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Diabetes, Sugar-Coated but Harmful to the Brain

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Introduction

The damaging effects of Type 2 Diabetes Mellitus (T2DM) on the kidney and the heart have been well characterized. T2DM has long been known to cause microvascular disease such as retinopathy, nephropathy and peripheral neuropathy [1] as well as macrovascular disease including coronary heart disease and stroke [2]. Up until some 15 years ago the brain was thought to be in a privileged position where it would preferentially receive all the nutrients it needed irrespective of what was occurring in the periphery. The brain abnormalities observed were written off as a consequence of the atherosclerosis that frequently accompanied T2DM, namely a “plumbing problem”. In recent years, significantly more interest has been dedicated to the effect of diabetes on the brain. When compared to healthy controls, individuals with type 1 diabetes (T1DM) have cognitive deficits which correlate with decreased white matter volume [3]. A meta-analysis of studies on T1DM and cognition found that the observed cognitive dysfunction was characterized by a slowing of mental speed and a diminished mental flexibility, whereas learning and memory were spared [4]. Many studies have similarly found that T2DM has a negative impact on cognition. When the cognitive functioning and brain imaging of individuals with T1DM were compared to individuals with T2DM, T1DM patients with more than 30 years of disease had a similar cognitive profile and better MRI ratings than age- and education-matched T2DM patients with only 7 years of disease [5]. Lobnig et al. found mild cerebral atrophy and impaired psychomotor speed in individuals with T1DM, but failed to demonstrate the hippocampal volume reductions seen in those with T2DM [6]. Moreover, in a large very recent study of brain integrity among children with T1DM, Tamara Hershey’s group failed to find differences using voxel-base-morphometry (VBM) between children with T1DM and controls. However she did find some associations between severity of illness and volume losses within the diabetic group [7]. Thus, the brain findings in type 2 diabetes differ from the findings in type 1 diabetes, which is not surprising since they are two diseases with different etiologic origins, physiology, and outcomes [8]. In this article we will focus on the effects of type 2 diabetes on the brain.

Type 2 Diabetes and the Brain

Type 2 Diabetes Mellitus has been associated with cognitive deficits, including psychomotor efficiency, learning and memory, intelligence, and executive functioning [9–11]. Prospective

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studies have found that women with diabetes had lower baseline cognitive scores than those without diabetes, and over time, they experienced an accelerated cognitive decline even after accounting for confounding factors such as hypertension, depression, stroke, smoking, and physical activity [12]. There appears to be an association between severity of T2DM and the degree of brain involvement. Diabetic insulin users, who needed more than oral agents to control their diabetes, had a higher risk of major cognitive decline [12]. The increased availability of imaging has allowed researchers to study the anatomical basis for loss of cognitive function in T2DM. Most of the literature to date has noted cortical and subcortical atrophy and increased white matter lesions coupled with impaired cognitive performance in T2DM, even after controlling for hypertension [13]. However, these studies have included elderly individuals mostly in poor diabetic control. Similarly, Akisaki et al found that impairments in psychomotor efficiency and memory were associated with white matter hyperintensities (WMH) and subcortical brain atrophy in elderly diabetic patients [10], but these investigators did not account for potential confounding variables such as vascular causes of WMH's.

We recently we investigated the early cognitive deficits and brain abnormalities in younger patients with well-controlled type 2 diabetes of less than ten years duration. We found specific deficits in hippocampal-based memory performance and selective MRI-based atrophy of the hippocampus relative to matched controls [14]. Furthermore, among these well-controlled individuals, hemoglobin A1c levels were inversely related to head-size adjusted hippocampal volumes [14], suggesting that severity of the illness may influence the degree of brain involvement. Thus, it appears that the hippocampus is particularly vulnerable even in early stages of type 2 diabetes, which may explain the memory deficits seen in type 2 diabetic individuals. Some studies of elderly subjects with type 2 diabetes have also found atrophy of the hippocampus and amygdala [15] and these associations were not due to vascular morbidity being more pronounced in persons with T2DM.

