Type 2 Diabetes Mellitus and Cognitive Impairment

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ABSTRAK

Diabetes melitus tipe 2 (DM T2) sangat terkait dengan kinerja yang lebih rendah pada beberapa domain fungsi kognitif dan dengan kelainan struktural otak. Dengan meningkatnya epidemi diabetes dan populasi yang menua, komplikasi saraf diabetes diperkirakan akan meningkat dan menjadi tantangan bagi implikasi kesehatan di masa depan. Memahami patofisiologi, faktor yang terkait dengan komplikasi ini, manifestasi gangguan kognitif dan berbagai penanda metabolik dan neuroradiologis yang mencerminkan kondisi patologis yang sangat penting dalam pengelolaan komplikasi DM T2. Ulasan ini akan membahas secara singkat aspek penting dari gangguan kognitif pada DMT2.

Kata kunci: *diabetes mellitus tipe 2, gangguan kognitif.*

ABSTRACT

Type 2 diabetes mellitus (T2DM) is strongly associated with lower performance on multiple domains of cognitive function and with structural abnormalities of the brain. With the growing epidemic of diabetes and aging population, neural complications of diabetes are expected to rise and becoming a challenge for future health implications. Understanding pathophysiology, factors associated with this complication, manifestation of cognitive impairment and various metabolic and neuroradiologic markers suggestive of this pathologic condition is crucial for proper management of this potentially debilitating complication of T2DM. This review will discuss briefly important aspects of cognitive impairment in T2DM.

Keywords: *type 2 diabetes mellitus, cognitive impairment.*

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is characterized by hyperglycaemia, insulin resistance, and relative insulin deficiency. Currently there are 366 million people with diabetes mellitus world-wide, with more than 23 million people live in the United States. This number will reach the number 552 million by 2030. Type 2 DM is associated with many chronic complications, involving many organs including brain and nervous system.[1] Central nervous system-related complications of diabetes has been known for more than 100 years by researchers and clinicians as people with diabetes frequently complained of worsen memory and attention.[2]

Existing evidence suggested that T2DM was strongly associated with reduced performance on multiple domains of cognitive function and with structural abnormalities in the brain.[1,2] Cognitive decline in this case can manifest as mild cognitive impairment (MCI), Alzheimer's disease (AD), vascular dementia (VD) and many other form of dementias as measured by neuropsychological testing compared to non-diabetic controls. T2DM is associated with 50% increased risk of dementia.[2]

In a longitudinal studies, diabetes in midlife was associated with a 19% greater cognitive decline over 20 years compared with no diabetes in the ARIC study cohort. In a large prospective population-based cohort study of more than 6000 elderly subjects, T2DM almost doubled the risk of dementia.[2] Mayeda et al.[3] conducted a 10 year cohort study involving 1617 non-dementia older participants from Sacramento Area Latino Study on Aging. After adjusting for competing risk of death, either treated or untreated diabetes patients showed an increased risk of dementia/ mild cognitive impairment compared to healthy control group. Another meta-analysis estimated that T2DM people have a relative risk of vascular dementia of 2.5 (95% CI 2.1-3.0) and that of Alzheimer disease is 1.5 (95% CI 1.2-1.8) relative to individuals without diabetes.[4] Of the kinds of dementia, Alzheimer's disease (AD) is the most prevalent pathology. Clinically, AD is characterized by the loss of memory, change in personality and other cognitive functions necessary to perform complex daily activities. Alzheimer's disease (AD) is estimated to cost American society of 214 billion dollars in direct medical expenses, and is predicted to reach 1.2 trillion dollars by 2050.[5]

