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Impaired cerebrovascular responsiveness and cognitive performance in adults with type 2 diabetes

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ABSTRACT

Aim: Cognitive deficits in type 2 diabetes mellitus (T2DM) may be partly attributable to stiffness in cerebral arteries and impaired vasodilator function, limiting the ability to increase blood flow in brain regions to meet cognitive demands. We undertook a comparison of cerebrovascular responsiveness (CVR) and cognitive performance in adults with and without T2DM.
Methods: Older adults with (50) and without (Herath, Cherbuin, Eramudugolla, & Anstey, 2016) T2DM underwent transcranial Doppler ultrasound measurements of basal cerebral mean blood flow velocity (MBFV) and pulsatility index (PI), a measure of arterial stiffness, in the middle cerebral arteries (MCA). A battery of tasks assessing domains of working memory, executive function and information processing/motor speed was then administered while MBFV was recorded. CVR to cognitive tasks was calculated as a percentage increase in MBFV from the basal level.
Results: There was no difference in basal MBFV between groups. However, PI was 14% higher in the T2DM group ($P < 0.05$), who performed poorer across all cognitive domains assessed and displayed poorer CVR in three tasks. Cognitive performance was inversely related to the PI/MBFV ratio, an indicator of intracranial stenosis.
Discussion: Impaired cerebral perfusion during mental tasks is accompanied by poor cognitive performance and stiffness in the cerebral vessels.

1. Introduction

The presence of type 2 diabetes (T2DM) may predispose an individual to accelerated cognitive decline later in life (Biessels, Staekenborg, Brunner, Brayne, & Scheltens, 2006). While advances in pharmacotherapy have been beneficial in preventing and treating classic micro- and macrovascular complications of the systemic circulation associated with T2DM, prevention of cognitive dysfunction in this at-risk population remains unresolved. Wong, Scholey, and Howe (2014) recently reviewed 9 clinical trials that compared performance in neuropsychological tests in a range of cognitive domains between adults with and without T2DM. They found that those with T2DM performed poorer in the specific domains of executive function, working memory, psychomotor and attentional functions, based on clinically significant effect sizes >0.50, which is indicative of impaired daily functioning in these tasks (Norman, Sloan, & Wyrwich, 2003). Competence in these cognitive domains is important for disease management and independent living in old age, as daily tasks may include measuring blood sugar, taking medications and remembering or planning medical appointments (Biessels, Deary, & Ryan, 2008).

The precise mechanisms underlying T2DM-related cognitive dysfunction or progression to dementia are yet to be elucidated; however, several mechanisms have been proposed. They include disruptions of the blood–brain barrier resulting in excessive amyloid-β plaque accumulation seen in Alzheimer's disease pathology (Biessels et al., 2006; Yan, Chen, Fu, Chen, et al., 1996), neuronal damage caused by diabetes-induced inflammation and chronic hypoperfusion at the neurovascular coupling unit (Mogi & Horiuchi, 2011; Umegaki, 2014). A common feature of these proposed mechanisms is disruption/damage of endothelial structure function caused by prolonged hyperglycemia and insulin resistance. Briefly, high blood glucose has both direct and indirect effects in the brain. It leads to the formation of advanced glycation end products (AGEs) which have potentially toxic effects on both endothelium and neurons (Goldin, Beckman, Schmidt, & Creager, 2006). Damage to the endothelium triggers an influx of inflammatory cytokines and proliferation of smooth muscle cells. The net result is narrowing of the lumen and increased arterial stiffness (Mogi & Horiuchi, 2011; Zhou, Zhang, & Lu, 2014). AGEs can also cause over-activation of microglia in the CNS resulting in neuronal damage. Additionally, insulin resistance leads to the downregulation of important proteins in the brain that are responsible for clearing amyloid-β, secondary to increased permeability of the blood–brain barrier (Mogi & Horiuchi, 2011).

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Previous studies using transcranial Doppler (TCD) ultrasound to assess blood flow in the middle cerebral arteries (MCA) have shown that, in adults with T2DM, basal blood flow velocity is reduced and the pulsatility index (PI; a measurement of cerebral arterial stiffness) is elevated (Park et al., 2008). In the brain, dynamic regulation of oxygen and glucose to match the metabolic demands of active neurons is achieved through concerted signaling actions by neurons, glial cells and the endothelium. They form a neurovascular coupling unit to regulate local blood flow through endothelium-dependent nitric oxide (NO) mediated vasodilatation (Mogi & Horiuchi, 2011). NO-mediated vasodilatation in response to a hypercapnic stimulus has been shown to be impaired in T2DM (Novak et al., 2006a), resulting in increased stiffness of cerebral vessels and limiting blood flow on demand to specific brain regions. Correspondingly, there is evidence that basal PI is higher in Alzheimer's disease, vascular dementia or multi-infarct dementia population groups compared with healthy controls (Keage et al., 2012). It is consequently not surprising that those with T2DM are at higher risk of Alzheimer's disease, vascular dementia and mild cognitive impairment than non-T2DM adults (Cheng, Huang, Deng, & Wang, 2012) and exhibit impairments in specific cognitive domains (Wong et al., 2014).

