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Relationship of Type 2 Diabetes to Human Brain Pathology

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Abstract

Type 2 diabetes (T2D) and Alzheimer disease (AD) are both highly prevalent diseases worldwide, and each is associated with high-morbidity and high-mortality. Numerous clinical studies have consistently shown that T2D confers a two-fold increased risk for a dementia, including dementia attributable to AD. Yet, the mechanisms underlying this relationship, especially non-vascular mechanisms, remain debated. Cerebral vascular disease (CVD) is likely to be playing a role. But increased AD neuropathologic changes (ADNC), specifically neuritic amyloid plaques (AP) and neurofibrillary tangles (NFT), are also posited mechanisms. The clinicopathologic studies to date demonstrate T2D to be consistently associated with infarcts, particularly subcortical lacunar infarcts, but not ADNC, suggesting the association of T2D with dementia may largely be mediated through CVD. Furthermore, growing interest exists in insulin resistance (IR), particularly IR within the brain itself, which may be an associated but distinct phenomenon from T2D, as possibly itself associated with ADNC. Other mechanisms largely related to protein processing and efflux in the central nervous system with altered function in T2D may also be involved. Such mechanisms include islet amyloid polypeptide (or amylin) deposition, co-localized with beta-amyloid and found in more abundance in the AD temporal cortex, blood-brain barrier breakdown and dysfunction, potentially related to pericyte degeneration, and disturbance of brain lymphatics, both in the glial lymphatic system and the newly discovered discrete central nervous system lymph vessels. Medical research is ongoing to further disentangle the relationship of T2D to dementia in the aging human brain.

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Conflicts of Interest

There are no conflicts of interest to disclose relevant to this paper.

Keywords

Alzheimer's disease; Cerebrovascular disease; Infarction; Pathology; Diabetes; Insulin Resistance; Amylin; Blood-brain barrier

Introduction

Type 2 diabetes (T2D) is a chronic disease characterized by progressive insulin resistance (IR) and hyperglycaemia with major complications including kidney disease, heart disease, retinopathy, neuropathy, and cerebrovascular disease (CVD) [1, 2]. Prevalence of T2D in 2013 was 410 million, a 133% increase over 13 years, the largest increase for any health condition [3]. Alzheimer's disease (AD) is a progressive neurodegenerative disease in which beta-amyloid plaques and hyperphosphorylated tau accumulate in the brain with associated cognitive decline, dementia, and eventual death [4]. AD cases are also increasing with an estimated global prevalence of about 80 million predicted by 2040 [5]. While deaths from heart disease and stroke decreased by 16% and 23% respectively between 2000 to 2010, deaths due to AD increased by 68% [6]. Both T2D and AD are chronic conditions comprising an enormous public health burden. Cost of dementia care in 2014 for those over the age of 65 in the United States was around 214 billion dollars [6], only slightly less than the total estimated cost for diabetes care in 2012 at 245 billion dollars, an increase of 41% since 2007 [7]. T2D has recently been established as a risk factor for developing all-cause dementia and dementia attributable to AD, demonstrated in several prospective longitudinal cohort studies [8–15]. Given that T2D appears to be a modifiable risk factor for dementia, significant interest exists in the reason for the association between the two conditions, with the hope that a common intervention might begin to address both problems. Two hypotheses at the forefront as plausible underlying mechanisms accounting for the observed association of T2D with dementia are CVD—including brain infarcts and vessel diseases—and AD neuropathologic changes (ADNC) – including neuritic amyloid plaques (NP) and neurofibrillary tangles (NFT). More recent study has turned beyond T2D, and more specifically to brain insulin resistance (IR) and its possible association with ADNC.

In addition to CVD and ADNC, other mechanisms remain possible. Islet amyloid polypeptide (IAPP), also called amylin, is a peptide hormone co-secreted with insulin from the pancreas. Amylin has been found to be elevated in the blood in persons with T2D, and deposited both in the brain itself and the microvasculature of the central nervous system [16], with unknown and possibly deleterious consequences. Further, growing interest has emerged in blood-brain barrier dysfunction (BBB) in the context of T2D, specifically how metabolic derangements may affect specialized pericytes, cells integral to the BBB. Lastly, the glymphatic system and newly discovered discrete lymph vessels in the central nervous system provide yet another avenue through which T2D may alter function and contribute to an association with dementia.

