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## Review Article

# Type 3 diabetes (T3D) and alzheimer's disease (AD)

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### ARTICLE INFO

### ABSTRACT

Alzheimer's disease (AD) is being referred as Type-3-Diabetes (T3D) as both have similar molecular and cellular features but it's still in a debate. Progression of Type 2 Diabetes Mellitus (T2DM) is called AD. AD is also called "diabetes of the brain".Insulin degrading enzyme (IDE) is very important in the shift of T2DM to T3D. Biochemical and molecular abnormalities of AD are mitochondrial dysfunction, chronic oxidative stress, amyloid-β deposits, neurofibrillary tangles, cell loss, dystrophic neurites, increased activation of signalling pathways and pro-death genes. This review aims to explain all these structural and molecular similarities between T3D and AD.

## 1. Introduction

There is a complex association between T2DM and AD which is interlinked by glycogen synthase kinase 3β (GSK3β), insulin growth factor (IGF) signalling, oxidative stress, amyloid beta (Aβ) formation from amyloid precursor protein (APP), insulin resistance, inflammatory response, acetylcholine esterase activity regulation and neurofibrillary tangle formation.[1–7] Hence it is termed as "Type-3-Diabetes". AD is a neurodegenerative disease with changes in personality and behaviour and decline in cognitive functions and memory progressively. In the United States AD is the $6^{th}$ leading cause of death. An estimated 5.8 million Americans age 65 and older are living with Alzheimer's dementia in 2020[8] and is estimated to reach 88 million by 2050[9–11] [Figure 1]
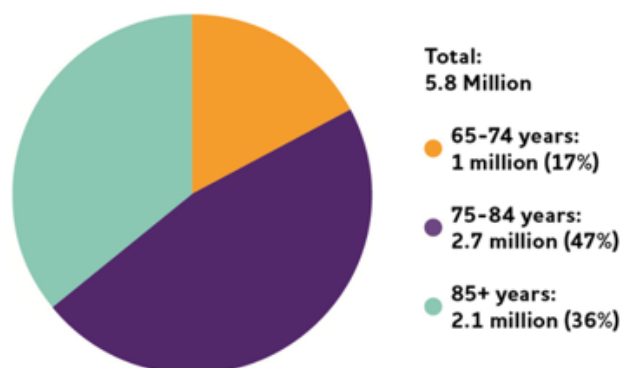


**Fig. 1:** Number and ages of people 65 or older withalzheimer's dementia, 2020. Created from data from hebert et al.[8]

### 1.1. Alzheimer's disease (AD)

The pathogenesis of AD includes both genetic and environmental factors. In some cases of AD, there is an autosomal dominant transmission of the disease and in early-onset familial AD cases, there is mutations

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in the genes of APP, presenilin 1 and presenilin 2. The major risk factor for AD is family history of dementia, previous depression, head trauma, vascular factors and female gender.[12,13] The diagnosis of AD is only through the post-mortem demonstration of neuritic plaques, neurofibrillary tangles, amyloid-β (Aβ) deposits in plaques and vessel walls and accumulation of amyloid precursor protein (APP) in the brain. The neurofibrillary tangles are due to the accumulation of hyperphosphorylated and polyubiquitinated microtubule-associated proteins, such as tau.[14–16]

## 1.2. Type 3 diabetes (T3D)

In 2005, Suzanne de la Monte coined the term type 3 diabetes when her team were examining the post-mortem brain tissue of AD patients. They termed type 3 diabetes, as it has elements of both types 1 and 2 diabetes i.e., both a decrease in the production of insulin and a resistance to insulin receptors.[17,18] Her team analysed 45 post-mortem brains of AD patients with Braak stages and found that insulin expression was inversely proportional to the Braak stage and there is a decrease in insulin receptors up to 80 % compared to normal subjects. The tau protein also reduced which is regulated by insulin and IGF-1.[18,19] This finally leads to neuronal cell death and AD exacerbation.

