

Title:

The clinical phenotype of vascular cognitive impairment in patients with type 2 diabetes mellitus.

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Abstract

Background:

Type 2 diabetes mellitus (T2DM) increases the risk of vascular cognitive impairment (VCI). It is unknown which type of vascular lesions and co-morbid etiologies, in particular Alzheimer pathology, are associated with T2DM in patients with VCI, and how this relates to cognition and prognosis.

Objective:

To compare brain MRI and cerebrospinal fluid (CSF) markers, cognition, and prognosis in patients with possible VCI with and without T2DM.

Methods:

We included 851 memory clinic patients with vascular brain injury on MRI (i.e. possible VCI) from a prospective cohort study (T2DM: n=147, 68.4±7.9 years, 63% men; no T2DM: n=704, 67.6±8.5 years, 52% men). At baseline, we assessed between-group differences in brain MRI

abnormalities, CSF markers of Alzheimer's disease and cognitive profile. After two years follow-up, we compared occurrence of cognitive decline, stroke, and death.

Results:

The distribution of clinical diagnoses did not differ between patients with and without T2DM. T2DM patients had more pronounced brain atrophy (total and white matter volume), and more lacunar infarcts, whereas microbleeds were less common (all $p < 0.05$). CSF amyloid- β levels were similar between the groups. T2DM patients performed worse on working memory (effect size: -0.17 , $p = 0.03$) than those without, whereas performance on other domains was similar. During follow-up, risk of further cognitive decline was not increased in T2DM.

Conclusion:

In patients with possible VCI, presence of T2DM is related to more pronounced brain atrophy and a higher burden of lacunar infarcts, but T2DM does not have a major impact on cognitive profile or prognosis.

Keywords:

Type 2 diabetes mellitus; vascular brain injury; MRI; cerebrospinal fluid; prognosis

Introduction

Type 2 diabetes mellitus (T2DM) is associated with an increased risk of cognitive dysfunction [1]. The etiology is likely to be multifactorial, with vascular disease as a key contributor [2].

Involvement of vascular disease in cognitive dysfunction, also referred to as vascular cognitive impairment (VCI), includes both ischemic and hemorrhagic changes in the brain, due to large or small vessel disease [3]. It is unknown if T2DM is associated with specific types of vascular lesions among patients with VCI.

Previous imaging studies have observed associations between T2DM and an increased burden of lacunar infarcts and a modest increase in white matter hyperintensities (WMH) volumes, but the burden of microbleeds and micro-infarcts was not increased [4]. T2DM predisposes to large (including cardio embolic) and small vessel causes of ischemic stroke [5]. These observations on vascular lesions in people with T2DM are mainly derived from population-based cohorts. The question is which of these lesions are the prime determinants of VCI in patients with T2DM. Moreover, Alzheimer's disease is an important co-morbid pathology in VCI [3]. The question is therefore also to which extent T2DM affects the balance between vascular brain injury and Alzheimer's pathology in VCI. Although the relationship between T2DM and vascular brain lesions and Alzheimer pathology has been addressed in several previous population based studies [4,6], it has not been studied in patients with clinically manifest VCI presenting at a memory

clinic. This is an important knowledge gap. We cannot take for granted that patterns of brain changes in the general population (i.e. those at risk for cognitive impairment and dementia) are the same as in those with clinical features of cognitive and dementia. Yet, the brain changes that contribute to the clinical phenotype of the latter groups should be the prime target for preventive measures and are also relevant for diagnosis and prognosis in clinical practice. The current prospective memory clinic study examined which patterns of vascular brain injury and cerebrospinal fluid (CSF) markers of Alzheimer's disease are associated with T2DM in patients with possible VCI. Moreover, we assessed how T2DM affects the prognosis of these patients.

Materials and methods

Study population

This study involved patients from the Utrecht-Amsterdam Clinical Features and Prognosis in Vascular Cognitive Impairment (TRACE-VCI) study, an observational prospective cohort study of 860 consecutive patients with vascular brain injury on MRI (i.e. possible vascular cognitive impairment [VCI]) referred to a memory clinic [7]. Patients were included from the Vrije Universiteit Medical Center (VUMC) (n=664) and the University Medical Center Utrecht (UMCU) (n=196) between September 2009 and December 2013. All patients had to have cognitive complaints and evidence of vascular brain injury on MRI, operationalized as the presence of at least one of the following neuro-imaging markers: a) WMH Fazekas scale ≥ 2

(Fazekas), b) Fazekas scale 1 and two vascular risk factors (i.e. hypertension, hypercholesterolemia, diabetes mellitus, obesity, current smoking, or a reported history of a vascular event other than stroke), c) ≥ 1 lacunar infarcts, d) ≥ 1 non-lacunar (sub)cortical infarcts, e) ≥ 1 cerebral microbleeds, f) ≥ 1 intracerebral hemorrhage.

