

Name of Disorder
DEMENTIA

Essay Title
COGNITION, BRAIN VOLUME AND DIABETES

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The burden of diabetes and dementia

The current WHO report made for sobering reading [1]. The global adult prevalence of diabetes is estimated to be 10%. People with diabetes require at least two to three times the health-care resources compared to people who do not have diabetes, and diabetes care may account for up to 15% of national health care budgets [2]. Type 2 diabetes (T2DM) is one of Australia's fastest growing chronic diseases, with a prevalence that has doubled during the past 20 years: 2 million Australian cases are expected by 2025 [3].

Add to this an estimated 1300 new cases of dementia diagnosed each week in Australia. The prevalence of dementia is projected to increase more than four-fold in the next four decades, from 245,400 people in 2009 to 1.13 million people by 2050 [4]. Worldwide, current dementia prevalence of 35 million is predicted to double every 20 years: an expected 66 million in 2030, 115 million in 2050 [5]. We are dealing with major global health issues, a present and future epidemic that will fundamentally affect health care provision in all high income countries, and increasingly burden middle- and lower-income countries [1].

The association between diabetes and dementia

People older than 70 years with T2DM have at least twice the likelihood of developing late life cognitive impairment or dementia compared to those without it [6, 7]. Data from the Rotterdam study suggests that DM doubles the risk of AD [8], with a three-fold increase in the relative risk in patients who had both clinical AD and cerebrovascular disease. Results from the Honolulu Asian Aging Study show that a diagnosis of diabetes – based on a midlife assessment – increases the risk of both vascular cognitive impairment and AD [9]. Many factors may contribute to this strong association, including increased stroke incidence, white matter microstructural changes leading to greater white matter hyperintensity (WMH) load (leukoariosis), hyperinsulinaemia and metabolic syndrome, as well as the cross-association of mid-life obesity and T2DM.

The failure of HbA1c for predicting cognitive decline

Unfortunately, there is little evidence that treatment of T2DM is associated with reduced dementia risk [10-12]. A Cochrane review found no link between any particular treatment forms or glycaemic control targets in reducing the risk of dementia [13]. The ACCORD-

MIND investigators assessed the effects of intensive glucose monitoring on brain structure and function [10], but found no evidence that intensive treatment altered cognitive outcomes. However, the study was halted due to raised mortality from cardiovascular events in the intensive arm [14]. Further complicating the situation, subsequent follow-up of these patients found an association between poor cognitive function and the risk of severe hypoglycemic events in T2DM patients [15]. Christman et al. from the ARIC group found that a single baseline HbA1c value in diagnosed diabetic patients did not predict cognitive decline over a 6 year period [12].

Cardiovascular risk, hypertension and diabetes

Depending on the age of the cohort, up to 80% of patients with T2DM have associated hypertension [16, 17]. LVH is a known independent predictor of cardiovascular risk in patients with hypertension [18, 19]. Even in the absence of hypertension, patients with diabetes have increased risk for development of cardiac dysfunction and heart failure. This appears to be the case even after adjusting for coronary artery disease and hypertension [16, 20].

In a relatively healthy, population-based sample of hypertensive adults, T2DM was associated with higher LV mass, more concentric LV geometry, and lower myocardial function, *independent* of age, sex, body size, and arterial BP. structural and functional abnormalities in addition to, and independent of, atherosclerosis [17]. A high prevalence of previously unknown heart failure and left ventricular dysfunction has been reported in patients with T2DM [21, 22]. The cause of this increased heart failure risk is multifactorial. Hypertension and diabetes are risk factors that predispose to the ischemic small vessel disease underlying lacunar infarction. The cognitive outcome of lacunar infarction results from selective damage to frontal-subcortical circuits subserving processing speed and executive function – the same deficits that are often observed in T2DM [23].

Structural brain aging and cognition

Structural brain aging is a term used to encompass a variety of brain changes that occur in the aging brain, and are increased in patients with cognitive decline and dementia [24]. These markers include magnetic resonance imaging (MRI) findings such as lower total brain volume, specific declines in critical brain regions, including hippocampi, and increasing WMH load. All of these MRI findings are correlated with performance on neuropsychological tests, and are powerful predictors of dementia in both community and clinic populations [25, 26].

The association between diabetes and brain atrophy

It is surprising that longitudinal brain volume changes have not been thoroughly examined in diabetes, given the wealth of knowledge that exists in other conditions. The Framingham cohort demonstrated a strong association between midlife vascular risk factors and structural brain aging [27]. Midlife diabetes was associated with an increased rate of progression of vascular brain injury, global and hippocampal atrophy, and decline in executive function a decade later. Results from the PROSPER study suggested that elderly non-demented patients with T2DM had accelerated progression of brain atrophy compared to non-diabetic subjects: further evidence for the hypothesis that diabetes exerts deleterious effects on neuronal integrity [28]. Metabolic syndrome is a term used for a clustering of risk factors for T2DM and CVD. It is associated with cognitive dysfunction and brain imaging abnormalities, including ischaemic stroke, white matter alterations, and altered brain metabolism [29].

How does cardiac disease cause brain atrophy and cognitive decline?

In a systematic review of all forms of cardiac disease and cognitive impairment, researchers found a strong association with impairment across many cognitive domains, but particularly in tests of executive function [30]. There are many potential mechanisms for the development of cognitive impairment associated with heart disease. Heart failure with low EF can lead to chronic cerebral hypoperfusion. Heart failure is strongly associated with cognitive impairment [31-33], being an independent risk factor for AD and cerebrovascular disease [27], especially in association with reduced ejection fractions (EF). Dilated cardiomyopathies or segmental hypokinesia from myocardial ischaemia are associated with stroke. The presence of cardiovascular disease is strongly associated with cerebrovascular disease. Myocardial ischaemia is associated with the development of arrhythmias, especially atrial fibrillation: a strong risk factor for stroke.

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