## 1.3. Dementia due to alzheimer's disease

It is characterized by a noticeable thinking, behavioural or memory symptoms which impairs a person ability to function in daily life. Dementia may vary from mild to moderate to severe depending on the person.[11] In the mild stage, people can function independently in some areas (drive, work) but require assistance in some instances to be safe. In the moderate stage of Alzheimer's dementia, they have personality and behavioural changes like agitation and suspiciousness. They face difficulties in daily activities like bathing and dressing.[11] In the severe stage of Alzheimer's dementia, they likely to require around-the-clock care, and they become bed-bound. There may be blood clots, skin infections, sepsis and organ failure. There will be difficulty in eating and drinking, as there is a damage in the brain which controls this, which results individuals swallowing food into windpipe instead of food pipe. This causes deposition of food particles in the lungs and causes lung infection called aspiration pneumonia, which is a major cause of death in AD patients.[11]

### 1.3.1. Oxidative stress (OS)
The fundamental process which occurs in aerobic metabolism is oxidative reaction in all the cells in the mammalians. They are very essential for life, in the same way if they are uncontrolled it may lead to diseases like T2DM, AD and Huntington's disease (HD).[20] If there is

an imbalance between reactive oxygen species (ROS) and reactive nitrogen species (RNS) production to counteract the free radicals, it leads to Oxidative stress (OS).[21] OS is the major cause for AD and T2D, hence AD is called as T3D by Suzanne et al.[22] Free radicals are maintained by antioxidants to maintain cell integrity and prevent apoptosis.[23] OS causes apoptosis of various cells like mitochondria, cell membranes, etc.

### 1.3.2. Hyperglycaemia and oxidative stress
Hyperglycaemia is caused due to the decreased production of insulin or impaired insulin receptors, which cause accumulation of advanced glycation end (AGE) products leading to ROS generation and cell damage. These hyperglycaemia and OS cause increase in the free radicals due to the variations in the antioxidants like catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px).[24] The resulting imbalance in the antioxidants and OS is observed in T2DM and AD.

### 1.3.3. Advanced glycation end (AGE) products
Maillard reaction produces the protein molecules called AGEs.[25] These are found in both types of diabetes and accumulate with aging. It causes AD neurotoxicity by promoting amyloid oligomer aggregation.[26] AGEs also modify neurofibrillary tangles and plaques as implicated in AD. T2DM increase the production of AGEs, which in turn causes the development of AD. toxic AGEs in serum or CSF may be a biomarker for the early detection of AD.

## 1.4. Mitochondrial dysfunction

ROS and RNS are produced in the mitochondria, as it is permeable it can enter the cytoplasm. These are converted into water/oxygen in the presence of dismutase enzyme, which prevents cell damage. Mitochondrial dysfunction may lead to oxidative imbalance, which results in increased production of ROS as seen in AD and T2DM.[27] Amyloid beta may directly disrupt the mitochondrial function, it increases the production of free radicals and cause neuronal damage in the brains of AD mice as stated in a recent study.[28] [Figure 2]

## 1.5. Impaired insulin and IGF actions in the brain

IGF signalling and insulin mechanisms are important in cognitive function. Insulin receptor (IR) is expressed in both glia of the brain and in the neurons.[30,31] When IR is bound by the insulin, several tyro sine residues are activated by auto-phosphorylation, which are important for insulin receptor substrate (IRS) 1 and 2 which in turn initiates signalling cascades like Wnt signalling, GSK3β signalling and phosphatidylinositol 3-kinase (PI3K) signalling. This suggests that insulin is not only involved in the glucose metabolism but also in neurotransmission
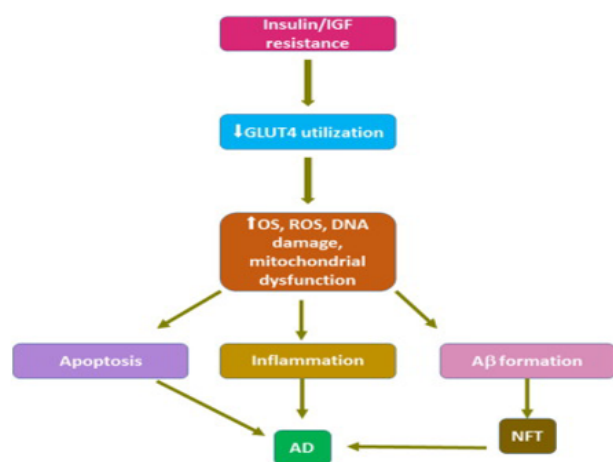
**Fig. 2:** Insulin resistance decreases glucose metabolism and plays a pivotal role in mitochondrial damage, DNA damage and ROS formation.[29]