Neuropathologic study provides insight about pathophysiologic processes by allowing direct comparison of tissue of the healthy and diseased brain on a scale ranging from the molecular to the macroscopic level. Autopsy study provides a direct, albeit cross-sectionally sampled,

window into the cells and tissues that are abnormal in brain diseases. In the present review, we focus on insights provided by neuropathologic studies in understanding how T2D affects the aging human brain, exploring both the more abundant data regarding the relationship of T2D to CVD and ADNC as well as more novel possible links including contributions of IAPP dyshomeostasis, BBB and pericyte dysfunction, and alterations in the brain lymphatic system.

Cerebral Vascular Disease Pathology

T2D is a well-established risk factor for CVD [17]. Presence of macroscopic infarcts accounted for about a third of dementia cases in a cohort study which examined both ADNC and brain infarcts [18]. A systematic review performed on vascular risk factors, stroke and dementia shows unequivocally that CVD is a risk factor for dementia [19]. That T2D is associated with all-cause dementia and possibly even dementia attributable to AD through CVD is a plausible mechanism. As is now well recognized, the most common neuropathology of dementia on autopsy is mixed pathology of ADNC and CVD [20, 21]. Given the very strong relationship between T2D and CVD, and that mixed pathology is the rule rather than the exception in dementia, we first examine T2D's relationship with neuropathologically verified CVD, including brain infarcts, as well as cerebral vessel diseases including atherosclerosis and arteriolosclerosis.

Infarcts

Different methodologies are used to explore the relationship of T2D to infarcts on autopsy, with the simplest approach involving examining whether T2D is associated with the presence of any neuropathologically verified brain infarct. Not surprisingly, across several different studies, T2D has been consistently associated with a 1.5- to 2.5-fold increased risk of at least one infarct on autopsy [22–26]. The largest study to date with autopsy-confirmed infarcts included nearly 2400 older women and men, and found a 1.57 increase in the odds of infarct [25], in agreement with the findings of four prior smaller studies [22–24, 27].

To better understand what type of vascular insults may confer the most susceptibility to cognitive decline, infarcts may be examined separately by size [e.g., microscopic (microinfarcts) versus macroscopic (macro or gross infarcts)] and location [e.g., cortical versus subcortical]. Size is categorized in some studies using the criterion of greater than 1cm considered a large infarct with those smaller than 1cm as a lacunar infarct. Two well-characterized clinical-pathologic cohort studies, one of more than 1200 women and men and another of men only [the Honolulu-Asia Aging Study (HAAS)] both found significant associations of T2D and large infarcts, using the criterion of being visible to the naked eye (odds ratio [OR]=1.53) and greater than 1cm (OR=1.8) respectively [9, 26]. These results disagree however from two other studies which evaluated the association of T2D with large infarcts [23, 25]. Small infarcts, both using the microscopic and lacunar designations, are also associated with T2D on autopsy [25, 27] but the discrepancies in study results are also noted. In a smaller autopsy cohort study, T2D was associated with microinfarcts but not lacunar infarcts [23], directly contrasting with a large combined cohort study, which found a significant association with lacunar but not microinfarcts [25]. However, the larger study

reported 23% missing microinfarct data among persons with T2D. One study, separating subjects into four groups based on both diabetes and dementia status, found that microinfarcts were more common in those with both T2D and dementia compared to those either with T2D and no dementia as well as those with dementia but no T2D [27].

Few studies have analysed infarcts by cortical versus subcortical location. Subcortical infarcts appear to have a stronger association with T2D than cortical infarcts. Subcortical infarcts were 1.8 times more likely in those with T2D compared to those without T2D, whereas no significant association with cortical infarcts was found in the same study [26]. Other research however does demonstrate an association between T2D and cortical infarcts [22, 27]. In a sub analysis using both size and location, both micro (OR=1.65) and gross (OR=1.79) subcortical infarcts are associated with T2D [26]. Figure 1 shows typical findings in human brain tissue of a person with T2D, with notable gross and microscopic evidence of CVD, and in particular with brain infarcts in subcortical regions (Figure 1, Panel A).

