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"UNDERLYING POTENTIAL MECHANISMS OF DIABETES-RELATED ALZHEIMER'S DISEASE"

- A PERSPECTIVE APPROACH

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Abstract
A build-up of senile plaques (SPs) and neurofibrillary tangles (NFTs) in the brain is the pathological hallmark of Alzheimer's disease (AD), the primary cerebrovascular illness that causes dementia. Diabetes mellitus is a condition marked by improper carbohydrate metabolism and increased blood glucose levels. It is caused by a malfunction in the body's capacity to create or respond to the hormone insulin. There is growing recognition that cognitive impairment is a significant comorbidity of diabetes mellitus. There are many stages of diabetes-related cognitive impairment, each with unique cognitive characteristics, affected age groups and prognoses, and most likely distinct underlying processes. Additionally, mounting data points to a number of linkages between the neuropathology underlying DM and AD, and evidence even points to the possibility that experimental production of DM might result in cognitive failure, even in rodent animal models. Deficits in spatial learning are correlated with unique modifications in hippocampus synaptic plasticity in animal models of diabetes. Although the complex pathophysiology of diabetic encephalopathy is not fully known, it is evident that it has characteristics with the pathophysiology of diabetic neuropathy and brain aging. Chronic hyperglycemia-related alterations in metabolism and blood vessels are present, and there may also be abnormalities in the brain's ability to use insulin. Thus, insulin treatment may have a direct impact on the brain in addition to addressing hyperglycemia. Therefore, insulin therapy may have a direct impact on the brain in addition to treating hyperglycemia. It is not yet known why AD typically occurs in older people, despite genetic research demonstrating that the primary component of SPs, β-amyloid peptide (Aβ), is the critical element causing AD pathogenesis.

Index terms: **Senile plaques, Neurofibrillary tangles, Alzheimer's disease, Diabetes mellitus, Dementia, Synaptic plasticity, β-amyloid peptide.**

I. INTRODUCTION

Dementia, a collective term for memory loss and other cognitive skills severe enough to impair with day-to-day functioning, is most commonly caused by Alzheimer's disease, which is acknowledged as the fifth leading cause of death for those 65 years of age and beyond [1]. Senile plaques (SPs) and neurofibrillary tangles (NFTs) are the two main pathological features of AD [2-4]. Though research is ongoing, there is currently no cure, however there are treatments for the symptoms. Among the most obvious abnormalities associated with AD include deficiencies in neurotransmitters, damaged neurons, synaptic dysfunction, extracellular accumulation of Aβ, and intracellular neurofibrillary tangles (NFT) [5]. This progressive disease is thought to be the cause of the memory deficit that first manifests clinically, then the progressive loss of judgment, verbal fluency, reasoning abilities, and other cognitive processes. β-amyloid protein (Aβ) aggregates are deposited extracellularly and are known as SPs. The brains of AD patients have massive SP accumulation in the cortices, which activates microglia and astrocytes to cause inflammatory reactions. Furthermore, a growing body of research indicates that Aβ is the cause of synaptic degradation, which in turn causes cognitive

impairment [6]. Conversely, NFTs are the intracellular build-up of aggregated tau, a protein that binds to microtubules [7–10]. According to established research, tau aggregation is triggered by hyperphosphorylation, and in AD patients, the degree of NFT accumulation is positively correlated with both neuronal loss and dementia [10].

One of the most prevalent endocrine diseases, diabetes mellitus is linked to a cluster of metabolic disorders that include persistent hyperglycemia and abnormalities in the metabolism of proteins, carbohydrates, lipids, and oils, as well as glycosuria, ketosis, and acidosis brought on by deficiencies in the action or secretion of insulin [11]. Diabetes mellitus can cause long-term harm, malfunction, and organ failure, with the eyes, kidneys, nerves, heart, and blood vessels being particularly vulnerable [12]. Diabetes, a serious degenerative condition that affects people worldwide, is quickly rising to the third rank of all diseases that kill people. It affects 16 million people in the US and up to 200 million people globally, making it the most prevalent endocrine disorder [13, 14]. Every one of the three forms of diabetes is on the rise; by 2035, type 2 diabetes alone might rise by 55% [15].