FACTORS ASSOCIATED WITH COGNITIVE IMPAIRMENT

Cognitive decline in T2DM has been associated with duration of diabetes, poor glycemic control, obesity, retinopathy and some other factors. These factors promote cognitive decline by some mecahnism: chronic hyperglycemia causing osmotic insults, oxidative stress, formation of advanced glycation end products (AGEs), activation of deleterious microglia and other mechanisms. All these factors load to direct toxicity on neurons.[6] Morris et al.[7] used data from Alzheimer's disease neuroimaging initiative (ADNI) to assess the impact of baseline glycemic status (fasting glucose) on cognitive performance and brain structure in MCI subjects. Changes in clinical dementia rating-sum of boxes, cognitive performance testing (global cognition), brain volume (whole brain and hippocampal volume), fluorodeoxyglucose-positron emission tomography and conversion to AD were assessed. Subjects with normoglycemia at baseline had less functional and global cognitive decline over 2 years; less whole brain volume loss and lower conversion from MCI to AD compared to subjects with impaired glycemia. This study suggested the role of glycemic control on cognitive decline in T2DM. A multivariate regression analysis found that HbA1C level was the only significant predictor of hippocampal atrophy in T2DM patients. However, in the ACCORD-MIND sub-study, there was no difference of cognitive performance or brain MRI outcomes between intensive glycemic control group compared with standard glycemic control group after 80 months of follow-up.[8] Another study linked obesity as a significant predictor of smaller hippocampal volume in T2DM.[9] In the ACCORD-Eye substudies of ACCORD-Mind, there was an association between baseline diabetic retinopathy and severity of retinopathy with decline in global cognitive function and processing speed over 40 months follow-up. This association was due to the similarity of embriology and anatomy between retinal and cerebral small blood vessels, causing vulnerability of both organs to the vascular factors such as T2DM.[2]

PATOPHYSIOLOGY

The pathophysiology of cognitive impairment in diabetes is still not fully understood. However, until now the most important mechanism underlying this condition is insulin signaling dysfunction leading to failure of glucose absorption in the neurons needed for energy production. Studies in AD revealed that this failure is associated with many mechanisms, such as insulin resistance, insulin growth

factor (IGF) signaling, inflammatory response, oxidative stress, glycogen synthase kinase 3β (GSK3β) signaling mechanism, amyloid beta (Aβ) formation from amyloid precursor protein (APP), neurofibrillary tangle formation, and acetylcholine esterase activity regulation.[1] Insulin resistance as a key link between type 2 DM and cognitive impairment refers to a condition where brain tissues do not respond sufficiently to physiological insulin concentration. Usually early type 2 DM patients have hyperinsulinemia but poor insulin sensitivity.[5] Long-term consequences of insulin resistance states include cellular energy failure, elevated plasma lipids, and hypertension.[10]

Secreted by pancreatic beta cells, insulin enters the central nervous system by crossing the blood-brain barrier.[5] Like in most organ systems, insulin and insulin-like growth factors (IGFs) play many important roles for optimal brain functions. They maintain homeostasis, energy metabolism and cell survival and support neuronal plasticity and cholinergic functions needed mostly for learning, memory and myelin maintenance.[10] In adipocytes and myocites, insulin regulates glucose transport by controlling translocation of the glucose transporter 4 ($Glut_4$).[5] In the brain, the virtually same mechanism of insulin and IGF signal transduction regulates metabolic activities. $Glut_4$ mediates glucose uptake in the brain tissue for energy production, which is abundantly expressed along with insulin receptors in the medial temporal lobe and other targets of AD. Both of this protein regulate glucose utilization and ATP production in the brain tissue. Impairment of these signaling, caused by receptor resistance or ligand deficiency will disrupt energy balance and disturb networks that support a broad range of brain functions.[10] Besides, this impairment makes neurons more vulnerable to metabolic stress, thus accelerating neuronal dysfunction.[5]

Both neurons and glia cells of the brain have insulin receptor (InsR) with more concentrated in neurons relative to glial cells and are especially high in post-synaptic densities. The areas with the highest density of insulin receptors are hippocampus, hypothalamus, cerebral cortex and olfactory bulb. Insulin binds to the extacellular α-subunit of InsR, resulting in autophosphorylation of the intracellular β-subunit. Activated InsR will activate and phosphorylates intracellular substrates especially several tyrosine residues on insulin receptor substrate (IRS) and Shc. These phospho-tyrosine residues are important for IRS 1 and 2 for initiating several signaling cascades such as phosphatidylinositol 3-kinase (PI3K), GSK3β signaling, mithochondrial regulation for energy production and etc. Phosphorylated tyrosine residues on IRS and Shc then recruit downstream signaling molecules containing Src homology 2 (SH2) domains, such as the p85 subunit of phosphatidylinositol 3 kinase (PI3K) which activates Akt-mediated signaling, and growth factor receptor-binding protein 2 (Grb2), which leads to the activation of mitogen-activated protein kinase (MAPK) signaling pathway. PI3K is associated with almost all of the metabolic actions of insulin.[1,5]

