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Cerebral haemodynamics, cognition and brain volumes in patients with type 2 diabetes

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ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) is associated with cognitive impairment and brain abnormalities on MRI. The underlying mechanisms are unclear. We examined the relationship between cerebral haemodynamics (cerebral blood flow (CBF) and cerebrovascular reactivity (CVR)) and cognitive performance and brain volumes in patients with T2DM, at baseline and after four years.
Methods: 114 patients with T2DM, aged 56–80 years, underwent a detailed cognitive assessment and MRI scan. In 68 patients the evaluation was repeated after four years. CBF (two-dimensional flow-encoded phase-contrast MRI) and CVR (carbogen breathing response middle cerebral artery; transcranial Doppler) were measured at baseline. Cognitive performance was expressed as composite z-score and regression based index score. Brain volumes were measured on MRI by automated segmentation. The relationship of haemodynamics with cognition and brain volumes was examined with linear regression analyses adjusted for age, sex and IQ.
Results: Mean CVR was 51.8% ± 18.0% and mean rCBF 53.3 ± 11.3 ml/min/100 ml brain tissue. CBF was associated with baseline cognitive performance (standardized regression coefficient β (95% CI): 0.17 (0.00; 0.32) and total brain volume (0.23 (0.05; 0.41)). No correlation was found between CVR and baseline cognitive performance. Neither CBF nor CVR predicted change in cognition (CBF 0.11 (−0.21; 0.44); CVR 0.07 (−0.21; 0.36)) or total brain volume (CBF 0.09 (−0.22; 0.39); CVR 0.13 (−0.13; 0.40)) over four years.
Conclusions: CBF was associated with impaired cognition and total brain volume in cross-sectional analyses, but did not predict changes in cognition or brain volumes over time. Apparently, alterations in cerebral haemodynamics play no major etiological role in cognitive decline or change in brain volumes in non-demented individuals with T2DM.

1. Introduction

Type 2 diabetes mellitus (T2DM) is associated with cognitive dysfunction and an increased risk of dementia (Biessels, Deary, & Ryan, 2008). On brain MRI this is accompanied by modest atrophy and a higher white matter hyperintensity (WMH) load (Biessels et al., 2008; Manschot et al., 2007). We have previously reported that T2DM-related cognitive changes and cerebral atrophy develop slowly over the course of years, at an average rate that is still within the range of that of normal aging (de Bresser et al., 2010; van den Berg et al., 2010). Nevertheless, people with T2DM are overrepresented among those older individuals with accelerated cognitive decline (Reijmer, van den Berg, Ruis, Kappelle, & Biessels, 2010). There is still uncertainty on the etiology, but vascular disease is likely to play a role (Biessels et al., 2008). Indeed clinically manifest atherosclerosis is associated with cognitive impairment in people with T2DM (Bruce et al., 2008; Manschot et al., 2007). Moreover, alterations in cerebral haemodynamics might affect the brain, also in people without clinically manifest cerebrovascular disease. In a cross-sectional study, we observed that cerebral blood flow (CBF) was related to cognition, but there were no differences in CBF between controls and patients with T2DM (Tiehuis et al., 2008). In the present longitudinal study, we further examined the relationship between cerebral haemodynamics, as reflected by CBF and cerebrovascular reactivity (CVR), and cognitive functioning and brain volumes on MRI in patients with T2DM. This relationship was assessed both at baseline and after four years of follow-up.

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2. Methods

2.1. Participants

Participants were included in the Utrecht Diabetic Encephalopathy Study (UDES), a study on determinants of impaired cognition in patients with T2DM. At baseline (2002–2004), 122 patients with T2DM were recruited through their general practitioners. Furthermore, 56 age, sex and IQ matched controls were recruited among spouses and acquaintances of the patients (Manschot et al., 2007). At inclusion, all participants were between 56 and 80 years of age, functionally independent and Dutch speaking. Diabetes duration had to be at least one year. Exclusion criteria were a psychiatric or neurological disorder (unrelated to diabetes) that could influence cognitive functioning, a history of alcohol or substance abuse or dementia, and a fasting blood glucose $\geq$7.0 mmol/l for control participants. Participants with a history of transient ischaemic attacks or non-disabling stroke could be included.

At follow-up four years later (2006–2008), seven participants had died, four could not be contacted and 59 were not willing or able to participate. Reasons for not participating were: lack of interest ($n=28$); comorbidity ($n=22$; three reported dementia (two patients, one control); and other reasons ($n=9$). One patient with T2DM was excluded because of severe comorbid disease and one control participant fulfilled the criteria for T2DM and was therefore excluded from the control group. Hence, 106 subjects (68 patients and 38 controls) participated in the follow up examination (van den Berg et al., 2010). Baseline characteristics (demographics, cognitive functioning and brain volumes) in participants ($n=106$) and non-participants ($n=70$) at follow-up were similar (for details see (de Bresser et al., 2010) and (van den Berg et al., 2010)). From 43 of the 70 non-participants at follow-up who were alive and could be contacted a cognitive screening test was obtained by telephone (the Dutch version of the Telephone Interview for Cognitive Status (Kempen, Meier, Bouwens, van Deursen, & Verhey, 2007)). Mean performance of non-participants (mean score 35.4$\pm$5.2) was similar to the participants (36.5$\pm$4.6) at follow-up (van den Berg et al., 2010).

