Neuroimaging and its Relevance to Understanding Pathways Linking Diabetes and Cognitive Dysfunction

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Abstract. Diabetes mellitus is associated with an elevated risk of cognitive impairment and dementia. Cerebrovascular disease and neurodegeneration are two major pathways that may explain the effect of diabetes on the brain and therefore deserve investigation. Neuroimaging provides an effective way to investigate the contribution of these pathways \textit{in vivo}, guiding further mechanistic research and providing biomarkers for clinical correlation or interventional studies. In this paper, we present a narrative review of the state of play with neuroimaging evidence in studies of people with diabetes mellitus, how these data are useful in understanding mechanistic links between diabetes and brain impairment, and possible ways that the field may develop in the future.

Keywords: Alzheimer’s disease, dementia, diabetes, neuroimaging

INTRODUCTION

Diabetes mellitus is characterized by hyperglycemia and is associated with an elevated risk of cognitive impairment and dementia [1]. Type 1 diabetes mellitus (t1D) is usually diagnosed early in life by the occurrence of hyperglycemia due to the autoimmune destruction of the insulin-secreting pancreatic islet beta cells. In contrast, Type 2 diabetes (t2D) is the presence of hyperglycemia secondary to the resistance of end-organs to the action of insulin. t2D often co-exists with obesity and other cardiovascular risk factors such as hypertension and hyperlipidemia [2]. While the links between t2D and cognitive impairment or dementia are well established, there is now greater recognition that t1D is also associated with cognitive impairment [3, 4]. Cerebrovascular disease and neurodegeneration are two major pathways that may explain the effect of diabetes on the brain and therefore deserve
investigation. Neuroimaging studies provide an effective *in vivo* method to investigate the contribution of these pathways, both in the context of diabetes and its antecedent conditions, such as obesity. Such studies therefore play an important role in guiding further mechanistic research into the diabetes-dementia relationship and in providing biomarkers for clinical correlation or interventional studies. In this paper, we present a narrative review of neuroimaging evidence of brain dysfunction in people with diabetes mellitus, how these data are useful in understanding mechanistic links between diabetes and brain impairment, and possible ways that the field may develop in the future. The review will address evidence pertaining to studies using brain magnetic resonance imaging (MRI) and positron emission tomography (PET). Since the mechanisms underlying this relationship may be different according to the type of diabetes, we discuss the evidence in each type in turn. Summaries of the details of the discussed studies are included in Supplementary Tables.

**EVIDENCE FROM BRAIN MRI STUDIES OF DIABETES**

MRI is now a widely available imaging modality for clinical and research purposes. Brain MRI provides the ability to measure structural (global and regional brain volumes [three-dimensional T1 images], brain tissue density [possibly a more sensitive marker of subtle, early gray matter changes than atrophy], white matter microstructure [T2 weighted images including fluid attenuated inversion recovery, FLAIR] and connectivity [diffusion tensor imaging]) and functional MRI (activation, networks) effects of diabetes. Additionally, MRI enables us to quantify cerebrovascular health in a structural (infarcts, white matter hyperintensities, microbleeds) and physiological sense (cerebral perfusion). The past decade has seen a surge in such studies in diabetes, with a predominance of evidence based on structural MRI and emerging data from functional MRI (fMRI) (Supplementary Table 1).

**DIABETES AND MRI MARKERS OF BRAIN ATROPHY AND CONNECTIVITY**

Brain atrophy on MRI is an established marker of neurodegeneration, and its presence and distribution can provide clinical insights into the underlying pathology, such as previous trauma, depression, schizophrenia, epilepsy, and dementia. For example, patients with Alzheimer’s disease (AD) dementia typically have reduced cortical volumes in the hippocampus, entorhinal cortex, precuneus, posterior cingulate, parietal, and temporal cortex [5, 6]. Furthermore, MRI cortical atrophy correlates well with memory decline [7, 8] and conversion from MCI to mild AD [7–9]. Brain volume measures in young people, on the other hand, may be useful as indicators of brain development and potentially of brain reserve [10]. There have been several studies conducted that firmly establish an association between diabetes and MRI measures of brain volumes.

