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DIABETES AND OTHER DISEASES-EMERGING ASSOCIATIONS (JJ NOLAN, SECTION EDITOR)

Diabetes Mellitus and Dementia

Toshiharu Ninomiya

Abstract Growing epidemiologic evidence has suggested that people with diabetes mellitus are at an increased risk for the development of dementia. However, the results for the subtypes of dementia are inconsistent. This review examines the risk of dementia in people with diabetes mellitus, and discusses the possible mechanism underpinning this association. Diabetes mellitus is associated with a 1.5- to 2.5-fold greater risk of dementia among community-dwelling elderly people. Notably, diabetes mellitus is a significant risk factor for not only vascular dementia, but also Alzheimer's disease. The mechanisms underpinning the association are unclear, but it may be multifactorial in nature, involving factors such as cardiovascular risk factors, glucose toxicity, changes in insulin metabolism and inflammation. The optimal management of these risk factors in early life may be important to prevent late-life dementia. Furthermore, novel therapeutic strategies will be needed to prevent or reduce the development of dementia in people with diabetes mellitus.

Keywords Diabetes mellitus · Dementia · Alzheimer's disease · Vascular dementia · Epidemiology · Prospective study

Introduction

Dementia is a syndrome that affects memory, thinking, behavior, and the ability to perform everyday activities. Among the dementia subtypes, Alzheimer's disease is the most common and has traditionally been considered a primarily neurodegenerative disorder characterized by neuritic plaques and the neurofibrillary tangles, which are the accumulation of amyloid beta protein and abnormally phosphorylated tau protein in neurons, respectively. Vascular dementia is the second most common type of dementia, and develops as a consequence of strokes or chronic brain ischemia generated by small vessel disease. These dementia subtypes are thought to have different etiologies. According to the report "Dementia: a public health priority," which was jointly published by the World Health Organization and Alzheimer's Disease International in 2012, the number of people with dementia worldwide is currently estimated at 35.6 million and will double to 65.7 million by 2030 and more than triple to 115.4 million by 2050 [1]. In addition, dementia accounted for 11.2 % of years lived with disability in people aged 60 years or older, and this percentage was higher than the contribution made by almost any other health condition, including stroke, musculoskeletal disorders, and individual cancers [2]. Therefore, dementia is widely acknowledged as a public health and social care priority worldwide.

The rising prevalence of diabetes mellitus is also a great public health concern, because diabetes mellitus can lead to complications in several organ systems. Today, 366 million people have diabetes mellitus worldwide, and the number is predicted to reach 552 million by 2030 [3]. Advances in prevention and treatment strategies for the macro- and microvascular complications of diabetes mellitus have improved life expectancy in individuals with diabetes mellitus, and this improved longevity is likely to increase the population at risk of geriatric health complications, including cognitive impairment and dementia [4•]. Several epidemiologic studies have suggested that people with diabetes mellitus are at an increased risk of developing cognitive impairment and dementia [5]. However, the results for the subtypes of dementia are

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T. Ninomiya (✉)
The George Institute for Global Health, Sydney University, Level 10, King George V Building, 83-117 Missenden Rd, Camperdown, NSW 2050, Australia
e-mail: tninomiya@georgeinstitute.org.au

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inconsistent across studies, partly because people with dementia sometimes have mixed neurodegenerative and vascular pathology, making it difficult to distinguish the subtypes [6, 7]. Therefore, the real relationship between diabetes mellitus and dementia is an area of controversy, and the determinants of the accelerated cognitive decline are less clear. Herein, we review the findings of population-based prospective studies addressing the association between diabetes mellitus and dementia, and discuss the possible mechanisms underpinning this association, which may be useful from a clinical and public health perspective.

Epidemiologic Evidence of an Increased Risk of Dementia in Patients with Diabetes Mellitus

A number of population-based prospective studies have reported an association between diabetes mellitus and the development of dementia. We performed a computerized search of the relevant studies using MEDLINE via Ovid (from 1946 through August 2013) with diabetes mellitus (exp diabetes mellitus/ or diabete$.tw), dementia (exp dementia/ or dementi$.tw) and epidemiologic studies (exp epidemiologic studies/) as the medical subject headings and test words, without language restriction. The literature search yielded a total of 795 articles, from which we excluded 622 articles that addressed irrelevant issues, 70 articles lacking a population-based prospective cohort study design, 29 review articles, and 10 duplicates in the abstract review process. The remaining 64 articles were fully reviewed. Among them, 41 articles did not include the relevant risk estimates, and 7 articles reported the risk estimates from a study population that was already represented in another included article, leaving 16 articles [8–21, 22•, 23], to which we added 2 studies [24, 25] that were identified from the review articles [4•, 5]. Thus, a total of 18 studies were identified (Table 1).

