CEREBRAL MICROVASCULAR LESIONS ON HIGH-RESOLUTION 7T MRI IN PATIENTS WITH TYPE 2 DIABETES

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Abstract

Cerebral small vessel disease, including microvascular lesions, is considered to play an important role in the development of type 2 diabetes mellitus (T2DM) associated cognitive deficits. With ultra-high field MRI microvascular lesions (e.g. microinfarcts and microbleeds) can now be visualized in vivo. For the present study, 48 nondemented older individuals with T2DM (mean age 70.3±4.1 years) and 49 age-, sex-, and education-matched control subjects underwent a 7T brain MRI scan and a detailed cognitive assessment. The occurrence of cortical microinfarcts and cerebral microbleeds was assessed on FLAIR and T1-weighted images and T2*-weighted images respectively, compared between the groups and related to cognitive performance. Microinfarcts were found in 38% of controls and 48% of patients with T2DM. Microbleeds were present in 41% of control participants, and 33% of patients (all $p>0.05$). Presence and number of microinfarcts or microbleeds were unrelated to cognitive performance. This study showed that microvascular brain lesions on ultra-high field MRI are not significantly more common in well-controlled patients with T2DM than in controls.

Introduction

Type 2 diabetes mellitus (T2DM) is associated with cognitive dysfunction and a twofold increased risk of dementia.(1) The aetiology is incompletely known, but vascular disease is likely to play a role.(1) In the general population vascular disease, in particular cerebral small vessel disease (SVD), is a major contributor to ageing related cognitive decline and dementia.(2) On conventional magnetic resonance imaging (MRI) SVD can be visualized as white matter hyperintensities (WMH), lacunar infarcts, and microbleeds.(3) However, these conventional markers of SVD do not capture the full burden of cerebral microvascular damage. Neuropathological studies have identified microinfarcts as another common microvascular pathology that is linked to ante-mortem cognitive decline and dementia.(4)

T2DM is a known risk factor for vascular disease, affecting both large and small vessels. Microvascular complications of T2DM appear in the retina, peripheral nervous system, kidney, and probably also the brain. Ultra-high resolution MRI now, for the first time, permits visualization of cortical microinfarcts in vivo (5) and also greatly enhances the detection of cerebral microbleeds.(6) We hypothesized that microinfarcts and microbleeds are more common in patients with T2DM than in controls and that these lesions are associated with cognitive dysfunction. The present study investigated the presence of cortical microinfarcts and cerebral microbleeds with 7 tesla (7T) in patients with T2DM and in age-matched non-diabetic controls, and explored the relationship between these microvascular lesions and cognitive performance.

Methods

Study population

Patients were recruited through six general practitioners as part of the second Utrecht Diabetic Encephalopathy Study (UDES2).(7) Eight hundred sixty-four randomly selected persons between 65 and 80 years of age (416 patients and 453 controls) received a letter to which they could respond if they were willing to participate. Two hundred sixty-three persons responded that they refused to participate; 168 responded that they were willing to participate, of which 63 patients with T2DM and 61 age-, sex- and education-matched controls met our inclusion criteria.

For inclusion, participants had to be 65-80 years of age, functionally independent and Dutch speaking. The diagnosis of diabetes had to be established at least one year prior to the study. Controls had to have a fasting blood glucose <7.0 mmol/l. Exclusion criteria were contraindications for 7T MRI, a psychiatric or neurological disorder that could influence cognitive functioning (including dementia), recent non-disabling stroke (<2 years) or any disabling stroke, major depression or alcohol abuse. All subjects underwent a standardized evaluation, including medical history, physical and neurological examination, neuropsychological assessment, laboratory testing and both a 3T and 7T MRI, all on the same day.

In 26 participants (15 T2DM, 11 controls) no complete 7T MRI could be obtained due to patient related factors (e.g. contra-indications for 7T MRI or claustrophobia) or technical issues. One control participant proved to have a neurological disease that was not detected upon initial screening, leaving 97 subjects (48 T2DM, 49 controls) for the present study.

The study was approved by the medical ethics committee of the University Medical Center Utrecht and all subjects gave written informed consent.

Medical history and biometric measurements

Medical history and medication use were assessed with standardized questionnaires. Blood pressure was measured at three different time points during the day and averaged. BMI was calculated as weight in kilograms divided by the square of height in meters. Fasting glucose, HbA1c and cholesterol levels were measured with standard laboratory testing. Impaired fasting glucose (IFG) was defined as fasting glucose levels of 5.6-6.9 mmol/L, according to the ADA criteria.

