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Diabetes Induced Cognitive Dysfunction, Type 3 Diabetes: A Perspective Study

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Abstract

Alzheimer's disease is triggered by insulin resistance in the brain termed as Type 3 diabetes. Type 2 diabetes is a risk factor for causing dementia, vascular dementia, Alzheimer's disease. Type 2 diabetes mellitus (T2DM) and Alzheimer's disease (AD) are two independent diseases, evidences from epidemiological, pathophysiological relationship between these diseases. As its pathophysiology resembles with T2DM and AD, which response insulin resistance and deficiency, protein aggregation, oxidative stress and advanced glycation end products, it is termed as "type 3 diabetes". Type 3 diabetes is diagnosed and treated by using anti-diabetic drugs and are successfully used to reduce the cognitive decline in AD patients.

Keywords: *Alzheimer's disease, anti-diabetic drugs, cognitive decline, type 3 diabetes*

INTRODUCTION

Diabetes mellitus (DM) is a group of metabolic disorders share the common features of hyperglycaemia. Hyperglycaemia in diabetes results from defects in insulin secretion, insulin action, or most commonly, both. The chronic hyperglycaemia and attendant metabolic dysregulation may be associated with secondary damage in multiple organ system, especially the kidneys, eyes, nerves, and blood vessels [1].

Types of Diabetes Mellitus

- Type 1 diabetes (β-cells destruction, leads to absolute insulin deficiency)
- Type 2 diabetes (insulin resistance with relative insulin deficiency)
- Type 3 diabetes (Alzheimer's disease AD)
- Gestational diabetes mellitus

Type 1 diabetes

Type 1 diabetes is characterized by an absolute deficiency of insulin caused by pancreatic β-cells destruction. It accounts for approximately 10% of all cases [2-5].

Type 2 diabetes

Type 2 diabetes is caused by a combination of peripheral resistance to insulin action and an inadequate secretory response by the pancreatic β-cells (relative insulin deficiency).

Type 3 diabetes

Type 3 diabetes is a term used when Alzheimer's disease (AD) is triggered by insulin resistance in the brain. This condition describes people who have type 2 diabetes and are also diagnosed with AD or dementia. It is often referred to as "type 3 diabetes".

Gestational diabetes mellitus

Gestational diabetes mellitus sometimes is referred to as type 4 diabetes, is diagnosed during pregnancy and is not clearly overt diabetes [6-10].

Effect of Diabetes on Cognitive Dysfunction

Hyperglycemia produces reactive oxygen species (ROS) as a result of glucose auto-oxidation, metabolism and the

development of advanced glycosylation end products. In fact, diabetes is typically associated with increased generation of free radicles and impaired antioxidant defence qualifications, representing a central contribution for ROS in the onset, progression, and pathological consequences of DM, namely, vascular complications, nephropathy and cognitive impairment or dementia [11].

Type 3 Diabetes Mellitus

Type 3 diabetes mellitus, is a term recently used by scientists and tried to define it as a metabolic syndrome that may lead to abnormalities linked to progressive brain insulin resistance with consequent impairment of central insulin signalling processes, accumulation of neurotoxins, neuronal stress, and resulting in a course of neurodegeneration [12-15].

Epidemiological Links between T2DM and AD

According to Global Health and Aging (2010), 8% of the world's population is over 65 years of age in 2010, and the number of people over 65 years of age is expected to rise to 16% by the year 2050. Both type 2 diabetes mellitus (T2DM) and Alzheimer's disease (AD) are associated with increasing age. Additionally, there are at least 347 million diabetic patients and 44 million people suffering from AD. These numbers are expected to become double by the year 2030. Similarly, according to the World Health Organization (WHO) in 2014, 13% of the world's population was obese, making obesity another challenging health issue as the pathogenesis of both T2DM and AD showed strong associations with obesity. Undoubtedly, these data are alarming and represent an emerging health-care issue because, without appropriate regulation, the combination of these two diseases is going to be one of the major socio-economic burdens of the future world population. T2DM and AD increases with increasing age, these diseases have become major alarming health issues for the elderly throughout the world. In 1999, Ott *et al*. [16] first established that the influence of T2DM on developing AD is almost double. A longitudinal study of the American population revealed that T2DM was the strongest risk factor for developing AD.

Causes

- People who have type 2 diabetes, they are up to 60 percent more likely to develop Alzheimer's or dementia. One study of over 100,000 subjects with dementia pointed out that women with type 2 diabetes had a higher probability of developing vascular dementia than men [17].