Most of the studies were conducted in Western countries, including the United States, Canada, and Europe, with various follow-up periods ranging from 2.1 years to more than 10 years. Two studies were conducted in Japanese populations [12, 22•]. Many studies ascertained the diagnosis of diabetes mellitus based on self-reports, medical records, and use of anti-diabetes medication, except 4 studies [8, 9, 12, 22•], in which the participants underwent an oral glucose tolerance test.

Fifteen studies reported the adjusted risk estimates for the development of all forms of dementia in individuals with diabetes mellitus. Diabetes mellitus appeared to confer an increased risk of all dementia, although the risk estimates did not reach statistical significance in 5 studies. Using these data, a meta-analysis was performed, in which pooled estimates were calculated using a fixed-effect model, and the heterogeneity across included studies was analyzed by using a Cochran Q test and the I^2 statistic. Overall, diabetes mellitus was associated with a 1.7-fold (95 % confidence interval [CI], 1.5–1.8) greater risk of all dementia, without any heterogeneity in the magnitude of the association (I^2=0.0 %, P=0.51) (Fig. 1, a). With respect to publication bias, the Begg's funnel plots did not show asymmetry (P=0.26) and the Egger's test was not statistically significant (P=0.14).

Substantially similar findings were observed in the subtypes of dementia, such as Alzheimer's disease and vascular dementia. Among 14 studies addressing the association between diabetes mellitus and Alzheimer's disease, only 5 studies demonstrated a significantly increased risk of Alzheimer's disease in people with diabetes mellitus, and the remaining 9 studies failed to reveal a significant association. These findings may be related to the methodological differences in the ascertainment of diabetes mellitus and dementia subtypes, as well as in the regional characteristics and ethnicities of the settings and patients. Certainly, the studies in which diabetes status was determined accurately using an oral glucose tolerance test demonstrated a significant association. On the whole, however, the risk for Alzheimer's disease in people with diabetes mellitus showed a fairly consistent pattern of being higher across studies (Fig. 1, b). The pooled hazard ratio for Alzheimer's disease in individuals with diabetes mellitus was 1.6 (95 % CI, 1.4–1.8). Similarly, a significant increase in the risk of vascular dementia was found in 7 of 12 studies, with a pooled hazard ratio of 2.2 (95 % CI, 1.7–2.8). There were no evidences of heterogeneity in the association for either subtype of dementia across the studies (both I^2=0.0 %, P>0.4). These findings provide convincing evidence that people with diabetes mellitus have a 1.5- to 2.5-fold greater risk of dementia than those without it among community-dwelling elderly people. Importantly, diabetes mellitus is a significant risk factor for not only vascular dementia, but also Alzheimer's disease.

Intriguingly, the results from the Hisayama study, in which diabetes status was determined by oral glucose tolerance test and approximately 75 % of the decedents of the town underwent autopsy, demonstrated that greater 2-hour post-load plasma glucose (2-hour PG) levels, but not greater fasting plasma glucose (FPG) levels, were linked to an increased risk of both Alzheimer's disease and vascular dementia in an elderly Japanese population [22•]. It is reasonable to postulate a close association between 2-hour PG levels and the risk of vascular dementia, because increased 2-hour PG levels are associated with the development of stroke [26, 27]. Meanwhile, the risk of Alzheimer's disease almost doubled in those with 2-hour PG of 7.8–11.0 mmol/L and tripled in those with 2-hour PG above 11.0 mmol/L compared with those with 2-hour PG below 6.7 mmol/L. These findings may suggest that hyperglycemia after glucose load plays an important role in the development of Alzheimer's disease, as well as vascular dementia.

