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The resting perfusion pattern associates with functional decline in type 2 diabetes

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ABSTRACT

We investigated the relationships between cerebral blood flow (CBF), cognitive, and mobility decline in type 2 diabetes mellitus (T2DM) over a 2-year period. Seventy-three participants (41 T2DM and 32 controls) were evaluated using volumetric CBF with arterial spin labeling perfusion magnetic resonance imaging at baseline and at the 2-year follow-up. Regions with significant CBF differences between T2DM participants and controls at baseline were detected using voxel-wise analysis. Correlation analysis was performed to investigate the association between regional CBF and cognitive or mobility performance over the 2-year span. Compared to controls, participants with T2DM had decreased CBF in the resting-state default mode, visual, and cerebellum networks. Greater decrease in longitudinal CBF values at these regions over a 2-year span was associated with worse gait, memory and executive functions, and higher baseline insulin resistance and worse baseline cognitive performance. In T2DM, impairment of resting regional perfusion is closely related to worse cognitive and mobility performance. Insulin resistance may further contribute to regional perfusion deficit in T2DM.

1. Introduction

Type 2 diabetes mellitus (T2DM) is associated with altered cerebral vasoreactivity (Chung et al., 2015; Last et al., 2007; Novak et al., 2011), cerebral atrophy (Franke et al., 2013; Novak et al., 2011; van Elderen et al., 2010), cognitive impairment (Chung et al., 2015; Wong et al., 2014), and functional decline (Chung et al., 2015). T2DM-related endothelial dysfunction secondary to a chronic state of hyperglycemia, inflammation, and insulin resistance (Brownlee, 2005; Kim et al., 2006; Starr et al., 2003) has been associated with alterations in the blood-brain barrier (Mogi and Horiuchi, 2011; Starr et al., 2003), neuronal damage (Umegaki, 2014), and arterial stiffness (Zhou et al., 2014), thus negatively affecting cerebral metabolism and cerebral blood flow (CBF) (Roberts et al., 2014).

Arterial spin labeling (ASL) is a functional magnetic resonance imaging (MRI) technique capable of quantifying regional CBF, among the several neuroimaging techniques. ASL is a noninvasive technique that magnetically labels the water in the blood vessels (Detre et al., 1992; Williams et al., 1992). ASL has been recently used to evaluate CBF in T2DM patients; however, the reports are contradictory. Some studies found that resting CBF is similar between T2DM patients and controls (Novak et al., 2011; Rusinek et al., 2015; Tiehuis et al., 2008), whereas others reported reduced CBF in patients with T2DM (Last et al., 2007; Nagamachi et al., 1994; Novak et al., 2006; Xia et al., 2015). The cross-sectional design of these studies, however, did not allow to investigate the association between T2DM and changes in brain perfusion or structure and cognitive or mobility functions over time. Pseudo-continuous ASL (PCASL), with great labeling efficiency (Dai et al., 2008; Wu et al., 2007) and recommended for clinical applications (Alsop et al., 2014), was adopted for the measurement of whole-brain CBF maps. Moreover, PCASL has been shown to have excellent test-retest reliability for both young and elderly subjects (Xu et al., 2010) and hence, can serve as a useful technique even for longitudinal studies.

In the present study, we used ASL CBF imaging to determine the effect of T2DM on CBF at baseline and the relationship between CBF and functional outcomes (cognition and gait) at baseline and after the 2-year follow-up. We hypothesized that (1) T2DM is associated with altered resting perfusion patterns and (2) impaired CBF is associated with alterations in cognitive function and gait.

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2. Methods

The current work is an analysis from our prospective study on cerebromicrovascular disease in elderly with T2DM. The study was conducted at the Syncope and Falls in the Elderly laboratory, Clinical Research Center, and MRI Center of Beth Israel Deaconess Medical Center (BIDMC) between August 2009 and July 2013. Participants were recruited from the greater Boston area using community advertisement. They were assigned to either the T2DM group or the nondiabetic control group.

2.1. Participants

A hundred thirty-one participants, 50–85 years, were enrolled in this 2-year study. All participants signed written informed consent approved by the Committee on Clinical Investigations of BIDMC. Of 131 participants, 73 participants, 41 T2DM and 32 nondiabetic controls were eligible and included in baseline analysis, according to the inclusion criteria of the study. Of those, 42 participants, 19 T2DM and 23 nondiabetic controls, who completed the 2-year follow-up were included in the follow-up analyses.