Patients were not primarily selected for inclusion in the TRACE-VCI cohort based on specific clinical diagnoses. Presence of co-existing neurodegenerative disorders (such as Alzheimer's disease) was accepted in line with earlier proposed VCI criteria [3]. Patients with a monogenic cause of cognitive dysfunction were excluded as were patients with other nonvascular and nondegenerative primary causes of cognitive dysfunction such as a brain tumor, extensive traumatic head injury, substance or alcohol abuse, multiple sclerosis, and patients with primary psychiatric disease, other than depression. Details on the inclusion and exclusion criteria of the cohort have been previously published [7].

Presence of T2DM was based on medical history, use of oral antidiabetic agents or a diagnosis of newly diagnosed diabetes. Patients were classified as having newly diagnosed diabetes if they had a nonfasting glucose of ≥ 11.1 mmol/l or an HbA1c ≥ 48 mmol/mol (or $\geq 6.5\%$) [8]. For the present study, we excluded 9 patients from the original TRACE-VCI cohort, seven because of a diagnosis of type 1 diabetes mellitus, and two others because a distinction between a diagnosis of type 1 diabetes mellitus or T2DM could not be made based on the available information. Hence,

the study population consisted of 851 patients with possible VCI, 147 of whom had T2DM (17%) and 704 whom did not have T2DM (83%). The study was approved by the institutional review board of the VUMC and the UMCU. All patients provided informed consent prior to research related procedures.

Interview, physical and neurological examination

Patients received a standardized diagnostic assessment performed by a neurologist or a geriatrician including an interview on cognitive complaints, an informant interview, a physical examination and a neurological examination. Hypertension was defined as present in medical history, the use of antihypertensive medication, or current blood pressure above 140/90 mmHg. Hypercholesterolemia was determined based on medical history or medication use. Obesity was defined as a baseline body mass index (BMI) ≥ 30 , calculated as weight in kilograms divided by height in meters squared. A vascular event other than stroke was defined as a history of myocardial infarction, cardiac surgery or endovascular treatment for coronary artery disease, any arterial occlusion or surgical intervention of a peripheral artery (such as an abdominal or leg artery) or carotid artery intervention (stenting or endarterectomy).

Blood samples

Glucose or HbA1c levels were available from 97.1% (826/851) of the patients. Plasma fasting or nonfasting glucose levels were collected in 84% (717/851) of the patients and HbA1c levels were

collected in 22% (190/851) of the patients. HbA1c levels were available in 43 of the 147 patients with T2DM (29%).

MRI assessment

Brain MRI scans were performed on a 3.0 tesla (94%, 800/851) or 1.5 tesla MRI scanner (6%, 51/851; GE Signa HDxt (45/851) 5%, other six on four other 1.5 tesla scanners). The MRI scan protocol included the following sequences: 3D T1-weighted, and 2D multi-slice T2-weighted, T2*-weighted/susceptibility-weighted imaging (SWI) and fluid-attenuated inversion recovery (FLAIR) sequences. The MRI sequence parameters are described elsewhere [7]. A total of 842 (98.9%) patients were scanned using all of these sequences. In nine patients (1.1%), no 3D T1-weighted and/or FLAIR sequence was available.

Visual MRI ratings and image processing

(Non)lacunar infarcts, cerebral microbleeds, and intracerebral hemorrhages were all rated according to the STRIVE (Standards for Reporting Vascular Changes on Neuroimaging) criteria [9]. WMH's were rated using the Fazekas scale [10] for patient classification. For the analyses WMH volumes were used. Ratings were performed by or under supervision of a neuroradiologist (in training).

The following stepped semi-automated processing pipeline was used to obtain WMH and brain volumes.

First, automated WMH segmentation was performed on FLAIR images using the kNN-TTP method [11]. All WMH segmentations were checked visually. Because of slight undersegmentation, minimal manual corrections were performed in eight patients (<1%).

Presence of WMHs can lead to misclassification of various tissue compartments in automated brain segmentation [12,13]. Lesion filling methods have been shown to reduce this misclassification and improve brain volume measurements [14,15]. Therefore, we performed WMH lesion filling on 3D T1 images using the SLF-toolbox

(<http://atc.udg.edu/nic/slfToolbox/index.html>) for Statistical Parametric Mapping 12 (SPM12, Wellcome Department of Cognitive Neurology, Institute of Neurology, Queen Square London) with default settings [16,17]. Since WMH segmentation was performed on FLAIR images, binary WMH segmentations were transformed using the elastix toolbox for image registration before feeding it to the SLF toolbox [18].

Next, lesion-filled 3D T1 images were automatically segmented using the Computational Anatomical Toolbox (CAT12, version r864, <http://www.neuro.uni-jena.de/cat/>) for Statistical Parametric Mapping 12 (SPM Wellcome Department of Cognitive Neurology, Institute of Neurology, Queen Square London; [13](http://www.neuro.uni-jena.de/hbm2012/HBM2012-</p></div><div data-bbox=)

Dahnke02.pdf; <http://www.neuro.uni-jena.de/hbm2016/GaserHBM2016.pdf>). Default settings were used to obtain probabilistic segmentations for each of the three tissue compartments (gray matter, white matter and CSF). Quality assessment was performed visually on all segmentations. No manual editing was found to be needed. Gray matter volumes, white matter volumes and CSF volumes were obtained from the probabilistic segmentations using MeVisLab (MeVis Medical Solutions AG, Bremen, Germany), [19].

