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Diabetes Mellitus And The Brain: Special Emphasis To Cognitive Function

Review Article

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Abstract

Diabetes mellitus (DM) is a major public health problem. Cognitive deficits are common with DM which range from subclinical or subtle to severe deficits as dementia. Both hypoglycemia and hyperglycemia are causes of cognitive impairment with DM. In patients with DM, not only severe hypoglycemia but also recurrent mild or moderate hypoglycemia have deleterious effect on the brain. Recurrent mild/moderate hypoglycemia is associated with intellectual decline, reduced attention, impaired mental abilities and memory deficits. Hypoglycemia may result in abnormalities of neuronal plasticity, synaptic weakening and scattered neuronal death in the cerebral cortex and the hippocampus. Chronic hyperglycemia in type 1 and type 2 DM is associated with low IQ (verbal, performance and total) and abnormalities in testing for different domains of cognitive function as verbal relations, comprehension, visual reasoning, pattern analysis, quantitation, memory, learning, mental control, psychomotor efficiency, mental and motor processing speed and executive function. The suggested mechanisms incriminated in the pathogenesis of hyperglycemia related cognitive dysfunction include, macro- and micro-vascular disease or vasculopathy, hyperlipidemia, hypertension, insulin resistance and hyperinsulinemia, stress response, direct toxic effect of chronic hyperglycemia on the brain, advanced glycation end products, inflammatory cytokines and oxidative stress. Hyperglycemia causes oxidative stress, amyloidosis, angiopathy, abnormal lipid peroxidation, accumulation of β-amyloid and tau phosphorylation, neuroinflammation, mitochondrial pathology, apoptosis and neuronal degeneration in the cortex and hippocampus. Depression has been identified as a risk for accelerated cognitive decline with DM. The knowledge that diagnosis at early age, frequency of hypoglycemia, poor glycemic control and presence of risk factors which negatively affect cognitive functions in DM, will have important implications for treatment and for research purposes.

Key Words: Diabetes Mellitus; Hypoglycemia; Insulin Resistance; Cognition; Vascular Disease.

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Introduction

Diabetes mellitus (DM) is one of the most common and most important metabolic disease worldwide. The incidence and prevalence of DM are increasing rapidly due to industrialization, inappropriate diet, sedentary life style and increased obesity [1]. Hypoglycemia, hyperlipidemia and vascular diseases (as angiopathy, nephropathy and cardiovascular, cerebrovascular and peripheral vascular diseases) are common complications of DM [2]. Cognitive deficits are common with DM which range from subclinical or subtle to severe deficits as dementia. Cognition refers to the set of integrated and inter-related mental processes and systems involved in acquiring knowledge and comprehending, storing, retrieving and using this knowledge to perform day-to-day activities.

Both hypoglycemia and hyperglycemia are causes of cognitive impairment with DM [3-39]. Intellectual decline, impaired mental abilities and memory deficits are common with recurrent hypoglycemic episodes [3-10]. Studies indicate that repetitive mild and moderate hypoglycemia cause impairment in synaptic plasticity with inability to induce long term potentiation (LTP) which has a crucial role in memory and this contributes to cognitive impairments [11,12]. Recurrent moderate hypoglycemia result in scattered neuronal death in the cerebral cortex [13,14] and hippocampus [15]. While severe hypoglycemia result in oxidative stress and wide spread neuronal death in the cerebral cortex and hippocampus [16,17]. In hyperglycemia, low IQ and reduced performance on various domains of cognitive function including verbal relations, comprehension, visual reasoning, pattern analysis, quantitation, digit forward, digit backward, memory, mental control, associate learning, psychomotor efficiency, problem solving, mental and motor processing speed, eye-hand coordination and executive function, are common [18-26]. The suggested mechanisms incriminated in hyperglycemia related cognitive impairment include: metabolic derangement, macro- and micro-vascular complications [27,28], oxidative stress [29,30] and diabetes-related depression [31-35]. Chronic hyperglycemia causes oxidative stress, amyloidosis, angiopathy, abnormal lipid peroxidation, increase the formation of advanced glycation end products, accumulation of β-amyloid and tau phosphorylation, neuroinflammation, mitochondrial pathology, apoptosis, neurodegeneration in the cortex and hippocampus and brain atrophy [36-39].

This review was performed through a comprehensive search in the PubMed, ISI web of science, Science Direct and Scopus databases from 1990 to 2013 using the following search terms: cognitive function in diabetes, hypoglycemia and cognition, type 1 DM (T1DM) and cognition and type 2 DM (T2DM) and cognition.

Data of epidemiological, longitudinal, prospective, double-blinded and clinical trial studies and case reports were considered. We also checked the reference lists of the retrieved studies for additional reports. In this review, we summarized the experimental and clinical evidence of cognitive dysfunction with DM, the possible mechanisms underlying cognitive dysfunction in DM, the relationship between DM and neurodegeneration and the clinical and research approaches with the aim to prevent and treat cognitive dysfunction with DM.