Diabetes and Dementia

The associations between T2DM and hippocampal atrophy, one of the clinical hallmarks of early Alzheimer's Disease (AD), have led some to hypothesize that T2DM is associated with a higher risk of dementia. In epidemiological population studies, there is an increase in the risk for dementia among individuals with T2DM [16]. However, epidemiological studies have to be interpreted carefully. Two epidemiological studies had reported that estrogen hormone replacement therapy [17] or use of nonsteroidal anti-inflammatory [18] may protect against dementia, whereas no such effects were found in prospective treatment studies [19;20]. Although in experimental rat models, the spontaneous onset of T2DM is associated with beta-amyloid and phospho-tau accumulation as well as neurite degeneration and neuronal loss [21], we have to bear in mind that the physiology of the rodent is very different than that of the human. There has been great progress in "curing" the pathological expressions of Alzheimer's disease in rodent models of the disease, but this has not really netted any major advance for the treatment of the human disease. Biessels et al recently conducted a systematic review of articles linking dementia and type 2 diabetes. He found that the incidence of "any dementia", including vascular dementia and AD was higher in individuals with diabetes than among those without diabetes. However, he reported that detailed data on modulating and mediating effects of glycaemic control, microvascular complications and comorbidity were largely absent in most reports [22]. Although it is intriguing to consider an etiological link between T2DM and Alzheimer's disease, there is as if yet no sound empirical data supporting such a link. More convincingly arguing against a link, autopsy neuropathology studies, which are the gold standard for Alzheimer's disease diagnoses, have failed to find an association between diabetes and Alzheimer's disease. A study of 233 older Catholic clergy in the Religious Orders Study found that diabetes was related to cerebral infarction, but was not

related to global AD pathology score, or to specific measures of neuritic plaques, diffuse plaques or tangles, or to amyloid burden [23]. There are only three other autopsy studies, two of which found no difference in the amount of AD pathology in patients with diabetes [24; 25] and a third study which found that persons with diabetes actually had fewer neuritic plaques and neurofibrillary tangles compared to persons without diabetes [26]. Therefore, to date a much stronger case needs to be made to show a possible etiological link between type 2 diabetes and Alzheimer's disease. We propose that perhaps the reported association in the population studies may actually be due to diabetes reducing brain reserve. The impact of diabetes on the brain may allow a preexisting subclinical Alzheimer's disease to be unmasked earlier in diabetics and thus allow for a diagnosis to be made. This would be akin to lower education, with the resulting lower brain reserve, being a risk factor for AD.

Comorbidities

Type 2 Diabetes often coexists with hypertension and dyslipidemia. The effect of such comorbidities on the diabetic brain remains to be identified. Hypertension has been associated with brain abnormalities such as white matter hyperintensities [27] as well as global atrophy and subcortical lesions [28;29]. Hypertension is also associated with cognitive deficits in memory, abstract reasoning, and attention [30]. We have demonstrated that hypertensive subjects have reductions in frontal lobe volume, but not hippocampal volume. Hypertensive subjects additionally had lower scores in a test of executive function when compared to normotensive controls [31]. Our findings are consistent with those of Raz et al., who also found smaller prefrontal cortex and increased frontal white matter hyperintensities and also failed to find a significant reduction in the hippocampus associated with hypertension [32].

The effects of dyslipidemia on cognition have been more contradictory. For example, van Exel found an association between low levels of HDL and cognitive impairment and dementia in elderly persons, independent of atherosclerotic disease. They did not demonstrate an association between LDL, cholesterol or triglycerides and cognitive impairment [33]. Conversely, Henderson et al found that higher LDL was associated with better memory. HDL in this cohort of middle age women was not associated with memory [34]. Others have noted that the use of HMG-CoA-reductase inhibitors (statins) is associated with a lower prevalence of dementia [35]. However, as the authors pointed out, there may be a selection bias influencing the observed relationship, since statins may be less likely to be prescribed to patients with dementia [35]. Another study examining the impact of plasma lipids on memory performance in healthy elderly individuals found no association between changes in cognition and plasma triglycerides, LDL or treatment with lipid lowering agents [36]. Consequently, given that this is still a very unsettled literature, it is difficult to ascertain the impact of dyslipidemia and its treatment on brain function. With that being said, although among our well-controlled middle-aged individuals with T2DM there was an inverse association between HgA1c and hippocampal volume that was independent of hypertension and statin treatment [14], it is likely that hypertension and possibly dyslipidemia contribute to the cognitive impairments seen in type 2 diabetes.

