

## Diabetes 2



## Diabetes and cognitive dysfunction

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Cognitive dysfunction in type 1 and type 2 diabetes share many similarities, but important differences do exist. A primary distinguishing feature of type 2 diabetes is that people with this disorder often (but not invariably) do poorly on measures of learning and memory, whereas deficits in these domains are rarely seen in people with type 1 diabetes. Chronic hyperglycaemia and microvascular disease contribute to cognitive dysfunction in both type 1 and type 2 diabetes, and both disorders are associated with mental and motor slowing and decrements of similar magnitude on measures of attention and executive functioning. Additionally, both types are characterised by neural slowing, increased cortical atrophy, microstructural abnormalities in white matter tracts, and similar, but not identical, changes in concentrations of brain neurometabolites. Disconcertingly, the rapid rise in obesity and type 2 diabetes in all age groups might result in a substantial increase in prevalence of diabetes-related cognitive dysfunction.

## Introduction

Around 171 million people worldwide have diabetes mellitus, and this number is estimated to double by 2030. The two primary forms of diabetes are type 1 diabetes—an autoimmune disorder characterised by an absolute or near total loss of insulin secretion—and type 2 diabetes, which is characterised by reduced insulin sensitivity and relative insulin deficiency. In both forms, chronic hyperglycaemia can lead to microvascular and macrovascular complications. Although most focus has been on end-organ disease affecting the kidney, eyes, and peripheral nervous system, the brain is also affected. Diabetes, its complications, and its treatment can induce transient or permanent cognitive abnormalities, which result from acute and chronic disturbances of blood glucose homeostasis.

Here, we focus on diabetes-related cognitive dysfunction rather than on other related effects of diabetes on the brain, such as glucose-sensing, the regulation of whole-body glucose homeostasis, or stroke, which have been reviewed elsewhere.<sup>1,2</sup> We consider the lessons learned from cognitive, neurophysiological, neuroanatomical, and neurochemical assessments of brain function in diabetes and compare results of studies of type 1 and type 2 diabetes. The increasing prevalence of diabetes and the decreasing age of diabetes diagnosis suggest that diabetes-related cognitive dysfunction will probably increase and have a substantial effect on society. Efforts to understand the pathophysiological changes that underpin the development and progression of diabetes-related cognitive dysfunction are of vital importance to develop treatments to reverse or prevent these cognitive complications.

## Type 1 diabetes

## Glucose control

Type 1 diabetes develops most often in childhood or adolescence and always needs insulin replacement therapy. Chronic hyperglycaemia associated with inadequate insulin replacement heightens the risk of microvascular complications such as retinopathy, neuropathy, and

nephropathy.<sup>3</sup> Intensive insulin therapy, designed to achieve near-normal glucose control, minimises the development and severity of these complications, but at the expense of increased severe hypoglycaemia (blood glucose concentrations so low that external assistance is needed for recovery).<sup>4</sup> Severe hypoglycaemia can be partly attributed to limitations of insulin regimens and profound defects in the physiological, symptomatic, and behavioural responses to hypoglycaemia that individuals with type 1 diabetes develop.<sup>2</sup> Recurrent hypoglycaemia causes cerebral adaptation, with resetting of glycaemic thresholds for symptom generation and counter-regulation—a syndrome known as impaired hypoglycaemia awareness. Thus, type 1 diabetes treatment is often beset by fluctuations in blood glucose concentrations that, along with associated hormonal and metabolic disturbances, might contribute to the development of diabetes-related cognitive dysfunction (panel 1).

## Cognitive dysfunction

Type 1 diabetes has a specific effect on a subset of cognitive domains in adults, including intelligence, attention,

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## Search strategy and selection criteria

A professional clinical librarian searched PubMed with the following MeSH headings, combined with a Boolean “or” operator: “diabetes mellitus”, “diabetes mellitus, type 2”, “diabetes mellitus, type 1”, “diabetes complications”, “hyperglycemia”, “blood glucose”, “hypoglycemia”, or “hemoglobin A, glycosylated” (set 1) and “brain”, “cognition”, “cognition disorders”, “dementia”, “memory”, “memory disorders”, “neuropsychological tests”, “executive function”, or “psychomotor performance” (set 2). These two sets were combined with a Boolean “and” operator and the search was restricted to human studies published in English between 1995 and 2012. Additional searches of authors were done and reference lists were reviewed after assessment of relevant studies identified from the PubMed retrieval. The final search took place on Jan 12, 2012.

### Panel 1: Factors contributing to the development of cognitive dysfunction in diabetes

Individuals with type 1 and type 2 diabetes can develop several microvascular and macrovascular complications that can contribute to cognitive dysfunction, which might be exacerbated by a genetic predisposition to neuroinflammatory brain disease.

