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COMMENTARY

Diabetes and cognitive performance: a story that is still unfolding

A. M. Jacobson

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Keywords Cognitive decline · Cognitive performance · Diabetes · Digit Symbol Substitution Test · Glutamate · Glycated haemoglobin · Hyperglycaemia · Hypertension · Hypoglycaemia · Insulin resistance

Abbreviations
ARIC Atherosclerosis Risk in Communities
DSST Digit Symbol Substitution Test

One question voiced by patients and clinicians is whether diabetes could lead to brain damage and cognitive dysfunction. Careful systematic studies are extremely important to ascertain the nature and extent of these central nervous system complications.

Macrovascular disease, when it results in a stroke, can clearly cause cognitive dysfunction. Traditional diabetes-related risk factors, such as hyperglycaemia, hypoglycaemia and hypertension, in the absence of a stroke, also may be associated with modest changes in cognitive performance, especially in domains of psychomotor efficiency and executive function [1, 2]. Recurrent, severe hypoglycaemia is the risk factor that has drawn the most attention in research to date. While findings from the Diabetes Control and Complications Trial (DCCT) and Epidemiology of Diabetes Interventions and Complications Study (EDIC) may allay concerns about the impact of recurrent, severe hypoglycaemic events among adults and adolescents with type 1 diabetes [3], the extent of their effects in young children are far from resolved. Older type 2 diabetes patients might also be at risk of dementia because of severe hypoglycaemia [4, 5]. Other research suggests that retinal microangiopathy, a presumed marker of chronic hyperglycaemia and central nervous system microvascular disease, is associated with decreases in cognitive ability [6, 7]. While there may be a link between insulin resistance associated with type 2 diabetes and dementia, it is as yet unclear if this is due to an increased risk of Alzheimer's or vascular disease [2]. Surprisingly, one study suggests that the presence of diabetes slows cognitive decline among individuals with Alzheimer's disease [8]. Thus, published research presents a complex and sometimes conflicting array of findings.

Research from the Atherosclerosis Risk in Communities (ARIC) study, published in this edition of *Diabetologia*, adds to our understanding about the impact of diabetes and hyperglycaemia on cognitive decline [9], but the study has important limitations. ARIC is a community-based study of 15,000 middle-aged adults followed over multiple data collection phases. Its prospective longitudinal design allows investigators to draw conclusions about the effects of key predictors on long term outcomes. Over 800 papers have been published on findings from ARIC.

The analyses presented by Christman et al. [9] examine the effects of a single baseline HbA_{1c} value and diagnosed diabetes on cognitive decline over a 6 year period. The diagnosis of diabetes was made at the baseline visit, based on a self-reported history of physician-diagnosed diabetes, use of a diabetes medication, or a fasting glucose level of ≥7 mmol/l. Cognition was assessed at baseline and 6 years later using the Digit

A. M. Jacobson
Winthrop University Hospital,
Suite 300, 222 Station Plaza North,
Mineola, NY 11501, USA

A. M. Jacobson (✉)
Harvard Medical School,
Boston, MA, USA
e-mail: amjacobson@winthrop.org

Symbol Substitution Test (DSST; measures executive function and processing speed), the Delayed Word Recall Test (assesses verbal learning and recent memory) and the Word Fluency Test (determines executive function and expressive language).

The authors report that at baseline both diagnosed diabetes and HbA_{1c} level were associated with cognitive performance on one measure—the DSST. Diagnosis of diabetes also predicted cognitive decline 6 years later on the same measure and was also associated with an increased risk of incident hospitalisation for dementia over a 14 year follow-up period. Surprisingly, they did not find an effect of HbA_{1c} level on cognitive decline or incident hospitalisation for dementia within the diabetes group. There are several potential reasons for this unexpected finding, including the possibility that glycaemic control is not the critical metabolic dimension of diabetes driving cognitive decline. However, such a conclusion would be quite premature. A single HbA_{1c} value may not be indicative of long-term glycaemic control. Therefore, it would not necessarily be linked to changes in the central nervous system and secondary effects on cognitive performance. Repeated assessments of HbA_{1c} are needed to increase the precision of the measurement and thereby address this question. The cross-sectional association of HbA_{1c} level with cognitive performance could represent an effect of glycaemic control on cognitive dysfunction, but also could reflect short-term, reversible effects. Of interest, daily variation in blood glucose levels seems to be independently associated with worse cognitive performance after adjusting for HbA_{1c} level [10]. One other highly relevant factor—namely, episodic severe hypoglycaemia—was not assessed in the ARIC study. Even though obtaining accurate information about serious hypoglycaemia is challenging in any study, and virtually impossible without very frequent reporting, it is a key missing piece of information on the participants with diabetes.