Akt molecules (Akt1, Akt2, and Akt3) is a serine/threonine kinase activated by PI3K downstream of growth factors and various cellular stimuli. Akt mediates the bulk of insulins action, including glycogen, lipid, and protein syhthesis, cell survival, and the anti-inflammatory response. The alteration or inactivation of Akt activity is one of the key characteristics of insulin resistance. Glut4 translocation is closely correlated with Akt2 activation through insulin-activated PI3K signals in adipocytes. Patients with type 2 DM have reduced Akt activation of adipocytes and skeletal muscle, leading to many damaging effects on neurons and glial cells. IRS proteins contain over 20 tyrosine residues and more than 50 potential serine/threonine phosphorylation sites. Activation of serine/threonine sites by phosphorylation will inhibit insulin signaling by antagonizing tyrosine phosphorylation. Multiple IRS serine kinases are activated in IR states, resulting in increased IRS serine phosphorylation and subsequently impaired insulin signaling. Decreased insulin signaling, including altered kinase activity and IRS expression, is getting worse with disease progression. In AD, interestingly the brain regions with the highest densities of InsR such as hippocampus and temporal lobe are also

the major targets of neurodegeneration in AD. Therefore insulin resistance in the brain can have profound effect on cognitive impairment and the development of AD. This condition exists not only in T2D, but also in the other insulin resistance states such as obesity, either in human or animal studies.[5]

MANIFESTATION OF COGNITIVE IMPAIRMENT IN T2DM PATIENTS

Data from prospective studies have shown that many people with T2DM perform less well than controls in the cognitive domains on information-processing speed, memory, attention and executive function. A longitudinal ARIC study showed cognitive decline in T2DM primarily in the domains of processing speed and executive function. Some studies have also shown change in mental flexibility and global cognitive function.[2] A case control study investigating drain volume abnormalities in older T2DM patients revealed a worse processing speed and memory performance in T2DM group compared with control subjects.[12] A 4 year cohort study conducted by Van den Berg *et al.* on non-demented T2DM patients found moderate decrements in information-processing speed and executive functions compared with controls at both of the baseline and the 4 year follow-up examination; however no evidence of accelerated cognitive decline over 3-6 years of follow up in T2DM groups.[13] On the contrary, other studies have showed accelerated decline in cognitive function over a follow up of 3-6 years in subjects with T2DM.[2]

In a large nationally representative cohort, The National Health and Aging Trends Study in US, 7605 elder participants were enrolled to complete immediate and delayed recall word list learning tests and Clock Drawing Test. In this study, analysis showed that baseline DM diagnosis was associated with decline on immediate and delayed word recall and the Clock Drawing Test. DM also predicted the incidence of dementia in older age groups at baseline.[14]

MARKERS OF COGNITIVE IMPAIRMENT IN T2DM

Metabolic Markers

The prominent hypothesis mediating T2DM with cognitive impairment is peripheral insulin resistance that promotes cognitive impairment by causing brain insulin resistance. Insulin resistance with dysregulated lipid metabolism leads to an increase in inflammation, cytotoxic lipid production, oxidative and endoplasmic reticulum stress, and worsening of insulin resistance. The role of cytotoxic ceramides that can promote inflammation, oxidative stress and insulin resistance are being investigated. Ceramides generated in liver or visceral fat can leak into peripheral blood because of local cellular injury or death, cross the blood-brain barrier, and initiate or propagate a cascade of neurodegeneration mediated by brain insulin resistance, inflammation, stress, and cell death.[10]

