An Update on Type 2 Diabetes Mellitus as a Risk Factor for Dementia

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Abstract

With the rapidly expanding evidence on brain structural and functional changes in type 2 diabetes mellitus (T2DM) patients, there is an increasing need to update our understanding on how T2DM associates with dementia as well as the underlying pathophysiological mechanisms. A literature search of T2DM and dementia or cognition impairments was carried out in electronic databases Medline, EMBASE, and Google Scholar. In this review, the chosen evidence was limited to human subject studies only, and data on either type 1 diabetes mellitus (T1DM) or non-classified diabetes were excluded. T2DM is a risk factor for both vascular dementia (VaD) and Alzheimer's disease (AD), although AD pathological marker studies have not provided sufficient evidence. T2DM interacts additively or synergistically with many factors including old age, hypertension, total cholesterol, and *APOE* ε4 carrier status for impaired cognition functions seen in patients with T2DM. In addition, comorbid T2DM can worsen the clinical presentations of patients with either AD or VaD. In summary, T2DM increases the risk for AD through different mechanisms for VaD although some mechanisms may overlap. Tau-related neurofibrillary tangles instead of β amyloid plaques are more likely to be the pathological biomarkers for T2DM-related dementia. Degeneration of neurons in the brain, impaired regional blood supply/metabolism, and genetic predisposition are all involved in T2DM-associated dementia or cognitive impairments.

T2DM and Dementia: introduction

Type 2 diabetes mellitus (T2DM) is one of the most common chronic metabolic diseases, which affects more than 300 million people worldwide [1]. With its defining characteristic of impaired glucose regulation, T2DM progresses clinically with slowly declining functions in multiple body organs and systems. Impaired cognitive functions are often seen in patients with T2DM. Dementia is a condition with impaired functions in language, memory, and execution functions. Based on etiology and clinical features, people with dementia can be classified into Alzheimer's disease (AD), vascular dementia (VaD), frontotemporal dementia, Lewy body dementia and non-specific dementia. In this review, T2DM will be examined for its associations with the two most common types of dementia: AD and VaD, which make more than 95% of all dementia cases. The underlying mechanisms of T2DM associated dementia will also be reviewed based on the expanding knowledge obtained from imaging and molecular pathological studies on brain structural and functional changes in patients with T2DM.

T2DM as a Risk Factor for Dementia

In 1996, a report from the Rotterdam study showed that T2DM was positively associated with dementia [2]. According to a 7-year follow-up study, patients with newly diagnosed T2DM had a 63% higher risk for developing dementia than those without T2DM [3]. From a retrospective study, hospital-admitted T2DM patients had a relative risk (RR) of 1.37 for dementia compared to controls [4]. By contrast, the RR for dementia diagnosis was 1.56 among newly onset T2DM patients compared to those participants without T2DM [5]. The increased risk for dementia in T2DM patients was

associated with many factors (Table 1), including age [6, 7], apolipoprotein E (*APOE*) ε4 carrier status [6], and medications, such as oral hypoglycemic agents and use of statins (lipid metabolism modifying agent) [6]. Other factors such as gender [7, 8], ethnicity [9], and body height [8] were also shown to be significantly associated with cognition changes in T2DM patients. Although *APOE* ε4 carrier status did not attain significance by itself [10, 11], these T2DM patients carrying one or two *APOE* ε4 allele had a significantly higher risk of dementia (both AD and VaD) than those who were negative for T2DM or *APOE* ε4 allele [12]. In addition, the dementia risk for patients with T2DM and stroke is eight times more possible to increase relative to that for those without T2DM or stroke [13].

