Dementia and cognitive decline in type 2 diabetes and prediabetic stages: towards targeted interventions

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Type 2 diabetes is associated with dementia, and also with more slight cognitive decrements. In this Review we discuss trajectories from normal cognition to dementia in people with type 2 diabetes, and explore opportunities for treatment. Slight diabetes-associated cognitive decrements and dementia affect different age groups and show a different evolution. These cognitive entities should therefore not be regarded as a continuum, although their effects might be additive. Vascular damage is a key underlying process in both entities. Glucose-mediated processes and other metabolic disturbances might also have a role. No treatment has been established, but management of vascular risk factors and optimisation of glycaemic control could have therapeutic benefit. We identify possible opportunities for intervention to improve cognitive outcomes in people with type 2 diabetes, and suggest how treatment can be tailored to individual risk profiles and comorbidities.

Introduction

It has been estimated that there will be more than 80 million dementia cases worldwide by 2040.[1] People with diabetes have a 50% greater risk of dementia than do those without diabetes.[2,3] Type 2 diabetes in midlife is also associated with an increased long-term risk of dementia.[2] With a prevalence of type 2 diabetes of 12–25% in people older than 65 years,[4,5] one in ten to 15 dementia cases worldwide are attributable to type 2 diabetes (population attributable risk). If prediabetes is also taken into account, these estimates increase to one in seven to ten dementia cases.[4]

In this Review, we address whether type 2 diabetes and prediabetic stages could be targets for the prevention of cognitive impairment. A particular focus will be on the trajectories from normal cognition to dementia, and from normal metabolism to diabetes. By drawing attention to different stages in these trajectories, risk factors, and underlying mechanisms, we aim to build a framework that can be used to identify treatment opportunities.

In the first section of the Review we define the scope of the problem. What is the association between diabetes and prediabetic stages and dementia? What are the trajectories of cognitive dysfunction in people with diabetes without dementia? We also review data from brain imaging studies in type 2 diabetes and describe structural correlates of impaired cognition. Next, we address risk factors for accelerated cognitive decline, and the possible mechanisms involved. Finally, we review results from treatment studies and suggest approaches to the development of targeted interventions against accelerated cognitive decline in people with diabetes, in which the ultimate goal is to establish the optimum treatment for the right individual at the right stage of their disease.

Diabetes, prediabetes, and dementia risk

Findings from many prospective population-based studies, including several meta-analyses using pooled data, have shown an increased risk of dementia in people with diabetes.[2,3] In the largest and most recent meta-analysis of type 2 diabetes and dementia risk, data was pooled from 19 published studies in 6184 individuals with diabetes and 38 350 without diabetes.[3] The combined overall relative risk (RR) for dementia was 1·51 (95% CI 1·31–1·74). Results of analyses that separated dementia outcome into the two most common subtypes—Alzheimer's disease and vascular dementia—suggest that type 2 diabetes confers a RR of 2·48 (95% CI 2·08–2·96) for vascular dementia and 1·46 (1·20–1·77) for Alzheimer's disease.[3]

Several epidemiological population-based studies have also assessed different markers of prediabetes and the risk of dementia. Results of prospective studies have shown that impaired fasting glucose, insulin resistance, and higher glycosylated haemoglobin (HbA_{1c}) concentrations predict increased incidence of dementia.[6,7] Results of epidemiological studies also suggest that both midlife total body obesity and abdominal obesity—another potential marker of prediabetes—increase the risk of both Alzheimer's disease and vascular dementia.[8,9]

Diabetes, mild cognitive impairment, and early dementia

Dementia is generally preceded by a stage in which patients have cognitive complaints and objective disturbances on cognitive testing, but in which their daily functioning is largely preserved. This stage is termed mild cognitive impairment (MCI).[10] MCI thus represents an intermediate stage between normal cognitive functioning and dementia, although not all people with MCI will develop dementia.[10] Prospective population-based studies link type 2 diabetes to an increased risk of MCI,[11,12] but not invariably.[3]

In people with MCI, diabetes is associated with a 1·5–3-times increase in the conversion rate to dementia.[13,14] This conversion rate could be even higher in people with MCI with prediabetes, compared with people with MCI without diabetes.[13] In patients with early Alzheimer's disease, diabetes might also increase the rate of functional decline,[15,16] although this effect seems to attenuate with longer duration of Alzheimer's disease.[16]

Cognitive trajectories in people with diabetes without dementia

Type 2 diabetes is also associated with slight cognitive decrements in people without dementia.[17,18] These decrements affect several domains, including verbal memory, information processing speed, attention, and executive functioning. Results of cross-sectional studies generally show slight effect sizes of about 0·3–0·5 SD units,[18] which implies that the cognitive performance of people with type 2 diabetes is around the 35th to the 40th percentile of that of control groups. This shift in performance is distributed quite evenly across people with type 2 diabetes[17]—ie, the reduced average performance is not caused by a few individuals with very low scores.