T2DM is associated with increased oxidative stress as a result of hyperglycemia and insulin resistance state. This systemic condition also involves the brain and cause pathological conditions affecting cognitive function such as proinflammatory networks causing organelle dysfunction, amyloid beta polypeptide precursor (AβPP) expression, neurotoxic fibrils production, activation of GSK-3β pathway which promotes tau phosphorylation leading to deposition of this pathologic substances.[10] There are many metabolic markers associated with oxidative stress, one of which is malondialdehyde.[15] Inflammation associated with obesity may contribute to hippocampal dysfunction and cognitive impairment. Besides, the hyperglycemia-associated production of reactive oxygen species and lipotoxicity leads to microvascular and macrovascular damage. In addition they may mediate T2DM and cognitive decline.[9]

Hyperglycemia can cause accumulation of advanced glycation endproducts (AGEs) leading to reactive oxygen species generation and cell damage. AGEs are peptide/protein molecules formed as a result of the Maillard reaction. These AGEs promote amyloid oligomer aggregation

and involve the formation AD neurotoxicity. AGE products produce superoxide and H_2O_2 resulting in lipid peroxidation and cell damage in the brain. The increase in free radicals in T2DM may be caused by varying levels of antioxidants such as superoxide dismutase (SOD), glutathione peroxidase (PSH-Px), and catalase (CAT). This imbalance in prooxidants and antioxidants causes oxidative stress in T2DM and AD. Lipid peroxidation can occur in the brain tissue because of human brain gas with abundant peroxidizable polyunsaturated fatty acids and the relative paucity of antioxidants and enzymes. Mitochondrial dysfunction caused by insulin resistance triggers inflammation response. Insulin resistance increases the levels of cytokines such as IL-6, IL-1β and IL-18, TNF-α, α-1-antichymotrypsin and C-reactive protein.[1]

Plasma homocysteine has been associated with an increased risk for cardiovascular events in type 2 diabetic patients independent of conventional risk factors. In a cross sectional study conducted in Nigeria including 70 patients with T2DM and 30 healthy controls found a significant increased level of plasma homocysteine in patients with T2DM compared to healthy control subjects.[16] A cross-sectional study including 1276 Japanese showed that estimated glomerular filtration rate (eGFR) dan serum creatinin level were strongly associated with homocysteine.[17] A descriptive case series study conducted in Pakistan found that chronic poor metabolic control of diabetes mellitus is associated with elevation of plasma homocysteine concentration. This study included 70 T2DM patients with 48 of them showed hyperhomocysteinemia condition.[18] In addition in a meta-analysis conducted by Huang et al.[19] showed a strong evidence on the causal association of homocysteine level with the development of T2DM. Some studies have reported the association of homocysteine and T2DM-related cognitive impairment. Tian et al.[20] investigated this association and found that increased plasma homocysteine level was significantly related to T2DM-associated mild cognitive impairment (MCI), especially executive dysfunction. This study include 140 patients with mild cognitive impairment and 145 healthy cognition controls. The MCI group exhibited significantly higher plasma total homocystein levels than control group.

Neuroradiologic Markers

T2DM alters brain function and structures. Many studies have shown associations of diabetes mellitus with volume abnormalities of brain. Brain regional volume abnormalities have been studied intensively. T2DM is associated with global brain atrophy and increased burden of small-vessel disease. Results of studies identified consistent relationship between T2DM and cortical and subcortical atrophy, especially the temporal lobes. Hippocampus and amygdala atrophy was also consistently associated with T2DM. Zhang *et al* conducted a study to evaluate brain gray matter (GM) volume changes in T2DM patients and healthy control using voxel-based morphometry (VBM) based on MRI data. T2DM patients both with and without mild cognitive impairment showed significantly decreased total GM volume. Furthermore, compared with healthy controls, T2DM patients without MCI also exhibited extensively decreased GM volume, including the superior and middle temporal gyrus (MTG), the superior and medial frontal gyrus and the middle occipital gyrus. This study concluded the hypothesis that brain structural changes in several regions of the brain underlie transition from normal cognition to MCI in T2DM patients.[21]