Next, (non)lacunar infarcts, intracerebral hemorrhages and incidental findings were manually segmented on FLAIR images using an in-house developed MeVisLab tool (MeVis Medical Solutions AG, Bremen, Germany;

<https://www.narcis.nl/publication/RecordID/oai:dspace.library.uu.nl:1874%2F287431>), [19].

These manual segmentations of infarcts, hemorrhages and other incidental findings were subsequently used as a mask to correct WMH segmentations, gray matter volumes, white matter volumes and CSF volumes.

A total of 814 (95.6%) scans completed the pipeline. Thirty-seven scans failed to complete the segmentation pipeline, due to missing or inadequate scan quality (n=12), due to processing errors during automated brain segmentation (n=10), due to inadequate quality of brain segmentations (n=8) and due to errors during manual segmentation (n=7).

CSF samples

CSF concentration of amyloid- β ($A\beta$), tau and/or total tau phosphorylated threonine 181 were measured in 63% (533/851) of the patients, at a central laboratory for clinics at the Department of Clinical Chemistry of the VUMC [20].

Cognitive assessment

The Dutch version on the Mini Mental State Examination (MMSE) was used as a measure of global cognitive functioning [21]. The severity of cognitive symptoms was assessed using the Clinical Dementia Rating (CDR; 0-3) global score [22]. All patients underwent an extensive neuropsychological examination. The tasks were summarized in five cognitive domains: (1) working memory, (2) memory, (3) attention and executive functioning, (4) processing speed, and (5) perception and construction. The domain working memory was assessed by the Digit Span of the Wechsler Adult Intelligence Scale – 3rd edition (WAIS-III) [23]. The domain memory was assessed by the Dutch version of the Rey Auditory Verbal Learning Test (RAVLT) [24] and the Visual Association Test (VAT) part A [25]. The domain attention and executive functioning was assessed using the ratio of the Trail Making Test part B and A (TMT-B and TMT-A) [26], the Stroop Color Word Test [27], and the category naming tasks (animal naming, 1 minute) [28] and lexical fluency tasks (letters, 1 minute) [28]. The domain processing speed was assessed by the TMT-A [26], the Stroop Color Word Test I and II [27], and the Digit Symbol-Coding Test (DSCT) of the WAIS-III [23] or the Letter Digit Substitution Test (LDST) [23]. The cognitive

domain perception and construction was made using the Visual Object and Space Perception Battery, administering two separate tests known as the Incomplete Letters and Dot Counting. Level of education was defined according to a 7-point scale (Verhage scale 1-7; low to high education) [29].

Clinical Diagnosis

Clinical diagnoses were established at multidisciplinary consensus meetings after the 1-day memory clinic evaluation. Patients were divided in three categories of severity of cognitive impairments: dementia, MCI and no objective cognitive impairment (NOCI).

Patients were diagnosed with dementia if there was a clear decline in cognitive function defined as a deficit in ≥ 2 cognitive domains at neuropsychological testing and interference in daily living [30]. Dementia was further classified due to its main etiology, based on internationally established criteria without knowledge of CSF biomarkers, in vascular, neurodegenerative or unknown origin [31–34]. A diagnosis of MCI was defined as complaints of deterioration in cognitive function from a prior baseline and objective evidence of impairment in at least one cognitive domain. Daily living activities were normal or mildly impaired [35]. Lastly, NOCI was defined as having cognitive complaints, but no objective cognitive impairments on neuropsychological testing (also referred to as subjective cognitive decline or subjective cognitive impairment) [36].

Follow-up Investigation

Patients with at baseline an MMSE score of ≥ 20 [37], a CDR of ≤ 1 [24] and no institutionalization were eligible for follow-up, i.e. those without moderate to severe dementia at baseline. These criteria applied to 698 (82%) patients of the baseline population. To avoid selective drop-out of patients who were not able to be re-assessed at the memory clinic, we chose outcome measures which could also be collected by telephone interview. These included accelerated cognitive decline, defined as a change in CDR of ≥ 1 or institutionalization due to cognitive dysfunction during the follow-up period. Occurrence of ischemic stroke or intracerebral hemorrhage during follow-up was also recorded.

Statistical Analysis

Demographic variables, vascular risk factors, measures of global cognitive status, distribution of clinical diagnoses, Fazekas scale, and CSF data were compared between possible VCI patients with and without T2DM using independent samples t-tests for parametric data, Mann-Whitney U tests for non-parametric data and χ^2 tests for proportions.