An important observation is that the effect size of cognitive decrements is quite consistent across age groups (figure 1). Moreover, effect sizes in studies of people with type 2 diabetes detected by early screening,[19] or in people showing early signs of the disease, such impaired glucose tolerance[20] or metabolic syndrome,[21] are quite similar to those of people with type 2 diabetes of longer duration. This similarity suggests that the cognitive decrements detected in people with type 2 diabetes probably start to develop in prediabetic stages and evolve only slowly thereafter, over many years. Findings from longitudinal studies support this concept.[22,23] The average rate of cognitive decline in people with type 2 diabetes over time is similar to or slightly greater than the rate of normal ageing-related cognitive decline.[22,23] The same seems to be true for metabolic syndrome,[24] although fewer longitudinal studies with detailed cognitive assessment are available.

Should these slowly progressive subtle diabetes-associated cognitive decrements be regarded as clinically relevant? Mean *Z* scores of –0·3 to –0·5 are much higher than the threshold for impaired cognition, which is typically defined as a performance below a *Z* score of –1·65—a score equivalent to the fifth percentile of reference values. Nevertheless, even subtle cognitive decrements can cause problems such as concentration difficulties, increased mental effort, or forgetfulness.

Slight cognitive decrements and dementia risk: continuum or additive effects?

What is the association between slight diabetes-associated cognitive decrements and the increased dementia risk in people with type 2 diabetes? In our opinion, slight cognitive decrements, at least up to the age of 65 years, are unlikely to indicate the earliest stage of a dementia process. Dementia typically occurs after the age of 65–70 years.[25] No evidence exists that diabetes increases the risk of early-onset dementia. In fact, the 50% increased dementia risk in people with type 2 diabetes translates into an average earlier onset of 2·5 years compared with people without diabetes; in the general population dementia incidence doubles with every 5 years of ageing.[25] Dementia is generally associated with notable cognitive decline that is clearly distinct from the normal rate of ageing-related cognitive decline. This accelerated decline becomes evident only in the years just before dementia diagnosis.[26] By contrast, slight cognitive decrements associated with type 2 diabetes occur in all age groups, in individuals much younger than 60–65 years,[18,27] and progress slowly over time (figure 1). These differences in affected age groups and cognitive trajectories indicate that the slight cognitive decrements associated with type 2 diabetes, and accelerated cognitive decline and dementia are separate processes, although their effects might be additive. Thus, the presence of

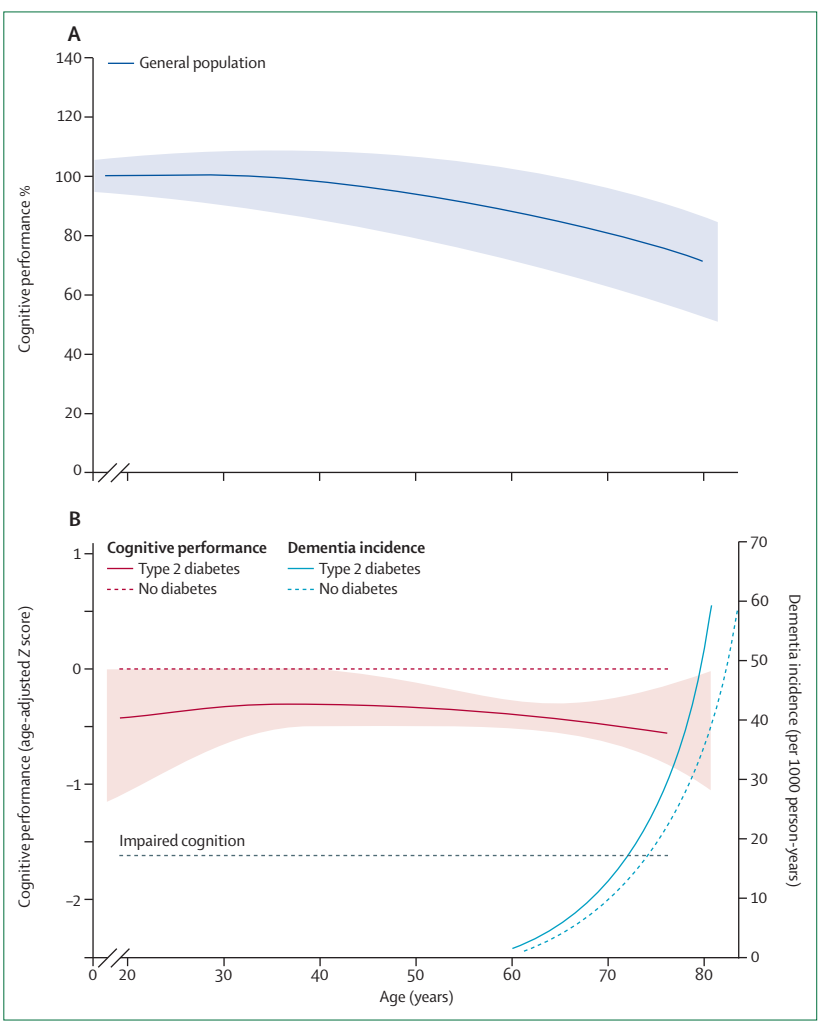

Figure 1: **Trajectories of cognitive decline in ageing and type 2 diabetes**
(A) In the general population, performance on most cognitive domains decreases slowly from midlife (about 40 years old) onwards. The shaded area represents the variation in the rate of decline between individuals. (B) The dashed red line shows mean performance of people without diabetes, normalised for age. The red line shows the slight decrements in people with type 2 diabetes across different age groups. Uncertainty of the estimates is highest in young and very old age groups, because of few studies. Mean performance in people with diabetes stays well above the threshold for impaired cognition. The blue curves on the right show the incidence of dementia by age, with incidence rates on the right y axis (based on Launer and colleagues[25]). The incidence of dementia by age is increased in people with diabetes compared with those without diabetes.[2,3] Unlike the slight diabetes-associated cognitive decrements, the incidence of dementia is strongly dependent on age.

slight cognitive decrements might reduce the threshold at which a dementia process becomes symptomatic.

