**Libyan International Medical University**

**Faculty of Basic Medical Science**

# Link Between T2DM And Alzheimer's disease

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***Abstract:*** The aim of this paper is to provide a comprehensive review of the epidemiological evidence linking that suggest a possible shared pathophysiology between type 2 diabetes mellitus (T2DM) and Alzheimer's disease (AD). It has even been hypothesized that AD might be 'type 3 diabetes'. The present review summarizes some of the evidence for the possible link including insulin processing, acetylcholine, Inflammation ,Obesity and metabolic syndrome ,Mitochondria and oxidative stress. The evidence for a connection between T2DM and AD is based upon a variety of diverse studies, but definitive biochemical mechanisms remain unknown. Additional study is needed to prove the existence or the extent of a link between T2DM and AD, but sufficient evidence exists to warrant further study.[2]

**Introduction:** Type 2 diabetes mellitus (T2DM) and Alzheimer's disease (AD) are both more prevalent with ageing, but it has generally been assumed that this is coincidental, not a reflection of co-morbidity. However, evidence suggests that patients with T2DM are at an increased risk of getting AD and that hyperinsulinaemia and insulin resistance hallmarks of T2DM can lead to memory impairment The latest research is focused on Alzheimer's disease, the most common neurodegenerative disorder that accounts for 60–80% of cases of dementia and one for which it's harder to figure out the precise relationship with diabetes. On this much, many scientists agree: The rate of Alzheimer's disease could be cut by close to half if diabetes could be abolished. The connection between the two is so strong that Suzanne M. de la Monte, one of the top researchers in the field, has said that many cases of Alzheimer's could be dubbed Type 3 diabetes.
People who haven't necessarily developed diabetes might still develop insulin resistance in the brain, said de la Monte, a professor of neurosurgery, pathology and laboratory medicine at Brown University.That's why she uses the term Type 3 diabetes.[2]

**Disscusion:** There have been reports and studies of links between T2DM and AD Some of these are:
**1-Insulin processing:** Insulin is primarily secreted by β-cells of the pancreas and normally is released into the circulation through the portal vein in response to a rise in blood glucose. Insulin-degrading enzyme (IDE) catalyses the catabolism of insulin in the liver, kidneys and muscles It is generally agreed that insulin located within the brain is mostly of pancreatic origin, having passed through the blood–brain barrier, although there is debate about the amount that is produced *de novo* within the CNS Insulin has a significant function in the hypothalamus and probably other brain regions. Major known actions of insulin in the brain include control of food intake (via insulin receptors located in the olfactory bulb and thalamus) and effects on cognitive functions, including memory. Possible common or interactive processes in T2DM and AD have been reviewed. Within brain, insulin binds to the α-subunit of the insulin receptor, activates tyrosine kinase phosphorylation of the β-subunit of the receptor, and leads to activation of several second-messenger transduction pathways. The neural Shc/MAP (Src homology collagen mitogen-activated protein) kinase pathway activates gene expression required for neuronal cell and synapse growth, maintenance and repair processes. It also serves as a modulator of hippocampal synaptic plasticity that underlies learning and memory. Another pathway involves binding of insulin receptor substrates 1 and 2 (IRS-1 and IRS-2) to phosphatidylinositol 3-kinase (PI3K), which is necessary for synaptic plasticity and memory consolidation, retrieval and extinction of contextual memory, and Aβ-induced memory loss. It also induces the synthesis of nitric oxide, which in turn plays a role in learning and memory processes. Insulin receptors also modulate neurotransmission by phosphorylation of NMDA

glutamate receptors (increasing the opening of the associated $Ca^{2+}$ channel), through influence on internalization of the AMPA receptor and by recruiting GABA receptors to the postsynaptic site. Abnormal insulin processing, insulin receptor defects or postreceptor defects can lead to CNS problems including AD, Parkinson's disease Huntington's disease malignancies ,migraine headaches and schizophrenia. [3]

