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Cognitive decline and dementia in diabetes: mechanisms and clinical implications

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Abstract

Cognitive dysfunction is increasingly recognized as an important comorbidity of diabetes mellitus. Different stages of diabetes-associated cognitive dysfunction can be discerned, with different cognitive features, affected age groups, prognosis, and likely also different underlying mechanisms. Relatively subtle, slowly progressive cognitive decrements occur in all age groups. More severe stages, particularly mild cognitive impairment and dementia, with progressive deficits, occur primarily in older individuals. The latter are clearly most relevant for patient management and are the focus of this review.

Evolving insights from studies on risk factors, brain imaging, and neuropathology provide important clues on mechanisms. In the majority of patients multiple etiologies likely determine the cognitive phenotype. Although both the risk of -clinically diagnosed- Alzheimer's disease and that of vascular dementia is increased in association with diabetes, the cerebral burden of the prototypical Alzheimer's pathologies is not. A major challenge is therefore to pinpoint from the spectrum of diabetes-related disease processes those that affect the brain and contribute to development of dementia beyond Alzheimer's pathologies. Observations from experimental models can help to meet that challenge, but this requires further improving the synergy between experimental and clinical scientists. Development of targeted treatment and preventive strategies depends on these translational efforts.

Worldwide the prevalence of diabetes is increasing, both in absolute and relative numbers[1]. Particularly for type 2 diabetes (T2DM), this is attributed to changing lifestyle factors, such as diet, overweight and physical inactivity[2]. Another key factor that adds to the prevalence of T2DM is increased longevity and aging of populations around the world. The latter is particularly evident in low and middle income countries[1]. These trends are expected to continue over the years to come. For dementia, we see very similar population trends[3]. As a

Literature selection

Due to the wide scope of this review, the references cited represent a selection of the available literature. Where possible, we referred to published (systematic) reviews, that provide a complete overview of available original studies. When original studies on a particular topic were quoted, and multiple studies were available, we quoted the first landmark studies and/or the most recent comprehensive studies that – in our view – represent a major advance to the field. For further background on specific topics the reader is encouraged to read the quoted papers and also explore the additional references provided in those papers.

consequence, there is an increased cooccurrence of diabetes and dementia. It has become evident, however, that diabetes and dementia concur more frequently than would be expected by chance alone. Epidemiological studies have established an increased risk of dementia among individuals with diabetes[4]. Diabetes is also linked to less severe forms of cognitive dysfunction[5]. This has important implications for patient management, particularly in older individuals where dementia and pre-dementia stages of cognitive impairment most commonly occur.

This review addresses the different manifestations of diabetes-associated cognitive dysfunction. Emphasis will be on dementia and pre-dementia stages of cognitive impairment in T2DM. Throughout the manuscript we will use the term diabetes if we refer to diabetes in general and T1DM or T2DM if we refer to these specific subtypes. We will show that studies on risk factors and on neuroimaging and neuropathology correlates of cognitive dysfunction provide important clues on underlying mechanisms, although many questions still remain. Experimental models may help to further unravel the etiology and identify treatment targets. A key strength of experimental models is clearly that they can single out individual causative pathways, in ways and at a level of detail that is impossible in humans. Technical progress provided tools that can boost studies of these pathways, from the level of specific molecular interactions to systems biology. It is of fundamental importance, however, that potential mechanisms identified in models are also evaluated in the context of other morbidities with which they may cooccur in patients. We will make the point that further improving synergy between clinical and experimental scientists can foster innovation in designing animal models that accurately replicate the complexities of the interaction between diabetes and dementia in humans.

While awaiting these further research developments, cognitive dysfunction in diabetes does already affect daily clinical care today. The final section of this review addresses clinical implications of the latest data on diabetic brain injury and future perspectives.

Cognitive dysfunction and diabetes: scope of the problem

There is strong epidemiological evidence for links between diabetes and cognitive dysfunction [5–7]. Importantly, cognitive dysfunction in relation to diabetes should not be regarded as a unitary construct. Manifestations and prognosis of diabetes-associated cognitive dysfunction vary depending on diabetes type and age[8].

In children with T1DM, for example, there may be subtle changes in cognitive development, particularly in those with an onset of diabetes before the age of 7[9]. Adults with T1DM also present subtle decrements in cognitive performance relative to age-matched controls, particularly affecting the domains intelligence (effect size Cohen's d= 0.7), psychomotor efficiency (d =0.6), and cognitive flexibility (d = 0.5)[10]. These decrements generally remain quite stable over time [11], although there may be subgroups of patients, particularly those with advanced microvascular complications, in whom the severity of cognitive impairment may worsen substantially over time[9,12].

In adults with T2DM, deficits in cognitive functioning can roughly be divided in three different stages, according to severity: diabetes-associated cognitive decrements, mild cognitive impairment (MCI), and dementia[5]. The term diabetes-associated decrements refers to subtle changes in cognitive function, that might give rise to cognitive complaints (usually expressed only by the patient), but should not affect activities of daily life or diabetes self-management[5]. The subtle cognitive changes may concern one or several domains, including processing speed, executive function, and memory, typically with a Cohen's effect size of 0.2–0.5 relative to people without diabetes at the group level (systematic reviews [13,14]). These decrements are likely to have an onset in pre-diabetic stages[15] and evolve only very slowly over the course of many years, at a rate that is up to 50% faster than that of normal cognitive ageing [13,15–18].

Mild cognitive impairment and dementia

Diagnostic constructs for mild cognitive impairment and dementia and their etiologies in people with diabetes are the same as in people without diabetes (text box 1)

Two prospective population-based studies, have reported quite comparable findings on the risk of MCI in patients with diabetes. One observed a hazard ratio (HR) of 1.5 (95% confidence interval (CI) 1.0–2.2) for amnesic MCI and of 1.2 (0.9–1.8) for nonamnesic MCI[24]. The other reported a HR of 1.6 (1.2–2.2) form amnesic and 1.4 (0.8–2.2) for nonamnesic MCI[25]. Prognosis of MCI is worse in patients with diabetes. Two meta-analyses, each containing seven - not completely overlapping - studies, reported a relative risk (RR) of conversion to dementia of 1.7 (1.1–2.4)[26] and 1.7 (1.1–2.6)[27] for patients with MCI and diabetes, compared to patients with MCI without diabetes.