#### Metabolic factors

- Chronic hyperglycaemia
- Acute hypoglycaemia
- Recurrent hypoglycaemia
- Protein glycation
- Changes in fuel metabolism and transport

#### Vascular disease

- Microvascular disease
- Macrovascular disease
- Endothelial dysfunction
- Inflammation
- Changes in blood–brain barrier permeability
- Rheological factors
- Dyslipidaemia

#### Endocrine factors

- Reduced insulin sensitivity
- Hyperinsulinaemia
- Hypothalamic–pituitary–adrenal axis dysregulation
- Increased antidiuretic hormone
- Hyperleptinaemia

#### CNS factors

- Genetic predisposition
- Amyloid disposition
- Oxidative stress
- Changes in neuronal calcium homeostasis
- Depression

psychomotor speed, cognitive flexibility, and visual perception (table).<sup>5</sup> The magnitude of cognitive dysfunction reported in most trials is moderate, with effect sizes (a measure of the strength of the difference between people with diabetes and healthy controls) ranging from 0·3 to 0·8 SD units. Most cognitive tests examine the participant's ability to respond rapidly, and mental slowing is thought to be the fundamental cognitive deficit associated with type 1 diabetes.<sup>6</sup> Toddlers<sup>7</sup> and children<sup>8</sup> with type 1 diabetes also show the same pattern of cognitive dysfunction as that shown in adults. By contrast, learning and memory, the cognitive domains thought to be most susceptible to early brain disease, seem to be unaffected even when patients have had a long history of poor glycaemic control. Thus, in type 1 diabetes, cognitive dysfunction emerges early in the disease course (within 2 years of diagnosis) and tends to have very circumscribed effects, particularly on intelligence and psychomotor speed. Age is also an important variable, and children's

brains might be more susceptible to the effects of diabetes than adult's brains, although this might be because glycaemic control is more difficult to achieve in this population. Individuals who develop type 1 diabetes early in life (younger than 7 years) are at a higher risk of developing more severe cognitive deficits than are those who develop diabetes at an older age.<sup>9</sup> One study in adolescents<sup>10</sup> reported that 24% of those with early-onset diabetes (diagnosed before age 6 years) showed clinically significant impairments in a wide range of cognitive domains compared with only 6% of the later-onset patients, and 6% of people without diabetes.

#### Neurophysiological and cerebrovascular changes

Neurophysiological changes underpinning cognitive dysfunction in type 1 diabetes are largely unknown, mainly because of the difficulties surrounding the study of specific brain regions in man. Nevertheless, studies of electroencephalograms in adults<sup>11</sup> and adolescents<sup>12</sup> with diabetes have noted significant reductions in fast brainwave ( $\alpha$ ,  $\beta$ , and  $\gamma$ ) activity, particularly in temporo-occipital regions, compared with people without diabetes, whereas slow wave ( $\delta$  and  $\theta$ ) activity was increased in several frontal areas. Reduced  $\gamma$ -band activity is associated with cognitive decline, whereas activity in the  $\delta$  and  $\theta$  areas is associated with subcortical lesions and metabolic encephalopathy. Magnetic encephalography detected abnormalities in functional magnetic fields and in the neural connectivity of the brain at the scalp in people with type 1 diabetes.<sup>13</sup> These abnormalities were present irrespective of microvascular disease status, but were greater when accompanied by retinopathy than when not. Magnetic encephalography has revealed similar changes in people with other brain diseases. Others have reported an association between neurophysiological abnormalities and peripheral neuropathy in people with diabetes, and suggested that this association represents a central neuropathy, although direct evidence is scarce.<sup>14</sup>

Measurement of cerebral blood flow with single-photon emission tomography in children<sup>15</sup> and adults with type 1 diabetes shows significant regional variation in cerebral perfusion (either increased or decreased compared with controls without diabetes) in many brain regions, but most noticeably in the cerebellum, frontal brain, and frontotemporal brain.<sup>16,17</sup> Changes in perfusion correlated most with poor glycaemic control and the presence of microvascular complications such as retinopathy. Although many cognitive studies have shown that changes in perfusion are related to poor glycaemic control or cognitive test results,<sup>18</sup> a strong relation has not been reported, and no evidence exists to suggest that perfusion abnormalities play an important part in the development of cognitive dysfunction in type 1 diabetes.

