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# Treatment of Alzheimer Disease with Anti-Diabetic Medications

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**ABSTRACT**

**AD and T2DM are widespread among elderly globally. Epidemiological studies suggest T2DM causes AD. AD brains have reduced glucose uptake, indicating insulin resistance. A plaques and tau tangles are AD pathology. Insulin resistance in T2DM directly exacerbates A and tau pathologies, while synaptic dysfunction, inflammation, and autophagy impairments are common to both illnesses and indirectly impact A and tau neuronal activity. Understanding how these diseases are linked can help find novel Alzheimer's drug targets.**

***Keywords-*** Alzheimer's disease, Type 2 DM, Neuro-protective, Insulin dependent.

## I. INTRODUCTION

Alzheimer's disease (AD) is a neurological illness that involves cognitive decline, memory loss, and behavioural abnormalities [1]. Alzheimer's disease (AD) affects 5.8 million Americans over 65, and that number is anticipated to climb to 13.8 million by mid-century. Alzheimer's is connected to APOE4 and amyloids [3,4]. 25% of the population carries APOE4 [5].

Diabetes mellitus (DM) is a widespread chronic metabolic illness with severe effects and an elevated risk of early death in the US. In 2019, 463 million individuals have diabetes [6]. Hyperglycemia and insulin resistance characterise type 2 diabetes (T2DM) [7].

Alzheimer's disease (AD) risk increases 45–90% in T2DM patients [8,9,10,11]. Rotterdam research found a link between T2DM and dementia. aMCI is more prevalent in T2DM [13]. AD and cognitive impairment appear to be affected by DM type and accompanying comorbidities, as well as antidiabetic medication [14]. T2DM's elevated insulin and IGF-1 levels impair cognitive function and development [15, 16]. Insulin and IGF-1 are essential. Recent investigations relate AD to neuroinflammation, AGEs, mitochondrial dysfunction, insulin signalling failure, and metabolic syndrome [17]. [18–20]. AD is a metabolic illness induced by insulin and IGF-1 resistance in the brain [18]. Diabetes type 3 is a failure of brain cells to recognise insulin, causing synaptic, metabolic, and immune system dysfunction. Intranasal insulin, metformin, thiazolidinediones (and incretins), and thiazolidinediones improve AD patients' cognitive ability (such as glibenclamide). According to studies, Alzheimer's disease (AD) can be treated with type 2 diabetes drugs [19,20,21]. There has been a lot of interest in exploring whether these medications can also treat AD [22]. AD and T2DM have similar pathophysiologies. Numerous human studies have examined how antidiabetic drugs affect AD pathology [23, 24, 25, 26, 27]. Animal studies show that antidiabetic drugs can also help with tau protein pathology [27, 28, 29], -amyloid pathology [29, 30], synaptic function [33], cognitive function [34, 35, 36], and neuroinflammation [37]. Alzheimer's or MCI patients engaged in research trials to investigate the idea that antidiabetic medicines could be neuroprotective. This review evaluates anti-diabetic drugs' effectiveness in treating Alzheimer's. Diabetes mellitus (DM) is a chronic illness that strains public health systems. 400 million people worldwide have diabetes, and 640 million are expected to have it by 2040 [1]. [2] Alzheimer's disease (AD) affects 26 million individuals worldwide [2], and the number is likely to climb [3]. Insulin resistance-induced AD is called "type 3 diabetes" because of the relationship between the two disorders [4, 5]. The Rotterdam trial showed a twofold rise in AD in DM and a tripled risk with insulin therapy [8]. Insulin resistance and inflammatory signalling pathways explain this association, but their pathophysiology links are unknown [9].

## II. EPIDEMIOLOGICAL STUDIES LINK TYPE 2 DM TO AD.

Insulin resistance and insufficiency, T2DM markers, are associated to AD. Oligomers bind to hippocampus neurons and remove dendritic insulin receptor substrates68. AD neuropathology revealed low insulin, IGF, and IRs. Non-diabetic AD individuals had insulin-resistant hippocampuses. 73 TNF- stimulates c-Jun N-terminal kinase74, which phosphorylates IRs-1.