II. DIABETES MELLITUS: A RISK FACTOR FOR ALZHEIMER'S

Chronic use of high-sugar and high-saturated fat diets combined with sedentary lifestyles leads to obesity and insulin resistance, which in turn promotes a range of metabolic illnesses, including metabolic syndrome and type II diabetes mellitus (DM) [16]. Elevated blood pressure, cardiovascular disease, dyslipidemia, hypercholesterolemia, and proinflammatory states are linked to these metabolic illnesses, which significantly shorten life expectancy [17, 18]. Insulin resistance, which is the term used to describe the widespread phenomena of target tissues not responding appropriately to insulin, is intimately linked to obesity. Insulin resistance usually occurs several years before type 2 diabetes (T2D). The most prevalent kind of dementia, AD, is associated with a higher risk of dementia due to T2D [19]. According to a number of recent epidemiological and clinical research, people with type II diabetes have a higher risk of cognitive impairment and greater vulnerability to AD [20–25].

According to recent research, persons with type 2 diabetes (T2D) who acquire the disease later in life have an increased chance of getting AD. Surprisingly, T2D exhibits many of the characteristics of AD, such as Aβ aggregation, elevated activity of glycogen synthase kinase-3 (GSK-3), unbalanced protein phosphorylation, aging-associated processes, elevated cholesterol, metabolic diseases, anomalies in blood vessels, elevated oxidative stress, heightened inflammatory response, association with apolipoprotein E ε4 allele, and glyceraldehyde-derived advanced glycation end-products derived from blood vessels[26]. Particularly in the case of abnormal insulin signalling, this lends credence to the notion that AD may be regarded as "type III DM" [27–32]. The brain's lower cerebral glucose metabolic rate, akin to AD, is the result of altered signalling pathway caused by abnormal insulin signalling [33, 34]. This is corroborated by histopathological data. In a number of animal models, the artificial introduction of DM exacerbates AD pathology, including SP and NFT formation [35–46].

III. CORRELATION BETWEEN T2DM AND AD

There is ample evidence that diabetes poses a significant risk to Alzheimer's disease pathogenesis by affecting synaptic connectivity, brain morphology (brain shrinkage), and memory processing (identification and retrieval) [19]. According to recent research, AD is a kind of diabetes that is specific to the brain [47]. kind 2 diabetes is the most prevalent and significant co-morbidity of AD, increasing the risk of AD by many times [48]. The symptoms of T2D include insulin resistance, hyperglycemia, hyperinsulinemia, metabolic dysfunctions, and chronic inflammation; interestingly, AD has all of these characteristics as well [48, 49]. Other important variables that connect AD [50] and T2D [51, 52] include aberrant energy metabolism, oxidative stress, mitochondrial differences, malfunctioning protein O-GlcNAcylation, and cholesterol modifications. Moreover, insulin is highly concentrated in the areas of the brain that are involved in the development and consolidation of memories, such as the hippocampal regions. Insulin is also vital in cerebral functions [53]. Changes in brain metabolism accompany a reduction in insulin signalling in the central nervous system caused by peripheral insulin resistance. Central insulin resistance is linked to increased Aβ toxicity, Tau hyperphosphorylation, oxidative stress, and neuroinflammation, all of which contribute to neurodegeneration. The study presents the fundamental mechanisms by which insulin resistance causes dysregulation of bioenergetics and progresses to AD as a mechanistic connection between AD and diabetes mellitus. This offers a viable and promising area for the development of therapies in AD through increased hypometabolism and modified insulin signalling [54–56].