#### Imaging studies

Neuroimaging has consistently shown slight structural changes in the brains of people with type 1 diabetes,

particularly in cortical grey matter.<sup>19</sup> In the largest study of its type so far, brain density in 82 adults aged 25–40 years with type 1 diabetes and 36 healthy participants was assessed with voxel-based morphometry—a well established, semi-automated quantitative MRI technique.<sup>20</sup> Those with type 1 diabetes showed reductions of 4–5% in grey matter density in several brain regions compared with controls, which correlated with lifetime glycated haemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) values, but the reduction in density was unrelated to cognitive test scores or history of recurrent hypoglycaemia.<sup>20</sup> That study excluded patients with proliferative retinopathy, but others<sup>21</sup> have shown that patients with retinopathy had substantial reductions in grey matter density in frontal gyri, occipital lobe, and cerebellum.

Studies using diffusion tensor imaging (DTI) have shown white matter microstructural abnormalities in middle-aged adults with long-standing type 1 diabetes. DTI measures the direction of water diffusion in tissues and is an index of the integrity of highly organised and constrained tissues such as white matter. DTI revealed abnormalities in the integrity of several white matter tracts, particularly the posterior corona radiata and optic radiations, and these abnormalities were correlated with increased duration of diabetes, raised HbA<sub>1c</sub> concentrations, and poor results in cognitive tasks that tested visuospatial analysis and hand–eye coordination.<sup>22</sup> Subsequent regional connectivity analyses showed that these white matter abnormalities were linked directly to a reduction in grey matter cortical thickness, suggesting that long-standing diabetes leads to concurrent microstructural changes to both grey and white matter, mainly in posterior cerebral regions.<sup>23</sup> In view of the possibility that these abnormalities underlie the mental slowing that is characteristic of many people with diabetes, DTI techniques clearly have a place in future research studies.

### Imaging brain metabolism

Several investigators have examined the effect of type 1 diabetes on whole-brain concentrations of metabolites and neurotransmitters. Unless done under controlled conditions, these studies can be difficult to interpret because the ratio of interstitial brain glucose to blood glucose (about 1:5) remains constant across a range of glucose concentrations, so measurements need to be made under similar glucose concentrations. However, correlations between lifetime glycaemic control and increased frontal brain glucose and neurotransmitter concentrations measured with proton magnetic resonance spectroscopy in adults with type 1 diabetes do suggest an underlying pathophysiological change.<sup>24</sup> Moreover, adults with type 1 diabetes had compromised memory and executive function and reduced psychomotor speed compared with controls. Studies using magnetic resonance spectroscopy have also shown that poor glycaemic control is associated with biomarkers of gliosis and altered neuronal integrity, and with high

|                       | Number of studies | n   | Effect size (SD units) | p value |
|-----------------------|-------------------|-----|------------------------|---------|
| Overall cognition     | 16                | 660 | 0.40                   | <0.001  |
| Intelligence          |                   |     |                        |         |
| Crystallised          | 5                 | 276 | 0.80                   | <0.01   |
| Fluid                 | 4                 | 168 | 0.50                   | <0.01   |
| Language              | 4                 | 144 | 0.05                   | NS      |
| Attention             |                   |     |                        |         |
| Visual                | 5                 | 195 | 0.40                   | <0.001  |
| Sustained             | 3                 | 217 | 0.30                   | <0.01   |
| Learning and memory   |                   |     |                        |         |
| Working memory        | 8                 | 244 | 0.10                   | NS      |
| Verbal learning       | 5                 | 204 | 0.20                   | NS      |
| Verbal delayed memory | 3                 | 157 | 0.30                   | NS      |
| Visual learning       | 5                 | 187 | 0.10                   | NS      |
| Visual delayed memory | 4                 | 157 | 0.10                   | NS      |
| Psychomotor speed     | 8                 | 368 | 0.60                   | <0.05   |
| Cognitive flexibility | 9                 | 364 | 0.50                   | <0.001  |
| Visual perception     | 5                 | 202 | 0.40                   | <0.001  |

Data are from a meta-analysis of 33 case-control studies of individuals aged 18–50 years.<sup>5</sup> The standardised effect sizes (Cohen's *d*) show differences between people with diabetes and those without. NS=not significant.

**Table: Characteristics of diabetes-related cognitive dysfunction in adults with type 1 diabetes compared with healthy controls**

concentrations of glucose in the brain in patients with type 1 diabetes with retinopathy.<sup>25</sup>

### Biomedical risk factors for cognitive dysfunction

Reports from the early 1990s suggested that cognitive dysfunction in type 1 diabetes might be more pronounced in individuals exposed to repeated severe hypoglycaemia, a finding consistent with anecdotal reports of severe hypoglycaemia inducing cortical changes in several brain regions such as the frontal and temporal cortex, basal ganglia, and hippocampus.<sup>26,27</sup> However, longitudinal epidemiological studies have tended to implicate chronic hyperglycaemia and microvascular disease in the pathogenesis of diabetes-related cognitive dysfunction.