Cognitive Dysfunction With Hypoglycemia

The brain is an energy-intensive organ. Glucose is the primary fuel of brain cells. Approximately 25% of total body glucose is required for proper brain function [40]. The normal range for human blood glucose concentration is 3.9 to 7.1 mM (1 mM = approximately 18 mg/dl). Hypoglycemia is defined as blood glucose level below which brain function deteriorates in most patients (i.e. less than 3 mmol/l or 54 mg/l00 ml) [41]. In patients with DM, not only severe hypoglycemia (blood glucose level below 2 mM) but also recurrent mild (blood glucose level is 3.2 to 3.6 mM) or moderate (blood glucose level is 2.3 to less than 3.2 mM) hypoglycemia have deleterious effect on the brain [3-11,13-17]. Hypoglycemia is common with intensive insulin therapy. It has been indicated that the oscillations in glycaemia, owing to the nature of subcutaneous insulin administration, are more common and result in increase in the frequency of hypoglycemia in those treated for DM [42]. Recurrent mild and moderate hypoglycemia are more common than severe hypoglycemia [7,10,43]. It has been reported that most hypoglycemic events were found to be asymptomatic in 90% of children treated with insulin, 98% of those occurring at night and the majority of untreated hypoglycemic events were associated with a relapse into hypoglycemia within 3 hours [44]. Attention, associative learning and mental flexibility are affected with acute hypoglycemia [5]. Recurrent mild and moderate hypoglycemia are associated with intellectual decline particularly performance IQ, impaired mental abilities and memory deficits [3,45]. It was reported that recurrent mild and moderate hypoglycemia in children younger than 5 years old with T1DM may develop reduced attention, spatial memory and intelligence in adolescence [6,8,46].

Experimental and clinical studies indicate that severe hypoglycemia for a least 10 minutes result in microglial activation and oxidative stress with the release of several neurotoxic substances, including superoxide, nitric oxide, and metalloproteinase and wide spread neuronal death in the cerebral cortex and hippocampus. While recurrent moderate hypoglycemia result in scattered neuronal death in the second and third cerebral cortex layers and hippocampal CA1 dendritic region and hippocampal thinning [14-16,47,48]. It has been suggested that cognitive impairment in children and adults with repetitive mild and moderate hypoglycemia is due to deterioration in synaptic injury with an inability to induce or persistent inhibition of long term potentiation (LTP) and facilitation of long term depression (LTD) at hippocampal CA1 (which plays a crucial role in memory) in the absence of apparent neuronal somatic injuries. This in turn results in activity-dependent synapse weakening and contributes to cognitive impairments [11,12].

Cognitive Dysfunction With Hyperglycemia

DM is defined by the presence of symptoms of hyperglycemia and presence of fasting plasma glucose (FBG) level ≥ 7.0 mmol/l or126 mg/dl or post-prandial blood glucose (PBG) ≥ 11.1 mmol/l or 200 mg/dl or a random plasma glucose ≥ 11.1 mmol/l or 200 mg/dl or glycated hemoglobin (HbA1C) ≥ 6.5% [49].

At the experimental level, detrimental effects on learning and memory were observed in streptozotocin (STZ) (rodent model of T1DM) and GK rat [50], db/db mouse and Zucker rat [51] (genetic models of T2DM) as observed with impaired performance in Morris water maze spatial test [51,52] and inhibitory [53] or active avoidance tasks [54] and an object-discrimination task tests [22], all are indicative of impairment in hippocampus and its related structures. At the clinical level, children and adults with DM demonstrate low IQ and reduced performance on various domains of cognitive function including verbal relations, comprehension, visual reasoning, pattern analysis, quantitation, digit forward, digit backward, short-term memory, memory for sentences, verbal memory, logical memory, mental control, associate learning, psychomotor efficiency, problem solving, mental and motor processing speed, eye-hand coordination and executive function [18-26,55-57]. Many authors reported that cognitive deficits were correlated with the degree of chronic hyperglycemia and improvement in performance of cognitive testing with improvement in glucose tolerance [58,59]. Wu et al. [23] observed that compared to treated patients, the untreated patients with DM had 2 points decline over 2 years on Mini Mental State Examination test (MMSE) with duration of illness <5 years and 6 points decline on MMSE with duration of illness ≥5 years. Cox et al. [24] observed that the increase of blood glucose >15mmol/l was associated with marked decline in cognition and poor performance in arithmetic tasks. The research showed that those with DM have a 1.2 to 1.5-fold greater rate of decline in cognitive function compared to those without diabetes [60]. At the neurophysiological level, studies also reported abnormalities in P300 component of event related potentials (ERPs), a physiological analogue of cognitive testing [25,61,62] and prolongation of I-III and I-V interpeak latencies of the auditory brainstem response (ABR), an indicative of central auditory pathway function [63], in patients with T1DM and T2DM and regardless of the recent metabolic derangement and disease duration. At the neuroimaging level, structural brain atrophy particularly in the limbic structures such the hippocampus and amygdala, smaller total brain volume, smaller gray matter volume, larger ventricular volume, larger white matter lesion volume and accelerated increase in ventricular volume over time and increased risk for incident brain infarcts, were seen in magnetic resonance imaging (MRI) of the brain of patients with T2DM and also in patients with early manifestation of impaired glucose tolerance (i.e. PBG ≥140 mg/dl or 7.8 mmol/L but not over 200 mg/dl or 11.1 mmol/L) [28,38,39,64-66]. Studies also reported that well-controlled middle-aged individuals with T2DM [20], non-diabetic individuals with insulin resistance (IR) (a pre-diabetic state) [67] had declarative memory deficits and specific hippocampal volume reduction and deficits in hippocampal synaptic plasticity [52] which were correlated with the present deficits in declarative memory.