68 Activated A oligomers block IRs-1. 75 AD may have type 3 diabetes or insulin resistance. 76 Insulin impacts A precursor expression in vivo and vitro. Insulin and IGF-1 decreased intracellular A by increasing its brain extracellular release and plasma membrane trafficking. Insulin and IGF-1 send A-binding carrier proteins to the brain, decreasing A. 79–81 Streptozotocin-induced insulin-deficient diabetes upregulates BACE1 and amyloid precursor protein. Insulin-degrading enzyme may interfere with extracellular proteolytic A degradation. Insulin resistance may inhibit insulin-degrading enzyme, aggravating AD. Insulin resistance and depletion promote GSK-mediated tau phosphorylation. -3 Insulin resistance/insufficiency may increase A damage to T2DM neurons. Insulin resistance and deficiency damage mitochondria and increase A. 88 Insulin resistance and deficiency may lead to sporadic AD (Figures 1 and 2).

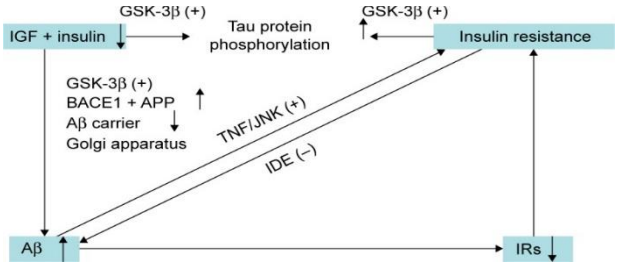


**Fig: 1 Insulin resistance and deficiency in Alzheimer's disease.**

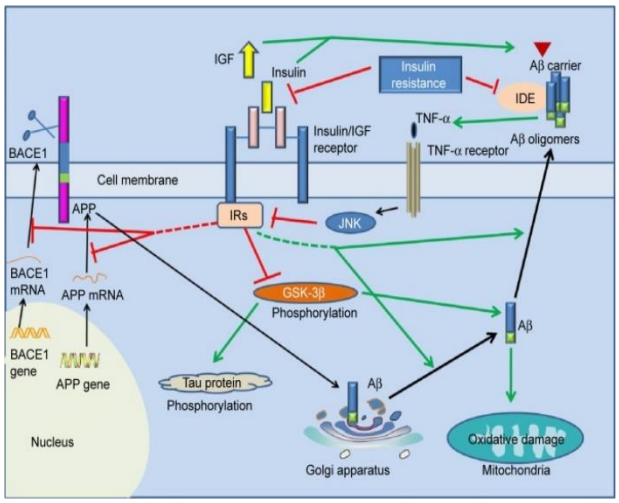


**Fig: 2 Alzheimer's and type 2 diabetes are linked.**

## III. IMPLICATION TREATMENT BETWEEN AD WITH OR WITHOUT DM

T2DM and Alzheimer's both impact glucose and energy metabolism. Both illnesses feature amyloidogenesis. Alzheimer's is characterised by amyloid plaques. IAPP is found in type 2 diabetics' pancreatic Langerhans islets (T2DM). Diabetes-induced oligomers and fibrils in diabetic mice overexpressing IAPP mimic AD mouse models overexpressing APP. Diabetes-related kidney, retina, and atherosclerotic plaques acquire AGE and RAGE under ER and oxidative stress.

