Original Article

Clinical and MRI features about two types of silent cerebral small-vessel disease in type-2 diabetes mellitus: a retrospective cross-sectional study in a tertiary hospital

Dan-Qiong Wang[1,2], Lei Wang[2], Xiao-Shuang Xia[1], Miao-Miao Wei[1], Xiao-Lin Tian[1], Liang-Fang Wang[3], Xin Li[1]

[1]Department of Neurology, the Second Hospital of Tianjin Medical University, Tianjin, China; [2]Department of General Medical, Shanxi Bethune Hospital, Shanxi Academy of Medical Sciences, Tongji Shanxi Hospital, Third Hospital of Shanxi Medical University, Taiyuan, China; [3]Department of Thoracic Surgery, Shanxi Bethune Hospital, Shanxi Academy of Medical Sciences, Tongji Shanxi Hospital, Third Hospital of Shanxi Medical University, Taiyuan, China

Contributions: (I) Conception and design: DQ Wang, XS Xia, X Li; (II) Administrative support: L Wang; (III) Provision of study materials or patients: LF Wang; (IV) Collection and assembly of data: MM Wei; (V) Data analysis and interpretation: XL Tian; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Xin Li. Department of Neurology, the Second Hospital of Tianjin Medical University, No. 23 Pingjiang Road, Hexi District, Tianjin 300211, China. Email: lixin_dhuf@163.com.

Background: The present study aimed to evaluate the frequency of silent cerebral small-vessel disease, especially lacunes and white matter hyperintensities, in patients with or without the impaired glucose tolerance (IGT) and type-2 diabetes mellitus, and to characterize the diabetes-correlated factors related to silent cerebral small-vessel disease.

Methods: This is a retrospective cross-sectional study. Totally 698 patients were included in this study, from January 2014 to December 2019, among which 270 patients were included in the diabetes mellitus group, 106 patients were included in the IGT group, and 322 patients were included in the Control group. All patients underwent magnetic resonance imaging to investigate the silent cerebral small-vessel disease: the lacunes and the white matter hyperintensities. All the baseline information and diabetes-related factors, such as glycated hemoglobin level, insulin usage, etc., were collected. Then correlation analysis and regression analysis were used to explore the correlation between diabetes with related risk factors and silent cerebral small-vessel disease.

Results: Lacunes and white matter hyperintensities were more common in the diabetes mellitus group than in the IGT group and the Control group, with an occurrence of lacunes of 83.3% *vs.* 70.8% *vs.* 70.4% (P=0.003), respectively, and an occurrence of white matter hyperintensities of 41.1% *vs.* 24.5% *vs.* 31.1% (P=0.003), respectively. The occurrence of lacunes was correlated with the duration of diabetes mellitus [odds ratio (OR) =1.483, 95% confidence interval (CI): 1.082–2.031, P=0.009] and the age (OR =1.141, 95% CI: 1.102–1.180, P<0.001), while white matter hyperintensities were independently correlated only with the age (OR =1.124, 95% CI: 1.094–1.155, P<0.001).

Conclusions: Lacunes and white matter hyperintensities, are more common in the diabetes mellitus patients than in the IGT patients or in the other patients. The occurrence of lacunes was correlated with the duration of diabetes mellitus and the age, while the occurrence of white matter hyperintensities was independently correlated with the age.

Keywords: Cerebral small-vessel disease (CSVD); type-2 diabetes mellitus; magnetic resonance imaging (MRI); lacunes; white matter hyperintensities (WHMs)

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Introduction

In China, the prevalence of type-2 diabetes mellitus (DM) is increasing annually, making China one of the countries with the fastest growing incidence of diabetes mellitus worldwide (1). In a recent study, the prevalence of DM was reported to be 10.9%, of which over 60% of those affected were unaware of their diagnosis. In addition, another 35.7% of the population was found to have abnormal glucose homeostasis (2,3). The marked increase in the prevalence of DM is mostly attributed to type-2 DM (4), which has resulted in an increased focus on metabolic disorders and vascular diseases caused by this disease.