**Type 1 diabetes and brain volumes**

Most studies of the association between t1D and brain volumes have been performed in people under 45 years of age [11–22], and only a handful in those aged <18 y [11–13, 18, 19]. In studies of children, the results have been inconsistent with some reporting no association between t1D and brain volumes [18, 19]. However, in a cross-sectional study comparing 27 children with t1D (mean age 7.0 y, standard deviation [SD] ± 1.4) to 18 without t1D (mean age 7.2 y, SD ± 1.6), the expected age-related increase in white matter volume was not observed in those with t1D [11]. In another study of 62 children with t1D aged <6 y, a high prevalence (16%) of mesial temporal sclerosis [13] was reported, but the small sample size and the lack of a comparison group prevented strong inferences being drawn about this observation. There has been only one longitudinal study [19] comparing 75 children with t1D (mean age 12.5 y, SD ± 2.8) to 25 children without t1D (mean age 12.5 y, SD ± 2.6). In that study, the authors reported no difference in brain and regional brain volumes over 2 years of follow up. However, in those with t1D, hyperglycemia was associated with greater decrease in gray matter volume, while severe hypoglycemia was associated with greater decrease in white matter volume. This raises interesting speculation about whether hyperglycemia and hypoglycemia have differential effects on brain structure and development. In young adults, on the other hand, most studies do report an association between t1D and lower brain volumes [14, 15, 20, 21], sometimes in specific groups such as those with diabetic retinopathy, suggesting a possible mechanistic role for cerebral small vessel disease. There are some data indicating regional vulnerability of the brain in t1D [16, 17] in young adults. In a study comparing 106 young adults with t1D (mean...
Type 2 diabetes and brain volumes

There have been several cross-sectional studies strongly supporting a relationship between the presence of t2D and lower brain volumes, and these have been extensively reviewed elsewhere [24, 25]. Surprisingly, there have been only three published longitudinal studies on this issue [26–28]. In two of these studies, t2D was associated with a 20%–50% greater rate of decline in total brain volumes over 3–5 years than in people without t2D, and a non-significant trend observed in the other [26, 27]. In the youngest of these three samples, the mean age was 65 years, suggesting that the negative effect of t2D commences before this age, but additional studies are required to explore this further. The hippocampus, temporal lobe, and cingulate cortex, regions known to play a prominent role in new memory formation and affected early in AD [29], appear particularly susceptible to the effects of t2D, but, additionally, frontal cortical regions and subcortical gray matter nuclei appear to be involved [30]. Although it is tempting to consider that some of this brain atrophy in t2D may be attributable to AD pathology, there is still uncertainty regarding this issue. The results of a recent large autopsy study (n = 2365) showed that brain infarcts, but not AD pathology, were more frequent in the brains of people dying with diabetes of either type [31]. By contrast, in a recent large in vivo study, t2D was associated with reduced cortical thickness and elevated cerebrospinal fluid (CSF) tau levels. This association between t2D and cortical thickness was partially mediated by elevated levels of phosphorylated tau (a marker of neuronal injury) [32]. Although this finding may suggest a link between t2D and AD pathology, it must be borne in mind that tau-related injury is found in neurodegenerative conditions other than AD. Moreover, there was no significant relationship found between t2D and CSF beta amyloid levels in the same study, although there may have been insufficient power to detect such an association.

WHITE MATTER MICROSTRUCTURE AND STRUCTURAL NETWORKS

Although brain volumes provide important insights into neurodegeneration, they are not sufficient to extend our understanding of the effects of diabetes on brain networks. Neurodegeneration does not usually occur in isolated locations, and the effects of disease in one location may affect the function of other regions to which they are connected by white matter tracts. Techniques such as diffusion tensor imaging (DTI) (Fig. 1) enable the study of structural brain connections by examining white matter microstructure based on the direction of movement of water molecules within white matter [33]. Damage to white matter through demyelination or axonal loss results in increased water molecule movement, and such loss of white matter integrity may be studied using measures such as fractional anisotropy (FA) and measures of diffusivity such as mean, radial, and axial diffusivity (Supplementary Table 2).