In summary, while some inconsistency with regard to specific size and location of the type of infarct exists, there appears to be an overall association of T2D with pathologically verified infarcts [14, 22, 23, 25, 26]. Methodological differences, including in sample size, are likely responsible for at least some of the inconsistencies in results. The two largest studies found the strongest associations with subcortical infarcts and lacunes [25, 26]. Interestingly, one large study included cognitive data from the six years prior to death, finding the most cognitive impairment in those with both T2D and lacunes, compared to those with T2D and no infarcts [25]. T2D is associated with autopsy verified infarcts, supporting CVD being at least partially responsible for the association between T2D and AD.

Cerebral Vessel Diseases

In addition to brain infarcts, CVD is characterized by cerebral vessel pathology. We will first discuss the relation of T2D with large artery disease, namely atherosclerosis. Cerebral hypoperfusion, of which atherosclerotic stenosis is a primary cause [28] is one posited contributor to the pathogenic process in AD. Both AD and atherosclerosis share several common risk factors including T2D, *APOE ε4*, and dyslipidaemia [29]. There is no dispute that T2D is associated with cerebral atherosclerosis at autopsy, which has been demonstrated for several decades now [30]. Consecutive autopsies of persons who suffered a fatal stroke (N=339) showed T2D was about twice as common in those with intracranial stenosis greater than 30% ($p<0.01$) [31]. Shared risk factors and hypoperfusion being possibly involved in AD pathogenesis prompts the question of whether atherosclerosis, which is clearly associated with T2D, might also be associated with ADNC. Data are mixed in this regard. Three studies, two looking at cerebral and the other at systemic atherosclerosis, found no association [29, 32, 33]. Four other studies however, did find that cerebral atherosclerosis was significantly associated with NP and NFT [34–37]. Thus, T2D is a risk factor for atherosclerosis, but if atherosclerosis in turn confers risk for ADNC remains an open question.

T2D is associated with subcortical infarcts [26] and subcortical lacunar infarcts are associated with arteriolosclerosis [38]. Furthermore, T2D is an established risk factor for

arteriosclerosis in the kidneys [39]. These data suggest that T2D might also be associated with arteriosclerosis in the brain. Figure 1, Panels B and C, show microscopic pathology, including arteriosclerosis, in T2D. A study of nearly 1400 subjects found no association of T2D and arteriosclerosis in either of two age groups dichotomized as ≥ 80 or < 80 [40]. However, there was a trend toward association in the younger age group. Further study on this topic is needed. Interestingly, genetic data add to advancing knowledge in this area. A study examining known single nucleotide polymorphisms (SNPs) associated with stroke or stroke risk factors with neuropathological outcomes of microinfarct, macroinfarct, or arteriosclerosis, found a significant association of the *JAZF1* gene with arteriosclerosis ($p=0.014$). The allele, encoding a zinc finger protein, is a known risk factor for T2D [41]. While more study is needed, existent data indicate that T2D is not likely associated with brain arteriosclerosis, which may be counterintuitive, given T2D's association with both peripheral arteriosclerosis and subcortical infarcts.

While our focus is on the consequences of T2D in the brain, the importance of indirect effects that T2D may exert on the brain by first damaging peripheral vasculature and other organs should not be discarded. Some evidence exists to this effect [42–44]. Microalbuminuria has been negatively associated with cognitive function, especially in those who also have peripheral artery disease [45]. Congestive heart failure, one of the most common complications of T2D, is also associated with cognitive impairment [46]. Peripheral vasculature damage leading to kidney disease and congestive heart failure along with other systemic complications of T2D likely contribute to cognitive decline in T2D.