Cerebral small-vessel disease (CSVD) is an age-related disease that affects the small vessels of the brain (5), and its imaging features are characterized by lacunar infarction (LI), white matter hyperintensities (WMHs), perivascular space enlargement, microbleeds, and brain atrophy (6). One study has confirmed that mild neuropsychological disturbances are not infrequent in acute lacunar infarcts (7). Brain structural abnormalities are considered to be an important pathway for brain diseases caused by type-2 DM. While previous studies have confirmed that type-2 DM is related to an increased risk of structural brain abnormalities such as LIs (8,9) and brain atrophy (9-12), findings on the relationship between type-2 DM and the markers of small-vessel diseases such as WMH (13-17) and cerebral microbleeds (18-22) have not been consistent. Some findings suggest that no difference in periventricular WMHs between patients with and without diabetes mellitus. In contrast, deep WMHs have been found only in the control group (23). No correlations between pre-DM and lacunes, cerebral microbleed (CMBs), WMHs, or smaller brain volumes have been observed in the older population (24).

The objective of the present study was to compare the frequency of CSVD in patients with impaired glucose tolerance (IGT) and type-2 DM and factors related to two types of CSVD, Lacunes and White Matter Hyperintensities. In addition, it aimed to evaluate the relationship between type-2 DM and CSVD at different courses and characterize the DM related variables related to CSVD in patients with type-2 DM.

We present the following article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-21-786/rc).

Methods

Participants

This is a retrospective cross-sectional study. From January 2014 to December 2019, patients who met the inclusion and exclusion standards as follows are retrospectively included in this study. Inclusion criteria: (I) patients were between 55 and 85 years old; (II) patients were hospitalized at the General Department of Bethune Hospital in Shanxi Province; (III) according to the diagnostic criteria for diabetes mellitus revised by the World Health Organization (WHO) in 1998 (25), the diagnosis of patients, with or without type-2 DM or IGT, was definitive: oral glucose tolerance test was completed, the results of fasting blood glucose and glycosylated hemoglobin were obtained in three month; (IV) patients underwent brain magnetic resonance imaging (MRI) scans. Exclusion criteria: (I) patients who had been admitted to the hospital as a result of an acute cerebrovascular accident; (II) patients who had had acute complications associated with type-2 DM within 3 months, such as ketoacidosis, severe hypoglycemia lead to loss conscious, and a hyperglycemic hypertonic state; (III) patients with a previous diagnosis of dementia, craniocerebral trauma, or macrovascular complications such as cardiac arrest, heart failure, numbness due to low blood supply to legs; (IV) patients who had recently been administered psychoactive drugs or hormones; (V) patients with incomplete clinical data needed in this study.

A total of 894 people met the inclusion criteria, including 351 people in the DM group, 138 people in the IGT group, and 405 people in the Control group. Total 125 patients refused to participate in the study, and 71 patients with incomplete data were excluded. After all, a total of 698 patients were included in this study, among which 270 patients were in the diabetes mellitus (DM) group, 106 patients were in the IGT group, 322 patients were in the Control group (see *Figure 1*).