Pathological Mechanisms Underlying the Impaired Cognition Functions

Impaired cognition functions in patients with T2DM were manifested in a variety of domains, such as attention [14, 15, 16], execution [14, 15, 16, 17, 18], information processing speed [9, 14, 16, 18, 19, 20], working memory [14, 15, 17, 18], and verbal memory [16, 20, 21, 22, 23]. Impaired cognition functions were associated with not only subcortical ischemic changes in the brain but also brain atrophy [14]. The atrophic brain changes associated with T2DM will be discussed in details in a separate section next. Worse execution function and memory are correlated predominantly with less gray matter density and reduced glucose metabolism in fronto-temporal areas [24]. The impaired execution function was also shown to be associated with the widespread white matter abnormalities [15]. T2DM patients performed significantly worse in language [25, 26] and visuospatial abilities [15, 19, 21, 25, 26] than those without

T2DM. In one study with a relatively small sample size, T2DM was found to be associated with a lower level of semantic memory in older adults than in those without T2DM, but not with episodic memory, working memory, visuospatial ability or global cognition [27]. Verbal memory impairment was associated with compromised microstructural integrity of the left parahippocampal gyrus [23].

The status of T2DM patients is usually described with its duration and overall glycemic control. Long duration of T2DM was associated with a poor cognitive function [28] especially on attention, working memory, and execution function [29]. For patients with T2DM, cognitive function was shown to be negatively associated with HbA1c [21]. The inverse relationship between HbA1c and cognitive performance was even seen in non-diabetic subjects [30]. Therefore, hyperglycemia is associated with both impaired cognition functions and atrophic changes of the brain. High plasma glucose levels within the normal range (<6.1 mmol/L) were associated with atrophy in the hippocampus and amygdala [31]. On the other hand, T2DM patients with normoglycemia lost less whole-brain volume and exhibited a lower rate of converting mild cognitive impairment (MCI) to AD than those with hyperglycemia [32]. Both advanced glycation end products (AGEs) and glycoxidations were elevated in patients with T2DM compared to controls [33, 34, 35], which are important for the pathogenesis of T2DM and diabetic compliations. In addition, serum levels of AGEs, and C-reactive protein (CRP) were significantly increased in elderly patients with both MCI and T2DM compared to those with T2DM only [36]. In AD patients, AGEs were found to be elevated in the central nervous system [37] and were present mainly with intracellular neurofibrillary tangles (NFTs) [38]. The evidence suggested glycation, oxidative stress

as well as inflammation were involved in the impaired cognition functions in patients with T2DM (Table 2). Although insulin treatment was shown to increase the odds ratio of dementia in T2DM patients [2, 7, 39], it might simply indicate a more severe status of diabetes.

T2DM patients with stable HbA1c levels over time had better cognition functions than those with fluctuating HbA1c levels [40]. Therefore, a fluctuating glucose level was suggested to be involved in the cognition decline in T2DM patients as impaired cognitions were seen among T2DM patients with hypoglycemic episodes as well [41, 42] (Figure 1). For instance, the risk of dementia in T2DM patients was positively correlated with the number of hypoglycemic episodes [41]. The RR was 1.6 for dementia in T2DM patients who had hypoglycemic episodes compared to those who did not have hypoglycemia after controlling for age and gender [7]. Moreover, severe hypoglycemia was associated with poor cognition functions and an accelerated cognitive decline in T2DM patients [42].

Other factors such as hypertension and vascular changes may also contribute to the cognition impairments seen in T2DM patients (Figure 1). Dementia was significantly and independently associated with hypertension in T2DM patients [43]. The cognitive impairment prevalence was found to be significantly higher in people with both T2DM and hypertension than in those normotensive T2DM patients [44]. Small vessel disease not only could predict future cognitive decline in elderly people with T2DM [45] but also was associated with the hippocampal atrophic changes [46] (Figure 1). Further, accelerated cognitive decline in patients with T2DM was associated with vascular damages [47]; arterial stiffness was increased and significantly associated with

cognition impairments in T2DM patients [16].

T2DM was also shown as a risk factor for VaD [48, 49, 50] and it affected VaD more than AD [2] (Figure 1). The high overlap rate between dementia and ischemic stroke suggested that vascular events play an important role in the pathogenesis of T2DM-associated dementia [3]. Lastly, patients with both T2DM and VaD showed a significantly earlier onset of VaD, a faster rate of cognitive decline, and a greater prevalence of neuropsychiatric symptoms than patients with VaD only [50]—these findings suggesting that T2DM had either additive or synergistic effects with VaD to worsen the clinical presentations.