Table 1 Population-based prospective studies addressing the relationship between diabetes mellitus and dementia

Authors	Study population	Mean age, y	Follow-up, y	Ascertainment of diabetes mellitus	Covariates	Hazard ratio (95 % confidence interval)		
						All dementia	AD	VaD
Leibson et al 1997 [8]	1455 people aged 40–99 in the Rochester Epidemiology Project (USA)	NR	15	OGTT, DM-Tx	Age, sex, and calendar year	1.7 (1.3–2.1)[a]	2.3 (1.6–3.3)[a]	NR
Ott et al 1999 [9]	6370 elderly people in the Rotterdam Study (Netherlands)	69	2.1	Non–FG, OGTT, DM-Tx	Age and sex	1.9 (1.3–2.8)	1.9 (1.2–3.1)	2.0 (0.7–5.6)
Luchsinger et al 2001 [10]	1262 elderly people in the Washington Heights-Inwood Columbia Aging Project cohort (USA)	76	4.3	SR, DM-Tx	sex, race, education, hypertension, low–density lipoprotein cholesterol, prior cardiac disease, and smoking	NR	1.3 (0.8–1.9) [b]	3.4 (1.7–6.9)
Hassing et al 2002 [24]	702 elderly people in the Old-Old-Twin Study (Sweden)	83	6–8	MR, DM-Tx	Age, sex, education, hypertension, hypotension, prior cardiovascular disease, and smoking	NR	0.9 (0.4–2.0)	3.6 (1.4–9.8)
MacKnight et al 2002 [11]	5574 elderly people in the Canadian Study of Health and Aging (Canada)	74	5.0	SR, MR, DM-Tx	Age, sex, education, hypertension, prior cardiovascular disease, and smoking	1.3 (0.9–1.8)	1.3 (0.8–2.0)	2.0 (1.2–3.6)
Peila et al 2002 [12]	2574 Japanese–American elderly men in the Honolulu-Asia Aging Study (USA)	77	3.0	SR, FG, OGTT, DM-Tx	Age, sex, education, midlife systolic blood pressure, diabetes medications, total cholesterol, body mass index, prior cardiovascular disease, ankle-to-brachial index, *ApoE* genotype, smoking, and alcohol	1.5 (1.01–2.2)	1.8 (1.1–2.9)	2.3 (1.1–5.0)
Arvanitakis et al 2004 [13]	824 older people in the Religious Orders Study (USA)	75	5.5	SR, DM-Tx	Age, sex, and education	NR	1.7 (1.1–2.5)	NR
Akomolafe et al 2006 [14]	2210 elderly people in the Framingham Study (USA)	70	12.7	Non-FG, DM-Tx	Age, sex, education, systolic blood pressure, body mass index, prior cardiovascular disease, plasma homocysteine, smoking and alcohol,	1.2 (0.7–2.0)	1.2 (0.7–2.1)	0.8 (0.2–3.7)
Hayden et al 2006 [25]	3264 elderly people in the Cache County Study (USA)	74	3.2	SR, DM-Tx	Age, sex, education, hypertension, hypercholesterolemia, obesity, prior cardiovascular disease, and *ApoE* genotype	1.6 (0.9–2.6)	1.3 (0.7–2.5)	2.2 (0.9–5.2)
Irie, et al 2008 [15]	2547 elderly people in the Cardiovascular Health Study Cognition Study (USA)	74	5.4	FG DM-Tx	Age, sex, education, hypertension, total cholesterol, body mass index, depressive status, ankle-brachial index, prior stroke, smoking, alcohol, and *Apo*E genotype	1.4 (1.03–2.0)[#]	1.6 (0.98–2.7)[c]	0.8 (0.3–2.1)[c]
Raffaitin et al 2009 [16]	7087 elderly people in the Three-City Study (France)	73	4.0	FG, Non-FG, DM-Tx	Age, sex, education, and city center	1.6 (1.1–2.4)	1.2 (0.6–2.1)	2.5 (1.2–5.7)
Alonso et al 2009 [17]	11,151 people aged 46–70 in the Atherosclerosis Risk in Communities Study (USA)	57	12.8	SR, FG, Non-FG, DM-Tx	Age, sex, education, study center, occupation, cognitive test, hypertension, hypercholesterolemia, body mass index, and, smoking	2.2 (1.6–3.0)	NR	NR

Table 1 (continued)