Total brain, gray matter, and white matter volumes (as % of ICV) were standardized into z-scores to allow comparison of effect sizes between different volumes. As WMH volumes did not follow a normal distribution, WMH volumes were log-transformed and then standardized into z-scores. Between group differences in brain volumes were calculated using analysis of covariance

(ANCOVA) with age, gender and scanner type as covariates. The occurrence of other cerebrovascular lesions was compared between groups using logistic regression with age and gender as covariates.

Raw cognitive test scores were standardized into z-scores per test, using the mean and standard deviation of the whole study sample. Subsequently, the test z-scores were averaged to create domain z-scores. If individual test scores were missing, the domain z-score was based only on the available tests. Between group differences in domain z-scores were calculated using analyses of covariance (ANCOVA) with age, gender, and level of education as covariates.

Follow up data was analyzed using Cox proportional hazard models, to assess the risk of T2DM presence on the time to event for each separate outcome (change in CDR of ≥ 1 , institutionalization due to cognitive dysfunction, stroke, and death). The Cox proportional hazard models were adjusted for age, gender and clinical diagnosis. For stroke, the model was additionally adjusted for vascular risk factor count (one point for each risk factor: hypertension, hypercholesterolemia, current smoking, obesity, history of stroke and history of reported vascular event other than stroke).

Sensitivity analyses were performed excluding patients with NOCI, in order to study specifically MCI and dementia. Furthermore, patients could be included in the TRACE-VCI cohort based on the criterion of a Fazekas scale grade 1 and the presence of ≥ 2 vascular risk factors, one of which

could be T2DM. In a second sensitivity analysis we therefore controlled for this potential selection bias, by excluding patients that were included in the cohort solely based on this criterion. Finally, to evaluate the influence of Alzheimer pathology on brain atrophy and occurrence of lacunar infarcts and cerebral microbleeds, we stratified the between group analyses on brain volumes for CSF Alzheimer profile (i.e. CSF ratio tau/A β > 0.52) [38].

Results

Demographic characteristics and vascular risk factors are shown in table 1. The proportion of men was higher in the group with T2DM. Patients with possible VCI with and without T2DM were similar with regard to age. Level of education was lower in the patients with T2DM. Patients with T2DM more often had hypercholesterolemia, obesity and a history of a vascular event other than stroke. There were no between-group differences in syndrome diagnosis (NOCI, MCI or dementia). Regarding dementia subtypes, most patients across both groups had a diagnosis of Alzheimer's disease (61% with T2DM versus 69% without T2DM). Of the 147 patients with T2DM, 102 (69%) used oral antidiabetic agents, and 26 (18%) used insulin. Thirteen (9% of all patients with T2DM) patients had newly diagnosed T2DM.

Brain MRI features at baseline are shown in table 2. Patients with T2DM had a lower total brain volume (as % of ICV: 71.0 ± 4.1 vs. 70.0 ± 4.1 , effect size: -0.21 [-0.36 ; -0.07], $p=0.005$) and a lower total white matter volume (% of ICV: 32.0 ± 2.3 vs. 32.5 ± 2.2 , effect size -0.22 [-0.39 ; -

0.06], $p=0.008$) than patients without T2DM. Difference in total gray matter volume did not reach significance (effect size -0.13 [-0.28 ; 0.11], $p=0.07$). Lacunar infarcts were more common in patients with T2DM than in those without T2DM (odds ratio 1.52 [1.01 ; 2.29]). There were no between group differences in WMH volumes, non-lacunar (sub)cortical infarcts or intracerebral hemorrhages. The occurrence of any microbleeds and strictly lobar microbleeds was lower in patients with T2DM (odds ratio 0.49 [0.33 ; 0.73], and odds ratio 0.50 [0.31 ; 0.78], respectively) than in patients without T2DM. The occurrence of strictly deep microbleeds was similar between groups.

Table 3 shows CSF features at baseline. CSF levels of A β , tau and phosphorylated tau did not differ between groups. Notably, although not significantly, CSF A β levels tended to be higher (i.e. less compatible with Alzheimer pathology) in patients with T2DM.

Table 4 shows the cognitive assessment at baseline. There were no between group differences in global cognitive status (MMSE and CDR scores). Patients with T2DM performed worse on the domain working memory (effect size: -0.17, 95% confidence interval [-0.32 ; -0.01], $p=0.04$) compared to those without. On the other four domains, cognitive performance was similar between both groups (effect sizes ranging from -0.02 to 0.12).

Out of the 698 patients who were at baseline eligible for follow-up, at least one outcome measure was available from 680 (97.4%); T2DM: 97.5%, no T2DM: 97.4%. Thirteen patients were lost to

follow-up and five gave no permission to collect follow-up data. Median follow-up duration was 2.1 years (range 0.2-3.0). Follow-up outcomes are shown in table 5. Patients with and without T2DM did not differ with regard to occurrence of death, accelerated cognitive decline, defined as a change of CDR ≥ 1 or institutionalization due to cognitive dysfunction, and risk of non-fatal stroke.