Data on microvascular complications were recorded. Retinopathy was defined as self-report of a physician diagnosis. Neuropathy was rated with the Toronto Clinical Neuropathy Scoring System,(8) but without a sensory test for temperature, so that the maximum score is 18 points. A score >6 was considered as indicative of neuropathy. A patient was considered to have macroalbuminuria in case of an albumin-to-creatinine ratio of >300 μg/mg (according to ADA criteria), based on laboratory testing of a first midstream urine sample in the morning.

A macrovascular event was defined as a clinical history of myocardial infarction, stroke (not including TIA) or endovascular or surgical treatment of carotid, coronal or peripheral arterial disease.

MRI scanning protocol

Scans were acquired on a 7T MR system (Philips Healthcare, Cleveland, OH, USA) with a volume transmit and 16 or 32-channel receive head coil (Nova Medical, Wilmington, MA). The standardized protocol included a dual-echo gradient echo sequence (repetition time (TR)/echo time (TE) = 20/6.9;15.8 ms, reconstructed voxel size 0.39x0.39x0.35 mm^3); a volumetric (3D) T1-weighted sequence (TR/inversion time (TI)/TE 4.8/1240/2.2 ms, reconstructed voxel size 0.66x0.66x0.50 mm^3); and a 3D fluid-attenuated inversion recovery

(FLAIR) sequence (TR/TI/TE: 8000/2325/300 ms, reconstructed voxel size 0.49x0.49x0.40 mm^3).

Scans on the 3T MR system (Philips Medical Systems, Best, the Netherlands) were acquired with a standardized protocol including, among others, a FLAIR sequence (TR/TI/TE 11000/2800/125 ms, reconstructed voxel size 0.96x0.95x3 mm^3), a 3D T1-weighted sequence (TR/TI/TE 7.9/955/4.5 ms, voxel size 1.00x1.00x1.00 mm^3) and a dual-echo T2-weighted sequence (TR/TE 3198/19;140 ms, reconstructed voxel size 0.96x0.95x3.00 mm^3). 3T MRI data were used for the detection of brain infarcts and the determination of brain volumes and WMH volumes.

Detection of microvascular lesions

Microvascular lesions were rated visually on 7T MRI scans by two independent raters, blinded to diabetes status and clinical information. In case of disagreement, consensus was obtained in a consensus meeting.

Cortical microinfarcts were defined as either small hyperintense (probably gliotic) lesions or hypointense with a hyperintense rim (probably cystic) lesions on the FLAIR image, corresponding with a hypointense lesion on the T1-weighted sequence (as previously described,(9) but without use of a T2-weighted sequence) (Fig. 1). Each lesion had to be detectable on sagittal, coronal, and transversal views, ≤3mm in length and restricted to the cortex to be classified as a microinfarct. Due to low signal-to-noise ratio on FLAIR images in the temporal lobes and cerebellum, these areas were not investigated.

Microbleeds were detected by the previously described semi-automatic method based on the radial symmetry transform (RST).(10) A slightly modified adaptation to the method was made by incorporating minimum intensity projection images. This improves the sensitivity and

reduces the number of suspected microbleed locations. The RST result was then censored visually to select true microbleeds.

The inter-rater agreement was good for number of microbleeds (ICC (95% CI): 0.83 (0.75; 0.88)) and moderate for number of microinfarcts (ICC=0.39 (0.21;0.55)).

Other MRI measures

WMHs, cerebral infarcts and brain volumes were determined on 3T MRI scans. WMHs were outlined manually on the FLAIR images and their volumes were calculated. Brain infarcts were rated visually on FLAIR and T1-weighted images and classified as large vessel infarcts (>1.5 cm) or lacunar infarcts. Gray and white matter volumes were computed automatically on the T1-weighted image using the Freesurfer software (http://surfer.nmr.mgh.harvard.edu). Volumes were expressed as a percentage of intracranial volume, which was outlined manually on the T2-weighted images.

Cognitive testing

All participants underwent a detailed standardized cognitive assessment as described earlier,(7) including tests for memory, information-processing speed and attention and executive function. For each cognitive test, raw test scores were standardized into *z*-scores and averaged to obtain one composite *z*-score per cognitive domain.

IQ was estimated with the Dutch version of the National Adult Reading Test, which is generally accepted to reflect the premorbid level of intellectual functioning.

Statistical analyses

Between-group differences in subject characteristics were analysed with an independent-samples *t*-test for continuous variables, χ^2 tests for proportions and Mann-Whitney U tests for

non-parametric data. Relationships between the presence of microvascular lesions and cognition were examined with linear regression analyses, adjusted for age, sex, estimated IQ, and group (control or T2DM). Because the numbers of microbleeds and microinfarcts showed a skewed distribution, three groups with 0, 1 or ≥1 lesion were distinguished.