Brain imaging studies

Over the past decade, findings from brain imaging studies, mostly using MRI and including people without dementia, have provided important insights into structural correlates of cognitive dysfunction in people with type 2 diabetes.[17,28] Slight brain atrophy—both cortical and subcortical—is a very consistent finding from MRI studies in people with type 2 diabetes.[28] Results of cross-sectional studies show reductions in average total brain volume of 0·5–2·0% in patients with type 2 diabetes compared with controls, which is equivalent to 2–5 years of normal ageing.[29–32] Relative increases in ventricular volume in people with type 2 diabetes are even more pronounced, ranging from 7% to 20%.[29,30] Results of cross-sectional analyses indicate that brain atrophy is associated with duration of diabetes;[32] longitudinal studies confirm this, although changes in brain volume in people with diabetes evolve only slightly faster than in controls.[29,30] In this way, the trajectories of brain volume changes and those of slight cognitive decrements are very similar. Brain MRI studies of other vascular risk factors, such as hypertension, also show very similar trajectories with brain changes that evolve slowly from early midlife onwards.[33] Generally, the pathological changes that underlie brain atrophy are heterogeneous and do not necessarily indicate neuronal loss or primary neurodegenerative processes, and could be secondary to vascular disease.[34] Therefore, the link between diabetes and brain atrophy cannot be simply assumed to be that diabetes accelerates neurodegenerative processes.

Diabetes is also associated with an increased occurrence of cerebral infarcts on MRI, particularly small subcortical (lacunar) infarcts that are mostly caused by small vessel disease.[28,35] Studies of other manifestations of cerebral small vessel disease detectable with MRI are less consistent. Some researchers have shown an increased volume of white matter hyperintensities in people with type 2 diabetes,[32,36] but others have not.[31] Some studies indicate that occurrence of cerebral microbleeds might be increased in people with diabetes,[37] but this topic needs further investigation.

New techniques can identify changes in brain MRI that cannot be detected by eye—eg, diffusion tensor imaging (DTI) enables assessment of the microstructure of the brain and the connections between different brain regions. In patients with type 2 diabetes, DTI shows abnormalities in white matter structure and network integrity that strongly correlate with cognitive performance (figure 2).[38] In line with these findings, results of functional MRI studies show alterations in functional connectivity between different areas of the brain.[39] These novel techniques will help to increase understanding of the structural and functional basis of cognitive decrements in type 2 diabetes. However, further evaluation of factors that might confound their interpretation—eg, abnormalities in neurovascular coupling in functional MRI—is warranted.

Modifiable risk factors for accelerated cognitive decline in type 2 diabetes

Vascular risk factors

In the general population, hypertension, hyperlipidaemia, and obesity in midlife are associated with increased risk of late-life dementia and cognitive decrements.[9,40,41] In line with these findings, elderly and middle-aged individuals with type 2 diabetes who are also hypertensive are at greater risk of dementia and cognitive impairment than are those without hypertension (figure 3);[42,43] treatment for hypertension could therefore lower this risk.[44,45] The link between hypertension and slight cognitive decrement is not consistently noted in cross-sectional studies in people with type 2 diabetes.[46] Nevertheless, results of longitudinal studies suggest that slight cognitive decrements might be linked to increased blood pressure 10–15 years earlier, in the prediabetic stages.[47]

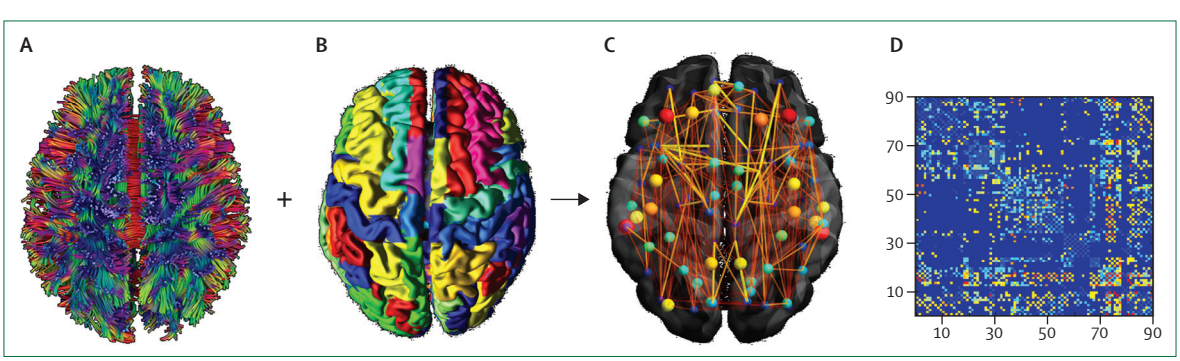

Figure 2: **Brain imaging abnormalities in type 2 diabetes**
The figure shows how cerebral networks can be reconstructed from diffusion tensor imaging (DTI) scans with graph theory. (A) DTI-based fibre tracts form the edges (connections) of the network. (B) Parcellated cortical and subcortical regions form the nodes (90 in total). Two brain regions are considered to be connected if a fibre bundle connects both regions. Each connection can be weighted by the microstructural integrity of that connection. (C) By use of this procedure a weighted brain network can be obtained, which can be represented by a 90x90 connectivity matrix (D). Reproduced with permission from Reijmer and colleagues.[38] Network metrics are affected by type 2 diabetes and form strong correlates of cognitive functioning, independent of MRI markers of atrophy and small vessel disease.[38]