Symptoms

- Memory loss that affects daily living and social interactions
- Difficulty completing familiar tasks
- Misplacing things often
- Decreased ability to make judgements based on information
- Sudden changes in personality or demeanour

People with severe symptoms can no longer:

- Understand language.
- Recognize family members.
- Perform basic activities of daily living, such as eating, dressing, and bathing.

Risk Factors

- A family history of diabetes.
- High blood pressure.
- Being overweight or obese.
- Certain chronic health conditions, such as depression and polycystic ovarian syndrome.

PATHOPHYSIOLOGICAL LINKS

Although type 2 diabetes mellitus (T2DM) and Alzheimer's disease (AD) are two

independent diseases, evidences from epidemiological, pathophysiological and animal studies have indicated a close pathophysiological relationship between these diseases. The pathophysiology of T2DM and AD includes:

- Insulin resistance and deficiency,
- Protein aggregation,
- Oxidative Stress and Mitochondrial Dysfunction,
- Advanced glycation end products.

Insulin Resistance and Deficiency

In T2DM, insulin resistance is caused by the failure of the insulin receptor to respond to insulin stimulation for blood glucose uptake, whereas insulin deficiency occurs due to impaired insulin secretion by pancreatic β-cells or low levels of insulin-secreting βcells in the peripheral liver and muscle tissues of T2DM patients. Although both insulin resistance and deficiency are core characteristics of T2DM, numerous studies have revealed their involvement in the pathogenesis of AD. In addition to the native insulin production in the brain, peripheral insulin enters the central nervous system via selectively distributed insulin receptor proteins. In the AD brain, insulin resistance develops due to the altered sensitivity of brain insulin receptors, which can affect the metabolic degradation as well as the expression of amyloid β peptide (Aβ) and tau proteins. In addition, Aβ oligomers were observed to bind with the hippocampal neurons and trigger the removal of dendritic insulin receptor substrates (IRS) from the plasma membrane, resulting in AD pathogenesis. As a result, these phenomena have recently been referred to as "type 3 diabetes"[18-22].

Protein Aggregation

Both T2DM and AD are protein (amyloid) aggregation-oriented diseases. In case of T2DM, amyloid deposition is progressively observed in pancreatic β-cells (Islets of Langerhans) leading to β-cell dysfunction followed by the disruption of glucose homeostasis. On the other hand, amyloid fibres are aggregated in AD brain causing neuronal cell loss followed by cognitive decline. Tau is a microtubule-stabilizing protein abundantly found in neurons. The hyperphosphorylation of tau can induce neurofibrillary tangles leading to AD [23-25]. Although the presence of hyperphosphorylated tau proteins is a common feature of AD, the proteins are also observed in pancreatic islet cells of T2DM in both rats and humans. Kim *et al*. reported that increased tau phosphorylation is one of the risk factors for the development of AD in T2DM patients.

Hyperinsulinemia

Hyperinsulinemia is an early hallmark of T2DM that has the potential to increase Aβ levels through various indirect mechanisms (*i.e.* Inflammation) leading to memory decline and subsequently to AD [26-30]. Although the structure and function of brain insulin receptors differ from those of peripheral insulin receptors, excessive levels of insulin were found to be associated with CNS functional decline.

In individuals with Type 2 diabetes mellitus (T2DM), hyperinsulinemia, hyperglycemia and insulin resistant conditions create an abnormal glucose metabolism that induces oxidative stress and subsequently activates inflammatory responses. In turn, Aβ plaques are synthesized in neurons due to inflammation in the brain via cytokines and interleukins, which are also responsible for tau hyperphosphorylation followed by neurofibrillary tangles. In addition to destroying β-cells and causing insulin deficiency, oxidative stress further obstructs normal auto phagocytosis of amylin (in the pancreas) and Aβ (in the brain) resulting in the sustainable accumulation of protein aggregates and the progression of T2DM and Alzheimer's

disease (AD), respectively. Deficiency of ape and mitochondrial dysfunction are also responsible for obstructing auto phagocytosis, resulting in unregulated deposition of Aβ. Common genetic and epigenetic factors also directly link T2DM and AD [31-34].