Results

Subject characteristics are summarized in Table 1. Controls and patients with T2DM did not differ in age, sex, and estimated IQ. Patients with T2DM used significantly more often antihypertensive and cholesterol lowering drugs and had a higher BMI than controls. Patients with T2DM performed slightly worse than controls on all three cognitive domains (mean differences in standardized *z*-scores (95% CI) between patients and controls for information-processing speed: -0.24 (-0.58;0.11); attention and executive functioning: -0.21 (-0.50;0.09); memory -0.14 (-0.44;0.17), all p>0.05), but differences were not statistically significant.

MRI findings are described in Table 2. Cortical microinfarcts were found in 19 (38%) controls (5 subjects showed >1 microinfarcts) and in 23 (48%) patients with T2DM (7 subjects showed >1 microinfarcts), p>0.05 (Fig. 2). Microbleeds were present in 20 (41%) controls (10 subjects showed >1 microbleeds), and in 16 (33%) patients with T2DM (10 patients showed >1 microbleeds), p>0.05 (Fig. 2). Microbleed distribution (i.e. presence and number of lobar and deep/infratentorial microbleeds) was also similar between the groups.

Cerebral gray matter volumes were smaller and lateral ventricle volumes larger in the patients than in the controls, but WMH and white matter volumes and occurrence of brain infarcts did not differ between the groups (Table 2).

Across the two groups, cognitive performance on the three cognitive domains was not related to microvascular lesion load (Regression coefficient B (95% CI) information processing speed: microinfarcts 0.06 (-0.17;0.29), microbleeds 0.11 (-0.08;0.31); attention and executive

functioning: microinfarcts 0.04 (-0.16;0.23), microbleeds 0.02 (-0.14;0.19); and memory: microinfarcts 0.10 (-0.11;0.31), microbleeds 0.06 (-0.12;0.24), all p>0.05).

When control participants with IFG (n=25; 51%) were excluded, microbleeds were present in 11 (46%) and microinfarcts in 10 (42%) of the remaining 24 controls. Between group comparisons on MRI markers and cognition for controls without IFG and patients with T2DM did not show results that were different from the main analyses (data not shown).

Discussion

In this study on microvascular brain lesions in people with T2DM at ultra-high field MRI we did not observe an increased occurrence of microinfarcts or microbleeds compared to controls. Presence and number of microinfarcts or microbleeds were unrelated to cognitive performance.

Previous estimates on the occurrence of cerebral microinfarcts are solely based on autopsy studies, which identified them in around 24% of nondemented older individuals, with no significant differences between patients with T2DM and controls.(11) However, in autopsy studies that specifically addressed people with dementia, microinfarcts were more common in patients with T2DM than in those without.(12;13) In autopsy studies not specifically focusing on T2DM, microinfarcts have been related to cognitive impairment and dementia diagnosis before death.(14;15) These results suggest that the relationship between microinfarcts and cognition only becomes evident in cognitively symptomatic individuals. This may explain why we did not find a relation between microinfarcts and cognition in the present study.

Studies on the prevalence of microbleeds specifically in patients with T2DM are scarce. A few population-based studies showed diabetes mellitus to be associated with microbleeds (OR 2.2, 95% CI 1.2-4.2).(16) Two recent studies, including the AGES-Reykjavik study, specifically addressed patients with T2DM. They showed no difference in overall microbleed

occurrence between patients with T2DM and controls.(17;18) Although, an increased likelihood of ≥2 microbleeds in diabetic patients (7%) compared to controls (4%) was reported.(18) Both studies used 1.5T MRI and have found much lower prevalences compared with our study. Microbleeds did not mediate the association of diabetes and worse cognitive performance.(18) In previous large population-based cohorts, not specifically addressing T2DM, only weak associations between microbleeds and cognitive deficits have been reported (19;20), for example 0.4 MMSE points, for people with ≥5 microbleeds relative to those without.(20) These studies are in line with our results showing modest or no relationships with cognition, despite the high sensitivity of high field strength MRI to detect microbleeds.