High midlife total body adiposity and central adiposity is associated with cognitive decrements and increased risk of dementia;[8,9] however, studies of association between high adiposity in late life and short-term risk of dementia have produced mixed results.[9,48] Because central adiposity is common in prediabetic stages, these findings are highly relevant for type 2 diabetes. Adiposity might also be associated with cognitive decrements within populations with established type 2 diabetes, although this possibility has not been well explored. In a study investigating total fat mass and central adiposity, researchers reported an association between high adiposity and increased risk for cognitive decline during a 2 year period in elderly people with type 2 diabetes.[49] By contrast, results of an earlier study showed that central obesity was associated with a reduced risk of cognitive decline and dementia in people with type 2 diabetes, whereas no association was shown between body-mass index and cognitive decline in other studies.[44,50] Hence, although many mechanisms are plausible for why central adiposity in an individual without diabetes could be associated with cognitive decrements (by-products of visceral adipose tissue, adipocytokines, insulin resistance, fatty liver), whether obesity increases the risk of cognitive impairment in addition to the overarching effect of type 2 diabetes itself is unclear.

In the general population, increased total cholesterol in midlife, but not late life, is associated with increased risk of cognitive decline.[9,41,51] Some research suggests that low concentrations of high-density lipids in late life are associated with cognitive impairment.[51] Consistent with this finding, a study of elderly Japanese individuals with type 2 diabetes recorded that low concentrations of HDL were associated with high cognitive decline over 6 years.[43] By contrast, findings from another study showed that raised cholesterol was associated with a decreased risk of cognitive impairment in people with type 2 diabetes.[50]

Socioeconomic and lifestyle factors, and depression

Occupation, low level of education, and socioeconomic status have been linked to the occurrence of both dementia[40] and type 2 diabetes[5] (see appendix for further references). However, although evidence for a link between low education level and increased dementia risk is accumulating,[41,52] investigators of a systematic review[40] concluded that the evidence for other socioeconomic factors is inconclusive. Observational studies in the general population provide evidence that an association might exist between selected nutritional factors and physical activity, and decreased risk of cognitive decline.[40] Smoking, however, is associated with increased risk of cognitive decline.[40,53] In a large, long-term study of 1500 elderly women with type 2 diabetes, physical activity was not associated with decreased risk of cognitive decline,[54] but low intake of saturated fat and trans-fat, and high intake of polyunsaturated fat since midlife, were associated with reduced cognitive decline.[55]

Results of two large cohort studies showed that risk of dementia is doubled in elderly individuals with type 2 diabetes with depression compared with those with type 2 diabetes without depression, even after adjustment for complications of diabetes and glycaemic control.[56,57] By contrast, results of a pooled analysis of three cohort studies showed no association between depressive symptoms and slight diabetes-associated cognitive decrements.[58] Importantly, a bidirectional association might exist between prediabetes and depression, in which both conditions predispose to each other.[59,60] Furthermore, both cognitive dysfunction and depressive symptoms could hamper adherence to diabetes treatment and glycaemic control.[60,61]

Diabetes-specific risk factors

Several studies have shown that longer diabetes duration is associated with both an increased dementia risk[44,50,62,63] and with slight cognitive decrements.[17] Findings supporting the association between glycaemic control and cognition are inconsistent. In one study, for example, researchers reported that fasting glucose and HbA_{1c} were not associated with dementia in patients with type 2 diabetes,[50] whereas another study found that uncontrolled diabetes (defined as a random blood glucose ≥11·0 mmol/L) was associated with increased dementia risk independent of vascular comorbidities.[64] With regard

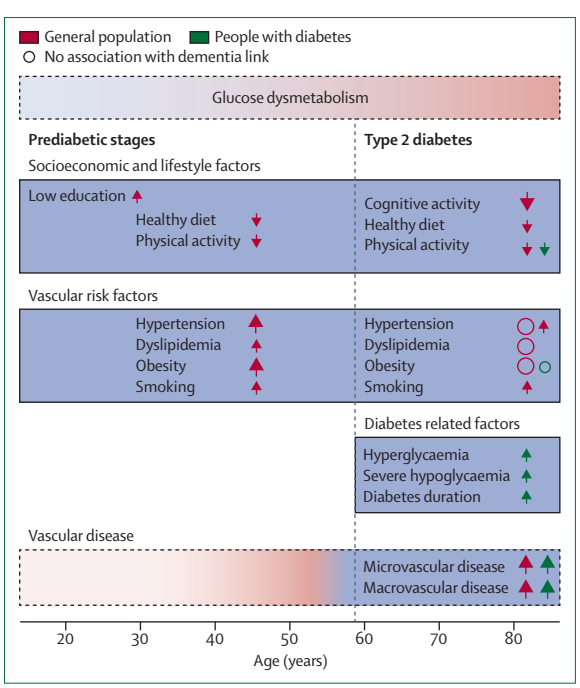

Figure 3: **Risk factors for late-life cognitive decline in diabetes**
The figure summarises data for several potentially modifiable risk factors for late-life accelerated decline in people with (green arrows) and without (red arrows) type 2 diabetes. Risk factors for late-life cognitive impairment can already be identified in midlife, in prediabetic stages. The upward arrows indicate increased risk of late-life dementia, and the downward arrows decreased risk, with the size of all symbols indicative of the level of evidence. Note the dynamics in the risk factors with age, where some factors convey increased risk when present in midlife, but not later in life.