Type 1 diabetes, white matter microstructure and structural networks

The effect of t1D on white matter microstructure is becoming increasingly recognized in DTI studies [34–36], and these studies are beginning to provide direction and insights into pathways leading to t1D-related brain complications. In a study comparing 25 people with t1D to 25 age- and sex-matched people without t1D, those with t1D (mean age 45 y) had...
lower mean FA in the posterior corona radiata, optic radiation, and splenium of the corpus callosum [35]. In a follow-up analysis of the same sample, there was strong relationship between areas of white matter disruption and posteriorly distributed regions of reduced cortical thickness [37]. This raises the possibility of a mechanistic link between the loss of white matter integrity and cortical atrophy, although it is unclear which phenomenon occurred first [37]. In another study of similarly-aged people with t1D (mean age 42 y) but with microangiopathic complications (proliferative retinopathy), more widespread reductions were seen in FA [36], suggesting that microvascular pathways may be important in the pathophysiology of t1D-related brain disease. An important potential mechanistic factor underlying brain complications in t1D is glycemic control and its impact on white matter integrity, and this is now being explored in greater detail using DTI. Two such studies in younger people (<22 y) [34, 38] and one in adults (mean age 45 y) [35] demonstrated that greater duration of t1D and/or greater HbA1c (reflecting longer term glycemic control) were associated with changes in mean diffusivity (MD) and FA, suggesting that cellular metabolic stress related to chronic hyperglycemia may play an important role in white matter injury.

**Type 2 diabetes, white matter microstructure, and structural networks**

Compared with t1D, there are a larger number of studies describing the relationship between t2D and white matter tract changes [39–44]. They describe t2D to be associated with widespread changes in white matter microstructure, particularly involving temporal and frontal white matter [42]. There is a strong positive association between DTI measures of white matter integrity and cognitive performance in t2D independent of the effects of white matter hyperintensities (WMH) and infarcts [40, 41, 44]. In a recent study comparing people with (n = 40) and without t2D (n = 38), those with t2D had lower white matter tract volume between the hippocampus and frontal lobe and also demonstrated slightly reduced memory performance [45]. A similar result was described in an earlier study, comparing 46 people with t2D to 50 people without t2D (mean age 59 y) [46]. In this study, the authors reported that those with t2D had mean diffusivity abnormalities in both white and gray matter, predominantly affecting the left hemisphere and, particularly, the hippocampus and parahippocampus. Others have reported t2D to be associated with white matter tract changes, but do not report differences in cognitive scores between those with and without T2D [39, 41]. Reduced white matter fractional anisotropy in the frontal lobe has also been reported in people with a pre-diabetic state (metabolic syndrome) compared with age-matched controls [47], suggesting that DTI may provide a sensitive way to detect pre-clinical brain changes in the context of diabetes. Now the thrust of investigations in t2D should focus on longitudinal studies to better understand the causal relationship between white matter tract injury and cognition, and the underlying biological mechanisms.

**FUNCTIONAL CONNECTIVITY**

While the study of brain structure is valuable, functional imaging can provide important insights into the effect of disease on distributed neural networks. The relatedness of these networks can be evaluated by measuring regional changes in the blood-oxygen-level-dependent (BOLD) signals on fMRI. Such
techniques can be performed either at rest or in response to specific tasks. Statistical relationships, such as correlation, between BOLD signals from different regions can be used to infer the presence of functional brain networks. Differences in the nature of the statistical relationship for a network between disease and non-disease groups can be an indication of difference in underlying brain function. Studies of this nature are typically described as “functional connectivity” studies, with “reduced functional connectivity” referring to a reduction in strength of the statistical relationship. The presence of functional connectivity does not necessarily imply direct connection between these brain regions, a necessary requirement for effective connectivity [48]. There is great interest in the study of specific networks (e.g., default mode network) to understand differences between diseased and non-diseased groups in neurodegenerative diseases, such as AD [49]. In the past decade, such techniques have also begun to be used to study people with diabetes mellitus (Supplementary Table 3).