There have been many studies on the risk of dementia in relation to diabetes. Systematic reviews and meta-analyses[4,6,7,28], including over 25 original studies with well over 2 million participants, estimate the RR for all type dementia at 1.73 (1.65–1.82)[6], for Alzheimer's disease (AD) at 1.53, (1.42–1.63)[7], and for vascular dementia at 2.27 (1.94–2.66)[6] for people with diabetes compared to those without. A large recent cohort study from Canada indicates that dementia risk is already increased in those with newly diagnosed diabetes (HR 1.16 (1.15–1.18))[29]. Moreover, elevated glucose levels in individuals without diabetes have also been linked to increased dementia risk[30].

When stratified by ethnicity, the RR of AD in Western populations and Eastern populations were 1.36 (1.18–1.53) and 1.62 (1.49–1.75), respectively[7]. When stratified by sex, the RR of all type dementia in women with diabetes was 1.62 (1.45–1.80) and in men 1.58 (1.38–1.81)[28]. For vascular dementia the RR was 2.34 (1.86–2.94) in women and 1.73 (1.61–1.85) in men, translating into a 19% greater risk for the development of vascular dementia in women with diabetes than men[28]. Of note, few previous studies have addressed such potential modifying effects of sex and ethnicity (e.g. [7,28,31]), and these topics needs further exploration.

Trajectories of cognitive dysfunction

Based on current evidence, we would argue that the different stages of cognitive dysfunction in patients with diabetes should not be regarded as a continuum[15]. Diabetes- associated decrements, the mildest stage, can occur in all age groups, from young adults and even adolescents with T2DM[32,33] to the oldest old[34]. Further cognitive decline over time is generally slow over the course of many years[15]. These decrements affect the patients with diabetes as a group. In other words, there is a subtle shift in average cognitive performance across individuals and the difference compared to people without diabetes is not due to poor performance of a small subgroup of patients pulling the average performance of the patients down. At an individual level, due to the subtle nature of the deficits, it is difficult to establish if a patient is affected based on formal cognitive testing. Dementia, on the other hand, is characterized by poor cognitive performance where an individual stands apart from what is considered normal cognitive performance. In other words, it affects individuals. It is primarily a condition of old age[3] and mostly involves relentless, year-by-year, cognitive decline. Although diabetes may also increase the risk of young-onset dementia (i.e. before the age of 65)[35,36], the vast majority of individuals with diabetes who develop dementia are well over the age of 65, just like people without diabetes[3]. Hence, considering the marked differences in affected age-groups clinical manifestation, and trajectories of cognitive decline, diabetes-associated cognitive decrements and dementia should be regarded as different entities, likely with different underlying mechanisms.

Mechanisms of cognitive dysfunction – observations in humans

In light of the increasing prevalence of diabetes, population trends in ageing, and the impact of cognitive dysfunction on affected individuals and society as a whole, preventive treatment is warranted. However, insight in potential therapeutic targets and underlying mechanisms is still incomplete, although there is an evolving scientific literature that does provide important clues.

An important trend is that recent studies not only provide data on risk factors and brain imaging correlates of diabetes-associated cognitive decrements, but increasingly also on dementia. While the latter is clearly most clinically relevant, it is also much more challenging to address with epidemiological studies. It requires huge cohorts to acquire a sufficient number of cases of patients with T2DM and incident dementia[31]. Fortunately, large collaborative autopsy studies[37] and novel biomarkers of dementia etiology have also stimulated progress in this field. This section will summarize this literature, focusing on T2DM.

Risk factors

The main picture that emerges from the many studies on the risk factors for cognitive dysfunction in diabetes is that there are many different factors involved, with (very) small effects each[15,38].

Glycaemic control has received a lot of attention. Converging evidence shows that higher A1C levels are associated with diabetes-associated cognitive decrements, but the strength of

the relation is weak[39]. A1C levels (or repeated glucose measurements) have also been linked to dementia risk in people without diabetes[30]. Whether A1C levels are also related to dementia risk among people with diabetes is less clear. There are few available studies [39] and there are indications of non-linearity, where both low and high levels related to dementia risk[30]. There also is an emerging literature indicating that apart from chronically elevated glucose levels fluctuations or peaks in glucose levels may be linked to cognitive decrements as well as dementia risk[39,40].

Observational studies have reported potential benefit for cognition of some glucose lowering compound over others[41], which suggests the need to assess outcomes other than blood glucose and A1C levels to understand the effect of anti-hyperglycemia drugs on cognition A recent large registry study in veterans with T2DM <75 years of age[42], for example, found metformin use to be associated with a lower risk of subsequent dementia than sulfonylurea use, while adjusting for known confounders. Yet, randomized controlled intervention studies thus far do not support that intensive glycaemic control or any particular glucose lowering agent is associated with better cognitive functioning[39,43], or dementia[44]. Occurrence of hypoglycemic episodes, on the other hand, is clearly linked to cognitive decline and increased dementia risk[29,31,38,39].

Vascular risk factors, in particular hypertension and dyslipidemia, may be associated with cognitive decrements among people with T2DM, although the evidence is inconsistent despite a substantial number of studies[38]. Few studies have addressed how vascular risk factors affect dementia risk among patients with T2DM[29,38]. Yet, because many studies in the general population have demonstrated the importance of (midlife) vascular risk factors for dementia risk [45,46], and because T2DM is associated with an adverse vascular risk factor profile, also in prediabetic stages[1], it is reasonable assume that these factors contribute to dementia risk among patients with T2DM and are thus a lead for prevention. It is also clear that patients with manifestations of microvascular (e.g. diabetic retinopathy) or macrovascular disease (e.g. myocardial infarction, stroke) are more likely to have worse cognitive performance[15,38] and are at increased dementia risk[29,31]. Other studies have identified insulin resistance, inflammation, and depression as potential risk factors for cognitive dysfunction in people with diabetes[38,39].