The etiology of cognitive impairment in people with hyperglycemia is multifactorial. Vascular [27,28] as well as neurodegenation [65,66] contribute to cognitive dysfunction with chronic hyperglycemia. The followings have been suggested as causes of hyperglycemia-induced cognitive impairment: chronic complication as macro- and micro-vascular complications (diabetic vasculopathy) [20,27,28], hyperlipidemia [68,69], hypertension [70,71], insulin resistance (IR) and hyperinsulinemia [67], dysregulation of limbic-hypothalamic-adrenal pituitary axis (LHPA) with chronic

hypercortisolemia and impairments in hippocampal neurogenesis, synaptic plasticity and learning [72-74], direct toxic effect of chronic hyperglycemia on the brain [25,55], advanced glycation end products, inflammatory cytokines, oxidative stress [29,30] and diabetes-related depression [32-35].

DM is a risk for arterial stiffness and atherosclerotic and cerebrovascular diseases [27,28]. Experimental and human studies also indicate that chronic hyperglycemia result in brain injury with specific vulnerability to memory and learning processing, regardless of vascular pathology. In experimental models, it was observed that chronic hyperglycemia and spontaneous onset of T2DM cause blood brain barrier (BBB) disruption, alteration of insulin transporter and decrease in insulin receptors which are expressed in discrete neuronal populations in the CNS, including the hippocampus. Impairment of insulin function result in reduction in the uptake of glucose into the neurons, impairment of energy metabolism and impairment of brain's capacity to generate the connections vital to memory and learning. Reduction of insulin like growth factor 1 (ILGF-1) [75,76] and brain derived neurotrophic factor (BDNF) were observed in rat models of T2DM [77]. IGFs regulate adult brain mass by maintaining brain protein content and supports synapses and is required for learning and memory. It was observed that replacement doses of insulin and IGFs in diabetic rats can cross the blood-brain barrier, improve brain atrophy and prevent hippocampus-dependent memory impairment [75-77]. Researchers found that insulin and IGF-I were significantly reduced in the frontal cortex, hippocampus and hypothalamus but not the cerebellum in postmortem brain tissue from people with DM [45]. It has been indicated that hyperglycemia causes oxidative stress, amyloidosis, angiopathy, abnormal lipid peroxidation, increase the formation of advanced glycation end products, accumulation of β-amyloid and tau phosphorylation, neuroinflammation, mitochondrial pathology, increase in Bax expression (proapoptotic protein) and caspase-3 (apoptotic element) levels, reduction in Bcl-2 protein levels (antiapoptotic protein), increase in the ratio of Bax to Bcl-2, DNA fragmentation in the cortex and hippocampus, neuronal degeneration and brain atrophy [36,37]. Recently, it was reported that adults and middle aged patients with T2DM had higher concentrations of serum neuron specific enolase (NSE) (which is a marker of neuronal cell damage which was significantly correlated with cognitive deficits' regardless the level of glycemic control and after adjustment of confounders [25]), indicating direct brain injury due to chronic hyperglycemia. Several studies have shown higher serum and cerebrospinal fluid (CSF) levels of NSE and also their over-expression increases the vulnerability to neurodegeneration, cerebral hypoxic-ischemic injury and traumatic brain injury [78,79].

