

Mechanism Linking Cognitive Impairment and *Diabetes mellitus*

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Abstract: Diabetes mellitus is an important risk factor for mild cognitive impairment (MCI) and subsequent Alzheimer's disease (AD). Severe diabetes is more likely to be associated with poorly controlled blood sugar, which can damage nerve cells in the brain and lead to cognitive impairment. In addition, impairment in verbal memory was found to be associated with history and duration of Type 2 diabetes. The purpose of this article is to present a comprehensive review of the literature regarding the subject of cognitive dysfunction in diabetes mellitus. Hyperglycemia alters function through a variety of mechanisms including polyol pathway activation, increased formation of advanced glycation end products (AGEs), diacylglycerol activation of protein kinase C and increased glucose shunting in the hexosamine pathway. The same mechanisms may be operative in the brain and induce the changes in cognitive function that have been detected in patients with diabetes. The pathogenesis of cognitive dysfunction is only partially understood. Although many studies suggested that changes in cerebral structure and function in diabetes are related to hyperglycemia-induced end organ damage, macrovascular disease, hypoglycemia, insulin resistance and amyloid lesions may play a role in some patients. As new knowledge is gained and can be applied to develop a new and improved ways to prevent and treat all of the hyperglycemia-related complications of diabetes.

Key words: Cognition • Dementia • B-Amyloid • Alzheimer's disease • Insulin Resistance

INTRODUCTION

Diabetes mellitus is a complex metabolic disease that can have devastating effects on organs in the body [1-3]. Diabetes mellitus is associated with slowly progressive end-organ damage in the brain. Mild to moderate impairments of cognitive functioning has been reported both in type I DM and in patients with type II DM [4-5]. Abnormalities in cognitive function mediated by frontal lobe (executive functions), including a number of complex behaviors such as problem solving, planning, organization, insight, reasoning and attention are noted in patients with diabetes [6]. Glucose is the primary substrate for brain energy metabolism [7]. Neurons in brain are unable to store or synthesize glucose and therefore, the needed glucose is obtained from systemic circulation and subsequently transported across the blood brain barrier [8]. When diabetes strikes and insulin's signal is ignored by cells, the brain may not get the large amount of glucose energy it needs especially for memory. Loss of brain cells and memory function result

especially in the hippocampal region of the brain which involves in learning and memory [9]. Insulin is transported across the blood-brain barrier via specific receptors. It may inhibit synaptic activity in the brain. Insulin has been found to reversibly reduce cholinergic activity of striatal neuronal cultures and to accelerate turnover of monoamines in the brain [10]. Increased insulin concentrations also appear to boost the levels of beta-amyloid, a protein involved in the formation of senile plaques that can lead to Alzheimer's [11]. Certain organ systems are predisposed to greater levels of oxidative stress. The brain is one of the organs systems most susceptible to damage by free radicals because of its high oxygen consumption rate, its abundance of easily peroxidized lipid membranes [12]. Moreover, brain tissue which has relatively little antioxidant protection also contains high levels of polyunsaturated fatty acids (PUFA) making it more vulnerable to oxidative insult [13]. In diabetes condition, elevated levels of blood glucose and insulin may provide a pro-oxidant environment. Glucose reacts with oxygen to generate a range of reactive

oxygen species (notably super oxides, hydroxyl radicals and hydrogen peroxide) that can damage the constituents of cells. The higher the glucose levels the greater the damage. Thus people with poor glucose regulation are exposing their systems to potentially harmful oxidative stress and also as age increases, the harm continues to accumulate unless we actively counteract [14]. Oxidative stress has been shown to cause cell damage and neuronal death in animal models and cell culture [15]. The association of diabetes mellitus with impaired cognitive function suggests that diabetes mellitus may contribute to Alzheimer disease (AD) [16]. The purpose of this article is to present a comprehensive review of the literature regarding the subject of cognitive dysfunction in diabetes mellitus.