All in all, it is clear that multiple risk factors are involved[38]. It is also clear that there are still substantial knowledge gaps on how these interconnect, translate to potentially modifiable mechanisms, and also on which genetic factors are involved.

Patterns of brain injury

There is an expanding literature on brain imaging studies in patients with diabetes[47,48], although it should be noted that few studies included patients who were affected by MCI or dementia. As a framework for the interpretation of the findings, it is important to distinguish between imaging markers that primarily reflect brain injury, markers that reflect specific etiological processes, and markers that reflect both. Markers of injury include, for example, measures of atrophy and microstructural white matter integrity. Although patterns of injury may be suggestive of a particular etiology, they are by no means etiologically specific (e.g.

medial temporal lobe atrophy cannot be taken as proof for AD as a primary etiology). Markers of etiological processes include for example amyloid PET and measures of cerebral blood flow, although the latter may also change as a consequence of brain injury.

It is clear from the literature that T2DM is associated with brain atrophy (figure 1), although the regional pattern of brain volume changes varies between studies[47,48]. The magnitude of the volume reduction is modest, with effect sizes of 0.2–0.6 SD units, comparable with 3–5 years of normal aging[47]. Another emerging marker of brain injury in T2DM is diffusion tensor imaging (DTI). This technique allows to explore microstructural integrity of the white matter and related changes in brain networks. DTI studies show widespread changes in white matter microstructure and connectivity in relation to T2DM, which are clearly related to cognitive dysfunction[47,48].

Given the links between diabetes and vascular disease, manifestations of so-called cerebral small vessel disease on MRI are clearly of interest. These include lacunes, white matter hyperintensities, visible perivascular spaces, microbleeds and microinfarcts[49]. Although widely accepted as markers of vascular injury, these MRI visible lesions have limited specificity for particular underlying etiological processes[49]. White matter hyperintensities, for example, can develop as a consequence of different underlying vascular pathologies, but also as a consequence of non-vascular processes such as inflammation[50]. Based on the current literature, T2DM is associated with an increased occurrence of lacunes and a modest increase in the volume of white matter hyperintensities (Figure 1)[47]. There may be an increased occurrence of microbleeds in patients with T2DM, but evidence is not consistent[47,5152]. There have been very few imaging studies on the relation between T2DM and perivascular spaces[53,54] and microinfarcts[55] thus far.

Etiological markers and neuropathology

As also indicated in the preceding section, diabetes is clearly associated with vascular brain injury on MRI. Indeed, neuropathological studies also report an increased burden of cerebrovascular lesions in people with diabetes. This particularly concerns lacunes[37,56]. In contrast, neuropathological studies do not report a clear increase in the burden of large artery infarcts or microinfarcts in patients with diabetes[37,56]. The increased occurrence of lacunes might be attributable to abnormalities in the small cerebral perforating arterioles, such as arteriolosclerosis, lipohyalinosis, or fibrinoid necrosis[57]. Indeed, there are studies in human autopsy material that show arteriolar abnormalities in patients with diabetes[58,59], but it should be noted that to date the impact of diabetes on the different blood vessel types of the brain has not been assessed systematically. Also with regard to cerebrovascular dysfunction in T2DM there are still uncertainties. There are reports of reduced cerebral perfusion and impaired cerebrovascular reactivity, but results of different studies have been conflicting, likely due to differences in study populations, imaging techniques and variation in dealing with confounding factors like cerebral atrophy[60].

Evidently, AD is another key etiology to consider. Converging evidence from brain autopsy studies from the past decade shows that the core neuropathological features of AD are not more common in subjects with than in those without T2DM[61]. Several recent studies of

large autopsy cohorts report that the occurrence of neuritic amyloid plaques (Odds ratio (OR) 0.96 (95% CI 0.68–1.36)[37]; 1.08 (0.84–1.38)[56]; 0.97 (0.68–1.38)[62]) and tau tangles (0.82 (0.61–1.11)[37]; 0.85 (0.66–1.11)[56] 1.12 (0.81–1.54)[62]), p = 0.48) is not increased in T2DM. Studies on in vivo biomarkers of AD pathology are completely in line with these observations. T2DM is neither associated with CSF or PET biomarkers of cerebral amyloid nor tau pathology[63–65]. Yet, despite these findings, T2DM is associated with higher levels of MRI and PET biomarkers of neurodegeneration[65], suggesting that T2DM accelerates neurodegeneration via non-AD mechanisms.

Another emerging concept in mechanistic studies is the potential role of cerebral insulin resistance[66,67]. Insulin signaling in the brain has important roles in brain physiology and cognition[66,67]. Moreover, disturbances in insulin signaling have been noted in brain tissue of people with AD, irrespective of T2DM (review[67]). This gives rise to the possibility that a core feature of T2DM, disturbed insulin signaling, causing insulin resistance, not only affects systemic metabolism, but also directly impacts the brain, by disturbing cerebral insulin pathways. Other etiological leads from studies in humans that warrant further investigation are accumulation of advanced glycation end products (AGEs)[68] – for which skin autofluorescence is a non-invasive proxy – and increased blood-brain barrier (BBB) permeability[69], pointing to possible roles of inflammation and endothelial dysfunction.

Diverging observations, converging pathways?