Authors	Study population	Mean age, y	Follow-up, y	Ascertainment of diabetes mellitus	Covariates	Hazard ratio (95 % confidence interval)		
						All dementia	AD	VaD
Ronnemaa et al 2009 [18]	1125 elderly men in the Uppsala Longitudinal Study of Adult Men (Sweden)	71	12.0	FG, DM-Tx	Age, education, systolic blood pressure, total cholesterol, body mass index, and smoking	1.6 (1.1–2.3)	NR	NR
Xu et al 2009 [19]	1248 elderly people in the Kungsholmen project (Sweden)	81	5.1	Non-FG, MR, DM-Tx	Age, sex, education, systolic and diastolic blood pressure, anti-hypertensive medication, body mass index, prior cardiovascular disease, survival status, baseline MMSE, and *Apo*E genotype	1.4 (0.9–2.1)	1.2 (0.7–2.1)	3.2 (1.2–8.6)
Ahtiluoto et al 2010 [20]	355 elderly people in the Vantaa 85+ study (Finland)	88	3.7	SR, MR, DM-Tx	Age, sex, education, and *ApoE* genotype	2.1 (1.3–3.3)	NR	NR
Mejia–Arango et al 2011 [21]	5398 elderly people in the Mexican Health and Aging Study (Spain)	69	2.0	SR	Age, sex, and education	2.1 (1.6–2.7)	NR	NR
Ohara et al 2011 [22•]	1017 elderly people in the Hisayama Study (Japan)	69	10.9	OGTT, DM-Tx	Age, sex, education, hypertension, total cholesterol, body mass index, waist-to-hip ratio, electrocardiogram abnormalities, prior stroke, smoking, alcohol, and physical activity	1.7 (1.2–2.5)	2.1 (1.2–3.6)	1.8 (0.9–3.7)
Cheng et al 2011 [23]	1488 elderly people in the Washington Heights–Inwood Columbia Aging Project cohort recruited in1999 (USA)	76	3.9	SR, DM-Tx	sex, ethnicity, education, hypertension, non–HDL cholesterol, HDL–cholesterol, cardiovascular disease, and *ApoE* genotype	1.5 (0.9–2.4)	1.4 (0.9–2.4)	3.7 (1.1–12.6)

AD Alzheimer's disease, *DM-Tx* use of anti-diabetes medications, *FG* fasting glucose level, *MMSE* Mini-Mental State Examination, *MR* medical records, *Non-FG* non-fasting (casual) glucose level, *NR* not reported, *OGTT* oral glucose tolerance test, *SR* self-report, *VaD* vascular dementia.

[a] Relative risks were estimated by means of a Poisson regression analysis.

[b] In the data for an average 5.5-year follow-up, the hazard ratio for Alzheimer's disease was 2.0 (95 % confidence interval 1.4–2.9) after adjusting for hypertension, prior cardiac disease, and smoking [73].

[c] Hazard ratios for people with diabetes mellitus only vs people with neither diabetes mellitus nor *APOEe4* genotype are shown.

Morphologic Changes of the Brain in Elderly People with Diabetes Mellitus

The morphologic changes of Alzheimer's disease occur in the hippocampus, amygdala, and medial temporal lobe in the early stages of the disease [28]. The assessment of hippocampal and amygdalar volume on magnetic resonance imaging (MRI) of the brain provides a good estimate of the degree of Alzheimer neuropathology [29], which shows that patients in the early stage of Alzheimer's disease have smaller volumes of the hippocampus and amygdala on MRI compared with healthy control patients [30–32]. In the Rotterdam Scan Study, the association between diabetes mellitus and hippocampal and amygdalar atrophy on MRI was investigated in elderly people without dementia. People with diabetes mellitus had smaller volumes of the hippocampus and amygdala on MRI than people without diabetes mellitus. The associations were not due to vascular morbidity being more pronounced in persons with diabetes mellitus [33].

Supportive findings were also found in the pathologic studies addressing the association between the diabetes-related factors and the neuropathology of Alzheimer's disease [12, 34]. In the Honolulu Heart Program, people with diabetes mellitus and *APOEe4* allele had a higher number of hippocampal neuritic plaques (odds ratio [OR] 3.0 [95 % CI, 1.2–7.3]) and higher numbers of neurofibrillary tangles in the cortex (OR 3.5 [95 % CI, 1.2–7.3]) and hippocampus (OR 2.5 [95 % CI, 1.5–3.7]) than those with neither of these risk factors [12]. There were no clear associations between diabetes mellitus and these neuropathologies of Alzheimer's disease in *APOEe4* noncarriers. This study also showed that the risk of the presence of cerebral amyloid angiopathy was significantly higher in people with diabetes mellitus and the *APOEe4* allele than in those without them. Finally, the study found that the presence of cerebral amyloid angiopathy was associated with worse cognitive function in people with Alzheimer's disease [35]. This finding implies that the pathologic link between diabetes mellitus, *APOEe4*, and Alzheimer's disease may be partially due to an increased risk of the formation of cerebral amyloid angiopathy.