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study

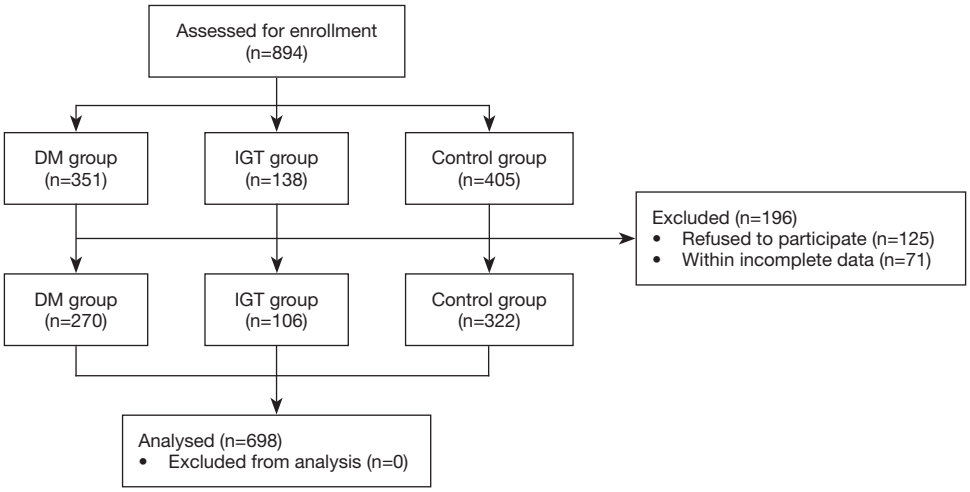

Figure 1 The flow chart of enrollment. DM, diabetes mellitus; IGT, impaired glucose tolerance.

was approved by Ethics Committee of the Shanxi Bethune Hospital (SBQLL-2021-066) and informed consent was taken from all the patients.

Clinical data

Basic information of patients such as age, gender, and body mass index (BMI) are recorded; the latest results of serum triglycerides (TG), cholesterol (TC), and creatinine (SCr) are recorded; diabetes-related factors such as diabetes course, fasting blood glucose level, HbA1C level, and insulin usage are recorded; cardiovascular and cerebrovascular risks factors such as smoking history, blood pressure status and blood pressure control methods, history of coronary heart disease (CHD), etc. are extracted from the medical system. Hypertension is classified by systolic blood pressure (SBP) according to the accepted standard (26). SBP below 140 mmHg is regarded as normal blood pressure. The three intervals of SBP about 140–160 mmHg, 160–180 mmHg, and above 180 mmHg are defined as grade 1, 2, and 3 hypertension respectively. All participants take the brain magnetic resonance imaging (MRI) scanning.

MRI scanning protocol

A unique Siemens Skyra 3.0T superconducting MRI machine was used for scanning, consisting of an axial T1-weighted sequence [repetition time (TR)/echo time (TE): 1,800/9 ms], an axial T2-weighted sequence (TR/TE: 3,710/99 ms), an axial fluid-attenuated inversion recovery sequence (TR/TE/TI: 8,000/81/2,372 ms), and a diffusion-weighted imaging sequence (B: 0/1,000 s/mm^2).

Image processing and evaluation

Images were evaluated by two experienced radiologists, and every MRI image of participants was assessed three times by each radiologist to ensure the CSVD markers: lacunes and WMHs. The Fazekas scale, which score ≥1 was considered as significant (27), was used to determine the WMH. The neuroradiologists involved had no knowledge of the clinical data or whether the participants had diabetes mellitus.

Statistical analysis

All results are analyzed by using IBM's SPSS software (version 22.0; IBM, Armonk, NY, USA). The statistical significance is considered to be $P<0.05$.

Firstly, the general characteristics of the patients in three groups are compared. The parametric variables are presented as means ± standard deviation (SD) and are compared between the three groups by *Analysis of Variance* (ANOVA). The nonparametric variables are analyzed using a Mann-Whitney U test, showing as medians (interquartile range). The categorical variables are analyzed using the χ^2 test or Fisher's exact test, as appropriate.

Secondly, the patients in the DM group and in the IGT group are seen as a combined population, trying to find the potential risk factors related to the occurrence of lacunes and WMHs. The clinical data of the population with or