Alzheimer Disease Pathology

Prospective studies demonstrate T2D to confer about a twofold increased risk for developing all-cause dementia, and also dementia attributable to AD [8–11, 14]. AD is the single most common cause of dementia [47]. It has been of particular interest to researchers whether T2D exacerbates, either directly or indirectly, the NP and NFT of ADNC, which would then lead to accelerated cognitive decline in aging. Supporting this idea are common risk factors and overlapping biochemical pathways of metabolic syndrome (including T2D, hypertension, hyperlipidaemia, and obesity) and ADNC [11, 48–52]. Additionally, young asymptomatic *APOE ε4* carriers have altered glucose metabolism in certain areas of the brain on FDG-PET imaging [53]. Animal data demonstrate that IR and a high fat diet are associated with increased levels of beta-amyloid [54, 55], that tau is hyperphosphorylated in T2D [56], and that an abnormally phosphorylated insulin receptor substrate 1 (IRS-1) is associated with increased tau pathology [57]. The animal data have prompted speculation that perhaps central IR, whether with or without systemic IR and the broader syndrome of T2D, may be associated with ADNC.

Type 2 Diabetes

The preponderance of evidence from prior studies does not support T2D being associated with ADNC- either NP or NFT. Associations have been sought with a variety of methods, looking at overall brain pathology, specific brain areas, regional approaches, and finally analyses for interactions with *APOE ε4*. Initial smaller studies largely found no differences

in the degree of NP or NFT among those with and without T2D. Heitner et al. (N=103) analysed NP and NFT counts in both the hippocampus and entorhinal cortex, while in the HAAS (N=216) counts of both types of pathology were examined in the hippocampus and cerebral cortex. Both studies produced null findings [9, 58]. These results are in line with two subsequent community-based studies, one where NP, NFT, and diffuse plaques (DP) were assessed in the superior/midfrontal gyrus [59]. The other looked at both individual (NP, NFT, and DP) and composite measures of AD pathology in the brain globally, as well as in specific regions [22]. There were no significant associations in either study for any analyses performed.

The few studies showing a relation of T2D with AD pathology found lower levels of ADNC in those with diabetes compared to those without. These results are in the opposite direction from what would be expected if ascribing the T2D dementia link to ADNC. One study found fewer NP in those with T2D in both the cortex and hippocampus compared to those without T2D [60]. The same group included analyses on medications in a follow-up study and found those with T2D on any type of antihyperglycaemic to have fewer NP in the hippocampus, entorhinal cortex, and amygdala again compared to controls without T2D [61]. There were no associations with NFT in either study. Two studies found fewer NP by CERAD [62] criteria in those with T2D [23, 24]. Again, no significant associations for NFTs were present. All four studies were relatively small, with total sample sizes ranging from 139 to 385.

Additional data on T2D and ADNC are available, and do not suggest an association. The Adult Changes in Thought study found no associations with either NP or NFT when separating subjects into four groups by both T2D and dementia status [27]. The community-based Arizona Study of Aging and Neurodegenerative Disease used CERAD and Braak [63] criteria for NP and NFT respectively in five different brain regions and produced no significant findings [64]. A recent, large autopsy study in Brazil analysing 1000 persons also demonstrated no significant relationship [65]. Furthermore, two large studies, albeit with some overlapping subjects, also produced no associations. One study of about 1200 subjects looking at individual measures of each NP, DP, and NFT in the mesial temporal lobe and neocortex as well as a composite measure of AD pathology in those regions, produced null results. An overall global AD pathology score likewise yielded no association [26]. An even larger combined cohort study from eleven community-based studies (N=2365) using little or no CERAD or Braak pathology as reference looking for associations of T2D with different degrees of ADNC also found no associations [25]. Importantly, while the abovementioned studies failed to report an association between T2D and ADNC, data suggest lower cognitive status in persons with T2D, and that persons with T2D have higher burden of neuropathology, and CVD in particular, in contrast to ADNC burden. Given the repeated absence of significant results, the fact that the few associations present are opposite the expected direction, and the presence of a different pathology that does correlate with T2D (CVD), the T2D dementia link appears less likely to be directly mediated through increased ADNC.