Relation Between Insulin and Cognitive Function:

Insulin resistance is a condition that impairs insulin function. AD has been called “type 3 diabetes” because a defect in insulin signaling is associated with the accumulation of patho-logical beta-amyloid peptide (A β) and hyperphosphorylated tau protein. IDE (insulin-degrading enzyme) is a protease involved in the degradation of A β and insulin and A β may compete for degradation. IDE expression found in the post-mortem hippocampus of AD patients who expressed the APOE ϵ 4 allele was reduced by 50% compared with ϵ 4 in AD patients and controls [17]. Oxidative stress and microinflammation mediate insulin resistance in the brain through the pathway of docosahexaenoic acid (DHA) and, thus, omega-3 fatty acids may also be protective [18]. Individuals with pre-diabetic states (e.g. impaired glucose tolerance or fasting hyperglycemia) or early type 2 diabetes typically have elevated circulating plasma insulin concentrations because of peripheral insulin resistance, which is in turn related to central obesity. Insulin receptors are found in high concentrations within the

limbic system of the brain; in epidemiological studies of non-diabetic adults, hyperinsulinaemia has been associated with poorer cognitive performance and an increased risk of AD.

Linkage Between Acute Hyperglycemia and Cognitive Impairment:

Hyperglycemia has also been proposed to cause end organ damage through increases in reactive oxygen species, in particular superoxide, which could then lead to increased polyol pathway activation, increased formation of AGEs, activation of protein kinase C and increased glucose shunting in the hexosamine pathway [19]. Hyperglycaemia is the hallmark of all types of diabetes and could cause cognitive decrements by several different mechanisms. Acute changes in blood glucose are known to alter regional cerebral blood flow and could also cause osmotic changes in cerebral neurons. These same mechanisms may be operative in the brain and induce the changes in cognitive function that have been detected in patients with diabetes (Fig. 1).

Diabetic Complications and Cognitive Decline:

The first degree relatives of non-insulin dependent diabetes mellitus patients are at the risk of accelerated atherosclerosis and micro vascular disease [20]. The recognized association between type 2 diabetes and macro and microvascular disease is pertinent to the pathogenesis of dementia. The former could cause cognitive impairment because of the increased incidence of embolic stroke [21]. Many of the clinical complications of diabetes are caused by small and large vessel pathology [22]. In particular “peripheral” microvascular complications of diabetes arising outside the brain appear to be correlated with corresponding microvascular changes in the brain. For example, diabetic retinopathy and retinal microvascular abnormalities were associated with various MRI signs such as small focal white matter

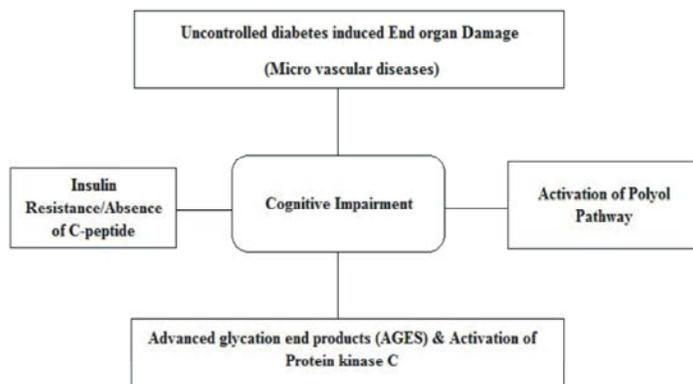


Fig. 1: Possible mechanisms related to cognitive decline in diabetes mellitus patients

hyperintensities and lesions. Likewise, the presence of micro albuminuria in the general population has been associated with significantly lower cognitive function score [23]. Investigations and subsequent clinical diagnosis of microvascular complications such as nephropathy, retinopathy and neuropathy are regularly made in patients with diabetes. However, early investigations of potential cognitive impairment at specialist memory clinics are not routinely undertaken in patients who do not show obvious signs of dementia. The early identification of clinically relevant cognitive impairment in diabetic patients is essential because of available symptomatic treatment, the need to educate patients and carers and the need to instate required supportive measures.