Table 1 General characteristics of the patients

Category	Control group (n=322)	IGT group (n=106)	DM group (n=270)	P
Male	194 (60.2)	66 (62.3)	183 (67.8)	0.160
Age (years)	72 [62–79]	67 [58–77]	70 [58–78]	0.113
BMI (kg/m^2)	24.191±3.028	25.314±2.967	25.839±3.495	<0.001*[a,b]
TC (mmol/L)	4.350±1.067	4.325±1.029	4.380±1.122	0.893
TG (mmol/L)	1.36 (0.93–1.82)	1.6 (1.08–2.303)	1.54 (1.113–2.3)	<0.001*[a,b]
SCr (μmol/L)	78.6 (68.75–87.85)	77.3 (67.475–85.025)	78.7 (67.7–90)	0.867
Hypertension history	201 (62.4)	78 (73.6)	201 (74.4)	0.004*[b]
BP satisfied controlled	166 (51.6)	54 (50.9)	113 (41.9)	0.048*
BP				0.005*[b]
Normal	121 (37.6)	28 (26.4)	69 (25.6)	
Grade 1 (>140 and ≤160 mmHg)	23 (7.1)	17 (16.0)	32 (11.9)	
Grade 2 (>160 and ≤180 mmHg)	52 (16.1)	20 (18.9)	62 (23.0)	
Grade 3 (>180 mmHg)	126 (39.1)	41 (38.7)	107 (39.6)	
CHD history	51 (15.8)	13 (12.3)	50 (18.5)	0.319
Using antihypertensive drugs	169 (52.5)	64 (60.4)	176 (65.2)	0.012*[b]
Using statins	96 (29.8)	31 (29.2)	105 (38.9)	0.042*
Using aspirin	86 (26.7)	29 (27.4)	108 (40.0)	0.001*[b]
Smoking	118 (36.6)	44 (41.5)	126 (46.7)	0.048*[b]
FBG (mmol/L)	5.070±0.483	6.160±1.185	7.716±2.583	<0.001*[a,b,c]
HbA_1C management				<0.001*[b,c]
<6	20 (74.1)	62 (58.5)	72 (26.7)	
≥6	7 (25.9)	44 (41.5)	198 (73.3)	
Lacunar infarction	233 (72.4)	75 (70.8)	225 (83.3)	0.003*[b,c]
White matter changes	100 (31.1)	26 (24.5)	111 (41.1)	0.003*[b,c]

Data are expressed as n (%), median (interquartile range), or mean ± SD. *, P<0.05, the difference is statistically significant. a, the difference between IGT group and Control group has statistically significant; b, the difference between DM group and Control group has statistically significant; c, the difference between DM group and IGT group has statistically significant. IGT, impaired glucose tolerance; DM, diabetes mellitus; BMI, body mass index; TC, total cholesterol; TG, triglyceride; SCr, serum creatinine; WMH, white matter hyperintensities; FBG, fasting blood glucose; CHD, coronary heart disease; HBP, high blood pressure; BP, blood pressure.

without lacunes and WMHs are analyzed by independent samples *t*-test, Mann-Whitney U test, χ^2 test or Fisher's exact test, as appropriate.

Thirdly, the variables showed significant differences in two steps before, especially the diabetic-related factors, are included in the Logistic regression analysis to determine independent associations between the type-2 DM and the lacunes and the WMHs (stepwise regression method, entry: P=0.05; removal P=0.10). The results are presented as an odds ratio (OR), a 95% confidence interval (95% CI) and a P value.

Results

The general characteristics of the participants

The clinical characteristics of the three groups are shown in *Table 1*. There were no significant differences in age and gender (P>0.05), but the BMI distribution was different. As expected, fasting blood glucose and HbA1C levels were higher in the IGT group and the DM group. There were no significant differences in fasting cholesterol and creatinine levels between the groups. The total frequency of hypertension was higher in the IGT group and the DM

group. After the classification of hypertension, it was found that grade 1 and 2 hypertension in the partial patients was higher than in the control group, and the control rate worsened as patients with impaired glucose tolerance and type-2 diabetes mellitus used less antihypertensive drugs, with a statistically significant difference (P<0.05). The type-2 DM group took more aspirin and statins than the other groups, and there were more patients with a history of smoking in the IGT and DM groups, but there was no statistically significant difference in the number of years of smoking when compared with the Control group (P>0.05). In terms of MRI manifestations, more patients with lacunes and WMHs were found in the DM group (83.3% and 41.1%, respectively), with a statistically significant difference in comparison with the Control group (P<0.05).