T2DM patients with severe diabetic retinal disease have a 42% increased risk of incident dementia [51]. On the contrary, one report showed that the severity of diabetic retinopathy was demonstrated to be inversely associated with the cognition impairments in T2DM patients [52]. In addition, the presence and number of microinfarcts or microbleeds were unrelated to cognitive performance in patients with T2DM [53]. Therefore, unlike other factors, the role of micorvascular changes is inconclusive for T2DM associated cognitive impairments.

T2DM and Atrophic Brain Changes

Atrophic brain changes in T2DM patients were manifested in volume changes either for the whole brain or for regional brain areas (Table 1). Whole brain atrophy was observed in many studies [19, 47, 54, 55, 56] except one [57] for patients with T2DM. The cerebral atrophy in T2DM patients was associated with an increased lateral ventricle volume [56, 58]. In addition, patients with AD and T2DM had more severe

cortical atrophy compared with the AD only group [59]. As sensitive early markers of AD-type neuropathology, hippocampal and amygdalar atrophy seen in T2DM were independent of vascular pathology [59, 60]. The atrophic hippocampus was reported in some studies [19, 22, 41, 54, 55], but T2DM-related brain volume reductions were reported to be restricted to the hippocampus in other studies [23, 61]. In one report, patients with T2DM had a greater whole brain atrophy but not hippocampal atrophy in comparison to controls [62]. T2DM was also reported to be associated with a lower bilateral frontal and parietal cortical thickness than in those without T2DM [63].

The association between T2DM and gray matter (GM) or white matter (WM) was also reported by many studies. For example, T2DM was associated with a smaller GM volume [58]. T2DM patients showed extensively decreased GM volume compared to healthy controls in certain brain regions, including the superior and middle temporal gyrus, the superior and medial frontal gyrus and the middle occipital gyrus [64]. T2DM-related GM loss was seen mainly in medial temporal, anterior cingulate, and medial frontal lobes, whereas WM loss was distributed in frontal and temporal regions [19].

To summarize, T2DM was associated with atrophic brain changes, and variations in atrophic brain regions might reflect the interaction of many factors including T2DM duration, genetic predisposition, age, gender, and age at onset of T2DM [65].

T2DM and MCI

MCI is generally considered to be a transitional phase between normal cognition and dementia. The MCI manifests as a stage of cognitive dysfunction with a mini mental status examination (MMSE) score falling between 23 and 27 out a toal of 30 points. On

average, the presence of T2DM at baseline shortened the duration of conversion from normal cognition to MCI by seven years [66]. Further, T2DM was associated with a higher MCI prevalence than in the general population [67, 68]. Patients with both T2DM and MCI had a faster cognitive deterioration process than patients with MCI only [32]; this finding suggested an interaction between T2DM and MCI. However, the association between T2DM and non-amnestic MCI was attenuated after socioeconomic and vascular risk factors were controlled [68].

Age [69, 70], blood pressure [69], body mass index (BMI) [71], gender [72], current smoking status [27, 67, 71], duration of diabetes [67, 71, 73], fasting blood glucose (FBG) [67], HbA1c [67, 71], high-density lipoprotein cholesterol [71], immunoreactive insulin [67], total cholesterol [71], and triglycerides [71] were involved in developing MCI in T2DM patients. Age, education, and systolic blood pressure were significantly associated with an increased risk of MCI in older patients with T2DM [69]. High blood pressure [73] and older age [70] were risk factors for cognition impairments while education had a protective role against dementia [70]. Older age (>75 years) and long duration of diabetes are major risk factors for converting MCI to dementia, while the use of oral hypoglycemic agents or statins was associated with a significantly reduced risk for converting MCI to dementia [74]. T2DM has been found to be associated with MCI or MCI subtypes in middle-aged (50-65 years old) subjects but not in elderly individuals (66-80 years old) [72]. However, T2DM was shown to be associated with an increased risk of MCI in an elderly group of subjects (70 years and older) in another study [75]. High BMI, high 2-hour postprandial glucose, and poor glycemic control were significant independent predictors of cognition impairments in patients with both T2DM