In addition, the Hisayama Study revealed that the likelihood of the presence of neuritic plaque increased significantly with increasing 2-hour PG levels (OR 1.7 [95 % CI, 1.0–2.8] per 1 mmol/L increment), fasting insulin (OR 2.0 [95 % CI, 1.1–3.7] per 1 μU/mL increment) and homeostasis model assessment of insulin resistance (OR 2.0 [95 % CI, 1.1–3.7] per 1 unit increment), but not FPG level (OR 1.4 [95 % CI, 0.9–2.3] per 1 mmol/L increment), after adjusting for known cardiovascular risk factors [32]. The magnitudes of these associations were significantly greater in people with the *APOEe4* allele than in those without it. This suggests that hyperinsulinemia and insulin resistance are likely to deteriorate the neuropathology of Alzheimer's disease, especially in *APOEe4* carriers.

Possible Biological Mechanisms Underpinning the Association Between Diabetes Mellitus and Dementia

The exact mechanisms underlying the association between diabetes mellitus and dementia are unclear. However, the association is likely to be multifactorial in nature, reflecting the metabolic complexity of diabetes mellitus. It is increasingly recognized that the brains of people with dementia are likely to show mixed pathologies of subtypes of dementia. Several factors related to diabetes mellitus—namely, cardiovascular risk factors, glucose toxicity, changes in insulin sensitivity resulting in insulin resistance, and inflammation—can lead to different pathologies. In addition, demographic and socioeconomic factors (eg, aging and education), other comorbidities (eg, depression), and genetic factors (eg, *APOEe4* genotype) could also be important determinants of increased risk of dementia in people with diabetes mellitus. These combined mechanisms could cause a mixture of pathologies, which would complicate the clarification of the biological mechanism.

Cardiovascular Risk Factors

Diabetes mellitus is known to be a risk factor for ischemic stroke and small vessel disease [36]. Type 2 diabetes mellitus can be associated with multiple cardiovascular risk factors, including obesity, insulin resistance, atherogenic dyslipidemia, hypertension, and proinflammatory states. The clustering of these risk factors accelerates stroke, small vessel disease, and subsequent vascular dementia [37, 38]. Chronic exposure to hyperglycemia in diabetes mellitus also induces abnormalities in the cerebral capillaries [39]. Stroke and small vessel disease repeatedly disrupt the brain's supply of oxygenated blood, leading to accumulated damage to brain tissue and function. Therefore, good control of cardiovascular risk factors could be expected to reduce the risk of dementia. Nevertheless, current evidence from randomized control trials, few of which were conducted in people with diabetes mellitus, suggest that the standard strategies of cardiovascular risk reduction (eg, anti-hypertensive agents, anti-platelet therapy, and statin treatment) among elderly populations are not effective in reducing the development of dementia [40–42]. However, a long exposure to poorly controlled cardiovascular risk factors presumably worsens arteriosclerotic changes and lipohyalinosis in the deep subcortical white matter circuits, which may be less reversible by treatment once these changes are established [43, 44]. Moreover, these studies did not address the treatment effect according to the subtypes of dementia. Based on its etiology, Alzheimer's disease might