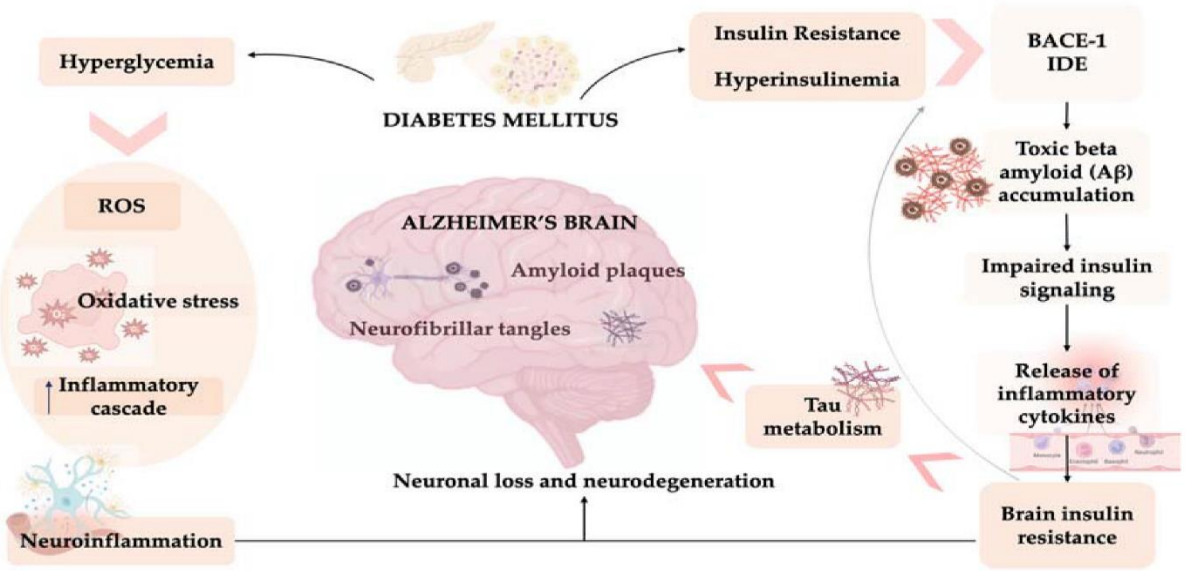

Figure 1: Correlation between DM and AD

IV. PHYSIOPATHOLOGICAL LINKS

4.1 Insulin Resistance

Hyperinsulinemia caused by insulin resistance in AD and diabetes can saturate the insulin-degrading enzyme (IDE), which in turn causes the breakdown of Aβ and insulin [57, 58, 59]. As a significant predictor of type 2 diabetes, insulin resistance may result in impaired neuronal and cognitive processes together with an excessive surge in insulin and comparatively decreased peripheral insulin activity [60, 61]. Neuritic plaque formation, hippocampal shrinkage, decreased cerebrocortical glucose metabolism, and cognitive decline follow, all of which may be strongly correlated with memory deficits [62].

Insulin binds to the α-subunit of the insulin receptor in the brain, causing tyrosine kinase to phosphorylate the receptor's β-subunit. This process activates a number of second-messenger transduction pathways. The Shc/MAP (Src homology collagen mitogen-activated protein) kinase pathway in the brain stimulates the production of genes necessary for the development, maintenance, and repair of synapses and neuronal cells. Furthermore, it acts as a modulator of the learning and memory-supporting hippocampus synaptic plasticity [63]. An further route entails binding insulin receptor substrates 1 and 2 (IRS-1 and IRS-2) to phosphatidylinositol 3-kinase (PI3K), which is required for memory consolidation and synaptic plasticity [64], contextual memory retrieval and extinction [65], and memory loss caused by Aβ [66]. Additionally, it triggers the production of nitric oxide, which is involved in memory and learning processes [67, 68].