The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) cognitive follow-up study<sup>28</sup> of 1144 participants showed no evidence for cognitive dysfunction in eight cognitive domains (assessed with a comprehensive battery of cognitive tests) in patients who had experienced one or more episodes of severe hypoglycaemia (defined as blood glucose concentration lower than 2.8 mmol/L accompanied by seizure or coma) during an 18.5-year follow-up. Similarly, data from a systematic meta-analysis did not show any relation between recurrent hypoglycaemia and performance in cognitive tests.<sup>5</sup> By contrast, many studies using various measures of brain integrity have shown that microvascular complications are associated with

increased risk of cognitive dysfunction.<sup>29</sup> The DCCT/EDIC cognitive study identified five variables that independently predicted reduction in psychomotor speed throughout the 18·5-year follow-up: old age, low number of years in education, high lifetime HbA<sub>1c</sub> concentrations, and two clinically significant microvascular complications (proliferative diabetic retinopathy and renal complications).<sup>18</sup> Additionally, increased carotid intima-media thickness (a marker of early macrovascular disease) was marginally associated with decreased performance in cognitive tests. In this study, retinopathy was most strongly associated with cognitive dysfunction, a finding also reported in type 2 diabetes. A limitation of the DCCT/EDIC cognitive study is that it has examined a young population (aged <50 years) of low-risk adults with type 1 diabetes that are in relatively good control in whom cognitive sequelae of repeated hypoglycaemia might not yet have emerged. However, findings from trials such as DCCT/EDIC suggest that, at least within this younger diabetic population with reasonable glycaemic control, any cognitive decline throughout follow-up was small and, as such, likely to have progressed very slowly.

Overall, a growing body of research suggests that moderate-to-severe hypoglycaemia does not seem to result in substantial cognitive dysfunction, although that might not be true for some high-risk groups such as children diagnosed within the first few years of life.<sup>30,31</sup>

### Type 2 diabetes Cerebrovascular disease

Type 2 diabetes is a heterogeneous metabolic disorder, characterised by reduced insulin sensitivity and relative insulin deficiency. Coexisting disorders, including obesity, hypertension, and dyslipidaemia, contribute to the severity of type 2 diabetes. By contrast with type 1 diabetes, macrovascular disease causes about 80% of mortality in people with type 2 diabetes. Interventions to reduce blood glucose in people with type 2 diabetes significantly lower the risk of microvascular, and possibly macrovascular, disease.<sup>32</sup> The brain is a target end-organ in type 2 diabetes and prediabetes, but the cause of diabetes-related cognitive dysfunction is difficult to establish because of the prevalence of several comorbidities, each of which might affect cognitive function (panel 1). Perhaps the most important of these comorbidities is cerebrovascular disease. Diabetes is associated with a 1·5–2·0-fold increased risk of stroke,<sup>33</sup> with a stroke relative-risk increase of 1·15 (95% CI 1·08–1·23) for every 1% rise in HbA<sub>1c</sub>.<sup>34</sup> Cerebrovascular disease, when present, probably contributes substantially to cognitive dysfunction in type 2 diabetes.

### Cognitive dysfunction

Although changes in psychomotor speed and other cognitive modalities have been reported, learning and memory deficits are the cognitive abnormalities that most clearly differentiate adults with type 2 diabetes

from those with type 1. Effect sizes are small, ranging between 0·25 and 0·5 SD units.<sup>35,36</sup> Additionally, the highly variable extent of cognitive dysfunction seen in adults with type 2 diabetes might be caused by the presence of several comorbid disorders, such as hypertension and obesity. Indeed, a study of elderly people with type 2 diabetes showed that their learning and memory skills were significantly disrupted, but when the analysis was adjusted for the presence of hypertension this difference was not significant.<sup>37</sup>

In cross-sectional studies of older adults (aged 60–85 years) with type 2 diabetes, extent of cognitive dysfunction was associated most strongly with long disease duration and poor metabolic control.<sup>37,38</sup> Surprisingly, diabetes might not increase the rate of cognitive decline over time. When people aged 56–80 years with diabetes were followed up for 4 years, their overall cognitive decline, measured by a comprehensive battery of cognitive tests, did not differ significantly from age-matched participants without diabetes (figure 1),<sup>39</sup> although people with diabetes did more poorly overall.<sup>39,40</sup> People with type 2 diabetes aged 85 years followed up for 5 years had the same pattern of results (ie, similar rate of decline to controls, but poorer overall performance at each timepoint of assessment than non-diabetic controls).<sup>41</sup> Although these follow-up periods were quite short, the findings suggest that cognitive dysfunction in type 2 diabetes might have a demarcated onset—similar to a traumatic brain injury, which impairs cognitive performance absolutely, but does not otherwise affect the rate of change over time. Whether dysfunction takes place during a critical period, perhaps soon after or even before the diagnosis of diabetes or the emergence of microvascular complications,<sup>42</sup> is unknown. This hypothesis suggests that therapeutic intervention and reversal of diabetes-related cognitive dysfunction is possible, provided the main underlying pathophysiological changes can be identified.