and MCI [76]. T2DM patients with MCI had a longer duration of diabetes [77, 78, 79], fewer years of education [77], higher HbA1c [78, 79], higher low density lipoprotein (LDL) cholesterol [78], higher triglyceride [78] and higher fasting blood glucose (FBG) [77] than T2DM patients without cognitive impairment. Cognition functions were inversely correlated with T2DM duration [77], FBG [77], history of hypertension [77], non-high-density lipoprotein cholesterol [71], and total cholesterol [78]. Insulin treatment was associated with a lower level of cognitive performance level in T2DM patients with MCI than in patients with T2DM only [79], however, the insulin treatment might simply indicate a more severe status of diabetes, as stated earlier.

T2DM may worsen the clinical presentation of patients with MCI by impairing psychomotor functions [80]. In addition, patients with both MCI and T2DM had a worse outcome in attention, information processing speed, and memory than non-diabetic MCI patients [81]. T2DM patients with MCI were shown to have a lower volume of the left middle temporal gyrus (MTG) than patients with T2DM only [64]. The atrophic changes in MTG were correlated positively with the cognitive performance score of Montreal Cognitive Assessment (MoCA) [64]. Therefore, structural changes can be observed in certain brain areas in the patients with T2DM who showed an early stage of cognitive impairment.

T2DM as a Risk Factor for AD

As the most common type of dementia, AD progresses clinically with impaired cognition functions, including memory. T2DM was shown to be associated with an increased risk of AD [82]. In 1999, the Rotterdam study reported that T2DM could double the risk of

AD [39]. More recently, T2DM was shown to be associated with a 60% increase of AD risk [83]. The association between T2DM and AD was not observed in one study with very old T2DM subjects (≥80 years old) (48). The association between T2DM and AD was probably specific with the age at onset of T2DM as the same relationship was observed between the age at onset of T2DM and MCI (72). Although the cortical atrophy in T2DM was reported to resemble the pattern as in preclinical AD [19], the presence of T2DM does not affect amyloid and neurofibrillary tangle burden in a sample of clinically and pathologically confirmed AD cases [84]. In addition, diffuse and neuritic plaques were not more common in T2DM than in control subjects [85]. The 11C Pittsburgh compound B (11C-PiB) (an amyloid plaque marker) retention ratio was similar in diabetic individuals versus non-diabetic individuals [86]. This finding suggested that the amyloid load was not significantly influenced by T2DM status. Moreover, the cognition impairments in T2DM were not associated with the AD-type pathology [87]. On the contrary, the T2DM was shown to be negatively associated with AD but positively associated with VaD [88]. For example, fewer neuritic plaques and NFTs in the cerebral cortex and hippocampus have been shown in diabetics than in the non-diabetics [89]. Hypometabolism in AD signature regions was two times more likely to be seen in diabetics than in nondiabetics [86]. It is likely that abnormalities in glucose metabolism interact with genetic predisposition leading to cognition decline in patients with T2DM (Figure 1). For instance, T2DM and *APOE* ε4 allele synergistically increased the number of pathological changes, such as neuritic plaques in hippocampus, NFTs in the cortex and hippocampus, and amyloid angiopathy in the brain [49]. Therefore, T2DM may accelerate the already existing cognitive impairments,

and the deteriorating effects of T2DM are more prominent in people with certain genetic predispositions (Figure 1). For example, individuals with both T2DM and *APOE* ε4 allele had a risk ratio (RR) of 5.5 for AD compared with those with neither of them [49]. Lastly, a higher prevalence of T2DM or impaired glucose metabolism in patients with AD than in control subjects supported the involvement of impaired glucose metabolism in AD development [85]. On one hand, T2DM could worsen already impaired cognition functions through additive or synergistic effects with AD [90]. On the other hand, insulin therapy was shown to be effective in slowing cognitive decline in patients with both AD and T2DM [91].