for synaptic plasticity. Evidence suggests that peripheral and neuronal insulin sensitivity is defective in T2DM. The insulin resistant patients with no hyperglycaemia (pre-diabetes)[32,33] shows neurodegeneration and cognitive decline which indicates that hypoglycaemia is important as loss of insulin action. In AD type dementia, it is to be proved whether neurotoxicity of hyperinsulinemias or neuronal insulin resistance is responsible for that.

### 1.6. The role of type 3 diabetes in glucose homeostasis

In T3DM glucose homeostasis is affected due to impaired glucose uptake which in turn results in impaired glucose metabolism in the brain. These abnormalities are due to the intracellular glucose metabolic disturbance and brain insulin resistance. This leads to cerebral glucose hypometabolism in T3DM. A report says that hyperphosphorylation of tau is due to decreased glucose transporters (GLUT).[34] Therefore, impaired insulin signalling also causes neuronal cell death in addition to alteration in systemic glucose blood levels.[35] Insulin resistant patients have features like apoptosis, neurodegeneration and decline in cognition. In T3DM, neuronal insulin receptor desensitization is a major cause and brain glucose uptake is impaired.[36] T2DM is characterized by insulin resistance, it also has a pathological feature of neuroendocrine disorder i.e., T3D.[37] This is how glucose homeostasis is a key factor in T3D. thus, T2DM and neurodegenerative brain disease is called T3D.

### 1.7. Therapeutic approaches to type 3 diabetes in alzheimer's disease

Multitargeted drug therapies and lifestyle interventions are used to treat T3D particularly aimed at improving insulin sensitivity.[29] It includes polyphenols, nutraceuticals, omega-3 fatty acids, antioxidant activity[38] as well as the

brain–gut connections.[39] In nutraceuticals, curcumin targets abnormal protein aggregates.[40] When metformin is coupled with curcumin and piperine supplementation, it enhances signalling, insulin sensitivity and better systemic glucose tolerance[40] in AD patients. Fruits and vegetables have anti-inflammatory benefits like reducing inflammatory damage by antioxidant action.[41] They also contain carotenoids, vitamins, flavonoids and polyphenols which protects "against cognitive and brain neuropathology from dietary oxidative stress".[42] Nutritional therapy for AD patients includes foods rich in omega-3 fatty acids and low in omega-6 fatty acids.[43] The ketogenic diet reduces inflammation, clears beta amyloid plaques and convalescing damaged mitochondria.[44] Exercise increases the quality of life in AD and T2DM patients, it also clears Aβ plaques in certain individuals.[45]

## 2. Conclusion

In the earlier days, T2DM and AD were considered as different metabolic disorders but the researches have shown that there is an inter-relationship between the two pathologies which is termed as T3D. The evidence prove that AD is a neuroendocrine disease caused by impairments in insulin and IGF signalling mechanisms and also accompanied by oxidative stress, DNA damage, mitochondrial dysfunction and activation of inflammatory mediators. The biochemical and molecular abnormalities overlap with T1DM and T2DM, hence the term T3D for AD is justified.

## 3. Source of Funding

None.

## 4. Conflict of Interest

None.

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