Potential risk factors related to Lacunar infarction in the DM group and IGT group

A comparison of the clinical characteristics in patients in IGT groups and DM groups with or without lacunes is shown in *Table 2*. There were significant differences between the two groups in relation to diabetes mellitus duration, HbA1C, and the use of insulin. The incidence of lacunes increased remarkably after ≥5 years of diabetes mellitus, but there were no significant differences in the history, grading, and management of high blood pressure (P>0.05) between the two groups. However, it was observed that there was a higher incidence of hypertension in the patients with lacunes, and there were more patients with grade 2 and 3 hypertension than in the control group. The medication ratio in the patients with lacunes in these two groups was higher, but the proportion of patients with poor blood pressure control in the two groups was higher than that of the control group. There were with difference in the history of CHD, the use of statins, and the use of aspirin between the two groups.

Potential risk factors related to WMHs in the DM group and IGT group

The comparison of the clinical characteristics of the patients with impaired glucose tolerance and type-2 diabetes mellitus with or without WMHs is shown in *Table 3*. There were significant differences in the diabetes mellitus duration and the use of insulin between the two groups; the incidence of WMHs increased remarkably after ≥10 years of diabetes mellitus. There was no difference in the HbA1C control between the two groups. In addition, there were no significant differences in the history of hypertension, hypertension management, and the use of antihypertensive drugs (P>0.05) between the two groups, but the incidence of grade 2 hypertension was higher among the patients with WMHs following the classification of hypertension (P<0.05). There were differences in the history of CHD, statins, use of aspirin, history of smoking, and years of smoking between the two groups.

The relationship between the diabetes-related factors and brain changes (lacunes, WMHs) in patients in the DM group

Table 4 set out the results of the regression analysis. The occurrence of lacunes was correlated with the duration of diabetes mellitus [odds ratio (OR) =1.483, 95% confidence interval (95% CI): 1.082–2.031, P=0.009] and the age (OR =1.141, 95% CI: 1.102–1.180, P<0.001), while WMHs were independently correlated only with the age (OR =1.124, 95% CI: 1.094–1.155, P<0.001). So, the duration of diabetes and the age of patients are risk factors for the silent CSVD.

The management of HbA1C levels, history of CHD, smoking history and years of smoking, aspirin use, and the use of statins were not correlated with brain changes in diabetic patients. In addition, no differences in brain changes were found between the type-2 diabetics using oral hypoglycemic drugs and those using insulin.

Discussion

Current studies demonstrate that compared with the control, type-2 diabetes mellitus is correlated with the classic MRI markers of CSVD (lacunes and WMHs). Diabetes mellitus duration is correlated with the occurrence of lacunes rather than WMHs, while the occurrence of WMHs is independently correlated with age. However, HbA1C management and use of insulin are not correlated with either type of CSVD.

Previous studies have demonstrated that patients with diabetes mellitus are more prone to suffer from LI, and diabetes mellitus and being older than 65 are independent risk factors (28) for LI. Type-2 diabetes mellitus is correlated with a higher risk of lacunar stroke (29), while prediabetes mellitus and persistent HbA1C are significantly correlated with an increased risk of LI or WMH (11). After an adjustment for multiple factors, type-2 diabetes mellitus

Table 2 Potential risk factors related to Lacunar infarction in the DM group and IGT group