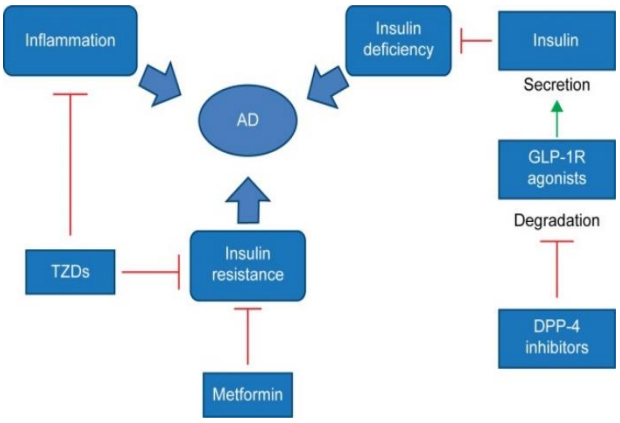


**Fig: 3 Anti-diabetic medications may have a role in the treatment of Alzheimer's disease.**

Glycated A and tau form neurofibrillary tangles in AD transgenic animals and post-mortem brains. AD and T2DM have synaptic dysfunction, inflammatory pathway activation, and autophagy impairment. In the first half of this review, we will analyse how T2DM impacts A and tau and discuss the possible mechanisms that link AD and T2DM in synaptic dysfunction, inflammation, and autophagic impairment.

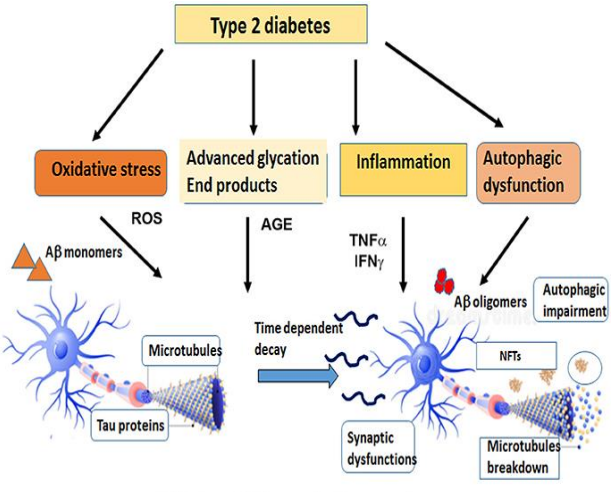


**Fig: 4 Type 2 diabetes causes Alzheimer's in many ways. Chronically high blood sugar in the brain and other target tissues causes oxidative stress, inflammation, advanced sugar glycation products, and autophagic failure in Type 2 Diabetes patients. These mechanisms release ROS that kill neurons. Insulin resistance affects downstream signalling pathways, not just A oligomers or hyperphosphorylated tau. Synaptic loss and neuronal death come from the cumulative effects of these variables on neurons.**

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## IV. ANTI-DIABETIC DRUG WORK AS ALTERNATIVE IN ALZHEIMER DISEASE

Given the multiple links between DM and AD, it is not surprising that several drugs currently approved for DM could also have a role in treating AD [32]. Different studies have explored the possible neuroprotective mechanisms of antidiabetic medications, and some of them have also been tested in clinical trials in AD and mild cognitive impairment (MCI) subjects. Here, we summarize some of the evidence from preclinical and clinical studies.

***Insulin:***

Alzheimer's medications target cholinergic, NMDA, and Gliadin-like pathways. Memory loss drugs don't treat Alzheimer's. Amyloid-based therapies failed due to side effects, unfavourable pharmacological features, or clinical ineffectiveness. Find therapy targets that reduce symptoms and pathology with few side effects. Anti-diabetes drugs have showed potential in Alzheimer's animal models and human clinical studies. In AD animal models, anti-diabetic medications were effective. Insulin decreased synapses in vitro and PKR-mediated ER stress in AD mice. Transgenic AD mice, cynomolgus monkeys, hippocampus cultures, A oligomers, exendin-4, and liraglutide were examined for GLP1-R agonists. G-protein-dependent signalling helps insulin-related pathways. In APP/PS1 transgenic AD mice, reducing Ser312IRS1, Ser636IRS1, and JNK phosphorylation improved insulin signalling, memory, and amyloid plaque load. Liraglutide attenuated intravenous A oligomer-induced IR reduction and synapse loss in cynomolgus monkeys. Liraglutide decreases inflammation in AD transgenic mice, while exendin-4 prevents excitotoxicity in a rat model ICV insulin boosts brainpower.