See Online for appendix

to the slight diabetes-associated cognitive decrements, high concentrations of HbA_{1c} were associated with accelerated cognitive decline in a cohort of people aged 70–79 years with type 2 diabetes.[23] By contrast, in people older than 85 years with diabetes, high HbA_{1c} concentrations were associated with decelerated decline.[65]

Severe hypoglycaemic episodes have been associated with an increased risk of dementia in two cohort studies of patients with type 2 diabetes,[66,67] whereas findings from a smaller study[68] with a shorter follow-up did not confirm these findings. Conversely, results of several studies have shown that poor cognitive functioning increases the risk of severe hypoglycaemic episodes in people with type 2 diabetes.[66,69,70]

Non-modifiable risk factors, such as genetic factors (eg, the APOE genotype) are outside the scope of this Review. The appendix provides selected references in the supplementary material.

Underlying mechanisms of cognitive decline in type 2 diabetes

Accelerated cognitive decline: degenerative or vascular abnormalities?

Theories about the general causes of cognitive decline and dementia focus on the processes underlying the two major subtypes of clinical dementia—vascular dementia and Alzheimer's disease. Vascular dementia is caused by the accumulation of various forms of vascular damage in the brain. Alzheimer's disease is thought to be due to aberrant amyloid-β processing, involving generation of small, toxic amyloid-β oligomers, and aggregation of the microtubule-associated protein tau.[71] This aberrant metabolism of amyloid-β and tau results in the two core pathological hallmarks of Alzheimer's disease—amyloid plaques and neurofibrillary tangles, respectively.[71] However, the rarity of so-called causally pure forms of dementia is increasingly recognised. Results of neuropathological studies show multiple abnormalities in the brain of most older people with dementia, with vascular and neurodegenerative changes occurring simultaneously in most cases against a background of other ageing-related brain changes.[72] The combined burden of these abnormalities is, at least initially, counterbalanced by compensatory structural and functional processes, also referred to as brain reserve. When these compensatory mechanisms run out, the earliest manifestations of dementia become clinically apparent.

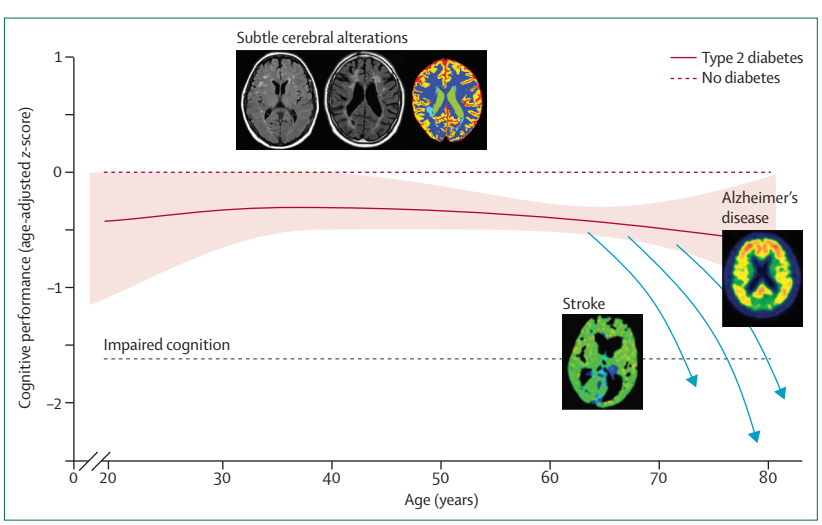

Figure 4: **Cerebral changes underlying cognitive trajectories in type 2 diabetes**
Slight cognitive decrements are related to subtle cerebral alterations including slight atrophy, disturbed white matter integrity, and vascular lesions (the picture shows two MRI scans and a segmentation of different brain tissues). These changes progress slowly, from midlife onwards, drawing on the reserve capacity of the brain. This progress increases vulnerability to the consequences of further incidents later in life, particularly (silent) stroke (the picture shows a left thalamic infarct on CT perfusion) and Alzheimer's-type abnormalities (the picture shows a PIB-PET amyloid scan, reproduced from Jack and colleagues,[79] by permission of Elsevier.) Individuals with such a combined burden of multiple abnormalities will have accelerated cognitive decline. Blue arrows indicate hypothetical cognitive trajectories of individual patients with multiple abnormalities.