Other factors are associated with an increased AD risk in T2DM patients. For instance, the use of statins might decrease the risk of AD in patients with T2DM while no benefit was observed in non-AD type dementia [92]. A low insulin response at baseline was associated with a higher cumulative risk of AD, and the association was stronger in subjects without the APOE ε4 allele [93]. Insulin resistance might be a signal of AD risk, which was associated with reduced cerebral glucose metabolism and subtle cognitive impairments at the early stage of T2DM, even before the onset of MCI [94]. Increasing insulin resistance was associated with more amygdalar atrophy in T2DM patients [60]. Patients with insulin resistance had increased the levels of Aβ and inflammatory agents in brain [95]. All these pathological changes could be responsible for the impaired cognition functions seen in T2DM patients (Figure 1 and Table 2).

At molecular and cellular level, the deficiency of insulin-PI3K-AKT signaling was more severe in individuals with both T2DM and AD than in those with either one alone [96]. The level of PI3K-AKT signaling was negatively correlated with tau phosphorylation

[96]. In addition, both neuronal membrane glucose transporter 3 and GlcNAcylation levels of tau were decreased in the brain of T2DM patients due to an increased tau phosphorylation [97]. In T2DM patients, an increased level of phosphorylated tau might cause neurons to degenerate by causing NFTs to accumulate in these cells.

T2DM and AD Biomarker Levels

Amyloid-β (Aβ) plaques and NFTs are pathological biomarkers for AD, while T2DM is characterized by the deposition of islet amyloid polypeptide (IAPP, also known as amylin) within beta cells of the pancreatic islets. All these biomarkers (Aβ plaques, NFTs and amylin) are in the form of mis-folded proteins. Aβ autoantibody levels increased 45% in patients with T2DM compared with age-matched controls [98]. However, T2DM was associated neither with ^{11}C- Pittsburgh compound B standardized uptake value ratio in any brain region for measuring Aβ plaques nor with cerebrospinal fluid (CSF) Aβ42 levels [63]. By contrast, T2DM was associated significantly with increased levels of CSF total tau and phosphorylated tau (pTau) [63]. Tau is a microtubule-associated protein, and the pTau level is closely related to the formation of NFTs. T2DM patients have a higher pTau level measured from frontal cortices than the control subjects [97]. So Tau and pTau instead of β amyloid plaques is more likely to be the sensitive pathological biomarker for T2DM- related dementia. However, studying biomarker changes longitudinally and/or pathological changes from autopsies is needed for disclosing relationship between T2DM and dementia.

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Factors Influence MCI or Dementia Risk	Abnormalities in Brain Structure and Metabolism	Impaired Cognition Functions in T2DM Patients
Age (6, 7, 69, 70, 72); Age at Onset of T2DM (65); *APOE* ε4 (6, 12, 49, 93); Blood Pressure (43, 44, 69, 73, 77); Blood Lipids (71, 78) Body Mass Index (8, 71, 76); Current Smoking Status (27, 67, 71) Duration of T2DM (28, 29, 67, 71, 73, 77, 78, 79); Ethnicity (9); Education (69, 77); Fluctuating Glucose Level and Glycemic Control (7, 21, 31, 32, 40, 41, 42, 67, 71, 76, 77, 78, 79); Gender (7, 8, 72); Medications (6, 74, 92); Stroke (13);	Amygdala Atrophy (31, 59, 60); Brain Atrophy (14,19, 47, 54, 55, 56, 58, 62); Cortical Atrophy (19, 59, 63); GM abnormality (19, 24, 58, 59, 63, 64); Hippocampus Atrophy (19, 22, 23, 31, 41, 46, 54, 55, 59, 60, 61); Increased Lateral Ventricle Volume (56, 58); Left parahippocampal Gyrus (23); Reduced glucose metabolism (14, 24); WM abnormality (15, 19);	Attention (14, 15, 16, 29, 81); Execution (14, 15, 16, 17, 18, 29); Information Processing Speed (9, 14, 16, 18, 19, 20); Language (25, 26); Psychomotor functions (80); Verbal Memory (16, 20, 21, 22, 23); Visuospatial Abilities (15, 19, 21, 25, 26) Working Memory (14, 15, 17, 18, 27, 29, 81);