Category	Patients with lacunar infarction in DM group and IGT group	Patients without lacunar infarction in DM group and IGT group	P
Male	189 (63.0)	60 (78.9)	0.009*
Age (years)	72 [63–79]	55 [48–62]	<0.001*
BMI (kg/m^2)	25 (23.2–27.175)	27.1 (24.975–28.850)	<0.001*
TC (mmol/L)	4.32 (3.6–4.92)	4.4 (3.83–5.06)	0.295
TG (mmol/L)	1.49 (1.06–2.23)	1.92 (1.3–2.93)	0.001*
SCr (μmol/L)	78.4 (67.2–89.5)	78.5 (69.5–86.9)	0.895
Hypertension history	227 (75.7)	52 (68.4)	0.197
BP			0.251
Normal	73 (24.3)	24 (31.6)	
Grade 1 (>140 and ≤160 mmHg)	36 (12.0)	13 (17.1)	
Grade 2 (>160 and ≤180 mmHg)	67 (22.3)	15 (19.7)	
Grade 3 (>180 mmHg)	124 (41.3)	24 (31.6)	
BP satisfied controlled proportion	128 (42.7)	39 (51.3)	0.175
Using antihypertensive drugs	194 (64.7)	38 (50.0)	0.019*
Using statins	121 (40.3)	15 (19.7)	0.001*
Using aspirin	124 (41.3)	13 (17.1)	<0.001*
CHD history	57 (19.0)	6 (7.9)	0.021*
Smoking	130 (43.3)	40 (52.6)	0.146
Smoking years			0.090
0	170 (56.7)	36 (47.4)	
≤20 years	42 (14.0)	15 (19.7)	
>20 and ≤40 years	65 (21.7)	23 (30.3)	
>40 years	23 (7.7)	2 (2.6)	
DM length			<0.001*
<5 years	48 (16.0)	29 (38.2)	
>5 and ≤9 years	52 (17.3)	8 (10.5)	
>10 and ≤19 years	75 (25)	7 (9.2)	
≥20 years	50 (16.7)	1 (1.3)	
HbA_1C management			
<6	99 (33.0)	35 (46.1)	0.034*
≥6	201 (67.0)	41 (53.9)	
Using insulin			<0.001*
No	211 (70.3)	70 (92.1)	
Yes	89 (29.7)	6 (7.9)	

Data are expressed as n (%) and median (interquartile range). *, P<0.05, the difference is statistically significant. IGT, impaired glucose tolerance; DM, diabetes mellitus; BMI, body mass index; TC, total cholesterol; TG, triglyceride; SCr, serum creatinine; WMH, white matter hyperintensities; FBG, fasting blood glucose; CHD, coronary heart disease; HBP, high blood pressure; HbA1C, Glycated hemoglobin test; BP, blood pressure.

Table 3 Potential risk factors related to WMHs in the DM group and IGT group

Category	Patients with WMHs in DM group and IGT group	Patients without WMHs in DM group and IGT group	P
Male	84 (61.3)	165 (69.0)	0.128
Age (years)	77 [70–82]	62 [55–73]	<0.001*
BMI (kg/m^2)	24.5 (22.65–26.825)	25.750 (23.8–28.4)	<0.001*
TC (mmol/L)	4.31 (3.57–5.07)	4.34 (3.68–4.95)	0.719
TG (mmol/L)	1.52 (1.06–2.25)	1.59 (1.1–2.34)	0.518
SCr (μmol/L)	78.7 (69.6–93.5)	78 (66.7–86.2)	0.174
Hypertension history	104 (75.9)	175 (73.2)	0.566
BP			0.002*
Normal	33 (24.1)	64 (26.8)	
Grade 1 (>140 and ≤160 mmHg)	9 (6.6)	40 (16.7)	
Grade 2 (>160 and ≤180 mmHg)	42 (30.7)	40 (16.7)	
Grade 3 (>180 mmHg)	53 (38.7)	95 (39.7)	
BP satisfied controlled proportion	58 (42.3)	109 (45.6)	0.539
Using antihypertensive drugs	90 (65.7)	142 (59.4)	0.228
Using statins	63 (46.0)	73 (30.5)	0.003*
Using aspirin	65 (47.4)	72 (30.1)	0.001*
CHD history	33 (24.1)	30 (12.6)	0.004*
Smoking	50 (36.5)	120 (50.2)	0.010*
Smoking years			<0.001*
0	87 (63.5)	119 (49.8)	
≤20 years	14 (10.2)	43 (18.0)	
>20 and ≤40 years	19 (13.9)	69 (28.9)	
>40 years	17 (12.4)	8 (3.3)	
Impaired glucose tolerance group	26 (19.0)	80 (33.5)	0.002*
DM length			<0.001*
<5 years	23 (16.8)	54 (22.6)	
>5 and ≤9 years	24 (17.5)	36 (15.1)	
>10 and ≤19 years	37 (27.0)	45 (18.8)	
≥20 years	27 (19.7)	24 (10.0)	
HbA_1C management			0.192
<6	43 (31.4)	91 (38.1)	
≥6	94 (68.6)	148 (61.9)	
Using insulin			0.001*
No	89 (65.0)	192 (80.3)	
Yes	48 (35.0)	47 (19.7)	