The preceding sections on studies in humans clearly do not point to a single mechanism underlying diabetes-associated cognitive dysfunction. The different stages of cognitive dysfunction in T2DM differ in severity, prognosis and likely have different underlying etiologies. Moreover, while diabetes is associated with several different imaging-manifestations of cerebral injury, one patient may show one manifestation and the next patient another. Furthermore, how can we understand that diabetes increases the risk of a clinical diagnosis of AD, while biomarker and neuropathological studies clearly indicate that the burden of AD pathologies is not increased? The likely explanation is that in the majority of individuals with diabetes the clinical phenotype of cognitive dysfunction or dementia is due to multiple pathologies (figure 2). Hence, although AD pathologies are not increased in T2DM, they are still considered the commonest cause of dementia, also in people with T2DM: over 40% of individuals with T2DM have intermediate to severe AD pathology in their brain at the time of death[37,62]. Yet, the elevated dementia risk in T2DM should be attributed to pathologies other than AD, which may often evolve on a background of AD pathology. The major challenge for etiological studies is thus to pinpoint from the diverse spectrum of diabetes-related disease processes those specific mechanisms affecting the brain beyond AD pathology. This clearly includes vascular disease, but likely also non-AD mechanism of neurodegeneration. The next section will summarize how animal models may contribute in meeting that challenge.

Mechanisms of cognitive dysfunction: experimental models

The diverse spectrum of findings identified in patients with diabetes with or without dementia is mechanistically explored using experimental models, including cell lines,

organoids and animal models ranging from rodents to non-human primates. Rodents are commonly used in both diabetes and dementia research owing to their genetic similarities to humans, including genome size, number of genes (99%) and synteny. Neither diabetes nor AD-like pathology develops spontaneously in rodents, unless specific gene manipulations or pharmacological interventions are used. Depending on the intervention, conditions associated with diabetes, dementia, or both can be induced in rodents (see Table 1). For the most part, insights from these interventions have been restricted to cerebral effects of inducing diabetes in normal rodents[70–81] (non-AD rodent models; Table 1) and in rodents genetically modified to accumulate β-amyloid (Aβ) in the brain[82–86] (AD rodent models; Table 1).

Here, we reviewed these rodent models with the objective of identifying pathophysiological processes that may contribute to an AD phenotype without entailing AD pathology. We also suggested characteristics that need to be captured in novel animal models in order to optimize our chances to uncover mechanisms underlying the dementia risk in diabetes.

Crosstalk between diabetes and AD-related processes

In mice without pre-existing AD pathology (Table 1; non-AD rodent models), induction of diabetes, genetically, pharmacologically (i.e., streptozotocin injection) or by diet, is associated with increased Aβ generation[75–78] and hyperphosphorylation of tau protein[71–74]. Similarly, diabetic AD mice showed accelerated cerebral Aβ formation[84,85] and cerebrovascular pathologies[82,83], including aneurisms and small strokes (Table 1; AD rodent models). In contrast to humans however, brains of diabetic AD mice had no brain atrophy [83]. In brains from diabetic AD mice generated by crossing AD mice with db/db mice, an increased vascularization was observed[83], which probably compensated for the leptin deficiency-mediated vascular disruption. Thus, inducing diabetic states lowers the threshold for neurodegeneration in AD mice via mechanisms that involve cerebrovascular pathologies[82–86].

Cerebral insulin resistance in rodent models of type 2 diabetes and AD

As mentioned earlier in this review, data from experimental models of demonstrate commonalities in abnormalities in signaling pathways between cerebral an in systemic insulin resistance, providing potential pathways that can link metabolic and cerebral changes in T2DM[67]. Moreover, experimental models show that brain insulin resistance may contribute to AD by promoting Aβ generation and hyperphosphorylation of tau protein [71–78,84,85]. Increased brain levels of Aβ correlated with altered insulin signal transduction and autophagy and increased beta-site amyloid precursor protein cleaving enzyme (BACE)1/β-secretase and γ-secretase activities[77,78]. The results suggest a role of insulin resistance and subsequent hyperinsulinemia in impairing Aβ clearance. Streptozotocin injection in mice, which results in insulin deficiency, characteristic of an advanced diabetic state, appears linked to abnormal brain levels of hyperphosphorylated tau protein[71,72,74,79].

Stimulating hippocampal insulin receptors by direct administration of insulin into the hippocampus improved learning ability in normal rodents[87,88]. A similar treatment had less

effect in diabetic rodents[88]. Brain levels of Aβ and tau hyperphosphorylation were reduced in AD mice by treatments that improved insulin availability or/and sensitivity (experimental work reviewed in[66]). Thus, brain insulin resistance plays a complex role in promoting AD pathology and is a promising therapeutic target to slow the progression of cognitive decline in humans.

Non-AD processes contributing to an AD phenotype in diabetes

Induction of diabetic states in non-AD rodents can cause memory and learning impairments[59,70,79–81,89]. Possible non-AD processes contributing to cognitive dysfunction in rodent models of diabetes are discussed below (see Table 2).

Vascular endothelial dysfunction

In diabetes, endothelial dysfunction is linked to vascular accumulation of toxic lipids[90], AGEs products[91] or/and aggregated proteins[59]. Proteinaceous deposition on blood vessel walls damages endothelial cells[59,91], increases the production of reactive oxygen species (ROS)[92,93] and impairs production of vasodilatory substances[92], which reduces the cerebral blood flow. Stalled blood flow can lead to neurovascular uncoupling and hypoxic neuronal injury[92–94]. Elevated ROS production can further damage cellular structures and activate matrix metalloproteinases inducing cytoskeletal reorganization and vascular remodeling[93]. Cytoskeletal reorganization affects the stability of tight junction proteins resulting in increased capillary permeability, depletion of energy resources and altered neural viability[92,93].

Inflammation and blood-brain barrier injury

Vascular endothelial dysfunction upregulates inflammatory mediators which can disrupt the BBB[59,89,93,94]. BBB disruption exposes the brain parenchyma to potentially neurotoxic blood proteins, thrombin, fibrin, plasmin and hemoglobin, as well as the iron from lysed red blood cells. A leaky BBB induces abnormal neuronal activity[93].

White matter disease of vascular origin

White matter disease has been clinically associated with vascular contributions to cognitive impairment and dementia[93,94]. It is also known as small blood vessel disease and may be the result of long term endothelial dysfunction, capillary loss and subsequent ischemia[93,94]. Indeed, recent results[59] from a rat model of T2DM demonstrated the association of periventricular white matter injury with chronic vascular endothelial dysfunction, microhemorrhages and reduced brain perfusion.