Despite epidemiological data linking type 2 diabetes with Alzheimer's disease and studies in experimental models linking aberrant cerebral insulin homoeostasis to formation of Alzheimer's-type abnormalities (amyloid-β plaques and neurofibriallary tangles),[73] autopsy studies mainly report associations between diabetes and vascular abnormalities, including both cortical and subcortical macroscopic infarcts,[74,75] and report decreased, rather than increased, burden of plaques and tangles in the brains of people with diabetes.[74,75] The latter could be due to competing risk of stroke, cardiovascular disease, mortality, and dementia, but this clearly does not support the idea that diabetes accelerates Alzheimer's-type abnormalities. In line with autopsy findings, results of a study that assessed brain amyloid-β burden in vivo, with carbon 11-labelled Pittsburgh compound B, also showed no association between measures of glucose and insulin homoeostasis and amyloid burden.[76]

Accumulation of amylin (rather than amyloid-β) oligomers and plaques has been found in cerebral blood vessels and the brain parenchyma of patients with diabetes and vascular dementia or Alzheimer's disease, and in the brains of people with Alzheimer's disease without diabetes.[77] Amylin (also known as islet amyloid polypeptide) oligomerisation and deposition in the pancreas are features of type 2 diabetes,[78] providing another potential connection between diabetes, amyloid, and dementia.

In summary, the increased risk of accelerated cognitive decline in older people with diabetes is probably due to many processes (figure 4). Subtle diabetes-related brain changes—shown on brain MRI as slight atrophy, disturbed white matter integrity, and vascular lesions—accumulate from midlife onwards, drawing on the reserve capacity of the brain. This process makes the brain more vulnerable to the consequences of further pathological changes, particularly cerebrovascular disease and Alzheimer's-type abnormalities (figure 4).

Cerebrovascular disease in diabetes

Type 2 diabetes and prediabetic stages, such as the metabolic syndrome, are strongly associated with microvascular and macrovascular disease, and links

between dysglycaemia, hypertension, and dyslipidaemia are well established. Diabetes and prediabetic stages are risk factors for stroke.[35] Diabetes is associated with atherosclerotic changes in the heart and the cerebropetal arteries, and with atrial fibrillation, which predisposes to large artery occlusive and thromboembolic strokes[35] and to cerebral small vessel disease.[28,35] Moreover, stroke outcome is worse and the risk of post-stroke dementia is increased in people with diabetes.[35,80] Vascular changes in the brain, particularly small-vessel disease, can initially be silent—ie, not causing acute focal symptoms. Small vessel disease is an important contributor to cognitive decline by causing neuronal ischaemia, disturbances in the cerebral white matter, or by aiding the leak of potentially neurotoxic mediators from the plasma into perivascular tissues.[81]

Epidemiological studies link both large vessel and small vessel disease to cognitive decline in diabetes, and in predementia stages. Data from the Edinburgh type 2 diabetes study[82] indicated that 4-year decline in cognition was associated with a baseline history of stroke, increased baseline carotid artery intima media thickness, and low ankle-brachial pressure index. Stroke and peripheral artery disease are also associated with increased dementia risk in patients with type 2 diabetes.[50,83] Retinal microvascular disease (which can be regarded as a surrogate marker of cerebral microvascular disease) has also been linked with lower cognitive performance in people with diabetes,[84,85] as has microalbuminuria.[44]

Other diabetes-related mechanisms

The associations between hyperglycaemia[23,64] and cognitive decline in people with diabetes could simply be a manifestation of hyperglycaemia-mediated increased propensity to microvascular and macrovascular disease. However, results of experimental studies into the effects of acute hyperglycaemia on cognition,[86] and short-term intervention studies of antidiabetic agents,[87] imply that short-term increases in blood glucose could have a direct effect on cognition. The mechanisms are unclear, but could involve changes in regional cerebral bloodflow, osmotic effects on neurons, or even alterations to metabolic pathways.

Insulin resistance and peripheral hyperinsulinaemia are thought to underpin many of the cardiometabolic abnormalities in type 2 diabetes and the metabolic syndrome. Additionally, insulin can cross the blood–brain barrier, and insulin receptors are found in several areas of the brain, including the hippocampus.[88] Insulin could play a part in the genesis of cognitive impairment through these central pathways by several mechanisms.[73] Amyloid β is broken down by insulin-degrading enzyme, and the increased concentrations of insulin that occur in insulin-resistant states could compete for binding sites on this enzyme, thereby reducing clearance of amyloid β.[73] Importantly, abnormalities in insulin signalling have been noted in the brain tissue of people with Alzheimer's disease without diabetes, leading to the classification of Alzheimer's disease as an insulin-resistant brain state.[73,89] Although there is a suggestion that cerebral insulin resistance also links type 2 diabetes to increased dementia risk, knowledge of cerebral insulin homoeostasis in type 2 diabetes is still incomplete.[88]

These putative mechanisms are based largely on in-vitro data, and the associations between dysglycaemia, insulin resistance, and cognitive impairment noted in epidemiological studies could be confounded by other factors not considered in the statistical models. Such factors include pro-inflammatory mediators and glucocorticoids. Type 2 diabetes and the metabolic syndrome are pro-inflammatory states, and increased concentrations of inflammatory mediators, such as interleukin 6 and tumour necrosis factor-α, could cause cognitive decrements.[90] Glucocorticoid concentrations are also raised in people with type 2 diabetes and the metabolic syndrome,[91] and glucocorticoid receptors are located throughout the brain.[92] Strong data link glucocorticoid excess to cognitive impairment in both animal and human studies,[92] and in people with type 2 diabetes.[93]

Can accelerated cognitive decline in diabetes be prevented?