While the focus of this review is on neuropathologic studies, other methods, including using imaging and CSF, have been applied to examine T2D, dementia and ADNC. Among

neuroimaging methods, recent advances in radiotracers have allowed for imaging select AD neuropathology in vivo. In a PET study of amyloid burden, results were consistent with that of the neuropathologic studies, and suggested no associations between T2D and level of radiotracer uptake of brain amyloid [66–70]. There is less data on imaged tau in T2D, however one study that examined the question failed to find an association [68]. While results were null for T2D, there are suggestions of possible vascular and/or metabolic influence on ADNC. One recent study found an increased number of midlife vascular risk factors (but interestingly not diabetes when assessed individually from other risk factors) being associated with higher amyloid burden when measured an average of 20 years later [71]. With regards to CSF studies, some investigators showed that while amyloid levels were similar among those with and without diabetes, total and phosphorylated tau was elevated in those with T2D compared to those without [70]. Overall, data using these complementary methods are largely consistent with the autopsy data, though there may be some discrepancy with regards to the relationship of T2D to tau. Selection and other biases may explain some of the difference in findings, and much more research is needed to clarify relations.

T2D does not appear to be associated with ADNC in general, however the data are less conclusive when considering *APOE ε4* status. Two studies found that persons with T2D and at least one copy of *APOE ε4* had increased ADNC [64, 65]. In one study, subjects with at least one copy of *APOE ε4* and T2D had more NP in all five regions analysed compared to those with T2D only [64]. In the other, *APOE ε4* carriers with T2D had increased NFT compared to controls [65]. In contrast, three studies looking for an interaction of T2D with *APOE ε4*, including the largest one to date, did not find an interaction (though two of the studies had some overlapping participants) [14, 22, 26]. Investigation of a possible interaction is limited by a 14% worldwide *APOE ε4* frequency [72] and because carriers with T2D tend to die at a younger age [61]. Even if an interaction exists, it does not account for the association of T2D in *APOE ε4* non-carriers. More study is needed on how T2D and *APOE ε4* may interact.

Insulin Resistance

Insulin is a critical polypeptide hormone, produced by pancreatic beta islet cells, secreted in response to elevated blood glucose [73]. As a key anabolic hormone, it readily binds to cell membrane receptors affecting a multitude of cellular and systemic processes, including glucose uptake, glycogen synthesis, gluconeogenesis, lipid metabolism, hunger, cell growth, and gene expression [74]. IR is characterized by decreased responsiveness of cells to the hormone, with associated hyperglycaemia and hyperinsulinemia [74]. IR is a central feature of T2D, though T2D involves many pathophysiologic processes beyond IR. In T2D, insulin secretion initially rises, compensating for IR, but over time pancreatic beta islet cell dysfunction progresses, insulin secretion decreases, and hyperglycaemia worsens. Different cell types and tissues react variably to insulin, so the degree and distribution of IR in tissues is not uniform. Thus, brain IR could exist in tandem with, or independently from peripheral IR and T2D. While much remains to be clarified in the field, both or either peripheral and central (brain) IR may be involved in the pathogenicity of AD.

The Homeostatic Model of Assessment for IR (HOMA-IR) is a widely used blood measure of peripheral IR. In an analysis of AD-related CSF markers, increased HOMA-IR is associated with greater total and phosphorylated tau in asymptomatic *APOE ε4* carriers, while non-carriers demonstrated a negative association. Main effects of HOMA-IR on both tau and amyloid-beta 42 (Aβ42) were not significant, nor were interactions of HOMA-IR with *APOE ε4* on Aβ42 cerebral spinal fluid (CSF) levels [75]. Results overall for CSF biomarkers are mixed, especially with regard to tau with some studies finding an association with HOMA-IR and increased tau [76,77] while others did not [78]. Higher HOMA-IR is also associated with lower glucose metabolism on FDG-PET in several brain regions, with the strongest association demonstrated in the left medial temporal lobe [79]. Lower glucose metabolism in the left temporal lobe is in turn associated with worse performance on immediate and delayed memory tests [79]. While main effects are not significant, increased HOMA-IR in normoglycaemic but not hyperglycaemic individuals is associated with greater [C-11] Pittsburgh compound B (PiB) uptake in the frontal and temporal lobes, reflecting increased amyloid deposition in those areas [79]. A post-mortem study of 135 persons found increased fasting plasma glucose, fasting insulin levels and HOMA-IR as positively associated with higher CERAD NP score 10 to 15 years later [80], though second study of 197 persons failed to replicate those results [81]. Dividing subjects into three categorical ranges of average glucose levels, with sub-analyses dividing subjects into 5-year age strata, also yielded no associations with ADNC [82]. The limited data are conflicted but IR's association with T2D may account for some of the T2D-dementia link; further investigation is called for.