Demyelination and axonal loss

Compared to normal rats, brains of diabetic rats have myelin loss, abundant white matter vacuoles and smaller volumes[59]. Demyelination and loss of axons can alter synthesis or/and release of neurotransmitters in the brain, which can further accentuate white matter disease and brain atrophy. Brain phenylalanine and tyrosine (precursors of catecholamine) were

reduced by >50% in diabetic rats compared to normal rats[95]. Thus, experimental diabetes can cause impairments of protein synthesis in the brain.

Peroxidative membrane injury, mitochondrial dysfunction and neurodegeneration

Exposure of unsaturated fatty acids to cytosolic ROS generates reactive aldehydes, such as 4-hydroxynonenal (4-HNE) and malondialdehyde (MDA)[96]. Elevated reactive aldehyde levels cause peroxidative membrane injury and have been used as biomarkers for neuronal oxidative damage[96]. Indeed, brain tissues from diabetic rats and from patients with diabetes and AD showed intraneural accumulation of 4-HNE-based adducts[97], indicating the peroxidative cell damage as a contributor to neurodegeneration in diabetes.

Accumulating evidence from experimental models of insulin resistance and T2DM indicates systemic mitochondrial dysfunction as a pathological mechanism contributing to health deterioration and cognitive decline. Specific mechanisms linking mitochondrial and metabolic dysfunction with neurodegeneration and AD were discussed in a recent review[98].

Neuronal Ca2+ mishandling, posttranslational modification of Ca2+-dependent proteinkinases

In diabetic rats, altered Ca2+ signaling contributes to neuron dysfunction via multiple mechanisms[99]. A recent study in brains (and hearts) of humans with diabetes and AD and in brains of diabetic rats identified posttranslational modification of Ca2+/calmodulin-dependent proteinkinase II (CaMKII)[100]. It was shown that diabetes induces O-GlcNAcylation (covalent binding of O-linked Nacetylglucosamine) of CaMKII, which activates the kinase[100]. Overactivity of CaMKII can cause neuronal excitotoxicity and dysfunction of ion channels involved in gene transcription and viability.

Amylin dyshomeostasis: a bridge between AD and non-AD processes?

Amylin is a pancreatic β-cell hormone co-secreted with insulin and plays a role in normal glucose homeostasis[101]. Amylin from humans (but not rodents[101]) is amyloidogenic and aggregates quickly when overexpressed. The majority of individuals with T2DM have large deposits of aggregated amylin in the pancreatic islets[101], kidneys[102] and heart[103]. Aggregated amylin induces cell dysfunction and apoptosis[101]. Accumulating data from several laboratories have confirmed that the brains of patients with T2DM and AD contain an abnormally increased level of aggregated amylin and mixed amylin-Aβ plaques[104–107] (see figure 3). A recent epidemiological study indicated also a genetic risk for developing mixed Aβ-amylin plaques in the brain[108]. The results indicate amylin dyshomeostasis as a possible new link between T2DM and increased risk of AD[104–108].

Amylin is oversecreted in individuals with prediabetic insulin resistance (i.e., hyperinsulinemia coincides always with hyperamylinemia) [101]. Overexpression (3-fold) of human amylin in the pancreatic β-cells of rodents (HIP rats and mice) results in pancreatic amyloid, β-cell apoptosis and overt hyperglycemia[109]. In addition to the development of

late-onset T2DM, HIP rats showed vestibulomotor dysfunction, altered balance, and impaired memory and learning ability[59,89]. Brain dysfunction in HIP rats correlated with amylin deposition in brain blood vessels[59,89] and brain parenchyma[59]. In contrast to diabetic AD mice generated by crossing AD mice with db/db mice[83], which showed brain microhemorrhages without parenchymal loss, HIP rats have brain microhemorrhages associated with white matter rarefaction and brain atrophy[59] (see Table 1). A recent study[110] demonstrated that HIP mice expressing a mutant form of the APP in neurons develop cross-seeding of amylin-Aβ pathology leading to accelerated brain dysfunction compared to transgenic mice expressing only amylin or the Aβ protein. These results suggest that systemic amylin dyshomeostasis is a trigger of mixed vascular-amylin-Aβ pathologies. Interaction of amylin with Aβ pathology was also documented in brains of patients with diabetes and AD[104,105]. These results suggest that not increased Aβ burden per se, but perhaps amyloid with a different composition may develop in brains of patients with diabetes and AD.

Next steps, challenges and further improvements of experimental models

Each animal model (Table 1) has certain limitations and no experimental model exists that accurately phenocopies the human brain condition in diabetes and AD. For example, transgenic mouse models of AD overexpressing the amyloid precursor protein (APP) do not only show exacerbated Aβ, but also elevated full length of APP and other fragments of the Aβ processing[111,112]. This might explain why the amyloid burden is increased in diabetic AD mice but not in patients with AD and T2DM.

The pathophysiology of T2DM encompasses a complex interplay of multiple deficiencies involving insulin resistance, relative insulin deficiency and pancreatic β-cell dysfunction that ultimately result in multiorgan impairments. Although AD is primarily a neurodegenerative process, it often occurs in the context of vascular risk factors, systemic cardiovascular disease and cerebral vascular pathology in humans [45,46,113].. Mice that accumulate Aβ in the brain do not demonstrate these vascular co-morbidities. Thus, to achieve progress in investigating and validating causative mechanisms of increased risk of cognitive decline in patients with T2DM, we think a vital tool will be animal models carrying significant heterogeneity of diabetes pathology along with a broad spectrum of phenotypes seen in patients with dementia. Novel lines of transgenic mice that are engineered to achieve inducible and reversible expression of human proteins involved with diabetic brain injury could be an important step to identify a cerebral pathologic substrate of diabetes.

Current implications for patient management

Manifestations of cognitive dysfunction in diabetes, as reviewed herein, are increasingly recognized. Recent clinical diabetes guidelines start to provide suggestions how cognitive impairment should be detected and how this should affect diabetes management[114–116].