Alzheimer's and MCI patients benefit from chronic intranasal insulin therapy (MCI). After insulin therapy, ApoE4 carriers had lower verbal memory recall, confirming the hormone's brain effects . Intranasal insulin enhanced MCI and early Alzheimer's patients' attention, memory, and function. Insulin intranasal works differently. Intranasal insulin improved women's cognitive function over men's. Intranasal insulin therapy improved memory and mood, but not weight, in obese patients. Eight unreported trials investigate intranasal insulin for Alzheimer's.

Preclinical research supports using GLP1-R agonists in clinical studies. Subcutaneous liraglutide delayed brain glucose intake without affecting A load or cognition. Two clinical trials are studying ligarglutide's neuroprotective potential in Alzheimer's (NCT01469351, NCT01843075). Alzheimer's disease is treated with rosiglitazone and pioglitazone. Rosiglitazone improved cognition and reduced phosphorylated tau in preclinical studies.

## V. METAFORMIN

Metformin boosts neurogenesis and reduces neuronal death in Alzheimer's mice hippocampus, preventing neuronal loss (AD). Metformin reduces A-induced apoptosis by inhibiting c-Jun N-terminal (JNK). Metformin inhibited db/db mice caspase-3 in vitro. Metformin restores caspase 3/9 activity and cytosolic cytochrome c release (hNSCs). Metformin blocks A25-35 SH-SY5Y apoptosis. Picone et al. observed that metformin accelerated neuronal mortality in C57B6/J mice brains. Non-diabetic and non-AD patients need more metformin safety study. PKC impacts rodent insulin and memory. Metformin activated aPKC-CBP signalling in neural progenitors, increasing human and rat neuron emergence. Metformin increased neurogenesis and spatial memory in 3xTg-AD mice by reducing the expression of monoacylglycerol lipase (Mgll), a hydrolase-producing arachidonic acid (ARA) precursor pool, by digesting 2-arachidonoyl glycerol (ACG) (2-AG). Mgll identifies Alzheimer's metformin responders. Metformin therapy enhanced APP/PS1 mice Bdnf, Ngf, and Syp. Metformin enhanced hippocampal plasticity in AD rats. Metformin lowers spine loss, basal synaptic transmission, and surface GluA1 expression in APP/PS1 mice. Metformin boosts glutamatergic transmission in C57BJ/6 CA1 pyramidal neurons. Metformin improves Alzheimer's synapses. Anti-oxidant Metformin treats Alzheimer's. Metformin decreased MDA and APP/PS1 SOD. Metformin reduced NO and MDA in scopolamine-impaired rats. Metformin reduced rat astrocyte AMPK and caveolin1, lowering inflammation and ER stress. mitochondrial dysfunction causes Alzheimer's. A influences hNSC development and mitochondrial function. Metformin and AMPK were unaffected. Metformin decreases APPc99 and pTau404 expression, enhancing mitochondrial function. Metformin increased TOM40, HKI, and VDAC levels in C57B6/J mice cortex, but it modified their shape, suggesting mitochondrial permeability transition pores and membrane channels may be disrupted, leading to mitochondrial dysfunction. Inhibiting Acrylcholinesterase (AChE) is anti-degenerative. In insulin-resistant neuroblastoma cells, metformin lowers AChE activity by 34.9%. Metformin reduces ChE in diabetic rats. In an Alzheimer's rat model, metformin reduced AChE activity. Metformin increased AChE activity in non-AD mice, suggesting it may moderate an AD-related pathophysiological change.