Of note, the ARIC group has previously examined the effects of other risk factors on cognitive decline in this population [11–18]. In separate manuscripts they have reported that insulin resistance in those without apparent diabetes [11] and hypertension [12] have modest, but significant effects on different aspects of cognition. Hypertension and a history of diagnosed diabetes also predicted subsequent incident hospitalisation for dementia [18]. Moreover, uncontrolled hypertension and sustained hypertension carried greater risks for cognitive decline than treated hypertension [17]. Across analyses and papers, different measures of cognitive function were affected by these predictors [11–18]. It is not clear whether these variations in effects result from specific pathogenetic links between a particular risk factor and a specific cognitive function or chance variation in the analyses.

Even though there is considerable interest in retinal microangiopathy as a marker of microvascular changes in the brain, the ARIC investigators have not directly examined the association of retinopathy with cognitive functioning. However, they have reported that retinopathy is associated with the presence of cerebral atrophy [16] and cerebral white matter lesions that may represent vascular damage [13]. Such white matter lesions alone were predictive of subsequent incident stroke. The risk of stroke was even greater in those individuals with both white matter lesions and retinopathy [13]. This is consistent with findings from other studies showing associations between retinopathy and cognitive dysfunction (for example, see [6]).

Because these papers were published over a long time frame and incorporated differing predictors and outcomes [11–18], it is challenging for the reader to integrate this new data with previous information into a coherent understanding of the entire body of ARIC findings about diabetes, the brain and cognition [9].

It does appear that findings from ARIC confirm and support most other research about diabetes and cognitive dysfunction. The effects (1) are generally modest; (2) have the greatest impact on measures of psychomotor efficiency and executive function; and (3) are secondary to more than one biomedical factor [9, 11–18]. The specific mechanisms that mediate these effects are not clear. Macrovascular and microvascular pathways may link factors such as hypertension and hyperglycaemia with altered brain structure and cognitive dysfunction [10]. More direct effects on neuronal integrity could also be involved [19, 20]. For example, hyperglycaemia could increase the concentration of glutamate, the activating neurotransmitter at the synaptic junction. High levels of glutamate can be neurotoxic and have been associated with central nervous system damage in other conditions [19]. Recent data suggest that insulin regulates brain cholesterol metabolism, and altered insulin levels in some brain regions appear to affect neuronal function [20]. Any of these mechanisms could account for both white and grey matter changes found in patients with diabetes [21, 22], and in turn lead to decreased cognitive performance.

As with most large survey studies, ARIC is hampered by limitations in the depth and richness of measurements of both predictors and outcomes, infrequency of testing, dependence on self-reported diagnoses and lack of information on highly relevant clinical factors such as occurrence of severe hypoglycaemia. These limits are balanced, in part, by having large, representative community samples, long-term follow-up, and the wide breadth of information about individuals without major illness. Clinical trials and small observational studies, depending as they do on carefully selected samples with more stringent exclusion criteria and samples of convenience, are more difficult to generalise into clinical

practice populations. Thus, ARIC provides important information that complements other types of studies and findings from ARIC are likely to reflect the scope and nature of the problems that are found in the community.

The commonly found coexistence of depression and diabetes could reflect the psychosocial stress of having a chronic illness, but may also be due to alterations in the structure of brain regions involved in affect regulation [19]. Even though cognitive and affective dysfunction may coexist, they have typically been studied separately as if they were distinct phenomena. Thus, among patients with diabetes, depressive disorder and cognitive dysfunction could have common underlying causal pathways [19].

It remains unclear whether patients with either type 1 or type 2 diabetes, as they live longer, healthier lives with better treatment, will face serious cognitive consequences in the absence of major events like stroke. Given this continued uncertainty about the effects of diabetes on the brain, further research is needed. Such research could include (1) clinical and epidemiological studies that evaluate the effects of metabolic factors on brain structure and function and their downstream impact on cognitive performance and affective disorder; and (2) animal studies to address alternative pathways linking the metabolic alterations of diabetes with behaviourally relevant outcomes and measures of brain structure, function and chemistry. The animal studies could fruitfully incorporate examination of insulin action in the brain, together with evaluation of hyper- and hypoglycemia on neuronal integrity. Studies of brain metabolism, diabetes and cognition would benefit from collaborations across previously distinct research lines.

Duality of interest The author declares that there is no duality of interest associated with this manuscript.

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