Type 1 diabetes and functional connectivity

In only a small number of studies, younger people (age 26–51) with t1D have been reported to display reduced functional connectivity than those without t1D, both during resting state [50, 51] and during specific cognitive tasks [52] in the absence of hypoglycemia. Interestingly, such reductions during resting state in people with t1D were greater in the presence of clinical microangiopathy, suggesting a microvascular basis for the observed differences [50]. The reductions in BOLD response seen during a cognitive task were accompanied by concomitant increased BOLD responses in other networks, even in the absence of overt cognitive differences [52], suggesting compensation for neuronal dysfunction. In addition to studying the effects of t1D on the brain, fMRI can also be used to interrogate the responses of the brain to critical physiological signals, such as hypoglycemia, which can be a frequent complication of t1D therapy [53]. In an elegant study comparing young adults (mean age ∼33 y) with and without t1D, the induction of hypoglycemia resulted in a greater level of bilateral widespread brain activation for a given working memory task and reduced deactivation of the default mode network in t1D, again indicating a reduced cerebral efficiency under physiological stress [54]. Overall, this small but growing body of fMRI studies in t1D suggests that there may be an early pre-clinical loss of functional connectivity in some networks, which may be compensated by increased functional connectivity in other cerebral networks to maintain cognitive performance. It remains to be seen whether such changes are a prelude to permanent cognitive loss, or whether t1D in the very young may affect cerebral development, and these questions can only be addressed by robust longitudinal studies.

Type 2 diabetes and functional connectivity

MRI studies have provided evidence of altered functional connectivity (especially in the default mode network) in people with AD and MCI [49], suggesting that fMRI may add to the biomarker armamentarium for the early recognition of dementia, as well as contribute to the understanding of disease mechanisms. Given the strong link between t2D and dementia, there are now a substantial number of such fMRI studies reporting on the relation between t2D, its precursor state of insulin resistance, and changes in functional connectivity. Most were designed to investigate the impact of t2D [55–57] or insulin resistance [58, 59] on resting state activity, but a few reports have recently emerged on the effect of t2D on brain activation during the performance of a cognitive task [60–63]. Overall, these studies indicate the presence of variations in resting state and task-related brain activation in those with t2D or insulin resistance compared to those without these conditions. In studies of the resting state, t2D has been shown to be associated with reduced functional connectivity of the default mode network with frontal and temporal cortices [59], hippocampus [64], and occipital cortex [65]. However, t2D has also been reported to be associated with increased connectivity in frontoparietal regions [62, 63]. In both of these studies, people with t2D had similar cognitive test performances to those without t2D but demonstrated greater activation of frontal networks, suggesting a compensatory mechanism at play. In those studies examining the effect of a cognitive task on changes in brain activation [60–63], t2D was shown to be associated with reduced functional connectivity in the task-relevant areas. Additionally, in two studies, those with t2D had an impaired ability to deactivate the default mode network [60, 61] while completing a cognitive task. The association of insulin resistance and glucose control on these relationships has been explored in one study [60] comparing 22 people with t2D to 29 people without t2D (aged 45–65 y). In this study, greater HbA1c and insulin resistance were each associated with activation of the default mode network,
sugestesing that both insulin and glucose signaling may mediate default mode network activation. Additionally, acute changes in glucose above 11 mmol/L were associated with impaired deactivation of the default mode network, further supporting the likelihood that glucose levels and insulin resistance may drive some of these functional connectivity changes.

DIABETES AND MRI MARKERS OF CEREBROVASCULAR DISEASE

Both t1D and t2D are clearly associated with a high risk of vascular disease, and cerebrovascular disease is a major determinant of dementia. Brain MRI is a sensitive and accurate method for quantifying cerebrovascular disease in people with diabetes and studying their impact on cognitive function. There are several cerebrovascular phenotypes related to dementia that may be of interest in the diabetes-dementia relationship. Acute stroke is the archetypal phenotype of cerebrovascular disease, common in aging populations and a major risk factor for dementia, with the magnitude of dementia risk greater in the setting of recurrent strokes [66]. Subclinical or “silent” strokes are also highly prevalent with aging and contribute substantially to the risk of future dementia [67]. Other radiological phenotypes representing smaller cerebral vessel disease are also of interest, given their association with the presence of dementia, including age-related white matter hyperintensities (WMH) (Fig. 1) and markers of amyloid angiopathy such as cerebral microbleeds and superficial siderosis [67]. With respect to cerebrovascular physiology, MRI with arterial spin labelling (ASL) (Fig. 1) enables the study of cerebral perfusion [68], which is becoming increasingly recognized as a potential pathway linking vascular risk factors such as diabetes with neurodegeneration [69]. Finally, more recently, direct visualization of cerebral microinfarcts and small deep cerebral vessels with high field imaging (7T MRI) [70] and the measurement of blood-brain barrier permeability (BBB) with dynamic contrast enhancing MRI are becoming possible [71]. These techniques may allow in-depth study of the effect of diabetes on microvascular structure and function in relation to the risk of dementia (Supplementary Table 4).