The sensitivity analyses excluding patients with NOCI (n=196) and excluding patients who were included in the cohort solely because of a Fazekas scale grade 1 and the presence of ≥ 2 vascular risk factors (n=205) showed essentially the same results as the main analyses.

In stratified analyses according to CSF markers (supplemental table 1), in patients without a CSF Alzheimer profile, those with T2DM had a lower total brain volume and a lower total gray matter volume than those without T2DM (n=240). By contrast, in patients with a CSF Alzheimer profile (n=293), brain volumes did not significantly differ between patients with and without T2DM, although the effect sizes were largely similar to the Alzheimer negative group. The relation between T2DM and lacunar infarcts and microbleeds was only observed in the Alzheimer negative group.

Discussion

In **memory clinic** patients with possible VCI, those with T2DM had a higher burden of lacunar infarcts than those without T2DM. Global brain atrophy and white matter atrophy were more

pronounced in patients with T2DM. CSF A β levels tended to be higher, i.e. compatible with a lower burden of Alzheimer's pathology, in patients with T2DM compared to those without T2DM, consistent with a less frequent occurrence of (lobar) microbleeds in patients with T2DM. This different pattern of brain tissue injury did not result in a markedly different cognitive profile or prognosis relative to patients without T2DM.

The main novelty of our study is that it was performed in a memory clinic setting, in contrast to most previous studies in brain imaging and cognition in T2DM, that were mainly population based. We consider this clinic based setting as important. Particularly in people presenting at a memory clinic, the pattern and severity of cognitive deficits, brain abnormalities on MRI, and CSF biomarkers guide the diagnosis and prognostication, but clearly also present the primary leads for the development of targeted treatment measures. Additional strengths of the study include the large sample size, the longitudinal design and the standardized and detailed recording of imaging markers, CSF biomarkers and cognitive performance. Our first objective was to compare patterns of vascular brain injury between those with and without T2DM. We identified only one previous memory clinic study addressing this objective. In line with our observations, that study observed that T2DM was associated with an increased occurrence of lacunar infarcts, but no increase in WMH compared to those without T2DM [39]. Other imaging studies on vascular brain injury in patients with T2DM were conducted in other population types, mainly case-control studies in participants without cognitive impairment and population-based cohorts.

In those studies, T2DM is also consistently associated with a higher burden of lacunar infarcts compared to controls [4,40] and in several studies also with a modest increase of WMH burden [4,40]. The association between T2DM and microbleeds is less clear, but most studies indicate that the microbleed burden is not increased in T2DM [4]. All in all, with regard to vascular brain injury, the burden of lacunar infarcts is consistently increased in T2DM, regardless of population type. The previous reported association between T2DM and WMH is less clear in a memory clinic setting. The observed lower burden of (lobar) cerebral microbleeds in our study is remarkable, but may be related to this memory clinic setting, where lobar microbleeds likely reflect cerebral amyloid angiopathy (CAA) [41]. Therefore, it appears that among patients with possible VCI, T2DM is associated with a lower CAA burden.

Previous memory clinic studies have found an association between T2DM and brain atrophy [39,42]. In concordance with these findings, case-control studies in participants without MCI or dementia and population-based studies observed that T2DM is associated with global brain atrophy [40]. The magnitude of the volume reduction is modest, with effect sizes of 0.2 to 0.6 standard deviation units [40]. Our findings are compatible with these previous studies. Of note, this indicates that even among patients with cognitive dysfunction, those with T2DM have additional brain atrophy.

CSF A β levels did not differ significantly between patients with and without T2DM in our study. If anything, CSF A β levels tended to be slightly higher in patients with T2DM, reflecting a possible lower burden of Alzheimer's pathology. In line with these findings, a previous large memory clinic study observed no association between T2DM and CSF A β levels [42]. The same study also found no association between T2DM and PET A β depositions [42]. Moreover, a population-based PET study also observed no association between T2DM and A β depositions [43]. Furthermore, in population-based autopsy cohorts, core pathological changes of Alzheimer's disease were similar, or, in line with the tendency of our observations, even decreased in T2DM relative to controls [6,44]. In sum, the burden of Alzheimer pathology is not increased, or if anything, is decreased in T2DM.

Despite the different pattern of brain injury in memory clinic patients with T2DM, detailed cognitive testing revealed that patients with T2DM had only a lower performance on working memory, whereas on the other four cognitive domains, their performance was similar to those without T2DM. Moreover, T2DM was not associated with accelerated cognitive decline. In apparent contrast with these findings, some [45–47], but not all [48] previous memory clinic studies found that T2DM was associated with accelerated progression from MCI to dementia within one to two years of follow-up. Furthermore, several previous population-based studies also observed accelerated conversion from MCI to dementia in patients with T2DM compared to patients without, during follow-up periods ranging from five to nine years [49–51] (but see [52]).