Clearly, detection and management of cognitive dysfunction in T2DM is not “ One size fits all”. The different stages of cognitive dysfunction, due to their different features and impact, require different approaches. Diabetes-associated cognitive decrements are by definition

subtle, without clearly affecting social or occupational functioning or diabetes self management[5]. It therefore suffices to act on cognitive complaints, rather than to strive for active detection strategies like screening. Approaches to diagnose and manage diabetes-associated cognitive decrements and to differentiate these subtle cognitive deficits from more severe stages of cognitive dysfunction, in particular MCI and dementia, have been proposed before[5]. First of all, age of the patient provides important context, as cognitive decrements occur in all age groups, whereas MCI and dementia rarely occur under the age of 60 to 65[20]. Secondly, the nature of the complaints should be compatible with decrements, in that the patient may express worries about his or her cognitive abilities, often focusing on memory, but that there are no obvious mishaps. Finally, the complaints should have developed insidiously, with limited progression over time, and there should be no alternative explanations. In such cases, it may often be sufficient to explain the patient that the complaints may be due to diabetes-associated cognitive decrements, that the complaints can be annoying, but that further marked decline is not expected to occur, particularly in patients under the age of 60 to 65. Yet, it should be acknowledged that a diagnostic label of "diabetes-associated cognitive decrements" always remains a probable diagnosis, purely based on the symptoms, as there are no definite signs on which it can be based[5]. Hence, reevaluation of the patient after 6 to 12 months is generally warranted, to verify if the course is indeed compatible with the diagnosis.

MCI and dementia clearly warrant another approach. These stages of cognitive dysfunction are associated with worse diabetes self-management and glycaemic control, with an increased frequency of hospital admissions and occurrence of severe hypoglycemic episodes, and with an increased occurrence of major cardiovascular events and death in patients with diabetes[44,117,118]. In order to try to avoid these adverse outcomes, screening for cognitive impairment in older adults with diabetes is being advocated[116]. Nevertheless, it should be acknowledged that there are still open questions regarding the actual target group and frequency for screening, the appropriate screening instrument, and – importantly – if early identification of cognitive impairment can indeed avert these adverse outcomes. With regard to the diagnostic approach of patients who are actually suspected of cognitive impairment the picture is much clearer: that should be no different from that in patients without diabetes[5]. As there are no diabetes specific features to MCI and dementia the same diagnostic tests are indicated as in patients without diabetes. Yet, the evaluation should consider how the cognitive deficits impact diabetes management. Particularly in patients with MCI, there should be serial assessments over time to monitor for changes in cognitive status[20], as some patients may progress to dementia, whereas others may remain stable or even improve.

At present there are no treatments that can halt the processes that underlie cognitive impairment, except from adequate cardiovascular risk factor management. Importantly, such prevention strategies apply to patients of all age groups. While we have argued that there may be little benefit of actively screening for cognitive deficits in young adults or in midlife, vascular risk factor management and lifestyle modifications likely have the highest impact if started early and maintained throughout life. Of note, in patients without earlier cardiovascular events guidelines for primary prevention apply. Yet, if an MRI is performed and manifestations of small vessel disease detected, cardiovascular risk factor treatment may

be modified according to recent recommendations[119]. Finally, it has been proposed that the less favorable risk benefit ratio of intensive glycaemic control in older individuals with diabetes with cognitive impairment is an argument to set glycaemic targets higher (for details see recent guidelines[115,120]).

Future perspectives

Cognitive dysfunction is now accepted as an important and common comorbidity -or even complication- of diabetes mellitus. Research over the past decades has delineated the clinical features and brain imaging correlates of diabetes-associated cognitive dysfunction in different age groups across the lifespan[5,8]. Insights derived from clinical research are increasingly being translated to daily clinical care for individual patients with diabetes, but there are still knowledge gaps. Current challenges include improving the delineation of the diagnostic construct of diabetes-associated cognitive decrements and development of effective strategies to detect undiagnosed frank cognitive impairment in vulnerable subjects.

Course-modifying treatment and prevention strategies for diabetes-associated cognitive dysfunction, in particular MCI and dementia, remain the highest unmet needs. Therapies should target diabetes-specific mechanisms of cognitive dysfunction. However, other contributing disease processes, not unique to diabetes, also need to be elucidated further, because disease processes that are not specific to diabetes and may not even be accelerated by diabetes, like AD, are still likely to be important contributors to cognitive dysfunction in people with diabetes, just like they are in people without diabetes. Thus, developments in the etiological treatment of AD and other dementia etiologies outside the field of diabetes are also highly relevant (e.g.[121]). From a prevention perspective, individuals with T2DM and a particularly elevated dementia risk can be identified with established risk scores (e.g.[31]). They may constitute a particularly relevant target group in dementia prevention trials. In the meantime, it is important that randomized controlled trials on prevention of diabetic complications consider cognitive outcomes, if not as a primary outcome, than at least as secondary.

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TEXT Box 1:

Diagnostic constructs for mild cognitive impairment and dementia

Mild cognitive impairment (MCI) refers to acquired objective cognitive impairment (mostly defined as a performance below 1 to 1.5 SD units of normative values) affecting one or more cognitive domains with largely preserved activities of daily life[19,20]. This construct captures a stage between normal cognition and dementia that identifies individuals at high risk of transition to dementia. Dementia, in turn, is defined as acquired objective cognitive impairment affecting multiple cognitive domains, severe enough to affect activities of daily life[21].

Of note, the diagnostic labels MCI and dementia do not refer to a particular etiology. In clinical practice as well as in most epidemiological studies, assumptions on the likely etiology are primarily based on the nature of the symptoms (e.g. acquired episodic memory deficit is suggestive of Alzheimer's disease) , while excluding other causes (e.g. a brain tumor). It is clear, however, that this approach has insufficient specificity and sensitivity in determining the actual etiology[22]. Therefore, particularly in research settings, the etiology of MCI and dementia is increasingly based on biomarkers (e.g. amyloid in the cerebrospinal fluid (CSF) or on PET-scans to demonstrate Alzheimer pathology)[23].