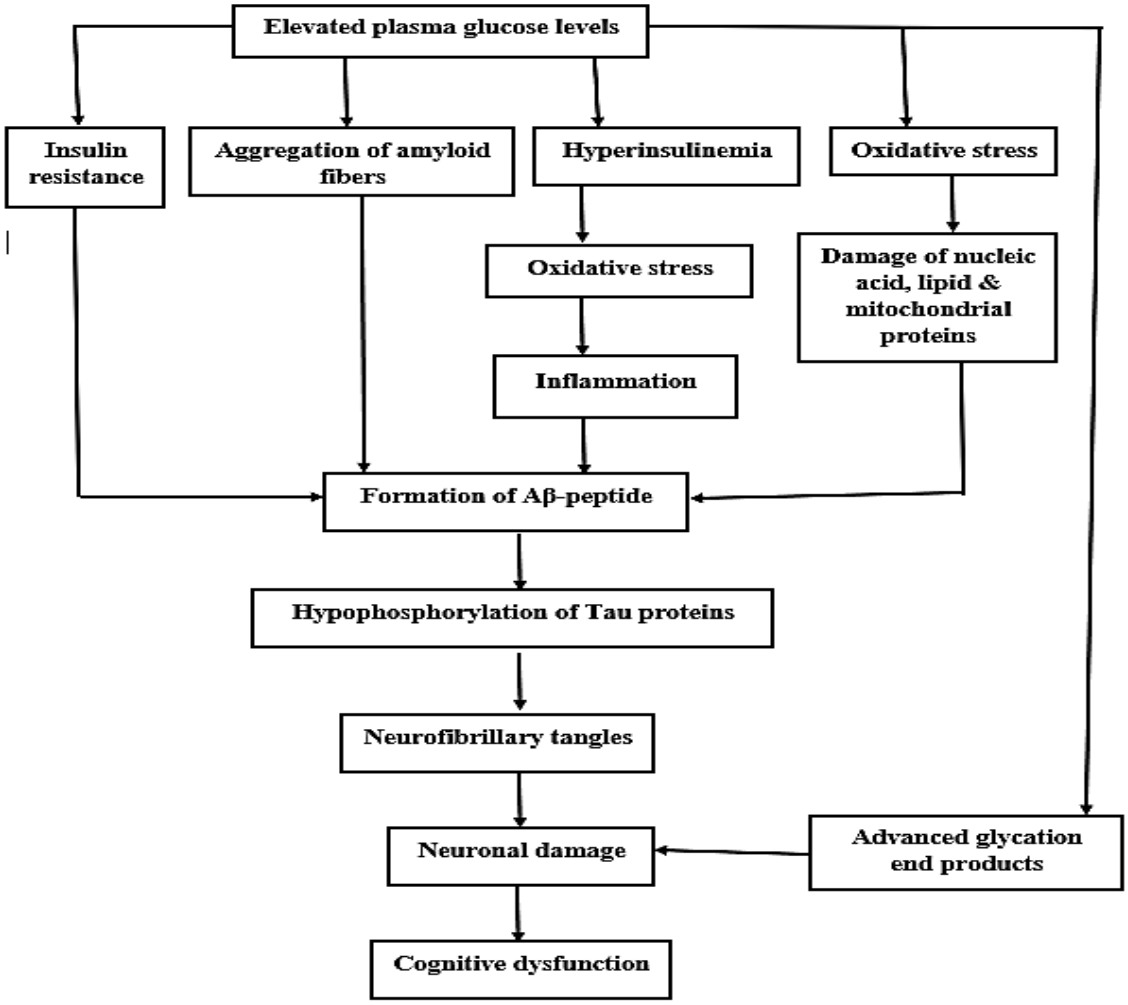

Figure 1: *Pathophysiology for T2DM and AD.*

Oxidative Stress and Mitochondrial Dysfunction

A pathophysiological link between T2DM and AD may also exist via oxidative stress and mitochondrial dysfunction. Abnormal glucose metabolism in the liver also affects the brain and tends to increase the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS). The overproduction of ROS and RNS further challenges the antioxidant capacity of cells via protein and/or lipid peroxidation leading to T2DM and AD. In case of AD, ROS [hydrogen peroxide (H_2O_2), hydroxyl ($HO^{\bullet}$) and superoxide ($O_2^{\bullet-}$)] targets and damages nucleic acids, lipids and mitochondrial proteins, which in turn amplify ROS production and trigger Aβ generation, tau phosphorylation and formation of neurofibrillary tangles. Although the brain represents only 20% of the body weight, it requires approximately 20% of the total body oxygen consumption. For the normal functioning of neurons, mitochondria utilize 90% of the generated adenosine triphosphate (ATP). However, due to mitochondrial dysfunction, metabolic ability is lost

leading to neuronal degeneration. Oxidative stress contributes as one of the most common pathogenic factors leading to insulin resistance and -cell dysfunction in T2DM. Increased oxidative damage was observed in the brains of experimentally induced hyperglycemic rats. Oxidative stress provokes inflammation and subsequently increases inflammatory mediators such as cytokines and ILs, which play further roles in the pathogenesis of AD. On the other hand, inflammation is recognized as an important pathophysiological finding in T2DM that may have a role in the susceptibility of T2DM patients to develop AD and in the progression of T2DM in AD patients [35].