The present study only concerns those patients with T2DM from whom baseline CBF or CVR data were available ($n=114$). Data from the control group served as reference values.

The study was approved by the medical ethics committee of the University Medical Center Utrecht and all participants signed an informed consent form.

2.2. Haemodynamics

Both CBF and CVR were measured at baseline. For CBF measurements a 2D-Phase Contrast MR section was positioned at the level of the skull base to measure volume flow in the internal carotid arteries and basilar artery (TR 16 ms; TE 9 ms; flip angle 7.5°; voxel size 0.98x0.98x5.00 mm^3, averages 8; velocity sensitivity 100 cm/s) (Spilt et al., 2002). Total CBF was defined as the sum of flow in both internal carotid arteries and basilar artery. Because total CBF is related to brain size, we calculated relative total CBF (rCBF), expressed as ml/min per 100 ml brain tissue (Appelman et al., 2008).

CVR was assessed with transcranial Doppler (TCD) as described previously.(van Oers, Manschot, van Huffelen, Kappelle, & Biessels, 2006) CVR in response to a rise in CO_2 was determined as the relative change in blood flow velocity in both middle cerebral arteries after 1.5 min of carbogen inhalation. Left and right CVRs were averaged.

2.3. Neuropsychological examination

Neuropsychological examination consisted of 11 tasks, covering 5 cognitive domains (i.e. attention and executive functions, information processing speed, memory, abstract reasoning, and visuoconstruction) (van den Berg et al., 2010). A division in these cognitive domains was made a priori, according to standard neuropsychological practise and cognitive theory (Lezak, Howieson, & Loring, 2004). For the present study we used a composite z-score of tests addressing the first three domains, because these are particularly sensitive to the effects of T2DM and vascular disease (van den Berg et al., 2010). These domains were assessed with the following tests: 1) *attention and executive functions*: Trail-making Test (Part B), Stroop Color–Word Test (Part 3), Brixton Spatial Anticipation Test, a letter fluency test using the 'N' and 'A' and category fluency (animal naming); 2) *information processing speed*: Trail-making Test (Part A), Stroop Color–Word Test (Part 1 and 2), subtest Digit Symbol of the Wechsler Adult Intelligence Scale 3rd edition (WAIS-3); 3) *memory:* forward and backward digit span of the WAIS-3, Corsi Block-tapping Task, Rey Auditory Verbal Learning Test, Location Learning Test, delayed trial of the modified Taylor Complex Figure (Manschot et al., 2006).

Raw test scores at baseline and follow-up were standardized into z-scores per test, by using the pooled mean of baseline scores of the whole group. The z-scores of each domain were calculated by averaging the test scores comprising that domain; these z-scores were averaged to obtain one composite z-score. In secondary analyses, each cognitive domain was addressed separately.

Change in cognitive performance over time was expressed as a regression based index (RBI) score, using the control group as a reference, taking age, sex and estimated IQ into account (Temkin, Heaton, Grant, & Dikmen, 1999). A negative RBI score reflects greater cognitive decline than expected from a control participant with a similar demographic profile and cognitive performance at baseline. The RBI score is preferred over using change in z-scores over time, because it reduces confounding by learning effects and regression to the mean (Temkin et al., 1999). Mean change in performance across the three domains was expressed as a composite RBI score. In secondary analyses, the RBI score of each cognitive domain was addressed separately. Pre-morbid IQ was assessed by the Dutch version of the National Adult Reading test (Manschot et al., 2006).

2.4. Brain volume measurements

MRI scans were acquired on a 1.5 T Philips MR scanner using a standardized protocol (38 contiguous slices, voxel size: 0.9 $\times$ 0.9 $\times$ 4.0 mm^3) and consisted of an axial T1 (repetition time in ms (TR)/ echo time in ms (TE): 234/2), T2 (TR/TE: 2200/100), proton density (TR/TE: 2200/11), inversion recovery (IR) (TR/TE/inversion time in ms (TI): 2919/22/410) and fluid attenuated inversion recovery (FLAIR) (TR/TE/TI: 6000/100/2000) (de Bresser et al., 2010).

After registration of all sequences to the FLAIR image and an inhomogeneity correction, a baseline brain mask was created by a k-means clustering algorithm with 8 clusters for every patient using all sequences. The baseline FLAIR image was rigidly registered to the follow-up FLAIR image within patients. The resulting transform parameters were applied to the baseline mask to create follow-up masks. The uncorrected FLAIR images were multiplied voxelwise times the mask images followed by an inhomogeneity correction. The IR and FLAIR images were used for a k-nearest neighbour-based probabilistic segmentation algorithm that measured total brain, lateral ventricular and WMH volumes on both time points (Anbeek, Vincken, van Bochove, van Osch, & van der Grond, 2005; de Bresser et al., 2010). Volumes were expressed as percentage of total intracranial volume to correct for between subject differences in head size. Volume changes between baseline and follow-up scans were calculated within participants.