TEXT Box 2.

Translational potential – enhancing cross-talk between clinical and experimental studies

Key features of cognitive dysfunction and dementia in humans with T2DM to be addressed:

- Cognitive dysfunction and dementia in T2DM are due to mixed etiologies, which mostly occur in the context of brain ageing
- Molecular or cellular processes involved in multiple etiologies (i.e. converging pathways) would be key targets for therapy
- T2DM does not accelerate the occurrence of AD pathologies. Yet, because AD pathologies are common, also in patients with T2DM, other etiologies will often occur on a background of AD pathology
- In addition to vascular pathologies, non-AD mechanisms of neurodegeneration should be a key focus of etiological research.

Insights from experimental studies to be considered:

- The intervention used to induce diabetes (Table 1) can impact the cerebral phenotype in rodent models, also apart from diabetes. Animal models that adequately capture the heterogeneity of diabetes seen in humans are essential to uncover a pathological substrate for cognitive dysfunction/dementia in T2DM.
- A number of non-AD processes (Table 2) appear to induce an AD-like phenotype in diabetic rodent models. For example, vascular lesions and mixed amylin-Aβ plaque formation occur in both rodent models of amylin dyshomeostasis and humans with dementia and T2DM. Understanding how these various pathways translate to cognitive dysfunction in humans with T2DM needs further investigation.

Key points

- Cognitive dysfunction in diabetes can manifest itself as diabetes-associated cognitive decrements, mild cognitive impairment (MCI), and dementia
- Because of marked differences in affected age-groups and trajectories of cognitive decline, diabetes-associated cognitive decrements and dementia should be regarded as different entities, likely with different underlying mechanisms
- Mechanisms of MCI and dementia in diabetes have mainly been studied in patients with T2DM and involve mixed vascular and neurodegenerative pathologies, often on a background of Alzheimer pathology, although T2DM does not increase the burden of the latter
- Key causative pathways in diabetes-associated cognitive dysfunction need to be identified in order to develop course modifying therapies
- Experimental models can single out individual causative pathways, in ways and at a level of detail that is impossible in humans
- It is of fundamental importance that potential mechanisms of brain dysfunction identified in experimental models of diabetes are also evaluated in the complex setting of other morbidities with which they may cooccur in patients

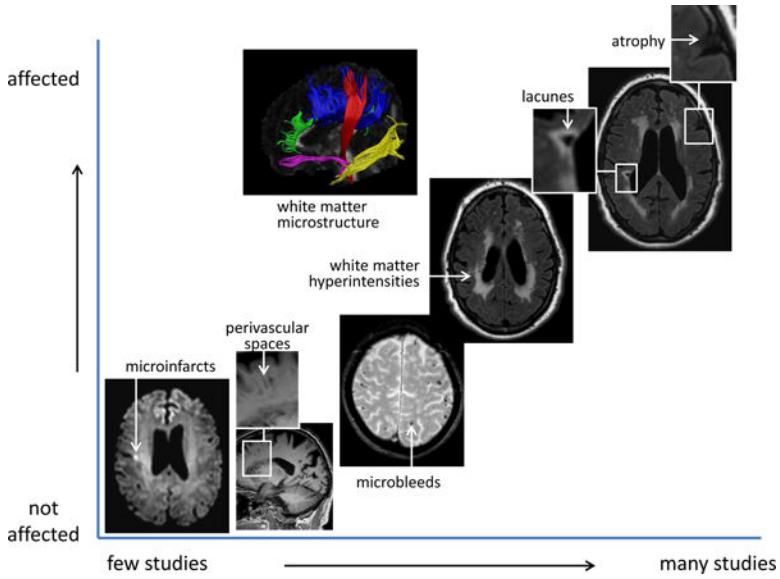

FIG 1.

Brain imaging findings in patients with T2DM

The figure summarizes findings form brain imaging studies in T2DM (for details and literature references see text). The position of each imaging marker on the X-axis reflects how intensively it has been studied in relation to T2DM. The position on the Y-axis reflects to which extent a marker is affected in individuals with T2DM relative to controls, based on the evidence from available studies. Image of white matter microstructure courtesy of Y Reijmer, UMC Utrecht.

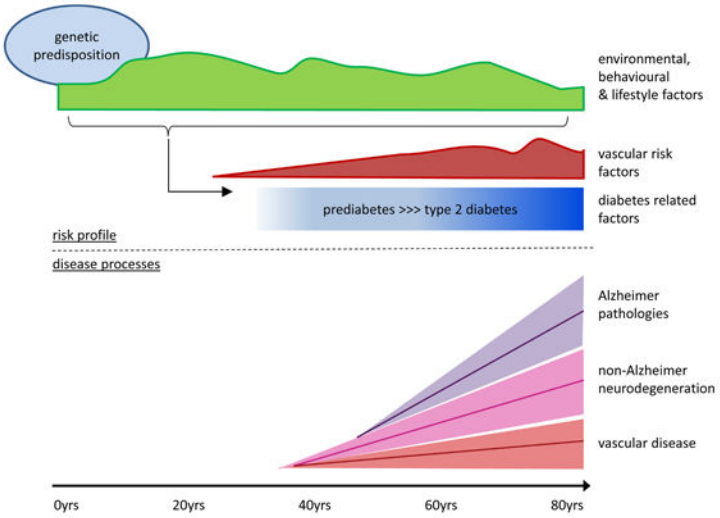

FIG 2.

risk factors and underlying pathologies for dementia in T2DM

The figure provides a life course perspective on risk factors and disease processes contributing to the development of T2DM and dementia. T2DM most commonly develops in mid- or late life, in the context of environmental, behavioural and lifestyle factors – that vary over the course of life - on a background of genetic risk. People with T2DM frequently have an adverse vascular risk factor profile, including obesity, hypertension and dyslipidemia, often already in prediabetic stages. Many of the factors that predispose and co-occur with T2DM, as well as factors that are related to having T2DM (e.g. elevated glucose, glucose lowering treatment) may affect the brain. Evidently, with so many factors involved there are marked interindividual differences in risk factor profiles and exposures.