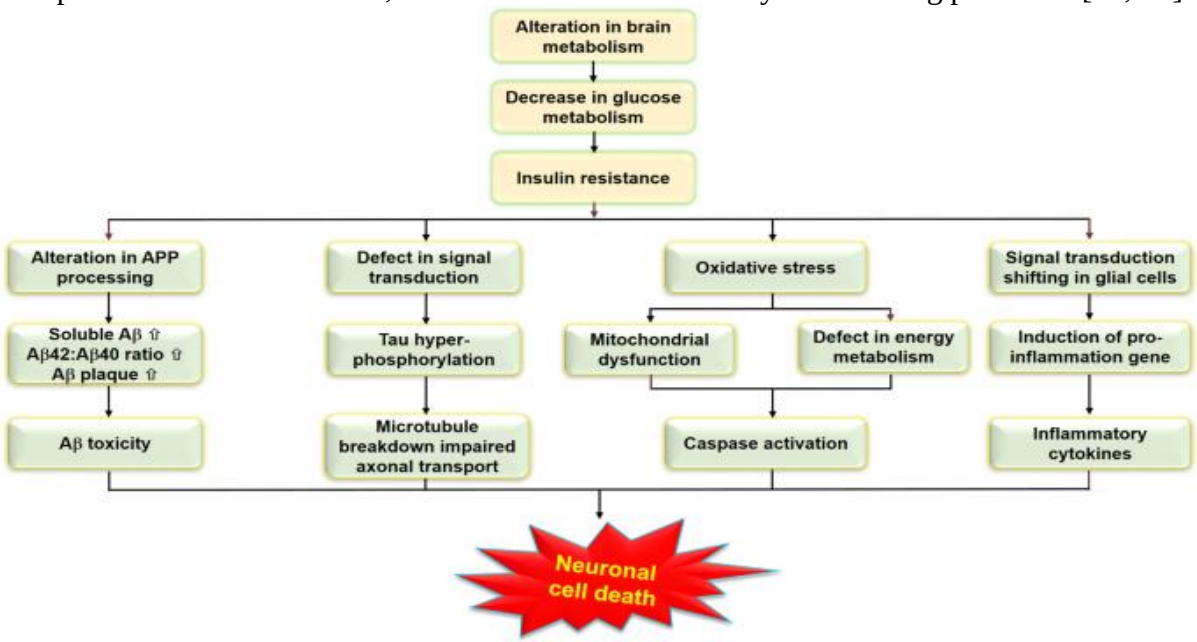

Figure 2: Role of Insulin Resistance in CNS

There are other theories explaining why diabetes and AD may be related, but generally speaking, the effects of poor insulin signalling are linked to brain metabolic problems that might result in brain dysfunction [69]. Insulin resistance causes Akt, a protein involved in several physiological functions, including glucose metabolism, to become less activated. It also inhibits GSK3β, one of the kinases that phosphorylates tau. Consequently, hyperphosphorylation of tau, a crucial element of neurofibrillary tangles present in AD patients' brains, may result from elevated GSK3β activation during insulin resistance [70, 71].