## VI. THIAZOLIDINEDIONES

NFTs Tau hyperphosphorylation causes hippocampal filaments. Tau stabilises microtubules [2]. Axonal transit, neuronal loss, and cognition are affected by tau phosphorylation [52]. Kinases and phosphatases phosphorylate tau. MAPK, ERK1/2, Cdk2/5, JNK, Akt, and PKA are involved (CaMKII). tau-phosphate Since

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there are no viable treatments for AD, future medications must target the disease's abnormal cellular and molecular signalling networks. Ineffective therapy and variable results [57, 58] make this uncharted ground. Understanding AD's pathogenic events could lead to a more effective therapy. TZDs have shown promise in treating AD [13, 17]. TZDs influence cell metabolism by activating PPAR (Figure 1). Neuroinflammatory damage, A clearance, and tau pathology are reduced by pioglitazone, rosiglitazone, and troglitazone. Different targets may explain why these medicines enhanced cognitive function in AD animal models and a mild-to-moderate AD human. Versatile TZDs are indicated for Alzheimer's. TZDs suppress Ser202, Ser396, and Ser404 phosphorylation in 4Rtau-transfected CHO [53]. Rosiglitazone reduced tau Ser396 and Ser202 phosphorylation [54]. Rosiglitazone reduced p-tau aggregation and tau phosphorylation in AD transgenic mice J20 [23]. PPAR activation in diabetic 2 rats' tauopathy (OLETF) [54]. Oral rosiglitazone reduced phosphorylated tau Ser396, Ser199, and Ser202 [54]. Pioglitazone helps ApoE4 mice phosphorylate tau [55]. In 3xTg-AD mice, pioglitazone decreased tau-phosphorylated neurons [24]. Pioglitazone or rosiglitazone inhibited tau phosphorylation [25]. SH-SY5Y and rat cortical neurons phosphorylated tau-Thr231 less [56]. TZDs don't inhibit GSK-3, PKA, or PP2A. Pioglitazone changed APP/PS1 Cdk5.

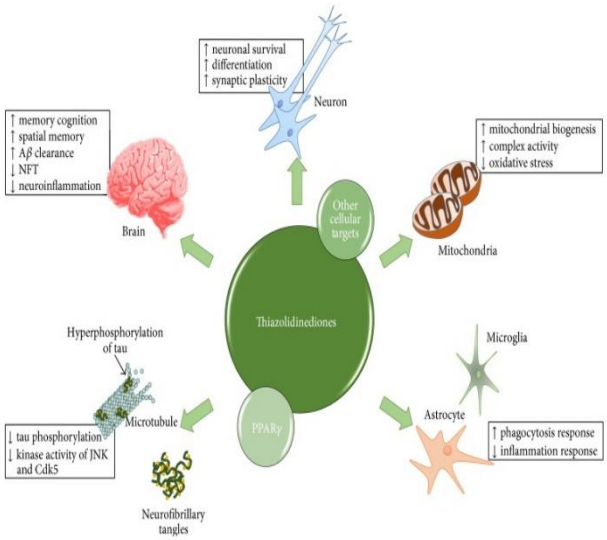


**Fig: 5 Alzheimer's thiazolidinediones TZDs bind to PPAR receptors and energy-regulating pathways in AD cell and animal models. These medications improve animal memory and diminish A deposits, accelerating amyloid plaque removal. TZDs promote neuronal survival, differentiation, and synaptic plasticity by boosting phagocytosis and reducing neuroinflammation in astrocytes and microglia. TZDs increase mitochondrial respiration and reduce oxidative stress. TZDs suppress tau kinases and neurofibrillary tangle formation.**

## VII. AD NEUROPROTECTIVE EFFECTS OF GLP1 AND DIPEPTIDYL PEPTIDASE-IV-INHIBITION

Food-stimulated intestinal L-cells generate GLP1[41]. Proteolytic cleavage makes GLP1 (1–37) active. GLP1 increases beta cell insulin production in hyperglycemic conditions and decreases alfa cell glucagon[43]. Seven-pass transmembrane GLP1 receptor sends GLP1 signals to AMPK and AMPK. GLP1 agonists activate AMPK in C2C12 myoblasts[44]. GLP1 receptor activates PI3K/AKT signal transduction, avoiding cell death[45]. Modulating mTOR kinase activity, GLP1 receptor regulates cell proliferation, survival, and protection. GLP1 receptor antagonists boost insulin activation via PI3K/AKT, activating mTOR and inhibiting GSK3-beta [46]. [47] GLP1 modulates autophagy, oxidative stress, and inflammation[47]. GLP1 and analogues may prevent CVD[48]. GLP1 receptor agonists reduce rat stroke infarct size, inflammation, and apoptosis[49].