Role of Amyloid and Insulin Resistance in Cognitive Dysfunction:

The mechanisms through which insulin resistance might alter cognitive function remain uncertain, but effects on neurotransmission and memory formation have been hypothesized [24]. Patients with Alzheimer’s disease have a decrease in cerebral spinal fluid insulin levels, suggesting that there may be impaired insulin transport across the blood brain barrier or increased insulin catabolism that accounts for the impaired central insulin action [25]. Another potential mechanism through which insulin resistance may indirectly contribute to cognitive dysfunction is by promoting the formation of senile plaques found in Alzheimer’s disease. Intracellular neurofibrillary tangles and extracellular senile plaques composed of β -amyloid are the pathological hallmarks of Alzheimer’s disease [26]. β - Amyloid is formed from the cleavage of amyloid precursor protein (APP), produced in neurons, by the enzymes β - and γ -secretase. β -Amyloid is eventually degraded by the insulin-degrading enzyme. In addition, there is a growing body of evidence that insulin and insulin resistance can affect the metabolism of APP and β -amyloid, thus potentially increasing the burden of cerebral senile plaques [27]. The pathophysiological mechanisms (Fig. 2) suggest how diabetes-related factors and comorbid conditions can affect the brain. Vascular disease and alterations in glucose, insulin and amyloid metabolism seem to be important factors and could be potentially modifiable.

Brain Structural Abnormalities: In autopsy series, macroscopic brain infarcts are more common in people with diabetes than in people without the disorder [28]. Additionally, diabetes is associated with pathological changes in the cerebral microvasculature, including

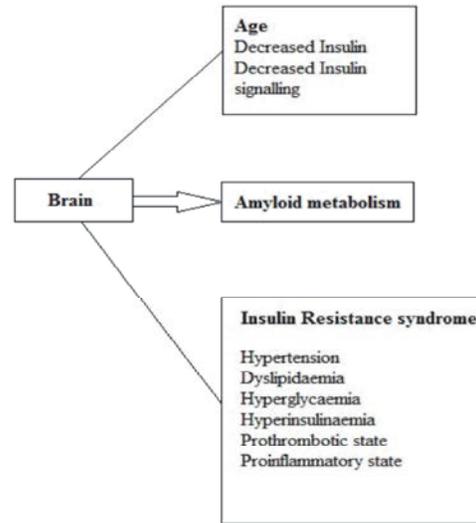


Fig. 2: Role of insulin in the pathogenesis of Cognitive impairment

amyloid angiopathy and capillary basement membrane thickening [29]. Several studies have also examined the incidence of Alzheimer’s type pathology in the brains of people with diabetes. Thus, the main anatomical alterations related to diabetes appear to be the consequence of elevated blood glucose and changes due to cerebral infarcts are linked to hyperinsulinaemia as a vascular risk factor. However, in contradiction to these statements, hippocampal volume was positively associated with the metabolic syndrome and with visceral fat volume in particular, in a group of 48 middle-aged to elderly non-dementia patients with diabetes [30]. Among these subjects, the metabolic syndrome was not associated with any cognitive alterations.

Recurrent Episodes of Hypoglycemia: Glucose is the predominant fuel utilized by the central nervous system. Because the brain cannot synthesize glucose nor store more than a few minutes’ supply as glycogen, the brain requires a continuous supply of glucose from the circulation. Therefore, disruption of the supply of exogenous glucose will rapidly cause functional disturbances [31]. Repetitive episodes of moderate to severe hypoglycemia have been implicated as one possible etiology of cognitive dysfunction in diabetes. This is significant because the risk of hypoglycemia increases as efforts to achieve the level of glycaemia necessary to minimize the risk of developing the micro vascular complications of diabetes are intensified [32]. During acute hypoglycemia episodes, it has been shown that performance on immediate verbal memory, immediate

visual memory, working memory, delayed memory; visual-motor skills, visual-spatial skills and global cognitive dysfunction are all impaired [33-34]. One possible reason that some studies found an association between frequent hypoglycemia and cognitive dysfunction and others did not is that the positive investigations may have included subjects with diabetes onset earlier in life. Patients with type I diabetes diagnosed at less than 5 year of age may have more severe and frequent hypoglycemia episodes than those diagnosed at ages older than 5 year, these younger patients have been found to have worse cognitive dysfunction.

CONCLUSION

In conclusion, Evidence from neurocognitive testing suggests that cognitive dysfunction should be listed as one of the many complications of diabetes, along with retinopathy, neuropathy, nephropathy and cardiovascular disease. In the clinical approach to individual patients with diabetes that present with complaints of cognitive disturbances a number of basic principles are important: first, diabetes should be regarded as “a risk factor” rather than as “the cause” of cognitive decline. Therefore, the diagnostic evaluation should be identical to that in other patients with cognitive complaints.

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