By contrast, large-scale longitudinal studies and systematic reviews suggest that diabetes increases the risk of developing dementia.<sup>38,43</sup> Diabetes is associated with a 50–100% increased risk of Alzheimer's disease and a 100–150% increased risk of vascular dementia.<sup>40</sup> Several endocrine, metabolic, and vascular abnormalities have been linked to diabetes and dementia, including ischaemic cerebrovascular disease, hyperglycaemia-associated neurotoxicity (glucose toxicity), changes in insulin and amyloid metabolism, increased oxidative stress, and increased release of inflammatory factors such as C-reactive protein, interleukin 6, and tumour necrosis factor  $\alpha$  (panel 1).<sup>41,42</sup> However, the causal pathway that underlies the statistical associations between type 2 diabetes and dementia is unknown.

Comparison of the results of neurocognitive assessments of individuals with type 1 diabetes with those of people with type 2 diabetes is useful. Brand and colleagues<sup>44</sup> compared age, sex, and estimated-IQ-matched patients

with type 1 and 2 diabetes and reported that patients with type 2 diabetes had significantly greater cortical atrophy and more lesions in deep white matter. The type 2 diabetes group had a much shorter duration of disease than did the type 1 group (7 years vs 34 years), better glycaemic control, and lower rates of clinically significant microvascular disease (laser-treated retinopathy, 8% vs 38%), but had higher rates of macrovascular disease and more atherosclerosis risk factors (eg, hypercholesterolaemia, hypertriglyceridaemia, hypertension, and high body-mass index). These findings implicate reduced insulin sensitivity and macrovascular disease in the pathogenesis of cortical atrophy and cognitive dysfunction in type 2 diabetes, by contrast with type 1 diabetes in which substantial disruptions in metabolic state and microvascular disease probably have a primary role.

### Neurophysiological and cerebrovascular changes

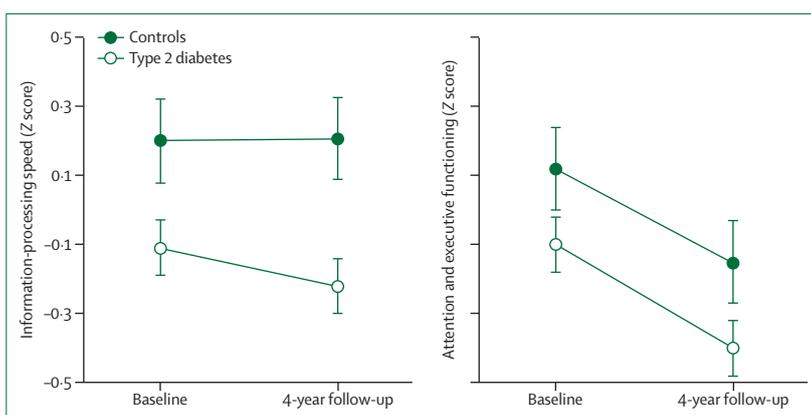
Adults with type 2 diabetes have evidence of neural slowing on recordings of sensory-evoked potentials. Neural slowing can occur soon after diagnosis and is indicative of metabolic status or perhaps subclinical disease<sup>45</sup> because it is significantly worse in patients with overt peripheral neuropathy.<sup>46</sup> The slowing of evoked potentials seems to proceed at the same rate as that in individuals without diabetes, but overall, adults with type 2 diabetes have 4–11% slower evoked potentials than do those without diabetes,<sup>47–49</sup> again supporting the notion of a crucial period for development of this complication. Furthermore, morbidly obese adolescents with diabetes performed more poorly in tests of several cognitive domains than did obese adolescents without diabetes, despite an average time of less than 2 years from diagnosis and no evidence of microvascular disease.<sup>50</sup> Structural brain abnormalities were also present.