Brain pathologies contributing to the development of dementia accumulate over the course of decades in the context of an individual's risk profile. In the majority of cases multiple pathologies cooccur, with variable proportions between individuals. Vascular pathologies are more common in individuals with T2DM than in those without and may thus contribute to the elevated dementia risk in T2DM. Of note, while Alzheimer pathologies are a key contributor to dementia in people with T2DM, the burden of these pathologies is not increased compared to people with T2DM. The excess dementia risk in people with T2DM is thus likely to be also attributable to additional non-Alzheimer neurodegenerative pathologies, which are yet to be identified (for details and references see main text).

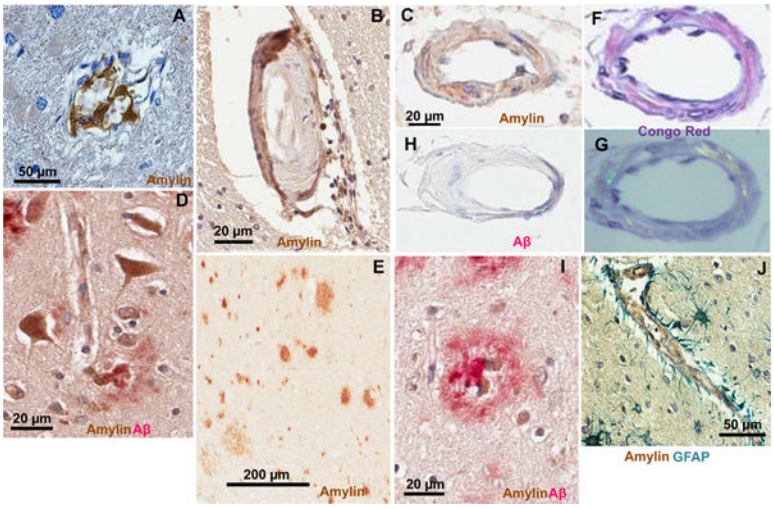

FIG 3.

Pancreatic amylin forms amyloid and interacts with Aβ in the brains of patients with T2DM

Sections through the brains of patients with T2DM and AD showing amylin-positive vascular wall contours in capillaries (**A**), small arterioles (**B** and **C**), neurons (**D**) and plaques (**E**). Vascular amylin deposits in (**C**) shows apple-green birefringence in the Congo red stain (**F** and **G**). Same blood vessel shows no Aβ immunoreactivity (**H**). Amylin interacts with Aβ forming cerebral mixed amylin-Aβ deposits (**D** and **I**). In **J**, vascular deposition of amylin (brown) and astroglial reaction (green stain for glial fibrillary acidic protein; GFAP) are shown. **A** and **J** are from Ref.[59], **B**,**C**, **F**, **G**, **H** and **I** are from Ref. [104], **D** and **E** are from Ref. [97].

TABLE 1

Cerebral effects of inducing diabetes or insulin resistance in normal rodents (i.e., non-AD rodent models) and in rodents genetically modified to accumulate Aβ in the brain (i.e., AD rodent models). Common interventions to induce diabetic conditions in rodents included recessive mutations in the obesity gene (ob, also known as Lep), defects in the leptin receptor (Ob-R), diet, and administration of streptozotocin. Rodents with pancreatic overexpression of human amylin spontaneously develop both type-2 diabetes and dementia-like pathology.

INTERVENTION	PATHOPHYSIOLOGY	FUNCTIONAL DEFICITS	REFERENCES
	NON-AD RODENT MODELS		
	AD RODENT MODELS		
• STREPTOZOTOCIN	• INCREASED *TAU* GENERATION AND PHOSPHORYLATION • ALTERED HIPPOCAMPAL SYNAPTIC PLASTICITY	• IMPAIRED MEMORY AND LEARNING	71-74
	• EXACERBATED CEREBRAL AMYLOIDOSIS • NEUROLINFLAMMATION • NEUROVASCULAR INJURY	• EXACERBATED IMPAIRMENT OF MEMORY AND LEARNING COMPARED TO NON-DIABETEIC AD RODENTS	79, 85
• HYPOTHALAMIC LEPTIN DEFICIENCY OR ACTION	• INCREASED Aβ GENERATION	• IMPAIRED MEMORY AND LEARNING	75-78
	• CEREBRAL Aβ PLAQUES • ANEURISMS • SMALL STROKES (NO BRAIN PARENCHYMAL LOSS)	• ACCELERATED MEMORY AND LEARNING COMPARED TO NON-DIABETEIC AD RODENTS	81-85
• DIET	• MILD CNS ALTERATIONS	• NONE	81
	• AGGRAVATED Aβ PATHOLOGY COMPARED TO CHOW DIET-FED AD RODENTS	• AGGRAVATED IMPAIRMENT OF MEMORY AND LEARNING COMPARED CHOW DIET-FED AD RODENTS	84
• AMYLIN DYSHOMEOSTASIS	• VASCULAR AMYLIN DEPOSITS • MICROHEMORRHAGES • BRAIN ATROPHY • MICROGLIA ACTIVATION • CEREBRAL AMYLIN PLAQUES • IMPAIRED SYNTHESIS OF NEUROTRANSMITTERS	• GAIT ABNORMALITIES • DIFICULTIES WITH MOTOR FUNCTION AND BALANCE • IMPAIRED MEMORY AND LEARNING	59, 87, 95, 97
	• MIXED Aβ - AMYLIN CEREBRAL PLAQUE FORMATION	• EXACERBATED IMPAIRMENT OF MEMORY AND LEARNING COMPARED TO AD RODENTS EXPRESSING RODENT AMYLIN	110

TABLE 2

Non-AD processes contributing to an AD phenotype in diabetes, as suggested from experimental studies in rodents. Color code: brown – AD rodent models; blue gray – Non-AD rodent models.