Treatment and cognitive outcomes in type 2 diabetes

In an observational study in a large cohort of people with type 2 diabetes not using insulin, use of metformin and sulfonylureas decreased dementia risk compared with patients with type 2 diabetes who did not take glucose-lowering drugs.[94] By contrast, other researchers reported increased dementia risk with metformin use (which was not recorded for other glucose-lowering drugs),[95] increased risk of dementia with insulin treatment,[96] or accelerated cognitive decline with thiazolidinedione use.[97] These heterogeneous findings show that results of observational studies assessing diabetes treatment should be interpreted with great caution because type of treatment is heavily confounded by severity and duration of diabetes. Rigorous pharmacoepidemiological studies of type 2 diabetes treatment incorporating new user design and propensity scores could help to address some of these issues.

Randomised controlled trials in people with diabetes also increasingly assess cognition, albeit mostly as a secondary outcome measure. Thus far, these trials have addressed mainly the slight diabetes-associated decrements, by comparing mean performance on cognitive tests between treatment groups. Because the rate of decline of mean performance on such tests in people with diabetes is not much accelerated compared with controls, this approach makes the a-priori chance of detection of a treatment benefit small. Results of the largest published randomised controlled trial—the ACCORD-MIND study[98]—did not show a difference in the rate of cognitive decline between patients assigned to receive intensive glycaemic control and those assigned to a standard treatment strategy. However, intensive treatment did slow the rate of brain volume loss. For

Panel: Lessons from the prevention of cardiovascular disease*

In view, at least in part, of the shared causes and risk factors of cognitive impairment and cardiovascular disease in patients with type 2 diabetes, lessons learned from the prevention of cardiovascular disease could be applied to the prevention of dementia.

Cholesterol-lowering treatment and blood pressure-lowering treatment are both very effective in reducing the risk of non-fatal myocardial infarctions, non-fatal stroke, and vascular death by 30–40%, as documented in clinical trials in various groups of patients ranging from low-risk to high-risk individuals, and in patients with diabetes or vascular disease, or both. No benefit of lipid-lowering or blood pressure-lowering treatment on relevant cognitive endpoints has been documented, but clinical trials in this specialty usually have a median follow-up of only 3–4 years and the mean participant age is generally about 60 years. There has been some indication of an effect of antihypertensive treatment on dementia prevention, although the effects are slight and not consistent across studies.

Randomised controlled trials of lifestyle changes—such as diet improvement, reduction of salt intake, weight reduction, increased physical activity, and stopping smoking—with clinically relevant vascular endpoints are either missing or poorly designed. Evidence for a causal association between these lifestyle modifications and occurrence of vascular disease is compelling, but comes from observational cohort studies. Cohort studies now provide similar evidence for dementia.

Medical interventions and lifestyle changes that lead to a lower risk for cardiovascular disease might also be effective in the prevention of cognitive impairment or dementia, also in patients with diabetes. The high-risk approach worked well in cardiovascular disease prevention, meaning that patients at the highest risk for developing vascular disease were the first to receive medical treatment and support for lifestyle changes. In patients with a high absolute risk at baseline, these interventions are most effective in terms of absolute risk reduction, with a relatively small number of patients needing to be treated to prevent one outcome event. Alternatively, a more general population approach can be used, targeting patients with an intermediate vascular risk (a 10-year risk of 10–20%). For dementia prevention, patients at high risk for developing dementia are usually also at high vascular risk, because of having diabetes or a vascular disease, or being elderly. These individuals should therefore already receive optimum treatment of vascular risk factors according to guidelines. Unless groups of patients with a high risk for dementia but without an increased vascular risk exist, the cardiovascular prevention guidelines can be used not only to optimally reduce the risk of vascular disease but also to reduce the risk of dementia. Nevertheless, randomised clinical trials assessing the effect of treatment of cardiovascular risk factors on the occurrence or progression of dementia are urgently needed. Cognitive impairment and dementia are diseases of elderly people, therefore strategies need to be developed to identify patients who will benefit most from preventive treatment.

*Please see appendix for references.

Search strategy and selection criteria

We searched PubMed for papers published in English from January, 1990, to August, 2013, with the terms (and synonyms thereof) "dementia", "Alzheimer's disease", "cognitive impairment", "diabetes", "metabolic syndrome", and "obesity", in combination with the key terms "epidemiology", "risk factors", "brain MRI", "prevention", and "treatment". We searched reference lists of papers identified and extracted relevant papers from our records. We also searched ClinicalTrials.gov. From the large amount of published work on these topics we selected mainly observational studies, systematic reviews or meta-analyses, and randomised controlled trials, published in core clinical journals in the past 5 years. Our final selection was based on originality and relevance to topics covered in this Review. When possible, we refer to reviews rather than to original studies. Additional references are listed in the appendix.

intensive treatment the HbA_{1c} target was less than 6·0% (42 mmol/mol); standard strategy targeted HbA_{1c} to 7·0–7·9% (53–63 mmol/mol). Another, smaller, randomised controlled study—comparing 6 years of intensive multifactorial treatment, targeting both glycaemic control and vascular risk factors, with standard care in people with early, screen-detected type 2 diabetes—did not show any benefit on cognitive performance.[99] By contrast, randomised controlled studies assessing the effects of short-term improved glycaemic control (over weeks and months) do suggest short-term benefits of glycaemic control on cognition.[87]

