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COMMENTARY

Cognitive functioning in type 1 diabetes: the Diabetes Control and Complications Trial (DCCT) revisited

B. M. Frier

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Abstract The Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) study has allowed an examination of the long-term effects of type 1 diabetes and intensity of treatment on cognitive function. The association observed between chronic hyperglycaemia and mild cognitive dysfunction, affecting motor speed and psychomotor efficiency, has been re-evaluated by Jacobson et al. (*Diabetologia* doi: 10.1007/s00125-010-1883-9) to determine the possible contribution of macrovascular risk factors, subclinical macrovascular disease and microvascular complications (retinopathy and nephropathy). This has revealed associations between mild impairment of psychomotor efficiency and hypertension, glycaemic control and the presence of retinopathy and nephropathy, while smoking history was associated with modest abnormalities in several cognitive domains. Neither macrovascular risk factors nor a history of severe hypoglycaemia was associated with the cognitive decrements; cerebral microangiopathy has been proposed as a possible underlying cause. Although the degree of cognitive impairment was mild and limited to a few domains, these decrements may influence the performance of everyday activities, such as driving.

Keywords Cognitive function · Hypoglycaemia · Psychomotor efficiency · Type 1 diabetes · Vascular risk

B. M. Frier (✉)
Department of Diabetes, Royal Infirmary,
Edinburgh, Scotland EH16 4SA, UK
e-mail: brian.frier@luht.scot.nhs.uk

Abbreviations

EDIC	Epidemiology of Diabetes Interventions and Complications
SDIS	Stockholm Diabetes Intervention Study

By providing indisputable evidence for the importance of glycaemic control to prevent and limit the severity of microvascular complications, the Diabetes Control and Complications Trial (DCCT) [1] caused a global sea-change in the clinical management of type 1 diabetes. This landmark study, in conjunction with its long-term follow-up, the Epidemiology of Diabetes Interventions and Complications (EDIC) study, continues to generate a wealth of informative data about type 1 diabetes. The paper by Jacobson et al. in this issue of *Diabetologia* presents further valuable findings [2].

In the original trial the long-term effects of type 1 diabetes and the intensity of its treatment on cognitive function were evaluated to address the unresolved question of whether exposure to recurrent severe hypoglycaemia, an almost inevitable consequence of intensive therapy and strict glycaemic control [1], led to intellectual decline [3]. The analysis of cognitive data in the DCCT after a mean follow-up period of 6.5 years did not demonstrate any adverse effect of recurrent severe hypoglycaemia on several domains of cognitive function [4, 5]. This finding was supported by a smaller contemporaneous Swedish trial, the Stockholm Diabetes Intervention Study (SDIS), in which the cognitive function of participants was reviewed after 10 years [6]. These observations were at variance with cross-sectional studies suggesting that severe hypoglycae-

mia exerted modest adverse effects on cognitive function in middle-aged adults with type 1 diabetes [7–10]. In view of the limited time of follow-up after exposure to severe hypoglycaemia, caution was expressed about the predictive value of the DCCT and SDIS data, as 6–10 years may not have been sufficient for any cognitive deficit to emerge. This problem was addressed by the DCCT/EDIC, in which the same exhaustive test battery of multiple domains of cognitive function was reassessed in 85% of the original cohort after a period of 18 years. The results confirmed that no significant cognitive decline had occurred during this time as a consequence of exposure to recurrent episodes of severe hypoglycaemia, not only in the group as a whole [11], but also in an adolescent subgroup [12]. These findings were not only reassuring but were consistent with the negative conclusions of a preceding meta-analysis of several studies that had examined the putative long-term effects of hypoglycaemia on cognitive function in type 1 diabetes [13].

However, an intriguing finding of the reassessment was a significant association between mild cognitive dysfunction affecting motor speed and psychomotor efficiency and chronic hyperglycaemia, as manifested by an elevated HbA_{1c} level [11]. The effect size was relatively small. For example, participants with HbA_{1c}>8.8% performed approximately 9% more slowly on measures of psychomotor efficiency than those with good glycaemic control (HbA_{1c}<7.4%). Modest cognitive deficits, principally in the form of slowing of mental speed and diminished mental flexibility, are recognised as occurring in type 1 diabetes [13], and mild cognitive impairment has been associated with the presence of microvascular complications, including retinopathy [14, 15] and peripheral neuropathy [15, 16]. The present study [2] has drawn on the wealth of biomedical data collected during the DCCT/EDIC studies to enable in-depth exploration of these cognitive deficits. The authors examined the role of macrovascular risk factors (hypertension, smoking, hypercholesterolaemia and obesity), subclinical evidence of macrovascular disease and the microvascular complications of retinopathy and nephropathy using appropriate statistical modelling.