Type 1 diabetes, cerebrovascular disease, and cognitive function

The cerebrovascular link between t1D and cognitive function is largely inferred indirectly from cross-sectional structural MRI studies of cerebrovascular burden with small samples (n = 80–172) of relatively young people (age 30–60 y) without acute (clinically-apparent) strokes. In these studies, the burden of silent brain infarcts [72] and white matter hyperintensities [72, 73] were found to be similar between people with and without t1D. The presence of proliferative retinopathy in people with t1D was associated with a greater prevalence of cerebral microbleeds, although the total numbers of cases with microbleeds was small (n = 8) [74]. Of interest, those with proliferative diabetic retinopathy were older, had a longer duration of diabetes, poorer glycemic control, and higher systolic blood pressure – indicating longer exposure to risk and more severe disease. Thus, more studies employing large enough samples with sufficiently long follow-up are required to definitively ascertain the impact of strokes, both clinical and subclinical, on the risk of dementia in people with t1D. Such studies will not only need to estimate the impact of t1D on cerebrovascular disease, but should also be designed to capture the cerebrovascular contribution of such disease on cognitive function and the risk of dementia relative to direct neuronal effects of t1D.

Type 2 diabetes, cerebrovascular disease, and cognitive function

It is well recognized that t2D is a risk factor for the development of acute cortical and subcortical infarcts [75–80], which are clearly associated with cognitive impairment and the risk of future dementia. However, the contribution of MRI-defined subclinical cerebrovascular lesions is less certain. Although T2D was associated with a higher prevalence of MRI infarcts in a large cross-sectional study (mean age ∼70 y), this excess prevalence did not appear to mediate the association between T2D and cognitive function [30]. Similarly, in a Japanese study of 1,543 neurologically normal individuals (mean age ∼62 y), the association between metabolic syndrome (central obesity and presence of two of: hypertension, diabetes, or dysglycemia) and lower executive function was independent of silent brain infarcts [81]. By contrast, in another smaller Japanese cohort study of 67 patients >65 y of age with t2D [82], the number of silent brain infarcts on MRI at baseline was associated with cognitive decline over 3 years. The development of high-field (7T) MRI also promises to contribute to our understanding of whether microinfarcts, previously only able to be visualized in autopsy
Fig. 2. Example of 7T MRI imaging. (A, B) Cortical cerebral microinfarct in a patient with type 2 diabetes which appears hyperintense on fluid attenuated inversion recovery (FLAIR) (A) and hypointense on T1-weighted imaging (B). (C, D) Cerebral microbleed in a patient with type 2 diabetes which appears hypointense on T2*-weighted imaging. Images courtesy of Dr. Susanne Van Veluw and Prof. Geert Jan Biessels, University of Utrecht, Netherlands.

studies, play a role in t2D-related cognitive impairment (Fig. 2). In the only 7T MRI study to date to explore whether t2D is associated with microinfarcts, the authors compared 48 people (mean age 70 y) cognitively normal with t2D and 49 age- and sex-matched people without t2D and found a similar prevalence of microinfarcts [70]. Further studies using 7T MRI in those with diabetes and cognitive impairment may help explore the potential contribution of microinfarcts.