Insulin Resistance and Cognition

Type 2 diabetes is an arbitrary evidence-based diagnosis based on evolving criteria of fasting glucose and insulin levels and peripheral insulin sensitivity. Type 2 diabetes is therefore at one end of a spectrum of impaired insulin sensitivity. Obesity is associated with a significant reduction in insulin sensitivity, as insulin sensitivity inversely correlates with BMI [37]. With the rapidly increasing prevalence of obesity worldwide, there is a corresponding increasing prevalence of insulin resistance. Given that insulin resistance is a pre-diabetic state that precedes T2DM [38], it is not unreasonable to surmise that insulin resistance may also be

associated with cognitive deficits. In fact, normoglycaemic individuals with increased two-hour glucose or insulin values on glucose tolerance testing also have deficits in learning and memory. For example, the patients with impaired glucose tolerance demonstrated the same neurocognitive deficits and degree of deficits as patients with type 2 diabetes [39]. This suggests that the cognitive deficits seen in type 2 diabetes are related to insulin resistance, although some investigators have argued that hyperglycemia can have toxic effects via overproduction of superoxides [40]. Non-diabetic patients with hyperinsulinemia have also been found to have lower scores on the MMSE, and there appears to be a “dose effect” with patients with type 2 diabetes performing even more poorly on the same tasks [41]. These differences between groups persisted even after accounting for the possible effects of atherosclerosis [41]. We have demonstrated that decreased peripheral glucose regulation was associated with decreased general cognitive performance, memory impairments, as well as hippocampal atrophy on MRI in non-diabetic elderly individuals, and these relationships existed even after adjusting for age and Mini Mental State Examination scores [42]. We now have novel preliminary data demonstrating cognitive deficits and brain abnormalities among obese adolescents with type 2 diabetes relative to non-insulin resistant obese controls, all years before there is any evidence of overt macrovascular disease (manuscript in preparation). In addition to the cognitive deficits in these adolescents with T2DM, which likely negatively affects their school performance, the implications for their future health are devastating. Early-onset type 2 diabetes in subjects younger than age 20 years is associated with a five-fold increase in the incidence of end stage renal disease and mortality [43], thus stressing the importance of early treatment and prevention.

Conclusion and Future Directions

The once uncharacterized effects of type 2 diabetes on the brain are now becoming a topic of great interest. Researchers have found that insulin resistance and T2DM are associated with impairments in cognition and abnormalities on neuroimaging, independent of comorbidities such as hypertension. These findings could impact numerous individuals given the recent rise in prevalence of T2DM. Following are some thought for future direction of the work in this area:

1. What is the mechanism for the cognitive impairments seen in T2DM?

Given that vascular reactivity plays an important role in substrate delivery across the blood-brain-barrier, and there is significant evidence that vascular reactivity is affected in T2DM and insulin resistance, it will be important to ascertain whether abnormalities in vascular reactivity as measured on MRI are associated with the cognitive impairments, and whether modifications in glucose control (insulin resistance) are associated with modifications in vascular reactivity. We have proposed a model for this possible mechanism [44].

2. Are the cognitive deficits reversible upon reversal of insulin resistance?

Weight loss is associated with improvements in insulin resistance [45]. Furthermore, significant weight loss in morbidly obese patients induces complete remission of the insulin resistance and prevents the occurrence of type 2 diabetes [46]. It has been suggested that improvement in glycaemic control in elderly patients with type 2 diabetes is associated with improvements in cognition [47]. We have some preliminary data (in preparation for publication) demonstrating cognitive impairments among adolescents with insulin resistance relative to obese, non-insulin resistant controls. The reversibility of the brain abnormalities seen in our data in insulin resistant adolescents remains unknown. It will be very important to ascertain whether the cognitive impairments and brain abnormalities associated with insulin resistance are reversible. In addition, it will be very important to determine whether reversal

of deficits with improvement of insulin resistance is possible at all ages, or whether it is restricted to adolescents where the brain may still be more plastic.

3. Are the peripheral to brain glucose ratios affected by insulin resistance?

Future studies should clarify the relationships between peripheral and brain glucose levels during steady state and during activation by using MRI spectroscopic techniques that allow such studies in real time. It will be important to ascertain whether these brain/periphery glucose ratios are affected by insulin resistance, and what the physiological and possible treatment implications for these observations would be.

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