Brain IR in conjunction with, or separate from peripheral IR and T2D, is hypothesized to be part of the pathogenic process of ADNC and dementia, however this remains poorly understood and controversial. Central effects of insulin are not completely understood, but it does appear to play a role in maintaining healthy synaptic transmission and plasticity by increasing synapse numbers and dendritic spine formation [83–85]. The majority of insulin is thought to enter the brain from the periphery through a saturable transport system of the BBB with some variation of permeability in different regions of the brain [86]. There is also significant evidence indicating at least some degree of insulin production within the brain parenchyma [86]. Differences exist between those with dementia attributable to AD versus cognitively normal brains with regard to insulin, insulin receptors, and downstream signalling molecules. For example, a post-mortem study demonstrated increased insulin receptor density and stronger immunohistochemical staining of insulin itself in the brains of those with ADNC [87]. Less insulin like growth factor-1 receptor (IGF-1R) and more IGF-1-binding protein-2 are found by western blot analysis in the temporal cortex of the brains of individuals with ADNC [88]. The same study also demonstrated increased IGF-1R in and surrounding amyloid plaques and decreased levels of the key insulin substrate adaptor proteins IRS-1 and IRS-2 in ADNC-affected neurons [88]. Phosphorylation of insulin receptor substrate 1 (IRS-1) is an early step in the cellular response to insulin receptor binding. In IR, an increasing amount of IRS-1 is abnormally phosphorylated and thought to be involved in downstream dysfunction [89]. Thus, abnormally phosphorylated IRS-1 may serve as a marker of IR. A post-mortem study found a decrease in the normal response to insulin and increased aberrantly phosphorylated IRS-1 in the hippocampus and cerebellar

cortex in AD cases in older subjects, including some without T2D [89]. In addition, abnormally phosphorylated IRS-1 correlates positively with NP and negatively with cognition, regardless of the presence or absence of T2D [89]. Another study of 157 autopsy cases demonstrated increased abnormally phosphorylated IRS-1 in the brain to be associated with pathologic tau in neurons [57]. Taken together, these data suggest brain IR can be a separate entity from peripheral IR and T2D, and that brain IR itself may be implicated as part of the pathogenic process in AD.

Amylin, the Blood-Brain Barrier, and Lymphatics

Data to date suggest that the T2D-dementia association is most likely multifactorial in aetiology. To illustrate this point, a schematic of plausible mechanisms linking T2D to dementia is provided in Figure 2. Of interest, several other mechanisms aside from or in addition to CVD and ADNC, might also be contributing to T2D-related dementia, and these are not mutually exclusive. Here, we consider the emerging data on T2D and how it may affect islet amyloid polypeptide (IAPP), the BBB and cerebral lymphatics, as alternative contributors to the association with dementia.