Strengths of our study include the advanced technique for the detection of microvascular lesions, with a substantial sample size for an ultra-high field MRI study. We also employed a comprehensive cognitive examination in a well-defined population-based cohort. Importantly, our scan protocol has the advantage over neuropathology that almost the complete supratentorial part of the brain can be assessed (except for the temporal lobes), while autopsy studies only sample a small portion of the brain microscopically. Moreover, in previous neuropathological studies, the temporal lobe has not been reported as a location of preference.(11) There are also limitations. Our MRI protocol can only detect the largest microinfarcts.(9) It is uncertain if detected lesions are a good representation of the complete lesion load in the brain. Moreover, particularly the assessment of microinfarcts is rater dependent. Nevertheless, because the raters were blinded we do not expect systematic errors in lesion counts for the groups. Finally, in the patient group glycaemia and vascular risk factors were relatively well controlled. Although this does reflect current clinical practice guidelines (21) it may have attenuated the contrast between the groups and may limit generalizability of our findings. Moreover, controls with IFG were not excluded from the

study which might add to this effect. Our findings may therefore underestimate the occurrence of microvascular lesions in less well controlled patient populations. Nevertheless, the patients in our cohort did have other brain MRI abnormalities that are typical for T2DM. They had a modest degree of brain atrophy, in line with the literature,(22) and we previously reported that these patients had disturbed white matter connectivity relative to controls (7;23), despite the observation that WMH volumes and the occurrence of brain infarcts did not differ between the groups, which has also been reported before.(24;25) Finally, the effect size of the difference in cognitive performance compared with controls of around 0.2, although not statistically significant, is in line with a recent meta-analysis of the literature, which reports effect sizes of 0.2-0.4.(26)

To conclude, this study showed no increased burden of cerebral microvascular damage in this well-controlled group of patients with T2DM compared to controls. Further studies should assess whether cerebral microvascular lesions do occur in patients who are less well controlled or have a high burden of microvascular complications elsewhere in the body.

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MB and GJB are the guarantors of this work, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Author contributions: MB acquired data, performed the analyses and wrote the manuscript; YDR acquired data and made critical revision of the manuscript; SJV and HJK researched data and critically revised the manuscript; PRL critically revised the manuscript; LJK and

GJB made substantial contributions to conception and design of the study, and critically revised the manuscript for important intellectual content. All authors gave final approval of the version to be published and agreed to be listed as authors.

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The authors have no conflicts of interest to declare.

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Table 1. Group characteristics

	Control participants n=49	Patients with T2DM n=48	*p*-value
Age (years)	71.1 ± 4.5	70.3 ± 4.1	0.36
Sex (% male)	30 (61)	26 (54)	0.48
Estimated IQ *	103 ± 13	101 ± 12	0.29
Systolic blood pressure (mmHg) †	146 ± 22	148 ± 13	0.69
Diastolic blood pressure (mmHg) †	81 ± 9	80 ± 10	0.78
Antihypertensive medication (%)	25 (51)	36 (75)	0.02
Total cholesterol (mmol/L)	5.4 ± 1.0	4.7 ± 0.9	<0.01
Cholesterol lowering drugs (%)	21 (43)	34 (71)	<0.01
Current smoking	8 (16)	5 (10)	0.62
BMI (kg/m^2)	26.1 ± 3.2	29.5 ± 5.1	<0.01
Antithrombotic use (%)	12 (25)	18 (38)	0.17
Fasting glucose (mmol/L)	5.6 ± 0.7	8.0 ± 2.0	<0.01
HbA1c (%)	5.7 ± 0.4	6.8 ± 0.8	<0.01
Diabetes duration (years)	-	11.0 ± 9.3	
Insulin/oral medication or diet (%)	-	15/33 (31/69)	
Macrovascular event (%) ‡	3 (6)	7 (15)	0.17
Retinopathy (%)	0 (0)	5 (10)	0.02
Peripheral neuropathy (%) §	5 (10)	10 (21)	0.15
Macroalbuminuria ‖	0 (0)	1 (2)	0.31
Cognitive performance ¶			

Information-processing speed	0.13 ± 0.57	-0.11 ± 1.07	0.18
Attention and executive functioning	0.09 ± 0.56	-0.11 ± 0.84	0.16
Memory	0.07 ± 0.73	-0.07 ± 0.76	0.37

Data are presented as mean ± SD or n (%) unless otherwise specified.

[*] Estimated by the Dutch version of the National Adult Reading Test.

[†] Mean values for three measurements; for one control subject blood pressure was not examined.

[‡] Defined as a clinical history of myocardial infarction, stroke (not including TIA) or endovascular or surgical treatment of carotid, coronal or peripheral arterial disease.

[§] Rated with the Toronto Clinical Neuropathy Scoring System (8)

[‖] Defined as an albumin-to-creatinine ratio of >300 μg/mg

[¶] Data are presented as mean standardized *z*-scores ± SD.