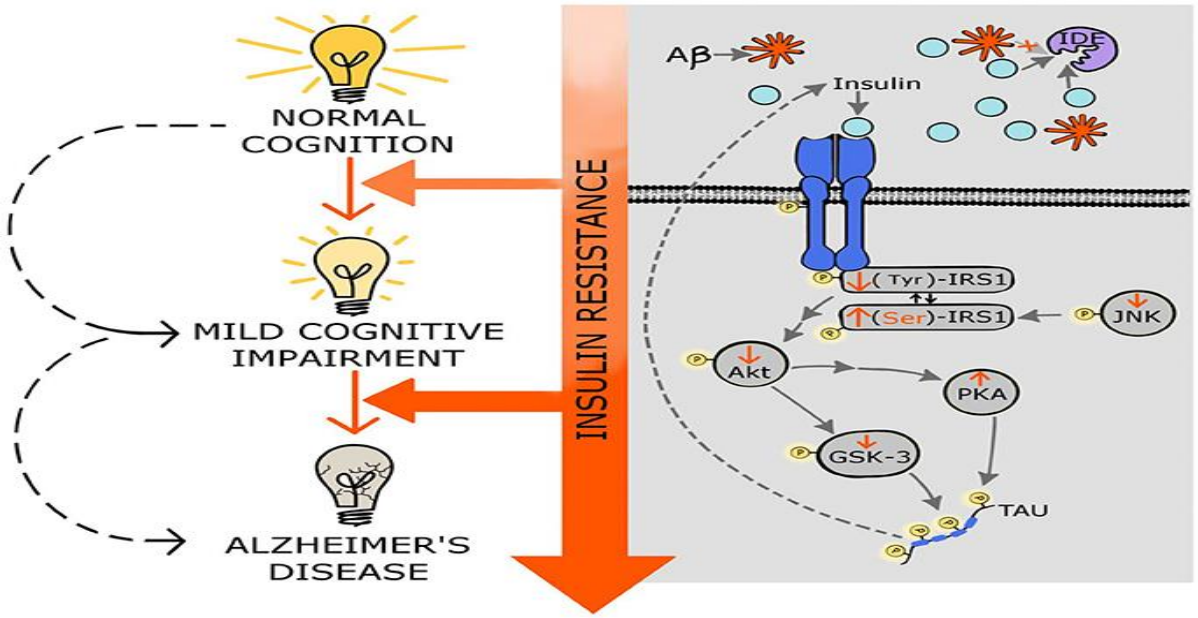

Figure 3: Defective insulin signalling pathway

4.2 Amyloid and Tau

Aβ, the predominant constituent of SP, arises from β-amyloid precursor protein (APP) via consecutive cleavages by β- and γ-secretases [72, 73, 74]. The γ-secretase complex, consisting of PS1 or PS2, nicastrin, anterior pharynx defective-1 (Aph-1), and presenilin enhancer-2 (Pen-2) is catalyzed by PSenilin 1 (PS1) [75-78]. Given that over 200 different PS1 mutations have been found, PS1 mutations are the primary cause of Familial AD (FAD) [79]. Additionally, several mutations linked to FAD have been found in APP [80]. As a result, several researchers use transgenic animal models in which the brains of the animals produce APP and/or PS1 mutations linked to FAD. Crucially, prolonged Aβ, or Aβ42, is produced in greater quantity by the majority of FAD-related mutations and is more likely to aggregate than the predominant Aβ40 species [81–83]. Growing data points to the early stage of AD pathology—synaptic dysfunction—being induced by soluble Aβ oligomers. For instance, brain-derived neurotrophic factor (BDNF)-containing vesicles and mitochondria's axonal transport are disrupted by Aβ oligomers [84–86]. Key components of synaptic transmission include mitochondria and BDNF. However, maintaining the proper balance of Aβ in the brain also depends on Aβ elimination. Many Aβ-degrading enzymes exist, including insulin-degrading enzyme (IDE), neprilysin (NEP), and endotherin-converting enzyme 1 (ECE-1) [87–89]. Rats given diabetes cause diabetes have lower levels of ECE-1 in their hippocampus and cortical areas of the brain, and their cortices also have lower amounts of IDE [90]. For this reason, a combination of elevated Aβ synthesis and reduced Aβ clearance may result in Aβ pathology when insulin insufficiency occurs.

While tau pathology in AD patients' brains is strongly correlated with their level of dementia and neuronal death, FAD-related genes are also linked to Aβ [91]. NFTs mostly consist of the microtubule-associated protein tau, whose hyperphosphorylation is thought to be the cause of the aggregation of NFTs [7–10]. GSK3β is a highly significant protein kinase that is implicated in the phosphorylation of tau [92–96]. Insulin and insulin-like growth factors (IGFs) bind to the insulin receptor (IR), causing it to become autophosphorylated and activated, which in turn mediates intracellular signalling pathways [97–99]. The activation of phosphoinositide-3 kinase (PI3K)/Akt signalling is caused by IR tyrosine kinases phosphorylating IR substrate (IRS) molecules [100-103]. Crucially, phosphorylating Ser9 of GSK3β and inhibiting its kinase activity is the outcome of activating the PI3K/Akt pathway [104]. These results imply that abnormal insulin signalling may change GSK3β activity, which in turn may cause Tau to become hyperphosphorylated.

4.3 Mitochondrial dysfunction and Oxidative stress

Since they can have either a positive or negative biological impact, reactive oxygen species and reactive nitrogen species, or ROS and RNS, serve a dual biological role in living systems [105]. Conversely, an imbalance between the intracellular antioxidant capacity and the generation of reactive oxygen species (ROS)/RNS as a result of mitochondrial dysfunction results in abnormally high ROS levels and oxidative stress (OS), which is accompanied by oxidative cell damage and, ultimately, death [106]. In fact, OS plays a key role in the etiology of diabetes and plays a major role in the onset and course of neurodegenerative diseases. [107]. Many study teams are actively examining the possibility that OS might serve as a bridge between T2DM and AD. The existence of cellular OS, aberrant mitochondria, and a deficiency in antioxidant defences are all strongly associated with T2DM and AD, according to available data [108–110].

When insulin transmission is resistant in T2DM patients, neurons become energetically deficient and more vulnerable to oxidizing or other metabolic insults that compromise synaptic plasticity [111]. Growing evidence points to the hypothesis that changes in mitochondrial function brought on by aging are what cause increased OS in T2DM and how AD pathogenesis develops and progresses [108, 112, 113, 114-116]. T2DM patients have lower antioxidant capacity and more oxidative stress [117], which may cause neuronal damage, targeting mitochondria specifically [118]. Oxidative modifications to mitochondrial proteins, lipids, and nucleic acids increase the generation of reactive oxygen species and cause cells to produce tau phosphorylation, Aβ synthesis, and neurofibrillary tangles [119].