Similarly, the links between t2D and WMH are also unclear. A previous meta-analysis examining 25 studies has shown an inconsistent relationship between t2D and WMH burden [24]. The reasons for this uncertainty may be variations in the sample used (e.g., community-based with possibly lower vascular risk factor burden) or differences in the scales used to rate the burden of WMH [24]. There has been disagreement in the findings of more recent MRI studies on the relation between t2D and WMH burden, with some
finding no differences and others showing an excess of WMH in people with t2D [83]. In the large Dallas Heart study (n = 2011), the combination of hypertension, diabetes, and body mass index was associated with greater WMH burden in those >50 y of age (p < 0.001) [84]. However, in those with t2D alone (n = 245), there was only a trend to greater WMH burden (p = 0.053), suggesting that the effect of t2D may be small and linked to other diseases that commonly co-exist with T2D, such as obesity and hypertension. The link between t2D, WMH, and cognitive function is also not definitively established. In the CDOT (Cognition and Diabetes in Older Tasmanians) Study, WMH volume did not explain the association between t2D and cognitive function [30]. Similarly, in a Dutch study comparing 89 people with t2D to 438 without t2D (mean age 75 y), those with t2D had greater cognitive decline over three years than those without t2D. However, there was no increase of progression of WMH during this time [26]. By contrast, the progression of WMH was associated with cognitive decline over 3 y in a similarly aged but smaller Japanese sample [82]. These inconsistencies in results are likely to be explained by variations in study methodology and sample characteristics.

Little is known about the importance of cerebral microbleeds in the t2D-cognition relationship. A previous review of 54 studies (n = 9073) showed that diabetes (type not known) was associated with a greater risk of cerebral microbleeds (CMB) in the general population (OR 2.2, 95% CI 1.2 to 4.2) [85]. Following this, an Icelandic study of 4,218 participants reported that those with t2D and retinopathy (indicating greater vascular disease) were more likely to have CMB than those without T2D and retinopathy [86]. By contrast, no associations were found between t2D and CMB in patients with acute stroke [87], as well as in the CDOT study [30]. However, the prevalence of CMB was similar in those with and those without t2D (mean age 70 y) in a recent small ultra-high field 7T MRI study [70], and neither the presence nor the number of microbleeds were associated with cognitive function across the two groups.

With the advent of techniques such as ASL and contrast-enhanced MRI, studies investigating aspects of cerebrovascular physiology (perfusion) and the integrity of the neurovascular unit are beginning to emerge, adding to information that can be gleaned from structural MRI (Supplementary Table 5). In a small sample (t2D: n = 26; non-t2D: n = 25), t2D was associated with lower regional brain volumes, perfusion, and vasoreactivity in frontal and temporal cortices [88]. In a larger sample comprised of those with insulin resistance (pre-diabetes) and well-controlled t2D, abnormalities in cerebral perfusion and vasoreactivity were strongest in those with insulin resistance and intermediate in t2D relative to healthy controls, suggesting a protective effect of t2D treatment [89]. Interestingly, in a small study comparing the effectiveness of intra-nasal insulin (to improve brain glucose utilization) on cognition and cerebral perfusion [90], intra-nasal insulin was associated with improved regional vasoreactivity and cerebral perfusion in the insular cortex and a concomitant improvement in cognitive performance. Taken together, these studies seem to support the possibility of hemodynamic mechanisms modulated by central insulin signaling pathways linking t2D, neuronal health, and cognition. However, it is difficult to explore whether cerebral perfusion changes occur before or after cerebral metabolic changes as measures of perfusion, such as ASL, and measures of cerebral metabolism, such as positron emission tomography (PET), correlate strongly with neurodegeneration and with each other.

Dementia is associated with disruption of the neurovascular unit (BBB), allowing leakage of plasma components and potential damage to surrounding tissue [91–93]. In animal models, t2D has been associated with BBB disruption, probably via pathways involving endothelial dysfunction [94–96]. In vivo imaging of the BBB is challenging, with some researchers adopting dynamic contrast-enhanced gadolinium MRI to study BBB permeability in the context of dementia [71]. In a preliminary study comparing BBB integrity between men with t2D >65 y of age and 10 non-t2D controls, those with t2D had greater BBB permeability, and furthermore, this was more pronounced in those who had a higher load of WMH irrespective of t2D status [97]. This technique, when combined with others including structural MRI and dynamic ASL, may cast greater light upon the role of microvascular disease in diabetes-related cognitive decline and the factors that may promote such disease.