Table 2. MRI findings

	Control participants n=49	Patients with T2DM n=48	*p*-value
Microvascular lesions *			
Cortical microinfarct presence (%)	19 (38)	23 (48)	0.36
Cortical microinfarct No.	0 (0-11)	0 (0-5)	0.35
Microbleed presence (%)	20 (41)	15 (33)	0.33
Microbleed No.	0 (0-5)	0 (0-13)	0.55
Strictly deep/infratentorial microbleeds (%)	3 (7)	1 (2)	0.32
Strictly lobar microbleeds (%)	11 (24)	12 (27)	0.76
Other MRI markers †			
White matter hyperintensity volume (mL)	6.9 ± 10.2	5.4 ± 5.5	0.36
Lacunar infarction (%)	13 (27)	10 (21)	0.51
Large vessel infarction (%)	2 (4)	3 (6)	0.63
Gray matter volume (% ICV)	39.1 ± 2.0	38.0 ± 2.2	0.02
White matter volume (% ICV)	30.5 ± 3.1	29.9 ± 2.4	0.30
Lateral ventricle volume (% ICV)	2.0 ± 1.0	2.7 ± 1.5	0.02

Data are presented as mean ± SD, n (%), or median (range). ICV = intracranial volume

* Determined at 7T field strength

† Determined at 3T field strength

Figure 1. An example of a cortical microinfarct, which appears hyperintense on FLAIR (A) and hypointense on T1-weighted (B) 7 tesla MR images.

Figure 2. Number of microinfarcts (A) and microbleeds (B) in controls and patients with T2DM. The number of microvascular lesions did not differ between the groups (Mann Whitney U test for number of microinfarcts: p=0.35; for number of microbleeds: p=0.55).

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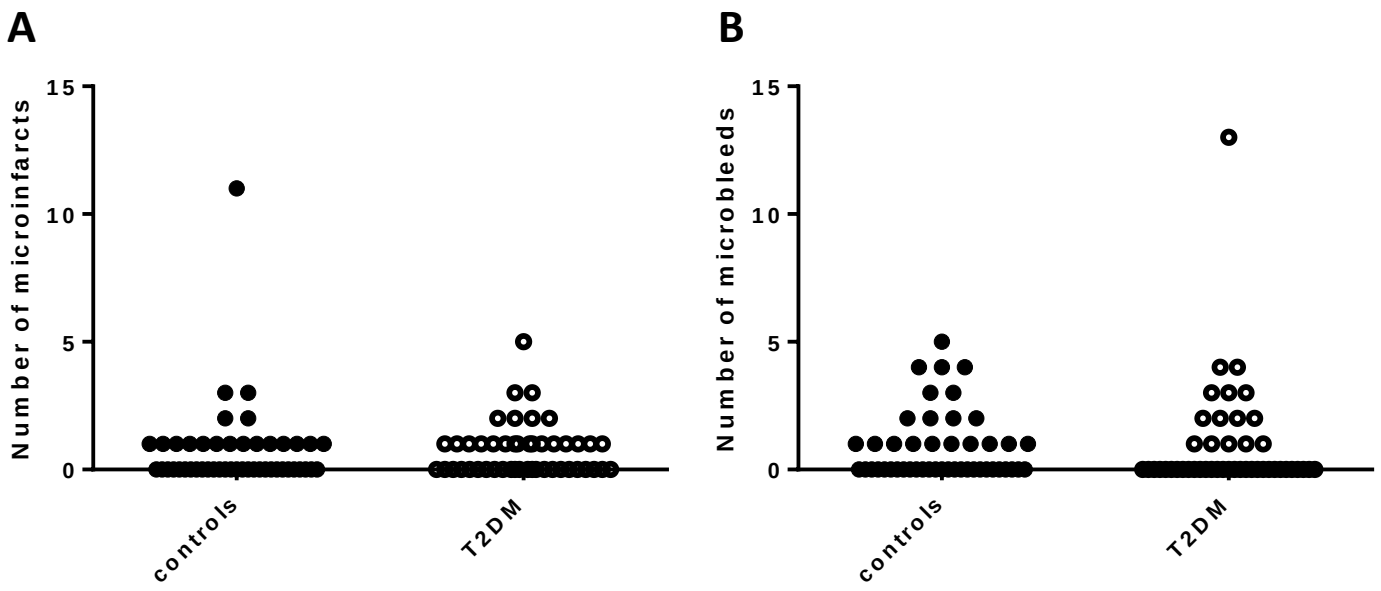
A
Number of microinfarcts
15
10
5
0
controls
T2DM
B
Number of microbleeds
15
10
5
0
controls
T2DM