The TCD technique can also be used to measure changes in cerebral blood flow velocity during mental activity to indirectly assess the integrity of the neurovascular coupling unit (Keage et al., 2012; Stroobant, Van Nooten, & Vingerhoets, 2004; Stroobant & Vingerhoets, 2000). We term this cerebrovascular responsiveness (CVR) to cognitive stimuli. This technique is applicable to a wide range of tests, such as those identified by Wong et al. (2014) for which alternative techniques such as fMRI are inapplicable. Early detection of cerebrovascular dysfunction in T2DM may provide a means of predicting cases at high risk of accelerated cognitive decline, yet no trials have examined CVR to cognitive task performance in this at-risk population.

In the current study, we used TCD to investigate whether impairments in the ability of the cerebral vasculature to supply blood in response to a battery of cognitive tests were associated with poorer cognition in T2DM compared with non-T2DM controls. Our aim was to provide novel insight into the relationship between CVR and cognition in T2DM. We hypothesized that T2DM participants would have higher basal PI, lower CVR and poorer performance to cognitive tasks.

2. Methods

A cross-sectional clinical evaluation was carried out at the University of Newcastle's Clinical Nutrition Research Centre in adults with T2DM and age- and gender-matched controls without T2DM. The study was approved by the University of Newcastle Human Research Ethics Committee and registered with the Australian New Zealand Clinical Trial Registry (ACTRN12613000457741). Written informed consent was provided by each participant before participation.

2.1. Study population

Men and post-menopausal women (self-report of >12 months since previous menses) aged 50 to 80 years were recruited from the Hunter Region New South Wales, Australia by media advertising and from the Hunter Medical Research Institute Research Volunteer Register. Inclusion in the T2DM group required a formal diagnosis by a medical practitioner, whereas inclusion in the non-T2DM group required fasting serum glucose ≤5.5 mM. To ensure an adequate range of disease severity, we aimed to recruit 50 participants with T2DM and compare them with 30 age and gender matched individuals without T2DM.

2.2. Initial screening

Initial contact was made by phone, email or post. Medical history including year of diagnosis, pre-existing medical conditions, use of medications, demographic information and lifestyle factors were obtained by administering a health and lifestyle questionnaire. Volunteers were excluded if they were unwilling to fast for 8 h, had suspected dementia, were receiving insulin therapy, were a smoker or on nicotine therapy, had a history of serious head injury, stroke, neurological conditions, cancer, were experiencing acute or terminal illness, could not read or speak English fluently, drank more than 4 standard alcoholic drinks per day, had established cardiovascular or liver disease, had severe depression or other mood disorder, were color blind, had no measurable TCD signal in left and right MCA, or had changed their diabetes medication in the three months prior to participation, or any other condition or circumstances, which in the opinion of the investigators, might confound the outcomes of the study.

Potential participants were referred to a commercial pathology collection center to provide an 8-h fasting blood sample to assess biomarkers of T2DM status, viz., serum glucose, insulin and glycated hemoglobin ($HbA1_c$) using routine analytical procedures. The latter was measured only in those with an initial diagnosis of T2DM. HOMA estimation of insulin resistance (HOMA-IR) was calculated as glucose x insulin/22.5 (Oxford Uo, 2015). Volunteers who met the desired entry criteria were then invited to attend the Hunter Medical Research Institute or the research clinic at the University of Newcastle after a 2-h fast (no food or beverage except water).

After measurement of, height, weight and waist circumference, four blood pressure readings were taken and an average of the final three was recorded for analysis. Blood pressure was assessed using an Omron M10IT Digital Automatic Upper Arm blood pressure monitor with a suitably sized cuff on the participant's non-dominant arm while seated after 10 min of quiet rest. Participants then completed the Mini Mental State Examination (MMSE). Those scoring >25/30 proceeded to TCD examination for recording of basal cerebral hemodynamics; a score of below 25 indicates suspected dementia (Folstein, Folstein, & McHugh, 1975).

2.3. Basal cerebral hemodynamics

Using a Doppler-Box™X system (Compumedics Germany GmbH), participants' left and right MCA were insonated from the temporal windows with 2-MHz probes. The left and right MCA were chosen for consistency with previous investigations of CVR in T2DM (Novak et al., 2006b), and for their ability to reflect changes of cerebral blood flow in a large proportion of the brain (Bishop, Powell, Rutt, & Browse, 1986). Once a suitable blood flow signal was obtained, participants were asked to sit quietly for 1 min with their eyes open while basal PI and MBFV (cm/s) in the left and right MCA were recorded. Basal cerebral hemodynamics (i.e., PI and MBFV) were determined by averaging the last 30 s of the 1 min recording. The PI/MBFV ratio (multiplied by 100 for ease of reporting) was also determined; it is a recognized index of cerebral microvascular disease (Wijnhoud, Koudstaal, & Dippel, 2011).

2.4. Cognitive performance and cerebrovascular responsiveness to a battery of neuropsychological tests

Participants then underwent a battery of neuropsychological tests which lasted for approximately an hour. The battery of tests consisted of 9 cognitive tasks in domains previously reported by Wong et al. (2014) to be compromised in T2DM and a motor speed task on their dominant hand. The order of tests administered was Digit Span Forward and Backward, Digit Symbol Coding, N-Back Task, Stroop Color-Word Task, Serial Subtraction 7 (SS7), Letter-Number Sequencing, Symbol-Digit Coding and Concept Shifting Task (see Table 1 for task description). Task performance was calculated as the percentage of correct scores out of the total possible responses on all tasks except for Concept Shifting Task. Overall performance was determined by a composite score (sum of Z-scores).

Prior each cognitive task, additional recordings for 30 s of quiet sitting with eyes open were made to establish pre-test MBFV before