**2-Acetylcholine:**

Recent research suggests a possible link between blood sugar, insulin resistance and inadequate production of acetylcholine (ACh). Synthesis of ACh involves the enzyme acetylcholine transferase (ChAT). Acetylcholine transferase is expressed in insulin and IGF-I receptor-positive cortical neurons; ChAT expression increases with insulin/IGF-1 stimulation; and ChAT co-localization in insulin or IGF-I receptor-positive neurons is reduced in AD. Therefore, low insulin levels and insulin resistance can contribute to a decrease in ACh levels, which represents a possible biochemical link between diabetes mellitus and AD. [3]

**3-Inflammation:**

Insulin resistance a key aspect of T2DM, is associated with inflammation specifically with elevated levels of the inflammatory mediators interleukin-6 (IL-6), C-reactive protein and α-1-antichymotrypsin .It is postulated that elevated levels of acute-phase inflammatory products are linked with immunological dysfunction, which leads to insulin resistance .

Likewise there is evidence that AD is associated with inflammatory processes .Inflammatory products accumulate at different rates in Alzheimer's patients compared with healthy control subjects the inflammatory cytokine IL-6 is present in senile plaques of AD patients and elevated immunoreactivity to IL-6 is found in lumbar and ventricular cerebrospinal fluid in patients with AD At least two studies link C-reactive protein with an increased risk of AD There are also reports of reduced incidence of AD in people who take non-steroidal anti-inflammatory drugs for chronic pain. Interestingly, peroxisome proliferator-activated receptor-γ (PPARγ) agonists, a class of antidiabetic drugs that reduce insulin resistance, appear to have anti-inflammatory effects .Such drugs should reduce the levels of IL-6 and other inflammatory mediators and might be beneficial in treating or preventing AD.[1]

**4-Obesity and metabolic syndrome:**

Obesity, especially central body obesity, is an independent risk factor for metabolic syndrome, a disorder of dyslipidaemia, insulin resistance and hypertension. Obesity and the metabolic syndrome are important risk factors for the development of T2DM The following evidence suggests that there may also be a link with AD: the Baltimore Longitudinal Study of Aging found that men with weight gain between the ages of 30 and 45 years and women with a body mass index >30 at ages 30, 40 and 45 years had an increased incidence of AD a Swedish study found that AD risk increased by 36% for every 1.0 increase in body mass index at age 70 years men and women with a midlife body mass index >30 kg $m^{-2}$ have a greater risk for AD and patients with AD have a significantly larger mean waist circumference, higher mean plasma concentration of triglycerides and glucose, and lower mean plasma concentration of high-density lipoprotein cholesterol. The significant role of leptin in regulating brain function might also be involved. As recently suggested by Han & Li the proposed link between T2DM and AD would be advanced by studying defective leptin signalling in the absence of perturbed insulin signalling .[4]

**5-Mitochondria and oxidative stress:**

Mitochondrial dysfunction and oxidative stress play key roles in the pathogenesis of both AD and T2DM, and represent a possible link There is increased oxidative stress in T2DM, with reduced

antioxidant capacity which has been suggested can lead to neuronal injury with mitochondria as specific targets In a rat model of T2DM, brain mitochondria display age-related impairment of the respiratory chain and an uncoupling of oxidative phosphorylation which is vital for ATP production. Since mitochondria provide about 90% of the ATP required for normal functioning of neurons, mitochondrial dysfunction results in neural degeneration and loss of metabolic control. As the CNS is heavily dependent upon ATP production, it is more susceptible than other systems. According to the 'mitochondrial cascade hypothesis', the rate of accumulation of mitochondrial damage is determined by the basal rate of production of reactive oxygen species by the electron transport chain, which in turn is determined by genetics. Oxidative changes in nucleic acids, lipids and mitochondrial proteins amplify production of reactive oxygen species and trigger cells to generate Aβ, tau phosphorylation and formation of neurofibrillary tangles.

In the end If there is in fact some biochemical link between T2DM and AD, then could it be possible that a drug currently approved for T2DM could also be useful for treating AD. Presently, AD patients might benefit from treatment with pharmacotherapy currently used to treat T2DM and clinical trials of such therapy are currently underway.[5]

**Conclusion**:

Diabetes and Alzheimer's disease have traditionally been thought to be independent disorders. However, the results of recent epidemiological and basic science investigation have suggested possible associations and some common pathophysiological mechanisms.

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