Advanced Glycation End Products (AGEs)

Ages (non-enzymatically produce by glucose-protein condensation reactions) are a group of heterogeneous molecules that carry irreversibly added adjacent groups with them. Although, generally, ages are normally synthesized during aging, the production rate is extremely high in patients with T2DM and AD. In T2DM, accelerated AGE formation is anticipated to occur as a result of high plasma glucose levels, while oxidation of glycated proteins is one of the major causes of AD. Gironès *et al*. observed high levels of carboxymethyl-lysine (an AGE) in both T2DM and AD patients, further strengthening the pathophysiological linkage between T2DM and AD via ages [36].

Diagnosis

There's no specific test for Alzheimer's or type 3 diabetes. Doctor will ask several questions about your family history and your symptoms. Brain imaging, like MRIs and CT scans, can give your doctor a picture of how your brain is working. Cerebrospinal fluid tests can also look for indicators of Alzheimer's. If you have the symptoms of type 2 diabetes and Alzheimer's and haven't been diagnosed with either one, you may be sent for a fasting blood sugar test and a glycated haemoglobin test. If you do have type 2 diabetes, it's essential that you begin treatment for it. Treating type 2 diabetes could minimize damage to your brain and slow the progression of Alzheimer's or dementia [37].

TREATMENT

Metformin

Metformin is a biguanide commonly used in the treatment of diabetes. It reduces hyperglycaemia and hyperinsulinemia by decreasing insulin resistance. Metformin primarily acts on the liver to decrease hepatic glucose output. Furthermore, it has been postulated to potentiate the actions of insulin or sensitize liver and skeletal muscles to insulin, possibly mediated by AMP-kinase.

Sulphonylureas

A commonly used class of drugs for the treatment of diabetes. Sulphonylureas work by interacting with ATP-sensitive potassium (K_{ATP}) channels in the pancreas to stimulate insulin secretion. K_{ATP} channels are also found in neurons as well as cardiac myocytes. Gliclazide is more specific for pancreatic in comparison to cardiac or neuronal K_{ATP} channels at concentrations used in clinical practice. Glyburide (glibenclamide) and glipizide have been investigated for their effects on memory and cognition in patients with diabetes [38].

Thiazolidinediones

Thiazolidinediones work by stimulating peroxisome proliferator activated receptor gamma (PPARs) and have anti-amyloidogenic, anti-inflammatory, and insulin sensitizing effects, which may play a role in delaying and reducing the risk of neurodegeneration. Thiazolidinediones are a class of drugs that improve the

sensitivity of skeletal muscles and adipose tissue to insulin. They also inhibit hepatic gluconeogenesis, improve glycaemic control, and reduce circulating insulin levels. The effects of rosiglitazone and pioglitazone on cognition in diabetes have been studied [39-40].

COMPLICATIONS

People with diabetes prone to number of serious health issues. Consistently high blood glucose levels can lead to serious diseases affecting the heart and blood vessels, brain, eyes, kidneys, nerves and teeth. Brain insulin resistance, T3DM, is quite similar to T2DM in terms of its complications. Additionally, both T2DM and impaired fasting glucose were clear in Alzheimer's disease (AD) patients than in non-AD individuals. The early abnormalities, seen in brain insulin resistance, are associated with impaired cognitive function including memory loss, learning difficulties and dementia. The DM and age-related neurodegeneration diseases usually compromise the trophic factor signalling in the brain.

Preventive Measures

- Exercise four times per week for 30 minutes per day.
- Eat healthy foods rich in protein and high in fibre.
- Carefully monitor your blood sugar according to your health team's recommendations.
- Take any prescribed medications on schedule and with regularity.
- Monitor your cholesterol levels.
- Maintain a healthy weight.

CONCLUSION

Enhanced plasma glucose levels (diabetes) leads to neuronal damage with subsequent reduction in cognitive abilities. This condition adversely affects the regular activities and reduces the quality of life. Correct diagnosis and use of appropriate treatment strategies helps to arrest the progression of the disorder.

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