Data are expressed as n (%) and median (interquartile range). *, P<0.05, the difference is statistically significant. IGT, impaired glucose tolerance; DM, diabetes mellitus; BMI, body mass index; TC, total cholesterol; TG, triglyceride; SCr, serum creatinine; WMH, white matter hyperintensities; FBG, fasting blood glucose; CHD, coronary heart disease; HBP, high blood pressure; HbA1C, Glycated hemoglobin test; BP, blood pressure.

Table 4 The relationship between the diabetes-related factors and brain changes (lacunes, WMHs) in patients in the DM group

Brain changes	Variables	Regression coefficient	OR value (odds ratio)	95% confidence interval (95% CI)	P
Lacunar infarction	Course of diabetes	0.394	1.483	1.082–2.031	0.009*
	HbA1C management	0.069	1.071	0.556–2.063	0.953
	Insulin use	0.881	2.413	0.801–7.27	0.133
	Age	0.132	1.141	1.102–1.18	<0.001*
WMH	Course of diabetes	0.161	1.175	0.956–1.444	0.127
	HbA1C management	–0.242	0.785	0.449–1.374	0.421
	Insulin use	0.613	1.846	0.937–3.638	0.078
	Age	0.117	1.124	1.094–1.155	<0.001*

*, P<0.05, the difference is statistically significant. WMH, white matter hyperintensities; DM, diabetes mellitus.

may be one of the key determinants of microangiopathy, which is dominated by white-matter lesions (30). When based on a longitudinal comparison, diabetes mellitus is correlated with larger white-matter high-intensity volume, and from a horizontal comparison perspective, diabetes mellitus is correlated with accelerated white-matter high-intensity accumulation (13); the volume of WMHs and the number of WMH lesions are significantly correlated with diabetes mellitus (31). Prediabetes mellitus and type-2 diabetes mellitus are associated with fewer white-matter connections and weaker white-matter network tissue (32), while insulin-like growth factor binding protein-3 is negatively correlated with the severity of WMHs in patients with type-2 diabetes mellitus compared with the control group (P<0.05) (33). However, some findings are not consistent, with no difference in periventricular WMHs between patients with and without diabetes mellitus. In contrast, deep WMHs have been found only in the control group (23). No correlations between prediabetes mellitus and lacunes, CMBs, WMHs, or smaller brain volumes have been observed in the older population (24), and most studies have demonstrated that lacunes or WMHs are more common in patients with type-2 diabetes mellitus. It is currently believed that insulin resistance in the blood–brain barrier reduces the amount of glucose reaching the brain, leading to neuronal damage. The diabetic state may lead to a hyperglycemic state in the brain, which leads to the formation of advanced glycation end products, further triggering the neuroinflammation (34,35); this may also be correlated with reduced cerebral blood flow, increased middle cerebral artery resistance, and inflammation (36,37). Chronic hyperglycemia changes cell-membrane permeability reduces local blood flow, and results in permanent cell damage. In the present study, people with type-2 diabetes mellitus, impaired glucose tolerance, and a control group were studied in relation to four MRI markers of CSVD: lacunes, WMHs, CMBs, and perivascular space. The results demonstrated that compared with the control group and impaired glucose tolerance group, the prevalence of lacunes and WMHs in the type-2 diabetes mellitus group was higher. However, there was no significant difference in the incidence of CMBs and perivascular space. There are also some studies suggesting that gender could lead to different stroke risks caused by cerebrovascular diseases between men and women, and women with diabetes have a worse prognosis (38,39). These results are of great significance for us to further understand diabetes and the risk of cerebrovascular diseases. Unfortunately, this study did not conclude that there are gender differences in risk factors, which may have a certain relationship with the method of inclusion in this study.

