	1,542 (1,445-1,664)	0.56
max IMT (mm)	1.50 (1.33-2.00)	1.53 (1.30-1.68)	0.08
EPA / AA ratio	0.32 ± 0.14	0.34 ± 0.21	0.82
DHA / AA ratio	0.77 ± 0.19	0.85 ± 0.46	0.55
Subcutaneous fat area (cm ²)	190.9 ± 84.9	226.6 ± 96.3	0.39
Visceral fat area (cm ²)	165.1 ± 79.0	111.8 ± 24.4	0.55
Diabetic retinopathy (<i>n</i>)	4	7	0.30
Diabetic nephropathy, stage 1 (<i>n</i>)	9	8	0.08
stage 2 (<i>n</i>)	0	4	
stage 3 (<i>n</i>)	3	1	
Medication of hypertension (<i>n</i>)	9	4	0.16
Statin treatment	6	2	0.08
smoking	7	9	0.57

Values are Mean ± SD or Median (IQR)

analyzed by student *t*-test or Mann-Whitney *U*-test or χ -square test

although the prevalence of SVD was similar, structural changes and decrease in signal intensity of LSA were highly determined in diabetic subjects compared with non-diabetic controls, suggesting that high-resolution MRA enables us to determine LSA impairment prior to the development of SVD. Our present observations are anticipated to shed light on the process of SVD progression in the subjects with diabetes.

A widely recognized major characteristic of brain imaging in subjects with diabetes is global brain atrophy, including smaller total brain volumes, smaller white matter volumes, smaller gray matter volumes, and larger cerebrospinal fluid volumes²⁶. On the other hand, the effects of diabetes on SVD, especially WMH and microbleeds, have yet to be clarified²⁶. This is in contrast to hypertension, which is well known to be an established risk factor for ischemic strokes involving both large arteries and small vessels²⁷. Even on neuroimaging analysis of 7 T MRI,

microvascular brain lesions were not found to be significantly more common in elderly subjects with type 2 diabetes than in normal controls²⁸. On the basis of prior studies, we hypothesized that the changes in the microvasculature, such as LSA, are possible contributors to the initial step of early stage cerebral atherosclerosis or lipohyalinosis in diabetes before the development of cerebral SVD. The results obtained in this study, include several promising findings, possibly explaining the initial hypothesis. First, diabetic subjects showed a high prevalence of impaired LSA visualization, suggesting decreased signal intensity due to blood flow reduction. A large number of studies confirmed the mechanisms underlying hyperglycemia-induced microvascular complications, mainly resulting from damage to endothelial cells caused by oxidative stress²⁹. Decreased LSA signal intensity detected by 7 T MRA might be involved in chronic hyperglycemia-induced microvascular endothelial dysfunction.

Second, ultra-high field MRA examinations revealed a decrease in the numbers of stems and branches of LSA in type 2 diabetes as compared with non-diabetic control subjects. It is well known that chronic hyperglycemia is accompanied by narrowing and occlusion of retinal microvessels, leading to the spread of the avascular area in the retina³⁰. Because these microvascular systems share many regulatory processes, a decreased number of LSA indicates that pathologic changes similar to those in diabetic retinopathy also occur in the penetrating arteries in the brain. It is intriguing and of major potential significance that the initial step in diabetic vascular complications can also be seen in the cerebral microvasculature.

Major vascular pathophysiologies observed in lacunar infarction are characterized by thickening of the arterial media in small penetrating brain arteries. LSA are a major source of the blood supply for the basal ganglia, and their impairment is considered to be a major cause of lacunar infarction^{11, 14}. Thus, impairment of blood flow in LSA, suggested by the signal intensity decrease detected by 7 T MRA, is recognized in the early phase prior to the development of lacunar infarction. On the other hand, there was no difference in the incidence of lacunar infarctions between subjects with type 2 diabetes and non-diabetic controls, although this finding was considered to be at least partially consistent with those of several previous reports^{8, 28, 31}. This seemingly contradictory outcome might be attributable to the number of patients in our study who had cerebral microvascular lesions being rather small as compared with prior reports using 7 T MRI. This is partly attributable to our having enrolled subjects under 60 years of age, relatively young as compared with those who commonly develop ischemic strokes. In addition, none of the subjects had either cognitive dysfunction or a prior history of atherosclerotic disease, suggesting a somewhat lower risk for vascular disease despite having type 2 diabetes. However, even in such diabetic subjects carrying moderate risk, their structural changes and decreased signal intensity of LSA were highly determined as compared with non-diabetic controls. These observations suggest LSA imaging with the use of high-resolution MRA to be a very promising strategy for the investigation of early stage cerebral vascular complications in diabetes.

CKD is an established risk factor for atherosclerosis, including stroke, in subjects with diabetes³². Decreased GFR was found to be related to the prevalence of SVD, independently of cardiovascular risk factors, such as age, blood pressure, smoking, and lipid profile³³. In East Asian populations, a decreased

GFR level was reported to be associated with an increasing burden of SVD, including lacunar infarction³⁴. Our results, revealing a correlation between a small number of LSA branches and low GFR, are consistent with those of previous studies. Further longitudinal studies with a larger patient sample are required to clarify the effects of decreased GFR on the cerebral microvasculature.

The major limitation of this study is its cross-sectional design, raising the possibility that our results show only associations. The relationships among structural changes of LSA and the development of SVD in type 2 diabetes must be confirmed by further longitudinal study. Second, most of the study subjects had hypertension, dyslipidemia, and/or other risk factors for atherosclerosis. Thus, the findings related to LSA did not clarify whether a direct effect of diabetes was present. Third, LSA signal intensity was evaluated by a single neuroradiologist and it is difficult to quantify the observation in this study. Finally, our sample size was too small to allow sufficiently powered statistical analyses to be performed, especially for the relationships between the number of LSA branches and the clinical parameters of type 2 diabetes patients.

Conclusion

In conclusion, this study is the first to reveal structural and visualization impairment of LSA, using high-resolution MRI, to be highly prevalent in type 2 diabetes. We anticipate that this advanced, noninvasive method for visualization of the cerebral microvasculature will be applied to early detection of LSA impairment prior to the development of SVD, allowing earlier interventions aimed at the prevention of atherosclerotic events.

Conflicts of Interest Statement

The authors have no conflicts of interest to declare.

Acknowledgments

Author's contributions are as follows: S. Y. recruited the patients, collected the data, and wrote the manuscript; K. N., A. C., and Y. T. designed the study and conducted the statistical analysis. Y. H. reviewed and edited the manuscript; H. K., I. U., and M. S. performed the MRI examinations and radiological analyses; K. O. recruited the patients and contributed to the discussion; and Y. I. managed the study, contributed to relevant discussions, and reviewed the manuscript.

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