Towards targeted interventions

Population trends show that the global population is in the midst of an epidemic of obesity, type 2 diabetes, and dementia. On one hand this epidemic is due to an increase in life expectancies, particularly in developing countries;[1] on the other hand, type 2 diabetes is now being diagnosed in adolescents and young adults more than ever before.[4] These trends provide challenges for prevention of type 2 diabetes-related complications, including dementia. Fortunately, cohort studies show a reduction in the prevalence of dementia in older people over the past decades.[100] This trend indicates that dementia risk might be modifiable and that dementia onset can, at the population level, be delayed, possibly as a result of societal changes such as improvements in education, and prevention and treatment strategies.[100]

Slowing of accelerated cognitive decline and prevention of dementia in late life should become important goals in the management of type 2 diabetes. With regard to opportunities for effective prevention and treatment for these late-life disorders, a lifespan perspective is needed—appropriate treatments tailored to the risk profiles and disease processes of individual patients from different age groups need to be developed. This development will also need new methods to show convincingly that these treatments improve clinical outcomes, because present approaches in clinical trials are poorly suited to assess, for example, the effects of lifestyle interventions in midlife on dementia incidence several decades later. These methods might include the use of proxies for the ultimate outcome that can already be assessed much earlier in life than the outcome itself. Whether the slight cognitive decrements or early MRI abnormalities that are associated with type 2 diabetes represent such proxies for late-life dementia is unclear.

Preventive measures from young adulthood to late midlife should probably consist of generic approaches, promoting a healthy lifestyle and a favourable cardiovascular risk factor profile. No arguments exist to approach prevention of dementia differently from that of other conditions, such as cardiovascular disease (panel). From midlife onwards, end-organ damage—particularly cardiovascular disease and microvascular diabetic complications—can become clinically manifest. These

manifestations should guide preventive measures, according to guidelines for their management.[35] Development of specific approaches for dementia prevention starting in midlife is probably neither feasible nor necessary.

Vascular and Alzheimer-type processes that ultimately lead to dementia generally start to develop in the brain from the age of 50–60 years onwards, one or more decades before dementia typically becomes clinically manifest.[101] At this stage, preventive treatments are likely to be most effective in those individuals at high risk of dementia, analogous to present approaches in prevention of cardiovascular disease that target individuals at high risk of vascular events (panel). Biomarker approaches such as brain imaging are not yet optimally suited to efficiently identify individuals at high risk of dementia at the population level. However, prediction models are becoming available that identify individuals at risk, on the basis of demographic variables and cardiovascular profiles. Such a prediction model has been established specifically for people with type 2 diabetes who are older than 60 years.[102] These prediction models can be used to select high-risk individuals for future dementia prevention trials. Such trials could include drugs that might delay cerebrovascular disease, but specific classes of glucose-lowering drugs, based on properties other than their primary glucose-lowering effects, might also be of interest. Such drugs could include those acting through the incretin system, because incretins have direct effects on the brain in experimental models, including delaying cognitive decline and reducing the burden of amyloid toxicity in mouse models of Alzheimer's disease.[103,104] Similar pleipotropic actions are reported for insulin. For these reasons, intranasally administered insulin is being tested in randomised controlled trials in people with Alzheimer's disease.[105]

Patients with type 2 diabetes and MCI or early Alzheimer's disease might also benefit from dedicated tailored treatment, because in these stages diabetes is still a risk factor for accelerated cognitive decline. However, once dementia becomes more advanced, diabetes-specific approaches are unlikely to delay further cognitive decline, because at these stages type 2 diabetes no longer seems to be an important determinant of disease progression and the clinical profile of dementia. Nevertheless, in these later stages reconsideration of the targets for diabetes management might be appropriate. That the risk–benefit ratio of tight glycaemic control is less favourable in people with type 2 diabetes and impaired cognition is becoming increasingly clear. Hypoglycaemic episodes, for example, seem to have a reciprocal connection with cognition in these patients, with cognitive dysfunction increasing the likelihood of severe hypoglycaemic episodes, and hypoglycaemic episodes increasing the risk of further cognitive decline.[66] This association is taken into account in guidelines for diabetes management, which recommend greater leniency with glycaemic control in patients with important comorbidities such as dementia.[106]

Contributors

GJB created the structure of the Review, searched for and selected references, and prepared the first draft and subsequent versions. RAW, MWJS, and FLJV helped to select references and contributed to writing. LJK, RAW, MWJS, and FLJV helped to refine the idea and structure of the Review, and commented on the drafts.

Conflicts of interest

GJB consults for and receives research support from Boehringer Ingelheim, consults for Takeda Pharmaceuticals, and has received speaker's fees from Eli Lilly. LJK has received consulting and speaker's fees from Bayer, Boehringer Ingelheim, and Bristol-Myer's Squibb. MWJS received speaker's fees from Novo Nordisk, Eli Lilly, Pfizer, and Bristol-Myer's Squibb, and received support for travel and accommodation at a scientific meeting from Sanofi-Aventis. RAW and FLJV declare that they have no conflicts of interest.

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