Cognitive Dysfunction With Hyperinslinemia

Insulin is a key protein in the control of intermediary metabolism. It organizes the use of fuels for either storage or oxidation. It influences carbohydrate, lipid, protein and mineral metabolism [40]. Binding of insulin to its receptors phosphorylates many intracellular protein and generating a biological response. Insulin acts on cells thoughout the body to stimulate uptake, utilization and storage of glucose. In the brain, as with peripheral insulin, insulin is in part responsible for the uptake of glucose into the neurons which is important for energy metabolism. Most of brain insulin originates from systemic blood circulation but to less extent, it is produced in the brain [80]. Insulin crosses the blood-brain barrier (BBB) using a saturable transporter [81]. Insulin-sensitive glucose transporters, insulin receptors and insulin downstream signaling molecules, are distributed throughout the human brain on both neurons and astrocytes [82]. Insulin receptors are densely expressed in the medial temporal lobe, hippocampus and prefrontal cortex, which mediate long-term memory and working memory [83]. Insulin affect a wide range of normal brain functions, such as reward, motivation, cognition, attention and memory formation. Insulin's anabolic effect in the brain includes stimulation of the growth, neuronal differentiation, survival (neurotropism) and remodeling (neuromodulation) [82]. The synapses (which transmit information between neurons) contain insulin receptors. Insulin serves as a vital element for normal synaptic structure and function and subsequently for the strength of connections between neurons. Insulin binds to receptors at the synapse and together with proper inulin signaling, both contribute to brain plasticity and formation of new brain circuitries essential for learning and memory [84]. Insulin in the brain is degraded by insulin degrading enzyme (IDE). IDE regulates the generation and clearance of amyloid β (Aβ) from the brain[85,86].

Hyperinsulinemia is a most common consequence of IR which is the main defect in T2DM. It has been indicated that prolonged exposure of the brain to higher than physiological levels of insulin may alter signaling and metabolic pathways in a manner that is deleterious to cognitive circuitry which mainly depends on proper metabolic processes [84]. Chronic elevation of insulin concentrations in the periphery may paradoxically causes a relative hypoinsulinized state in the brain and thus resultant hyperinsulinemia could actually impair cognition by disturbing insulin-mediated utilization of glucose by cells in the brain particularly the hippocampus, which is enriched with insulin receptors. Central hypoinsulinemia may promote central inflammation, β-amyloid generation and reduced neuroplasticity [85]. Decrease in levels of insulin degrading enzyme (IDE) was observed in rat models of T2DM. IDE, an enzyme responsible for insulin degradation in the brain, also degrades amyloid plaque. As insulin has a very similar molecular structure to amyloid plaque, thus the latter might compete for the benefits of IDE in presence of hyperinsulinemia [86]. Elevated insulin levels are implicated in the brain cells' failure to clear β-amyloid, formation of senile plaques and tau protein phosphorylation[87-89].

Depression Accelerates Cognitive Decline With Dm

Epidemiological studies suggested that diabetic patients are 2-3 fold more likely to develop depressive illness when compared to non-diabetic individuals. On the other hand, individuals with depression have an approximately 60 percent higher risk of developing T2DM [32-34] In general, the prevalence of depression with DM was estimated to be 31.1% [90]. Comorbid depression has been identified as a risk factor for accelerated cognitive decline among patients T2DM. Depression has been identified as a risk factor for dementia among patients with T2DM in all domains [35].

Clinical and Research Perspectives

The knowledge that diagnosis at early age, frequency of hypoglycemia, poor glycemic control and presence of risk factors which negatively affect cognitive functions in DM, will have important implications for treatment of DM and for research purposes. Preventive strategies include modification of lifestyle, patient education, diet orientations (i.e. eliminating high-glycemic foods, including processed carbohydrates and sweets, would sensitize

insulin receptors and correct hyperinsulinemia [91-94]), stopping smoking, maintaining a healthy body weight, mental and physical exercise [95], control of hypertension and dyslipidemia and treatment of brain infarcts, cardiovascular diseases and depression [70,96,97]. In hyperglycemia, it is important to regularly monitor the blood glucose level and to keep glycemic control with the aim is an HbA1C level of 6.5%, but should not be lower than that, and may be set higher [98]. Hypoglycemia should be treated with a defined dose of carbohydrates rather than a mixed meal. Insulin-sensitizing drug are able to slow down, prevent, or perhaps even improve DM-related cognitive decline. Neuroprotective strategies have to be included aside to the treatment of DM from the beginning to prevent the long-term diabetic complications, those include: free radical scavengers/antioxidants (as alpha lipoic acid (ALPA), evening primrose oil (EPO), vitamin C, vitamin E and vitamin B complex) [99], modifiers of mitochondrial dysfunction, anti-apoptotics, and neurotrophic factors [76]. Future studies has to be directed for better understanding of the pathophysiological mechanisms underlying the cognitive dysfunction in diabetes. There is also a need for construction of longitudinal studies that prospectively assess the relation of the disease process to cognition over time and randomized clinical trials that compare cognitive function in DM patients receiving memory enhancers, antidepressants, versus a control group of DM patients.

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