Table 1. Factors interact with T2DM to affect brain structure and functions of metabolism and cognition. *APOE* ε4: apolipoprotein E ε4; T2DM: type 2 diabetes mellitus; GM: gray matter; WM: white matter

Pathological Mechanisms for T2DM Related Dementia	T2DM Related VaD Pathogenesis	T2DM related AD Pathogenesis
Glycation (33, 36, 37, 38); Glycoxidation (34); Inflammation (36, 95) Vascular changes (16, 45, 46, 47	Cerebrovascular Events (3, 13);	Impaired glucose metabolism (85, 86, 94); Insulin Resistance (60, 93, 94, 95); Increased Tau phosphorylation (63, 96, 97)

Table 2. Pathological mechanisms for T2DM related Dementia, AD and VaD. MCI: mild cognitive impairment; T2DM: type 2 diabetes mellitus; AD: Alzheimer's disease; *APOE* ε4: apolipoprotein E ε4; VaD: Vascular dementia

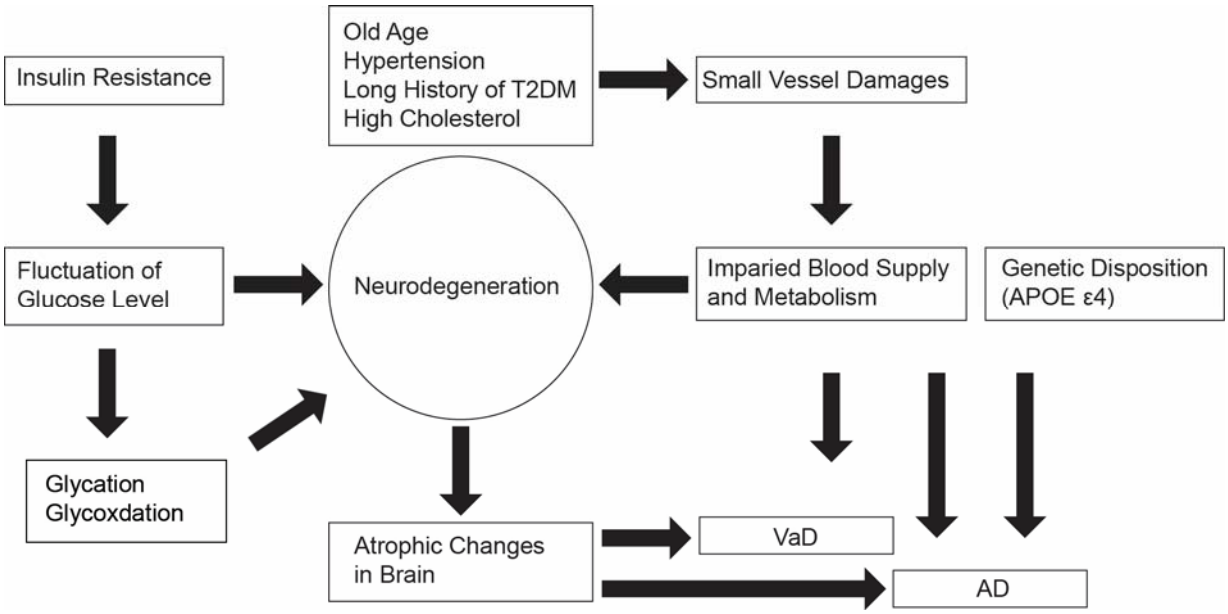

Figure 1. The possible pathological mechanisms for T2DM related dementia. AD: Alzheimer's disease; APOE: apolipoprotein E; VaD: Vascular dementia.