Currently, there are few studies on the metabolic and vascular determinants of brain imaging abnormalities in patients with type-2 diabetes mellitus. The present study found that in patients with abnormal blood glucose, the occurrence of lacunes was correlated with the duration of diabetes mellitus, HbA1C, and insulin use, but it was only independently correlated with the duration of diabetes mellitus. HbA1C levels were not correlated with brain structural features. It was not possible to assess the correlation between actual hyperglycemia or normal glucose duration and the effects of persistent or transient hyperglycemia on brain structural characteristics in patients with diabetes mellitus, as HbA1C levels only provide estimates within average glucose levels. A study similar to this study showed that compared with subjects

who had suffered from diabetes mellitus for less than 10 years, subjects who had been diabetic for 10 years or more had a greater number of lacunes (P<0.05) (24). However, another study showed that in a fully adjusted model, fasting glucose, HbA1C, and diabetes mellitus duration were not correlated with lacunes in subjects with type-2 diabetes mellitus (P>0.05) (40). In the present study, the use of antihypertensive drugs, statins, and aspirin was found to be greater in LI patients than in the control group (P<0.05), which may be related to the fact that all patients in our study were inpatients. Inpatients had increased opportunities to take these drugs when CSVD was diagnosed and confirmed.

In the present study, it was also found that in patients with abnormal blood glucose, the occurrence of WMHs was correlated to the duration of diabetes mellitus and use of insulin. Moreover, it was observed that the incidence of grade 2 hypertension was higher in the patients with WMHs (P<0.05). Some previous studies have shown that the duration of diabetes mellitus was correlated with the volume of WMHs (24,41) and that higher systolic pressure (beats per minute) was correlated with WMH progression (42,43). However, after multiple adjustments, the present study found that the occurrence of WMHs was only independently correlated with age. Some studies on WMHs using diffusion tensor imaging (DTI) technology have demonstrated (44) that diabetic patients presented with a loss of microstructures, which was reflected in a reduction in FA, rather than correlating with age (45). A study of healthy young adults showed that even in young adults, high blood glucose resulted in reduced white-matter integrity (46), and two studies on adolescents with type-2 diabetes mellitus and white-matter lesions also found a decrease in FA in the type-2 diabetes mellitus group (47,48). These results are not consistent with those of the present study. The next step in this study is to use MRI and DTI sequencing to further investigate the clinical determinants of WMHs in diabetic patients.

One advantage of this study is that it focuses on relatively older DM patients, who are more than 55 years old. Another advantage is that it focuses not only on diabetic patients, but also patients with impaired glucose tolerance. This study has some limitations. Firstly, this study is a retrospective study, limited by previous scan results, this study is unable to provide GRE and SWI scan results, and thus cannot study the perivascular space, cerebral microhemorrhage, and brain atrophy. Secondly, when the patients in the Control group were included, they were only concerned about whether the diagnosis of diabetes and impaired glucose tolerance was definitive, so only those who met the inclusion criteria, the oral glucose tolerance test was completed, the results of fasting blood glucose and glycosylated hemoglobin were obtained, were included. After the inclusion, the included patients were not further matched, resulting in poor comparability in the Control group and the possibility of selection bias. Thirdly, the possibility of unobserved confounding factors will affect the results of the study, and the cross-sectional study setting also limits the causal explanation. Fourthly, the statistical method used in this study is controversial. This study did not include all potential variables into the regression analysis, but only studied the correlation relationship between the four clinically concerned variables and the 2 types of CSVD in diabetes mellitus group, and the analysis about another variables were not sufficient.

The conclusions of the present study are that lacunes and WMHs are more common in type-2 diabetes mellitus than in the controls and patients with impaired glucose tolerance. The duration of diabetes mellitus and the age of patients are correlated with the occurrence of lacunes, but the occurrence of WMHs is independently correlated with age. More advanced multiparameter MRI technology will be used for future studies to investigate brain structural changes in patients with type-2 diabetes mellitus and their effects on cognitive function, as well as potential pathophysiological mechanism (49).

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-21-786/rc

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related

to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Ethics Committee of Shanxi Bethune Hospital (SBQLL-2021-066) and informed consent was taken from all the patients.

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