A case-control study in older individuals by Reijmer et al.[12] was conducted to investigate the association of T2DM with microstructural abnormalties in specific white matter tracts and relation of this structural abnormalities with cognitive functioning. Using 3 Tesla diffusion-weighted MRI scan and detailed cognitive assessment, 35 non-demented T2DM patients and 35 matched control subjects showed microstructural abnormalities in various white matter pathways in T2DM patients. And these abnormalities were related to worse cognitive functioning, primarily slowing information-processing speed and memory performance. Besides volumetry and microstructural abnormalities, the other radiology markers

associated with cognitive decline in T2DM were cerebral infarcts and microbleeds composed a pathology entity, cerebral microvascular disease.[9] T2DM cause microvascular disease throughout the body, including the brain tissue. The finding of progressive atrophy of medial temporal lobe, which houses the hippocampus, support this pathologic condition. Chronic microvascular injury caused by hyperglycemia-hyperinsulinemia is characterized by reactive proliferation of endhotelial cells, thickening of the intima, fibrosis of the media and narrowing of the lumens. Damaged blood vessels are leaky and permeable to toxins and contribute to increased frequencies of microhemorrhage and perivascular white matter tissue loss in T2DM and AD.

Despite most studies investigating brain abnormalities in T2DM focused on structural changes, functional imaging studies in conjunction with T2DM have been increasing. Those functional studies include cerebral blood flow measurement (CBF), glucose metabolism using PET, and resting-state functional MRI (rs-*f*MRI). Studies attempting to link T2DM to alterations in CBF showed mixed results. Initial studies found a reduction in CBF in T2DM patients relative to controls, but later studies with larger sample sizes showed inconsistent patterns of CBF change in T2DM patients. Additionally, measurement of CBF provides only a gross measurement of total blood intake, without reference to regional differences that may increase or decrease with disease pathology.[22]

Another novel marker associated with cognitive impairment is sympathovagal imbalance (SVI). It has been reported to be associated with metabolic derangements in T2DM together with autonomic dysregulation and decreased heart rate variability (HRV). A