Changes in cerebral blood flow, measured with a range of methods, are well documented in older adults (mean age 62 years) with type 2 diabetes. Advanced techniques, such as continuous arterial spin labelling MRI, have shown that patients with diabetes have significantly lower cerebral blood flow than do healthy controls, and have evidence of cortical and subcortical atrophy.<sup>51</sup>

People with type 1 and type 2 diabetes show similar neural slowing very early in the disease, and in both types this slowing is exacerbated by the presence of microvascular complications, suggesting that overall metabolic state and underlying vascular disease both contribute to neural activity. However, as in type 1 diabetes, the relation between these measures and cognition is poorly understood and, in many studies, neurophysiological function, cerebral blood flow, and cognitive function are not closely correlated.<sup>52</sup>

### Imaging studies

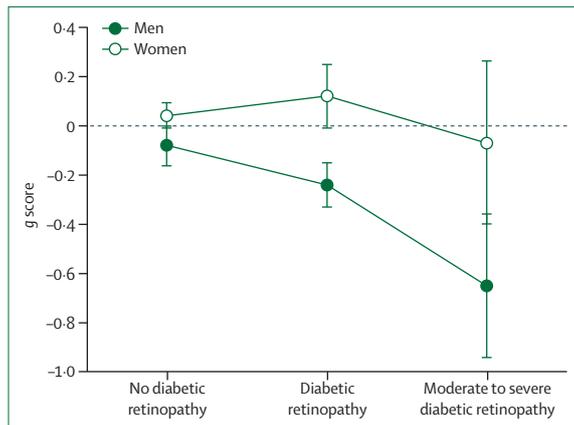
Pronounced structural changes in the brain have been noted in people with type 2 diabetes. Cerebral atrophy, white matter lesions, and infarctions are frequently



**Figure 1: Cognitive decline in people with type 2 diabetes compared with non-diabetic controls**  
Data are for people with type 2 diabetes (n=68) and matched non-diabetic control participants (n=38), followed up for 4 years.<sup>39</sup> A repeated-measures ANOVA (mean standardised domain score; error bars show SE of measurement) showed no significant decrease in information-processing speed over time for both groups (p=0.28), a significant main effect of group (p=0.02), and a non-significant time×group interaction (p=0.23), whereas for attention and executive functioning, both groups' performance decreased significantly over time (p<0.001), main effect of group was significant (p=0.04), but time×group interaction was not (p=0.37). Adapted from van den Berg and colleagues,<sup>39</sup> by permission of Springer on behalf of the authors.

reported,<sup>53,54</sup> and correlate with the presence of microvascular and macrovascular complications.<sup>55</sup> The rate of change in cerebral atrophy can be quite slow—eg, a 0.11% increase in ventricular volume over 4 years<sup>54</sup>—and is also similar to age-related changes, although the number of people examined in such studies is small and the follow-up times might have been too short to discern subtle differences in rate of increase in brain atrophy. Lacunar infarcts are also reported more frequently in people with type 2 diabetes than in those without diabetes.<sup>56</sup> Lacunar infarcts result from occlusion of penetrating arteries that supply arterial blood to deep brain structures. A meta-analysis of the few studies of cognitive function in patients with diabetes reported a significant association between diabetes and lacunar infarcts (odds ratio 1.3, 95% CI 1.1–1.6).<sup>56</sup> Lacunar infarcts are often silent (ie, the individual is unaware that they have had a stroke), but contribute to changes in mood, personality, and cognitive dysfunction.

Another consistent neuroimaging finding is the presence of hippocampal atrophy in patients with type 2 diabetes. Hippocampal atrophy is evident early in the course of the disease, and has even been documented in elderly people with prediabetes.<sup>57</sup> As much as a 10–15% loss in hippocampal volume has been reported in otherwise healthy middle-aged and elderly people with diabetes, despite them having similar frontal and temporal brain volumes to those without diabetes.<sup>36</sup> Hippocampal atrophy correlated with impairments in immediate memory, and was best predicted by HbA<sub>1c</sub> concentration, but not by hypertension.<sup>36</sup> The hippocampus is susceptible to acute metabolic changes such as hypoglycaemia,<sup>58</sup> suggesting that it might be particularly susceptible to diabetes-related metabolic and vascular change.



**Figure 2: Retinopathy and cognitive function in elderly people with type 2 diabetes**

Data are estimated means of general cognitive ability (g) scores of 1046 men and women aged 60–75 years with type 2 diabetes who underwent standard seven-field binocular digital retinal photography and a battery of seven cognitive function tests. The g score was generated by principal components analysis. In the total study population, mean g score was significantly lower for people with moderate-to-severe diabetic retinopathy ( $-0.44$ , 95% CI  $-0.73$  to  $-0.16$ ) than for those without retinopathy ( $0.05$ ,  $-0.03$  to  $0.12$ ;  $p=0.003$ ). Error bars show  $\pm 2$  SE. Adapted from Ding and colleagues,<sup>62</sup> by permission of the American Diabetes Association.

Hippocampal atrophy is one of the neuroanatomical features that differs between people with types 1 and 2 diabetes. Both have reduced grey matter density and white matter lesions, although cortical atrophy is generally more pronounced in type 2 diabetes (possibly because this population is older on average). Why the hippocampus is more affected in type 2 diabetes is unclear, particularly because this region is susceptible to acute metabolic change, which is a more prominent feature of type 1 diabetes. These findings suggest that age, associated comorbidities, and macrovascular disease or insulin resistance might be important risk factors for hippocampal atrophy.