Islet Amyloid Polypeptide

Islet amyloid polypeptide (IAPP), otherwise known as amylin, is a hormone co-secreted with insulin from pancreatic islet beta cells in the postprandial state [90]. IAPP helps regulate blood sugar by inducing satiation, delaying gastric emptying, and inhibiting glucagon secretion [91]. In addition to peripheral effects, IAPP readily crosses the BBB and acts centrally with receptors found in the area postrema and other locations in the brainstem [92]. As IAPP is secreted with insulin, its blood levels become elevated in those with IR and T2D. IAPP is toxic to pancreatic beta islet cells [92]. IAPP deposition may also negatively affect the brain and its vasculature however this remains unknown. Post-mortem data has shown IAPP deposition in the temporal lobe grey matter in those with diabetes, but not in controls, with some degree of IAPP and A β co-localization [16]. Interestingly, IAPP is found in both the parenchyma and blood vessels of patients with AD who do not carry a diagnosis of T2D in about the same concentrations as subjects with only T2D [16]. While IAPP in the aforementioned study was found extracellularly, a follow-up investigation used immunohistochemistry to demonstrate IAPP within neurons themselves, found in the absence of mRNA, excluding production of IAPP by the neurons [93]. A small study of 5 persons with ADNC and 6 controls found IAPP inclusions in the pericytes, cells involved with the BBB (discussed below), around the hippocampus and parahippocampal cortex [94]. Pericytes with IAPP inclusions had concomitant nuclear changes associated with cell death [85]. No statistically significant difference was found in the number of inclusions between AD cases and controls however [94]. Another study also found deleterious microvascular effects of hyperamylinemia, finding disruption of vascular wall integrity with associated IAPP deposition in the smooth muscle and arterioles of capillaries of patients with T2D and dementia [90]. Animal models included in the same study demonstrated more microhaemorrhages, white matter injury, and cognitive deficits in animals infused with IAPP or engineered to overproduce the protein [95]. A SNP in IAPP was demonstrated to interact with degree of PET-imaged cortical amyloid burden, showing a significant association with

decreased temporal lobe cortical thickness and cognitive decline [96]. Interaction of the SNP with A β in AD patients was confirmed on post-mortem subjects as well [96]. Growing evidence supports IAPP as potentially involved in the complex relationship of T2D and dementia.

Blood-Brain Barrier

The blood-brain barrier (BBB), a unique component of the central nervous system, is comprised of tight junction containing endothelium, astrocyte foot processes lining the microvasculature, and pericytes wrapping capillary endothelial cells [97, 98]. The structure is responsible for the brain being the most tightly regulated organ regarding what substances are able to enter and exit, requiring specific transporters and/or active processes to shuttle water soluble molecules and compounds into and out of the parenchyma. Downstream effects accompany alterations of transporter structure, number, and function. Decreased A β clearance by the BBB resulting from hyperglycaemia is one possible example of this. Animal models of T2D and AD demonstrate down regulation of the GLUT1 glucose transporter. The down-regulated transporter is in turn associated with increased levels of A β and progressive neuronal loss [99]. The BBB contains receptors for A β that bind and chaperone the protein through the BBB into systemic blood facilitating clearance and degradation [100]. Interestingly, APOE ϵ 4 competes with a key A β binding protein, low-density lipoprotein receptor-related protein 1, inhibiting its clearance [101].

Recent investigation in T2D and the brain considers pericytes, cells thought to be important to maintaining tight junctions and BBB integrity [102]. Hyperglycaemia in animal models induces tumour necrosis factor with an associated decrease of 60–80% of retinal pericytes [103]. A post-mortem human histopathologic study showed *APOE* ϵ 4 carrier AD patients with increased pericyte degeneration, higher levels of proinflammatory cytokines in the pericytes and greater BBB breakdown [104]. Another autopsy study demonstrated a 60% decrease in pericyte number and coverage in the cortex and hippocampus of AD subjects compared with controls ($p < 0.1$) [105]. More study is needed, but disruption of the BBB in the context of T2D, particularly through altered A β processing and loss of pericytes, could potentially be involved in the T2D-dementia association.

Central Nervous System Lymphatics

Recently discovered discrete lymphatic vessels in the dural sinuses of the central nervous system [106] and the better-described “glymphatic” system, are additional routes of clearance for toxic proteins possibly impacted by T2D with associated downstream cognitive effects. As only recently discovered, little to no data exist on how T2D affect the discrete lymph vessels within the central nervous system, however T2D is shown to affect lymphatic vessels in the skin [107]. T2D is associated with increased lymph vessel density and changes in gene expression patterns related to inflammation and remodelling of the vessels [107]. In the glymphatic system, CSF functions similarly to lymph fluid. CSF travels via perivascular spaces, the CSF water and solutes are transported via aquaporin 4 channels of astrocytes to the parenchyma, then interstitial fluid, and finally to veins and out of the central nervous system [108]. How T2D may affect glymphatics is an open question, and to our knowledge, no pathologic studies exist on the topic. However, a recent animal model demonstrated the

glymphatic CSF clearance in the hippocampi of rats with T2D to be three times slower than that of controls [109]. Furthermore, performance on cognitive tasks was inversely correlated to the retention of the tracers used to measure flow [109]. Brain lymphatic dynamics and protein removal are novel avenues to explore in better understanding the T2D association with dementia.