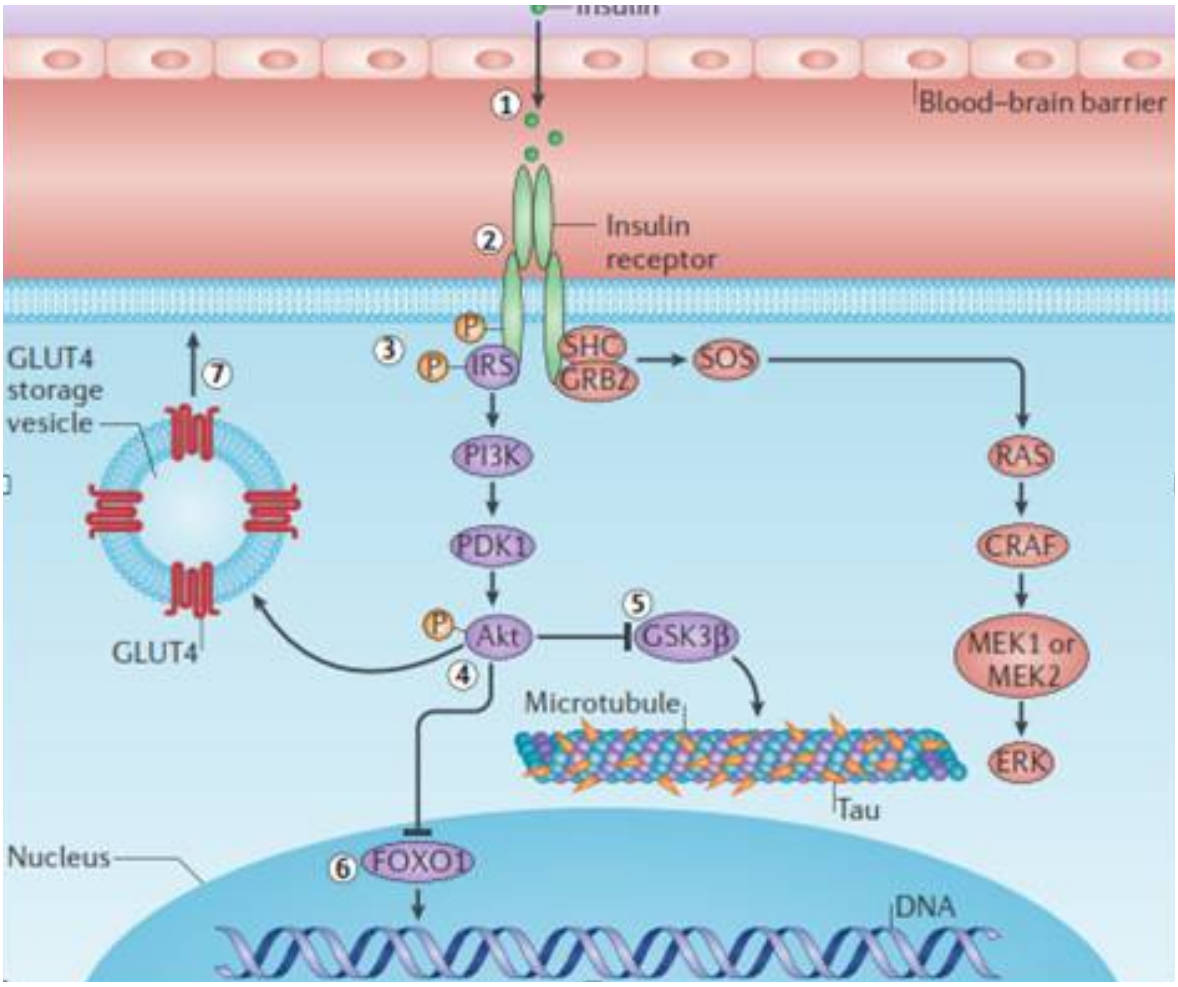

Figure 1. Insulin receptor signalling in the brain.[10]

clinical trial was conducted in 2018 to assess the association of SVI with cognitive function in T2DM. SVI was assessed by spectral analysis of HRV to calculate the ratio of low-frequency to high-frequency (LF-HF ratio) of HRV and cognitive function was assessed by recording the positive wave that appears in 300 milliseconds from application of stimulus in event-related potential tracing (P300). This study found that P300 latency was significantly prolonged in T2DM group compared with control group. LF-HF ratio of HRV was found to be correlated and linked with P300. It can be concluded that SVI could be the physiologic link to cognitive impairment in T2DM patients.[15]

THERAPEUTIC CHALLENGES

Intranasal insulin has emerged as a promising intervention for treatment of cognitive impairment in T2DM patients. Zhang et al.[23] conducted a randomized, double-blind, placebo-controlled study to evaluate the acute effects of intranasal insulin on resting-state brain functional connectivity in older adults with T2DM. After administrating a single 40 IU dose of intranasal insulin to 14 diabetic subjects and intranasal saline to 14 control subjects, resting-state functional connectivity between the hippocampal region and default mode network (DMN) was quantified using functional MRI (*f*MRI) at 3 Tesla. Following intranasal insulin administration, diabetic group demonstrated increased resting-state connectivity between the hippocampal regions and the medial frontal cortex (MFC) as compared with placebo. This trial proved that regulating memory with intranasal insulin use may modify functional connectivity among brain regions and complex cognitive behaviors. This trial also improved visuospatial memory and increased perfusion in the insular cortex compared with the control group. This acute improvements of cognitive function in T2DM patients may be related to vasodilatation in the anterior brain regions, such as insular cortex that regulates attention-related task performance.[24]

Future tasks of researchers include unravelling of the etiology of the brain complications of T2DM by integrating findings from different imaging modalities and detailed clinical phenotyping and by linking structural MRI abnormalities to histology. Understanding the underlying mechanisms is necessary to establish interventions that will improve long-term cognitive outcomes for T2DM patients.

CONCLUSION

The link between T2DM and cognitive impairment is still not well understood. Insulin resistance of the brain plays most important role of cognitive impairment in T2DM. Further studies investigating both markers associated with cognitive decline in T2DM and therapeutic interventions based on established linking pathophysiology are needed to achieve better outcomes in T2DM patients.

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