### Imaging brain metabolism

Adults with type 2 diabetes assessed with proton magnetic resonance spectroscopy had concentrations of specific brain metabolites that were different from those reported in older adolescents and adults with type 1 diabetes.<sup>24,59</sup> Myo-inositol is located in astrocytes and its concentration changes in brain disease. It is increased in the frontal white matter of elderly people with type 2 diabetes.<sup>60,61</sup> Concentrations of myo-inositol correlate with the presence of macrovascular disease and complications, but not with HbA<sub>1c</sub>, suggesting that frontal gliosis can arise secondary to cerebrovascular changes. People older than 60 years with type 2 diabetes do not show abnormalities in other neurotransmitters and metabolites, whereas younger adults with type 1 diabetes show abnormalities in concentrations of myo-inositol, choline, and N-acetylaspartate (a marker of neuronal damage).<sup>59</sup> Taken together, the differences between

these studies and those of patients with type 1 diabetes suggest that the neurometabolic changes occurring in the brain vary appreciably between these two disorders, with the greatest changes seen in adults with type 1 diabetes (who tend to have had the disorder for a much longer time). However, few studies have measured brain metabolites in these two populations, therefore clear conclusions are difficult to draw. More research is needed using magnetic resonance spectroscopy techniques to directly compare people with type 1 and type 2 diabetes to carefully ascertain the nature and extent of biomedical complications.

### Biomedical risk factors for cognitive dysfunction

Chronic hyperglycaemia and long duration of diabetes are both associated with increased development of cognitive dysfunction, as is the presence of vascular risk factors (eg, hypertension, hypercholesterolaemia, and obesity) and microvascular and macrovascular complications.<sup>29,62</sup> The Edinburgh type 2 diabetes study<sup>63</sup>—a cross-sectional survey of more than 1000 elderly people aged 60–75 years with type 2 diabetes—showed that age-adjusted and sex-adjusted general cognitive ability was significantly lower in people with moderate-to-severe diabetic retinopathy (mean  $-0.44$ , 95% CI  $-0.73$  to  $-0.16$ ) than in those without retinopathy ( $0.05$ ,  $-0.03$  to  $0.12$ ;  $p=0.003$ ; figure 2). Moreover, in men, but not women, diabetic retinopathy was associated with estimated lifetime cognitive decline.<sup>63</sup> Reduced insulin sensitivity, which is common in people with type 2 diabetes, might also affect cognitive processes via several mechanisms,<sup>64,65</sup> as might hypoglycaemia.<sup>66</sup>

### Therapeutic interventions for cognitive dysfunction in diabetes

Long-term prospective trials such as DCCT/EDIC suggest that cognitive decline in people with type 1 diabetes is likely to be slowly progressive and mild, at least in those with good glycaemic control. The correlation between lifetime HbA<sub>1c</sub> concentrations, retinopathy, and cognitive decline in DCCT/EDIC<sup>18</sup> suggests that intensive insulin therapy to improve overall glycaemic control is a prudent approach. DCCT/EDIC also showed a significant reduction in overall vascular events with improved glycaemic control<sup>67</sup> and a reduction in progression of carotid intima-media thickness, suggesting that this approach would be beneficial because it would reduce progression of cerebrovascular risk. Benefits of aggressive glucose management in type 2 diabetes are less clear. The Memory in Diabetes (MIND) substudy<sup>68</sup> of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial showed no benefit of intensive glucose-lowering therapy on cognitive function or total brain volume in a large population of people with type 2 diabetes during 40-month follow-up. Similarly, ACCORD,<sup>69</sup> ADVANCE (Action in Diabetes, and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation),<sup>70</sup>

and the Veterans' Affairs diabetes trial<sup>71</sup> reported that intensive glucose control had no significant effect on macrovascular disease in people with type 2 diabetes. By contrast, PROactive (PROspective pioglitazone Clinical Trial In macroVascular Events), which examined the effect of pioglitazone in a large cohort of people with type 2 diabetes, reported that, in a prespecified analysis, an HbA<sub>1c</sub> concentration difference of 0.5% was associated with a reduction in both fatal and non-fatal stroke (hazard ratio [HR] 0.53, 95% CI 0.34–0.85).<sup>72</sup>