Conclusions

T2D is a risk factor for all-cause dementia for reasons not completely understood, but given T2D's consistent association with pathologically verified infarct, CVD, particularly small subcortical infarcts, likely plays a role in the association. To date, the evidence does not support an association of T2D with ADNC, in light of most studies finding no association. However, IR, both peripherally and in the brain, may be a mechanistic link, as supported by emerging data showing that markers of both types of IR appear to be associated with ADNC. More data is needed to explore this area. In addition to CVD, ADNC, and IR, other mechanisms linking to T2D to dementia might be involved. T2D causes hyperamylinemia, amylin readily crosses the BBB, is deposited in both the brain parenchyma and microvasculature and co-localizes with A β . Amylin is also deposited in the specialized pericytes of the BBB. Dysfunction of the pericytes and the BBB, negatively affected by T2D, might alter efflux of toxic proteins, including those involved in ADNC, providing another possible link of T2D to dementia. Similarly, the lymphatic systems of the central nervous system help clear unwanted proteins, and may have altered function in those with T2D, contributing to dementia.

Ultimately, how T2D contributes risk to dementia is likely multifactorial and is a topic deserved of continued study. Better understanding the association is a necessary step to then be able to identify strategies to alleviate the negative effects of T2D on the brain. Even small advances may offer the opportunity to have an important influence on decreasing the large and growing burden of two of the most important public health challenges of the 21st century. Collaborative efforts, across different scientific disciplines and across all stakeholders including the public and governmental agencies, are underway to move toward improving the lives of those with, or at risk for, T2D and dementia [110].

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Abbreviations

AD	Alzheimer disease
ADNC	Alzheimer disease neuropathologic changes
Aβ42	amyloid-beta 42
BBB	blood-brain barrier
CERAD	Consortium to Establish a Registry for Alzheimer's Disease

CSF	cerebral spinal fluid
CVD	Cerebral vascular disease
DP	diffuse plaques
HOMA-IR	Homeostatic Model of Assessment for Insulin Resistance
IAPP	Islet amyloid polypeptide (amylin)
IR	insulin resistance
IRS-1	insulin receptor substrate 1
IGF-1R	insulin like growth factor-1 receptor
NFT	neurofibrillary tangles
NP	Neuritic plaques
SNP	single nucleotide polymorphism
T2D	Type 2 diabetes

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Figure 1.

Neuropathologic features seen at autopsy in an older woman who died at 95 years, with a history of type 2 diabetes and dementia (final Mini Mental State Exam score=17). Gross photograph of a coronally sectioned brain, at the level of the mid-striatum (A), showing a subcortical infarct measuring ~15mm in greatest dimension (red arrow). Photomicrographs in Panels B and C. B shows the area of cystic change (asterisk) in a low-power photomicrograph. C shows the inset region at higher power, depicting an arterial profile with arteriolosclerosis. Scale bars = 800 microns (B) and 200 microns (C)

Figure 2.

Conceptualization of mechanisms linking T2D to dementia, showing the likely multifactorial pathways. Plausible mechanisms include cerebrovascular disease (CVD, including infarcts), but also other recently studied pathways such as through amylin amyloidosis, BBB dysfunction, and brain insulin resistance. Rectangles reflect processes occurring outside the brain, while ovals represent processes inside the brain. IR = insulin resistance, T2D = Type 2 diabetes, BBB = blood-brain barrier, CVD = cerebrovascular disease, ADNC = Alzheimer's disease neuropathological changes.