Altogether, most memory clinic and population-based studies observed that T2DM is associated with accelerated progression from MCI to dementia. The differential findings in our cohort may be due to the fact that all participants were selected based on the presence of vascular brain injury.

The observation that overall cognitive performance at baseline was similar in both groups indicates that patients with T2DM did not attend the memory clinic in an earlier or later disease stage than those without. This also suggests that the overall burden of pathology, which in the majority of patients likely involved multiple etiologies, was similar between the groups. From this, it may be inferred that if some brain pathologies (i.e. lacunar infarcts and atrophy) were more common or severe in T2DM, other brain pathologies should be less common. This may be the explanation for the possible lower Alzheimer's pathology burden and the lower occurrence of lobar microbleeds in those with T2DM, indicating a lower CAA burden, in this setting probably mostly reflecting another pathological manifestation of the Alzheimer process [41]. The increased occurrence of lacunar infarcts in T2DM likely reflects an increased burden of arteriolosclerosis. The increased severity of atrophy, without increased Alzheimer pathology, suggest that also non-Alzheimer's disease types of neurodegeneration contribute to cognitive dysfunction in T2DM [53]. Further elucidation of such other types of neurodegeneration is an emerging research interest in the dementia field that is clearly particularly relevant for T2DM.

A possible limitation of our study is that we did not define a minimal threshold for severity of cognitive dysfunction for inclusion in our cohort. By contrast, most diagnostic criteria for VCI state that this construct only applies to patients with MCI or dementia [3,54]. The rationale for our approach is that some patients with cognitive decline as result of vascular brain injury may not present with cognitive deficits that are severe enough to be classified as MCI [7].

Importantly, we did perform a sensitivity analysis and showed that excluding patients without cognitive impairment did not affect the results in relation to T2DM status. Another limitation is that because all participants were selected for presence of vascular brain injury, we can only assess the relation between T2DM and the nature and burden of vascular injury, rather than its presence. Moreover, in 3.1% of the patients in the reference group no glucose or HbA1c levels were available and we may thus have missed some undiagnosed cases of T2DM. Yet, in light of this small percentage it is unlikely that that has affected our results. A final limitation is that we did not record detailed information about diabetes duration and rate of glycemetic control.

In conclusion, in memory clinic patients with possible VCI, those with T2DM, compared to patients without T2DM, had a higher burden of lacunar infarcts, likely attributable to accelerated arteriolosclerosis, and more brain atrophy, likely attributable to non-Alzheimer's disease types of neurodegeneration. Both disease processes may be targets for disease modifying treatment, particularly in VCI patients with T2DM. Of note, although the pattern of brain injury was

different in patients with VCI and T2DM, this was not associated with clear differences in cognitive profile of prognosis of cognitive functioning.

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Conflict of interest/Disclosure statement

Onno N. Groeneveld, Costanza Moneti, Rutger Heinen, Jeroen de Bresser, Hugo J. Kuijf, Lieza G. Exalto, Joeske M.F. Boomsma, Frederik Barkhof, Niels D. Prins, Philip Scheltens and Wiesje M. van der Flier have no competing interests to declare. L. Jaap Kappelle is a consultant for Boehringer Ingelheim. Geert Jan Biessels is a consultant for and receives research support from Boehringer Ingelheim. Compensation for these activities is transferred to their employer, the UMC Utrecht.

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Table 1. Demographic characteristics and vascular risk factors at baseline

	Possible VCI without T2DM n = 704	Possible VCI with T2DM n = 147	p-value
Demographics			
Gender, % men	367 (52)	92 (63)	0.02
Age	67.6 ± 8.5	68.4 ± 7.9	0.28
Level of education ^a	5 (3 - 7)	5 (2-7)	0.01
Vascular risk factors			
Hypertension ^b	588 (84)	132 (90)	0.06
Hypercholesterolemia ^c	273 (39)	106 (72)	< 0.001
Current smoker	143 (21)	29 (20)	0.91
Obesity ^d	136 (20)	40 (27)	0.04
History of reported stroke	58 (8)	17 (12)	0.20
History of reported vascular event other than stroke ^e	58 (8)	25 (17)	0.002
Clinical diagnosis			
No objective cognitive impairment	172 (24%)	24 (16%)	0.31 ^f
MCI	163 (23%)	44 (30%)	
Dementia	369 (52%)	79 (54%)	
Vascular dementia	25 (7%)	11 (14%)	
Alzheimer's disease	256 (69%)	48 (61%)	
Other neurodegenerative etiology ^g	68 (18%)	11 (14%)	
Unknown etiology ^h	20 (5%)	9 (11%)	

VCI; vascular cognitive impairment; T2DM, type 2 diabetes mellitus; MCI, mild cognitive impairment

Data are presented as n (%), means \pm SD, or median (10th percentile – 90th percentile).

^a Level 1-7

^b Based on a self-reported medical history, use of antihypertensive drugs, or a newly diagnosed hypertension defined as a systolic pressure > 140 mm Hg or a diastolic pressure > 90 mm Hg.