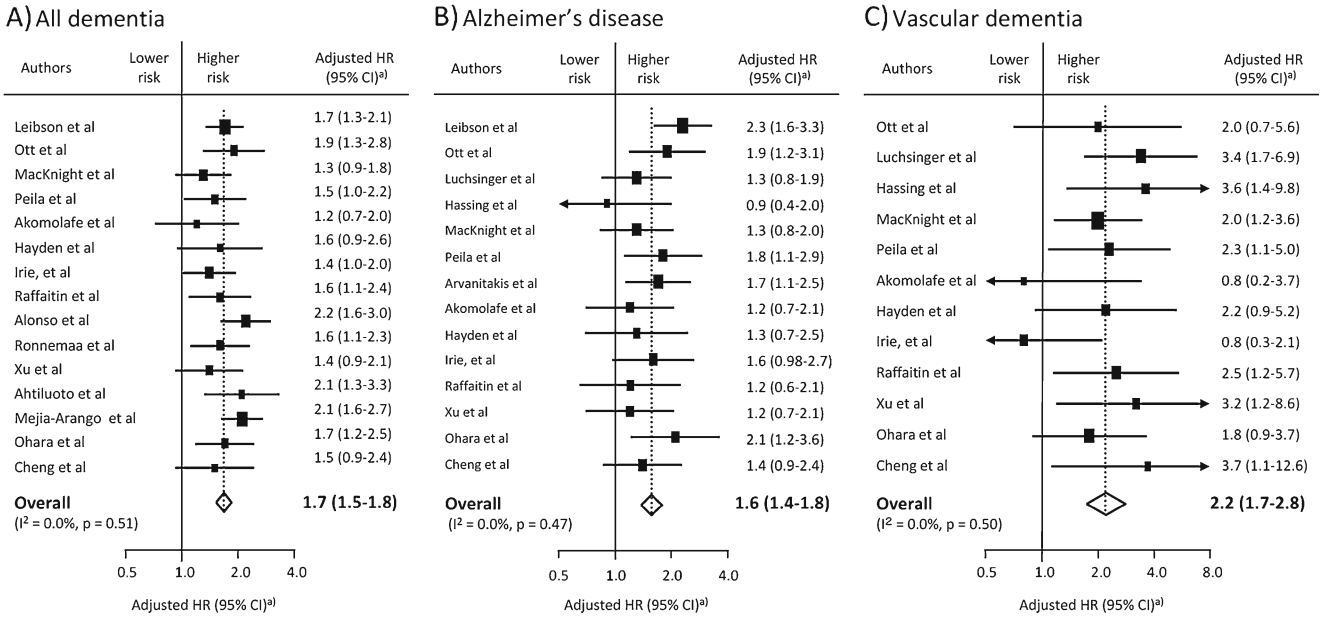

Fig. 1 Pooled risk estimates of diabetes mellitus on the development of all dementia (**a**), Alzheimer's disease (**b**), and vascular dementia (**c**); meta-analysis of population-based cohort studies. [a]The hazard ratio for each study was adjusted for the covariates shown in Table 1. *CI* confidence interval, *HR* hazard ratio

be expected to be less amenable to cardiovascular risk reduction strategies than vascular dementia, although these strategies might have a modest effect in reducing the rate of cognitive decline in people with Alzheimer's disease mixed with vascular abnormalities. Nevertheless, if these findings could be extrapolated to diabetic populations, the optimal management of the risk factors in earlier life and more prolonged therapy could provide cognitive benefits in later life in people with diabetes mellitus.

Glucose Toxicity

Hyperglycemia could cause decrements in working memory and attention, and could be associated with change of mood [45]. In the Diabetes Control and Complications Trials/the Epidemiology of Diabetes Interventions and Complications Study, higher glycated hemoglobin values were associated with moderate declines in motor speed and psychomotor efficiency among patients with type 1 diabetes during 18-year follow-up [46]. Chronic hyperglycemia may cause cognitive impairments and abnormalities in synaptic plasticity [47]. Glucose toxicity is mediated by an increased flux of glucose through the polyol and hexosamine pathway, an increased production of oxidative stress, and an accumulation of advanced glycation end-products [48]. These processes can lead to vascular damage, but can also affect the generation of neurodegenerative disorders in brain. Nevertheless, the effectiveness of tight glycemic control in the prevention of cognitive impairment is still controversial. The data from the Action to Control Cardiovascular Risk in Diabetes-Memory in Diabetes (ACCORD-MIND) study demonstrated that tight glycemic control significantly reduced the rate of brain atrophy over a period of 40 months compared with the standard glucose treatment, but there was no clear difference in the cognitive function between the treatment groups [49•].Further, intervention trials with more prolonged follow-up are required to elucidate this issue.