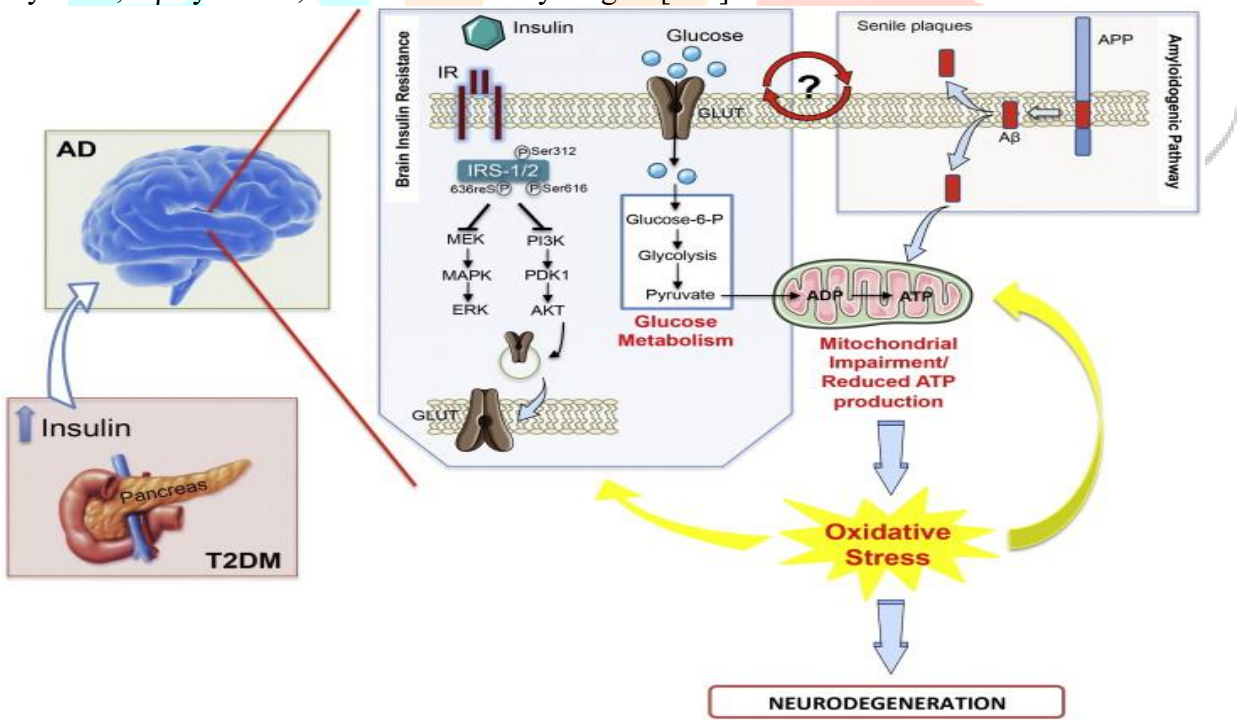

Figure 4: Role of oxidative stress

4.4 Advanced glycation end products (AGEs) and Neuroinflammation

Diabetes problems mostly arise from glucose toxicity, which is brought on by persistent hyperglycemia and dyslipidemia. A critical connection between diabetes and AD has been shown to be the AGEs produced by hyperglycemia [120–126]. Individuals with AD may experience cognitive impairment as a result of elevated levels of AGE in the blood and brain [127]. Rats with diabetes have been shown to accumulate AGEs, pentosidine, and glyceraldehydes-derived pyridinium (GLAP) in their brains [123]. Additionally, by activating NF-kB, pentosidine and GLAP cause the expression of BACE1, an enzyme essential to the production of Aβ. Not only can AGEs increase the cytotoxicity of Aβ, but they also facilitate the production of amyloid plaques and fibrillary tangles, two characteristics of AD. Aβ causes microglia to produce more AGE-albumin, which they then release [128]. Therefore, AGE build up in the brain represents a shared neurodegenerative mechanism that connects AD and diabetes.

As a fundamental feature of type 2 diabetes, insulin resistance is linked to inflammation [129], notably with increased concentrations of the inflammatory mediators a-1-antichymotrypsin, C-reactive protein, and interleukin-6 (IL-6) [130–132]. Additionally, there is proof that AD is connected to inflammatory processes [133–135). When comparing Alzheimer's patients to healthy control participants, the rates at which inflammatory products build vary [136], Alzheimer's disease patients' senile plaques contain the inflammatory

cytokine IL-6 [137], and individuals with AD had higher levels of IL-6 immunoreactivity in both lumbar and ventricular cerebrospinal fluid [138].

V. CONCLUSION

Diabetes generally advances in tandem with cognitive decline. Numerous epidemiological and experimental research have provided evidence in favour of the link between diabetes and dementia. Kind 3 diabetes may be the cause of dementia linked to diabetes, according to earlier experimental and epidemiological research. Finding the unique risk factors for diabetes-related dementia and preventing the two conditions from happening at the same time are the most crucial objectives. Consequently, altering the insulin signalling system might be a useful tactic to stop type II diabetes patients' cognitive deterioration and perhaps Alzheimer's disease.

VI. ACKNOWLEDGEMENTS

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