Particularly in type 2 diabetes, but also in type 1, treatment of hypertension and dyslipidaemia are important. The links between hypertension, ischaemic stroke, and cognitive dysfunction in type 2 diabetes suggest that modification of these risk factors will also ameliorate cognitive decline. Societies such as the European Stroke Organisation recommend a target blood pressure of 130/80 mm Hg in people with diabetes undergoing therapy that includes an angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker.<sup>73</sup> Statin use also reduces vascular risk. In a 5-year follow-up study of 1674 Mexican-Americans older than 60 years (about a third of whom had diabetes), those taking statins were about half as likely as were non-statin users to develop dementia or cognitive impairment (HR 0.52, 95% CI 0.34–0.80).<sup>74</sup>

### Recommendations for clinical practice

Cognitive dysfunction associated with diabetes is mild in most instances and rarely meets criteria for clinically significant impairment, but can occur in children as well as adults and is irrespective of diabetes type. Preliminary evidence suggests that cognitive changes begin early in the disease course and can worsen over time.<sup>40</sup> Reduction in mental efficiency might be sufficient to disrupt performance in the classroom, workplace, and home. If a patient reports that their performance in school or at work is worsening, or their ability to undertake activities of daily living is deteriorating, including diabetes self-management behaviours, or if they ask about the effects of diabetes on functioning, we recommend the approach to screening and assessment outlined in panel 2.

### Conclusions and future perspectives

In general, cognitive characteristics of people with type 2 diabetes are similar to those seen in people with type 1 diabetes. Both groups show evidence of mental and motor slowing (a nearly ubiquitous finding) and similar performance decrements on measures of executive functioning such as planning, attention, working memory, and problem solving (effect size is about 0.3–0.4 SD units). People with type 2 diabetes perform worse than healthy controls on learning and memory tests, unlike those with type 1 diabetes, who rarely have deficits in these domains; however, people with type 1 diabetes and those with type 2 show evidence of neural slowing, changes in cerebral perfusion, increased

#### Panel 2: Screening and assessment of cognitive dysfunction in diabetes

##### Discussion of the patient's cognitive complaints and level of functioning

Assessments should focus on perception of deficits relative to previous performance. Collation of information about their concurrent affective state (eg, depressed, anxious, stressed), metabolic status at the time of cognitive dysfunction (eg, hypoglycaemic or recently hypoglycaemic), and their overall level of metabolic control is important.

##### Identification of other potential biomedical causes of declining cognitive function

Common disorders include hypertension, hypercholesterolaemia, obesity, and poor sleep quality and each risk factor should be managed according to national recommendations.<sup>75–77</sup>

##### Counselling of the patient about possible causes of cognitive dysfunction

Several factors, such as poor glycaemic control, especially when associated with microvascular disease, might contribute to the development of cognitive dysfunction. If a connection between improved control and improved cognitive function is made, it might motivate patients to work more actively to improve glycaemia. Mood can also interfere with cognitive function.<sup>78</sup>

##### Referral for assessment by clinical neuropsychologist if necessary

If the patient reports having substantial difficulties with daily activities or undertaking tasks necessary for disease management, referral should be considered. The neuropsychologist can systematically document cognitive strengths and weaknesses, establish extent of impairment, and work with the health-care team to identify factors other than diabetes that might be disrupting cognitive functioning.

##### Consideration of cognitive remediation services

No study has examined whether cognitive rehabilitation is effective in reversal of diabetes-associated cognitive dysfunction, but studies of other disorders have suggested that these approaches might have some value when applied to patients with well documented cognitive dysfunction.<sup>79,80</sup>

##### Assistance of patients with accommodation to their new, normal level of functioning

If dysphoria or anxiety accompanies cognitive impairment, psychotropic drugs should be considered.<sup>81</sup>

cortical atrophy, and microstructural abnormalities in white matter tracts. Hippocampal atrophy seems to be a more prominent feature of type 2 diabetes than of type 1. Several biomedical risk factors might contribute to cognitive dysfunction in diabetes. In type 1 diabetes, evidence suggests that chronic exposure to high glucose concentrations and the presence of microvascular disease, in particular retinopathy, are major contributors to the development of the disorder. This finding is especially interesting and might be indicative of the structural homology between the retinal and cerebral blood supply. If this link is substantiated, digitised fundal photography might provide a non-invasive assessment of cerebral microcirculation. In type 2 diabetes, insulin resistance, dyslipidaemia, hypertension, and cerebrovascular disease seem to be of great importance to the development of cognitive dysfunction and should be addressed in the management of this disorder. The evidence suggesting that intensive glycaemic control improves cognitive outcomes is weak, although pioglitazone and metformin might prove effective through reduction of macrovascular risk. These

questions will only be answered by large, long-term intervention trials in which detailed cognitive assessment is combined with neuroimaging.

#### Contributors

RJM, CMR, and BMF contributed equally to the review of published work and to the writing and editing of this report.

#### Conflicts of interest

We declare that we have no conflicts of interest.

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