^c Based on medical history or medication use.

^d Defined as a baseline body mass index ≥ 30 , calculated as weight in kilograms divided by height in meters squared.

^e Defined as a myocardial infarction, surgery or endovascular treatment for coronary artery disease, any arterial occlusion or surgical intervention of a peripheral artery (such as an abdominal or leg artery) or carotid artery intervention (stenting or endarterectomy).

^f A Mann-Whitney U test for non-parametric data was performed.

^g Frontotemporal dementia, Lewy body dementia and others such as Primary Progressive Aphasia, Cortical Basal Syndrome, and Progressive Supranuclear Palsy

^h Dementia of unknown origin; further examination needed to state diagnosis

Table 2. Brain MRI features at baseline

	Possible VCI without T2DM n = 672	Possible VCI with T2DM n = 142	Standardized mean difference in z-scores between patients with VCI with and without T2DM ^a	<i>p</i> -value
Brain atrophy^b				
Total brain volume (% of ICV)	71.0 ± 4.1	70.0 ± 4.1	-0.21 (-0.36 ; -0.07)	0.005
Total gray matter volume (% of ICV)	38.5 ± 3.1	37.6 ± 3.0	-0.13 (-0.28 ; 0.11)	0.07
Total white matter volume (% of ICV)	32.5 ± 2.2	32.0 ± 2.3	-0.22 (-0.39 ; -0.06)	0.008
Cerebrovascular lesions^c				
WMH volume (ml)	6 (2-17)	7 (3-15)	0.03 (-0.13 ; 0.19) ^d	0.71
	Possible VCI without T2DM	Possible VCI with T2DM	OR (95% CI)^e	
Non-lacunar (sub)cortical infarcts	72 (10)	20 (14)	1.29 (0.75 ; 2.21)	
Lacunar infarcts	140 (20)	42 (29)	1.52 (1.01 ; 2.29)	
Intracerebral hemorrhages	12 (2)	3 (2)	1.20 (0.33 ; 4.33)	
Any microbleeds	320 (46)	44 (31)	0.49 (0.33 ; 0.73)	
Strictly lobar microbleeds	209 (30)	26 (18)	0.50 (0.31 ; 0.78)	
Strictly deep microbleeds	42 (6)	7 (5)	0.81 (0.35 ; 1.84)	
Mixed microbleeds	69 (10)	10 (7)	0.66 (0.33 ; 1.32)	

VCI; vascular cognitive impairment; T2DM, type 2 diabetes mellitus; ICV, intracranial volume; WMH, white matter hyperintensities; OR, odds ratio; CI, confidence interval

^a Data adjusted for age, gender, and scanner type.

^b Data presented as mean \pm SD.

^c Data presented as median (range) or n (%).

^d WMH volumes were log-transformed and then standardized into z-scores. The analyses were adjusted for age, gender, and scanner type.

^e Data adjusted for age and gender.

Table 3. Cerebrospinal fluid features at baseline

	Possible VCI without T2DM n = 454	Possible VCI with T2DM n = 79	p-value
CSF data			
A β 42 (pg/mL)	614 (460-929)	697 (479-928)	0.25
Tau, (pg/mL)	361 (255-631)	396 (231-650)	0.74
Phosphorylated Tau (pg/mL)	56 (39-82)	59 (39-82)	0.93
Tau / A β 42 ratio (pg/mL)	0.64 (0.28-1.29)	0.50 (0.28-1.03)	0.47

VCI; vascular cognitive impairment; T2DM, type 2 diabetes mellitus; CSF, cerebrospinal fluid; A β , amyloid-beta; AD, Alzheimer's disease

Data presented as median (range)

Table 4. Cognitive assessment at baseline

	Possible VCI without T2DM n = 704	Possible VCI with T2DM n = 147	<i>p</i> -value	
Measures of global cognitive status^a				
Mini-mental state examination	25 (22-28)	26 (21-28)	0.88	
Clinical dementia rating	0.5 (0.5-1)	0.5 (0.5-1)	0.92	
	Possible VCI without T2DM domain z-scores ^b	Possible VCI with T2DM domain z-scores ^b	Mean difference in domain z-scores between patients with VCI with and without T2DM ^{c,d}	<i>p</i> -value
Cognitive domains				
Working memory	0.04 ± 0.88	-0.20 ± 0.88	-0.17 (-0.32 ; -0.01)	0.03
Memory	-0.04 ± 0.88	-0.02 ± 0.92	0.10 (-0.05 ; 0.26)	0.18
Attention and executive functioning	-0.09 ± 0.76	-0.17 ± 0.81	-0.02 (-0.16 ; 0.11)	0.73
Information processing speed	-0.09 ± 1.05	-0.10 ± 0.94	0.08 (-0.11 ; 0.26)	0.42
Perception and construction	-0.04 ± 0.95	0.06 ± 0.74	0.12 (-0.06 ; 0.30)	0.20

VCI; vascular cognitive impairment; T2DM, type 2 diabetes mellitus

^a Data presented as median (range).