Inclusion criteria for the T2DM group were men and postmenopausal women aged 50–85 years, diagnosed with T2DM, and treated with oral agents and/or insulin for more than 5 years, with hypertension (blood pressure [BP] $\geq$140/90 mm Hg and/or treated for hypertension) or without hypertension (BP $<$140/90 mm Hg and no medical history of hypertension). Inclusion criteria for the control group were men and postmenopausal women with normal fasting blood glucose and glycated hemoglobin A1c (HbA1c) matched with the diabetes group by age $\pm$5 years, gender, and presence of hypertension. Exclusion criteria for both groups were type I diabetes mellitus, any unstable or acute medical condition, myocardial infarction or major surgery within 6 months, history of a major stroke, carotid stenosis $>$50% by medical history, Doppler ultrasound or by magnetic resonance angiography, hemodynamically significant vascular disease, arrhythmias, liver or renal failure or transplant, severe hypertension (systolic BP $>$200 and/or diastolic BP $>$110 mm Hg or subjects taking 3 or more antihypertensive medications), seizure disorders, malignant tumors, current recreational drug or alcohol abuse, active smoking, morbid obesity (body mass index $>$40), dementia (by history), or Mini–Mental State Examination (MMSE) score ($\leq$24). MRI exclusion criteria included incompatible metal implants, pacemakers, and claustrophobia.

Reasons for exclusion from baseline analyses included withdrew consent (n = 11), lost to follow-up (n = 10), smoking (n = 1), arrhythmias (n = 4), cancer (n = 2), MMSE score $\leq$24 (n = 3), stroke/transient ischemic attack (n = 2), heart failure (n = 1), MRI exclusion criteria (n = 1), renal failure (n = 1), T2DM $<$5 years (n = 3), poor glycemic and/or hypertension control (n = 7), undetermined neurologic disorder (n = 2), adverse event (n = 1), and incomplete data sets (n = 9). Reasons for exclusion after 2-year follow-up period included withdrew consent (n = 5), lost to follow-up (n = 25), and new diagnosis of dementia (n = 1).

2.2. Experimental protocol

Screening visit included medical history review, completion of autonomic function questionnaires, physical and neurological evaluation, electrocardiogram, and fasting laboratory measurements.

After enrollment, participants came for an inpatient 2-day baseline visit at the BIDMC Clinical Research Center. On day 1, participants had vital signs and anthropometric measurements taken, including height and weight, and a cognitive assessment battery testing. On day 2, a fasting blood draw was obtained, a cognitive assessment battery testing and walking test were completed, and MRI scans were performed. The same protocol was completed at the 2-year follow-up visit.

2.3. Cognitive assessment

The cognitive assessment battery that was used is a standard battery of cognitive tests that evaluate specific domains of cognition and daily living activities. It consists of measures of learning and memory (Hopkins Verbal Learning Test-Revised [HVLT-R] [Shapiro et al., 1999] and MMSE [Folstein et al., 1975]), measures of executive function (verbal fluency [VF] [Benton and Hamsher, 1989], Trail Making [Pugh et al., 2003], clock drawing [CD] [Grande et al., 2005]), and measures of attention (Digit Span [DS] [Wechsler, 1987]). HVLT-R includes a total recall (HVLT: total recall, total number of list items learned across trials), delayed recall (HVLT: delayed recall, total number of list items recalled after the delay), retention (HVLT: retention, percentage of items from HVLT: total recall that are subsequently recalled on HVLT: delayed recall), and Recognition Discrimination Index (HVLT: RDI, number of list items correctly identified among non-list items). MMSE assesses cognitive impairment. VF assesses phonemic and semantic fluency tasks. The phonemic fluency task requires the participant to generate as many words as possible beginning with a given letter (e.g., "S") for 1 minute. The semantic fluency task requires the participant to generate items of a given semantic category (e.g., animals) for 1 minute. Dependent variables for the fluency measures include the number of items generated for all 3 phonemic trials (e.g., F, A, S; VF FAS total) and the number of items generated for the semantic task (e.g., animals; VF: animals). A composite executive score was calculated from all 3 measures of executive functions (VF, Trail Making , and CD). DS assesses immediate memory/attention.

2.4. Gait assessment

Participants completed two 6-minute walking tests on a 75-m course of an 80 $\times$ 4 m indoor hallway. For the first test, participants were instructed to walk for 6 minutes at their usual and comfortable pace (normal walk), whereas for the second dual-task (DT) test, they were asked to perform the same while counting backwards. The time taken to complete each 75-m length and the total distance walked were recorded. No assistive devices were used for ambulation. The rate of perceived exertion (RPE) before and after each walking test was self-rated on a 10-point scale. Gait speed was calculated by dividing distance (m) by time (second).

2.5. Blood samples analysis

Serum/plasma glucose, insulin panels, and hematocrit were measured at Lab Corp (Laboratory Corporation of America Holdings, Burlington, NC, USA). The homeostatic model assessment of insulin resistance (HOMA-IR) was calculated as the product of fasting glucose (mg/dL) times insulin levels (mU/L) divided by 405 (Matthews et al., 1985).

2.6. MRI acquisition

All participants (73 participants at baseline and 42 participants at the 2-year follow-up) were scanned at the same 3-Tesla, GE HDxt scanner using a receive-only 8-channel head array coil and a body transmit coil. ASL images were obtained using the PCASL (Dai et al., 2008) with a 1.5 seconds labeling and 1.5 seconds post-labeling delay. Additional reference images for M_0 values were obtained for absolute perfusion quantification. All ASL and reference images