**DIABETES AND POSITRON EMISSION TOMOGRAPHY STUDIES**

PET imaging can be used to study mechanisms involved in the pathogenesis of dementia, even at a pre-clinical stage. Such studies may be focused on measuring cerebral metabolism, cerebral blood flow,
cerebral amyloid or tau accumulation, and neuroinflammation (Supplementary Table 6).

**Fluorodeoxyglucose PET (FDG-PET) studies in diabetes mellitus**

FDG PET is commonly used to measure the cerebral metabolic rate for glucose (CMRgl) as a surrogate marker of neuronal activity (Fig. 1). In patients with AD, CMRgl is consistently lower in the precuneus, posterior cingulate, parietal, and temporal cortex [98–100] and in some studies, found to predict cognitive deterioration or neuropathological diagnosis of AD [98, 101, 102]. There have been a few studies that have been conducted using FDG-PET in the setting of diabetes mellitus. When people with t1D were compared with those with t2D, [103, 104] no differences were seen in regional cerebral hypometabolism between groups in one study [104], whereas t1D was associated with lower regional glucose metabolism as well as lower blood flow (using the tracer $^{15}$O$\text{H}_2\text{O}$) in another study [103]. Interestingly, in the latter study, the authors then explored the contribution of reductions in blood flow to the reductions in glucose metabolism, reporting that vascular pathways explained only some of the association between t1D and glucose metabolism, suggesting other potential factors such as hyperglycemia may play a role.

A number of studies have explored the association between t2D and insulin resistance with cerebral glucose metabolism [105–108]. In a study of 58 people (mean age 75.1 y) with normal cognition, cognitive impairment, or mild dementia, t2D was associated with reduced glucose metabolism in several cerebral regions independent of other vascular risk factors [105]. In a study of 12 people with t2D, 11 with pre-diabetes and 6 without diabetes, greater insulin resistance was associated with cerebral hypometabolism in a pattern similar to that seen in AD [106]. Furthermore, those with pre-diabetes and t2D performed less well at a memory encoding task than those without diabetes, and in doing so exhibited more widespread activation of brain regions, suggesting insulin resistance may play an important role in the cognitive complication of t2D [106]. In the larger Mayo Clinic Study of Aging (n≈700), the authors found that the presence of t2D to be associated with a pattern of regional hypometabolism similar to that seen in AD [107], and that a greater HbA1c in those without t2D was associated with regional hypometabolism. In the similarly-sized Alzheimer’s Disease Neuroimaging Initiative (ADNI) sample, the authors reported that those with t2D and mild cognitive impairment (MCI) (n = 72) had lower metabolism in frontal lobe, sensorimotor cortex, and striatum than those with MCI but not t2D (n = 719) [108]. The younger age, smaller number of people with t2D, and the lower burden of cerebrovascular disease in the ADNI sample, compared to the Mayo Clinic Study of Aging, may all play a role in explaining why the regions of hypometabolism reported in these studies differ. As a result, it is important not to over-interpret the meaning of the regions of hypometabolism based on a single sample. These FDG-PET studies suggest an adverse effect of diabetes on cerebral metabolism that may be mediated by pathways related to insulin signaling and hyperglycemia.