^b Unadjusted data presented as mean ± SD.

^c Comparison of cognitive performance between patients with and without T2DM (without T2DM = reference).

^d Data adjusted for age, gender and level of education.

Table 5. Follow-up measurements

	Available follow-up data^a	Possible VCI without T2DM	Possible VCI with T2DM	HR (95 % CI)^c
Follow-up data^b				
Change in CDR \geq 1	No T2DM: n=477 T2DM: n=90	69 (15%)	13 (14%)	0.88 (0.48 ; 1.61)
Institutionalization due to cognitive dysfunction	No T2DM: n=529 T2DM: n=107	34 (6%)	3 (3%)	0.45 (0.14 ; 1.46)
Occurrence of non-fatal stroke ^d	No T2DM: n=554 T2DM: n=110	11 (2%)	6 (6%)	2.06 (0.68 ; 6.25)
Death	No T2DM: n=565 T2DM: n=115	56 (10%)	8 (7%)	0.60 (0.28 ; 1.27)

VCI; vascular cognitive impairment; T2DM, type 2 diabetes mellitus; HR, hazard ratio; CI, confidence interval; CDR, clinical dementia rating

^a Follow-up data was collected in 565/580 (97.4%) patients without T2DM and in 115/118 (97.5%) of the patients with T2DM

^b Data presented as n (%)

^c Data adjusted for age, gender and clinical diagnosis. For stroke, the model was additionally adjusted for vascular risk factor count (one point for each risk factor: hypertension, hypercholesterolemia, current smoking, obesity, history of stroke and history of reported vascular event other than stroke)

^d Defined as ischemic stroke and intracerebral hemorrhage

Supplemental table 1. Analyses stratified for cerebrospinal fluid Alzheimer profile^a

A. Between group analyses in patients with a CSF non-Alzheimer profile				
	Possible VCI without T2DM n = 199	Possible VCI with T2DM n = 41	Standardized mean difference in z-scores between patients with VCI with and without T2DM^b	p-value
Brain atrophy^c				
Total brain volume (% of ICV)	72.8 ± 3.8	71.7 ± 4.0	-0.36 (-0.65 ; -0.08)	0.01
Total gray matter volume (% of ICV)	40.0 ± 2.8	39.3 ± 2.7	-0.31 (-0.58 ; -0.05)	0.02
Total white matter volume (% of ICV)	32.7 ± 2.3	32.4 ± 2.2	-0.24 (-0.56 ; 0.09)	0.15
Cerebrovascular lesions^d				
			OR (95% CI)^e	
Lacunar infarcts	40 (20)	12 (30)	1.74 (0.81 ; 3.76)	
Any microbleeds	89 (45)	11 (27)	0.45 (0.21 ; 0.95)	
Strictly lower microbleeds	54 (27)	4 (10)	0.29 (0.10 ; 0.85)	
Strictly deep microbleeds	11 (6)	4 (10)	1.81 (0.54 ; 6.01)	
Mixed microbleeds	24 (12)	3 (7)	0.57 (0.16 ; 1.99)	
B. Between group analyses in patients with a CSF Alzheimer profile				
	Possible VCI without T2DM n = 255	Possible VCI with T2DM n = 38	Standardized mean difference in z-scores between patients with VCI with and without T2DM^b	p-value
Brain atrophy^c				
Total brain	70.7 ± 3.5	69.0 ± 3.9	-0.29 (-0.61 ; 0.03)	0.07

volume (% of ICV)				
Total gray matter volume (% of ICV)	38.3 ± 2.7	37.2 ± 2.8	-0.20 (-0.50 ; 0.10)	0.19
Total white matter volume (% of ICV)	32.4 ± 2.1	31.8 ± 2.3	-0.25 (-0.57 ; 0.07)	0.12
Cerebrovascular lesions^d				
			OR (95% CI)^e	
Lacunar infarcts	35 (14)	6 (16)	0.96 (0.37 ; 2.25)	
Any microbleeds	119 (47)	13 (34)	0.49 (0.23 ; 1.03)	
Strictly lower microbleeds	85 (34)	10 (26)	0.65 (0.30 ; 1.42)	
Strictly deep microbleeds	10 (4)	1 (3)	0.58 (0.07 ; 4.76)	
Mixed microbleeds	24 (10)	2 (5)	0.44 (0.10 ; 1.98)	

CSF, cerebrospinal fluid; VCI, vascular cognitive impairment; T2DM, type 2 diabetes mellitus; ICV, intracranial volume; OR, odds ratio; CI, confidence interval

^a CSF Alzheimer profile was defined as a CSF ratio tau/Aβ > 0.52 [39]

^b Data adjusted for age, gender, and scanner type

^c Data presented as mean ± SD

^d Data presented as n (%)

^e Data adjusted for age and gender