This new analysis has demonstrated an association between smoking history and modest cognitive decrements in several domains, while hypertension was associated with psychomotor slowing alone, and glycaemic control (estimated by HbA_{1c}) and the presence of retinopathy and nephropathy were each independently associated with impaired psychomotor efficiency. Interestingly, macrovascular risk factors were not implicated in any cognitive decrement, and a history of severe hypoglycaemia again failed to show an association. The absence of a relationship with sex and the *APOE* ε4 allele contrasts with a previous small study in which *APOE* ε4 appeared to confer a cognitive disadvantage on young women with type 1 diabetes, as they were found to perform less well on certain cognitive tests [17]. A relationship of psychomotor slowing with peripheral neuropathy has been described previously [18]. In the DCCT/EDIC study, the apparent relationship observed between the modest decrements in cognitive function and other diabetic microangiopathies, namely retinopathy and nephropathy, which can be regarded as surrogate markers of preceding chronic hyperglycaemia, provides more evidence that poor glycaemic control may have a detrimental effect on the brain, which is presumably as susceptible to the development of microvascular disease as other organs. The supposition that the cognitive impairment is linked principally to the development of cerebral microangiopathy, at least in adults, seems entirely plausible [19, 20] and structural abnormalities in the brain have been identified that may represent the presence of small vessel disease [14]. Increasing sophistication of neuroimaging techniques, applied in conjunction with careful cognitive assessment should permit correlation of functional and structural changes in the brains of people with type 1 diabetes and help to answer this important question.

In interpreting the results of the present study it is important to remember that the participants in the DCCT were not typical of the general adult population with type 1 diabetes. Those who were recruited were relatively young at entry into the trial, were well motivated, had diabetes of short duration, were carefully selected to have a low risk of severe hypoglycaemia and had no evidence of psychiatric morbidity. They also received much greater monitoring and clinical support throughout the course of the study than the average person with type 1 diabetes. This fact is alluded to by the authors, and the inherent selectivity of the group may have afforded some modicum of cerebral protection and so have limited the magnitude of cognitive impairment. In addition, although the observed degree of cognitive abnormality was mild and limited to a few domains, it is essential to determine whether these modest decrements could have a tangible effect on everyday functioning. The daily accomplishment of complex tasks that require rapid multi-modal integration of information, such as driving a car, depends greatly on the integrity of these particular cognitive skills. It may not require much impairment of the speed of information processing in the brain to affect an individual's performance.

Although it would appear from this and other studies that exposure to recurrent severe hypoglycaemia plays little part in affecting long-term cognitive function in adults, hypoglycaemia may interact with other established diabetic complications, such as peripheral neuropathy, to magnify the subsequent cognitive disability [21]. Furthermore, prospective studies of children with type 1 diabetes have

shown that severe hypoglycaemia has a deleterious effect on verbal IQ [22, 23] and on problem solving and psychomotor efficiency [23], indicating the vulnerability of the immature brain in early childhood. The cumulative effects of severe hypoglycaemia on the cognitive function of the increasing number of individuals with type 1 diabetes who survive into old age are unknown, and they may also be atypical of the average person with type 1 diabetes. Furthermore, although impaired cognitive function as a result of acute hypoglycaemia is usually short-lived and the adult brain appears to be resistant to exposure to recurrent severe hypoglycaemia, few studies have examined the long-term effects on cognitive function in people who have developed the hypoglycaemia-induced syndrome of impaired awareness of hypoglycaemia, which is associated with a very much higher frequency of severe hypoglycaemia [24, 25]. One such study has suggested that significant cognitive impairment occurs in affected patients [26].

The results of the present study [2] should not be compared with investigations of cognitive function in people with type 2 diabetes, who represent a very different population. Cognitive impairment certainly occurs in type 2 diabetes, but in addition to the effect of ageing per se, many other confounding factors such as hypertension and macrovascular disease can influence cerebral structure and function, and it is difficult to dissect the specific role of glycaemic derangement. Co-existing depressive illness can also interfere with assessment of cognitive abilities.

Like the eye and the kidney, the brain is probably a target organ for microvascular disease, but the functional effects may be subtle, insidious and take much longer to emerge. In a few people with a long duration of type 1 diabetes, premature and disabling cognitive decline becomes manifest in middle age—a condition that has been reported anecdotally [27]. If many years of exposure to chronic hyperglycaemia (implied by the presence of established microangiopathies) are associated with modest but progressive impairment in some cognitive domains, this may become more prevalent with increasing life expectancy. Research studies that direct attention towards how diabetes affects the brain are of major clinical importance, particularly as many people with type 1 diabetes of long duration now live well into old age. The declining prevalence of advanced microvascular complications of diabetes, such as sight-threatening retinopathy and end-stage renal failure, must not detract from the constant need for clinicians to encourage the maintenance of good glycaemic control to protect the brain in all people with type 1 diabetes.

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

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