Hypoglycemia

Several longitudinal studies suggested that severe hypoglycemia may be also a risk factor for cognitive impairments in patients with type 2 diabetes. Patients with recurrent severe hypoglycemic episodes have a 1.5–2.0 times greater risk of the development or deterioration of cognitive impairment [50–52]. Severe hypoglycemia can induce the permanent neurologic sequelae including neuronal cell death [53] and increase in platelet aggregation and fibrinogen formation [54], which may accelerate cognitive impairment. Older patients are thought to have less brain reserve or brain plasticity than younger patients [55, 56]. Therefore, it is plausible that hypoglycemia could cause neurologic changes that render an older patient more susceptible to dementia.

Changes in Insulin Sensitivity

Insulin resistance and compensatory hyperinsulinemia are typical characteristics of the early stage of type 2 diabetes mellitus. Insulin resistance and hyperinsulinemia are associated with impaired cognitive function, which is partially mediated by vascular disease. On the other hand, accumulated

evidence has suggested that insulin and insulin receptors play important roles in the cognitive performance via modification of the activities of both excitatory and inhibitory postsynaptic receptors and the activation of specific signaling pathways [57–59]. Insulin receptors are abundantly expressed in several specific brain regions, including the hippocampus and the cortex [57]. It has been found that prolonged hyperinsulinemia induces an impaired response to insulin through a decreased expression of insulin receptors at the blood brain barrier and brain, and consequently inhibits the insulin transport into cerebrospinal fluid and brain tissues [60]. These changes could cause deficits in learning and memory formation, probably due to a neuroglial energy crisis [57, 61]. Furthermore,, patients with Alzheimer's disease show disruptions in brain insulin sensitivity, such as lower insulin levels in cerebrospinal fluid, higher plasma insulin levels, and drastically reduced densities of insulin receptor in the brain compared with healthy adults [61]. Higher levels of plasma insulin provoke amyloid accumulation by limiting the degradation of amyloid beta protein via the direct competition for the insulin-degrading enzyme, which degrades both insulin and amyloid beta protein [5, 60]. Additionally, insulin and insulin-like growth factor-1 stimulate the transportation of amyloid beta carrier proteins such as albumin and transthyretin into cerebrospinal fluid and the elimination of amyloid beta protein from the brain. However, lower insulin levels in cerebrospinal fluid and the impaired response to insulin and insulin-like growth factor-1 inhibit the transportation of these carrier proteins and decrease the clearance of amyloid beta protein [62].

Inflammation

Chronic inflammation is thought to be involved in the initiation of insulin resistance and the development of diabetes mellitus [63–65]. People with type 2 diabetes mellitus also have higher levels of circulating inflammatory markers [66]. Several cross-sectional studies have investigated the associations between inflammatory markers and cognitive impairment and decline among community-dwelling elderly [67, 68]. Evidence of an activated inflammatory response of microglial cells has been observed in the brains of people with dementia [69]. Increased levels of interleukin-1, interleukin-6, tumor necrosis factor-α, C-reactive protein, granulocyte macrophage colony-stimulating factor, and eotaxin have been reported in brain tissue from patients with Alzheimer's disease [70]. Macrophage inflammatory protein-1α has also been detected in reactive astrocytes nearby Aβ plaques in the brain of Alzheimer's disease [71]. There are few studies addressing this association specifically in people with diabetes mellitus. However, a cross-sectional study showed that elevated circulating levels of inflammatory markers were associated with worse cognitive ability in people with diabetes mellitus [72]. These findings raise the possibility that chronic inflammation may play a role in accelerated cognitive impairment, either by a direct effect on the brain, or by influencing the development of vascular disease. However, the evidence of a causal association between inflammation and cognitive function remains limited.

Conclusions

Despite the methodological limitations of the observational studies, there is convincing evidence of an increased risk of dementia in community-dwelling elderly with diabetes mellitus. Notably, diabetes mellitus is a significant risk factor for not only vascular dementia, but also Alzheimer's disease. The etiology of cognitive dysfunction in people with type 2 diabetes mellitus is probably multifactorial, but the mechanisms underpinning this association are not yet fully clarified. Since the pathophysiological processes of dementia begin many years before any symptoms appear, the optimal management of risk factors as early as possible in the life cycle may be important to prevent late-life dementia in people with diabetes mellitus. Nevertheless, the standard therapeutic strategies may be insufficient to prevent the cognitive decline completely. Therefore, further research should attempt to explore novel therapeutic strategies to prevent or reduce the development of dementia in people with diabetes mellitus.

Compliance with Ethics Guidelines

Conflict of Interest Toshiharu Ninomiya declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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