**PET studies of amyloid, tau, and neuroinflammation in diabetes mellitus**

Cerebral amyloid-β (Aβ) and tau accumulation are key features of AD and serve as extremely useful imaging endpoints in establishing the link between diabetes and AD. A number of PET radioligands are now available to visualize Aβ plaque deposition, of which the most well-known is the [11C]-labelled Pittsburgh Compound B (PiB) [109] which has a high correlation between PiB retention and Aβ pathology on autopsy specimens [110]. Three studies have reported the absence of an association between t2D and cerebral amyloid imaging in vivo [32, 107, 111], raising questions regarding the magnitude of AD-specific pathophysiology in t2D-related dementia. The Baltimore Longitudinal Study of Aging examined associations between glucose tolerance and insulin resistance and brain PiB in 53 participants (mean age 79 y) [111]. The authors reported that there was no association between either glucose tolerance, insulin resistance, or frank diabetes and brain PiB amyloid load. In a study of the ADNI dataset, PiB-PET neuroimaging was available for 102 participants, of whom 19 had t2D [32]. In this group, there was a trend for PiB uptake to increase across the cognitive diagnostic range of health controls (n = 19), through MCI (n = 64) to AD (n = 19). However, PiB uptake was similar in those with t2D and those without t2D. Although it is possible that this result was due to the small numbers of people with PiB imaging available, in a larger study of 749 people without dementia (mean age ∼80 y) from the Mayo Clinic Study of Aging, PiB uptake was similar between those with
t2D (n = 154) and those without t2D [107], suggesting that diabetes may not drive the accumulation of cerebral amyloid. If other studies consistently find an AD-type signature of hypometabolism similar to that reported from the Mayo Clinic Study of Aging, pathways involving soluble amyloid oligomers, amylin deposition [112], or non-amyloid AD-pathways, such as cerebral tau accumulation, may be responsible. Supporting this hypothesis, the results of a study based on the ADNI cohort reported that when compared to those without t2D, t2D was associated with greater cerebrospinal fluid concentrations of tau and phosphorylated tau but not amyloid [32].

Cerebral tau accumulation may present a more viable marker for PET studies of t2D, given a strong association of t2D with the levels of phosphorylated tau in cerebrospinal fluid reported recently [32]. However, there have been no studies of this issue using tau-PET, which has only begun to be used for research in the last few years. Developing a ligand for tau imaging has been challenging for a number of reasons [113]. Tau aggregates are predominately intracellular, thus requiring that any successful ligand must cross the BBB and the cell membrane [113]. Furthermore, tau aggregates exist in six different isoforms and undergo multiple post-translational modifications, limiting the ability of a single agent to target all of the relevant polymorphisms [113]. Ligands targeting the more stable, paired helical filament tau are currently being developed [113], and once the results of such studies are made available, it may be useful to conduct studies of diabetes with tau-PET.

Neuroinflammation is a strong candidate to explain the increased dementia risk in t2D [114–117]. Many circulating inflammatory markers are elevated in t2D, including acute-phase proteins, cytokines, and chemokines. The most studied biomarkers include TNFα, IL-6, C-reactive protein (CRP), vascular cellular adhesion molecule-1 (VCAM-1), plasminogen activator inhibitor-1 (PAI-1), fibrinogen, and adiponectin [118]. In AD, increased microglial activation was reported to occur before the formation of neurofibrillary tangles and brain atrophy in mouse models [119]. Microglial activation is characterized by increased expression of Translocator protein 18 kDa (TSPO), and a recent study by Suridjan et al. [120] demonstrated a significantly higher binding of $^{18}$F—[FEPPA] (which has high affinity for TSPO) in the hippocampus, prefrontal, temporal, parietal, and occipital cortex in 21 patients with AD as compared to 21 control subjects. Moreover, they also showed a significant association between neuroinflammation in specific brain regions and specific cognitive deficits. Given the significant inflammatory components in both type 2 diabetes and AD, future studies should explore whether neuroinflammation in diabetes may prime the immune system to amplify the impact of neuroinflammation on changes from AD-related and/or vascular lesions.

CONCLUSION

Neuroimaging has contributed significantly to our understanding of the relationship between diabetes and dementia, but clearly much more work is required to complete this understanding. The contribution of cerebrovascular factors and neurodegeneration, their interactions, and their underlying mechanisms still require substantial elucidation. More research is also required to understand the influence of different diabetes treatments on dementia risk. Awareness of the cognitive complications of diabetes is increasing and, combined with more widely available neuroimaging imaging technology, one hopes that more studies of diabetes will include cognitive and multimodal neuroimaging measures. Current studies are predominantly cross-sectional in nature, and longitudinal studies will be required to explore the causal nature of some of the associations described in this review. The pathways through which diabetes contributes to cognitive impairment are numerous and likely interact with each other and with the time in life in which they occur. Large, cohort studies, requiring the pooling and sharing of data, and the use of advanced computational analyses will shine further light on these processes and help guide the development of therapeutic interventions.

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SUPPLEMENTARY MATERIAL

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REFERENCES