DPP4 degrades GLP1 in the brain, pancreas, liver, and stomach[50]. DPP4 inhibitors may increase GLP1's biological half-life, reducing blood sugar[51]. Linagliptin protects neurons against amyloid beta-induced cytotoxicity and tau hyperphosphorylation[52]. Linagliptin activated AMPK-Sirt1, reducing amyloid-beta-induced mitochondrial dysfunction and ROS. Sitagliptin raises brain GLP1 levels and decreases amyloid-beta formation in AD model mice[54,55]. Linagliptin decreases amyloid-beta-42 levels, possibly curing Alzheimer's [56]. Linagliptin increased nitric oxide and decreased apolipoprotein B[56]. DPP4 inhibitors diminish GLP1 degradation, lengthen GLP1's active life, and enhance insulin sensitivity to minimise hyperglycemia[57] and neuroprotection (Figure 3).

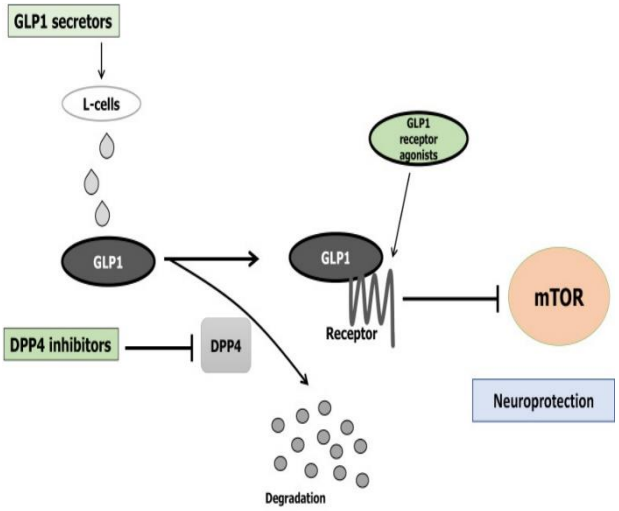


**Fig: 6 Neuroprotection from decreased dipeptidyl-peptidase-4, increased Glucagon-like peptide-1, and increased Glucagon-like peptide-1-receptor agonists.**

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## VIII. AMYLIN ANALOG

Amyloid is an extracellular -sheet protein aggregate. Amyloids cluster with related proteins due to their structure. AD causes A overproduction and aggregation [85]. T2D causes pancreatic cell death by amylin aggregation. Amylin and A may cause diabetes and Alzheimer's. Amylin pathogenesis and its interaction with other amyloids could assist study Alzheimer's and Parkinson's.

Insulin is important for A's metabolism. IDE degrades calcitonin, glucagon, and A. Liver, kidneys, and brain express IDE. APOE 4 lowers IDE by 50%. Reduced IDE induces A buildup. Insulin signalling promotes APP cleavage [88]. Extracellular A in the brain promotes CNS insulin resistance [89, 90]. Glycogen synthase kinase-3 requires insulin signalling [91]. Impaired insulin signalling causes hyperphosphorylation of tau, preventing Akt from regulating glycogen synthase-3 activity. Insulin signalling decreases neurodegenerative disease risk. T2D and AD have uncontrolled Amylin synthesis and signalling. Amylin maintains glucose homeostasis and has 37 amino acids. Islet hormone amylin [92, 93]. Amylin reduces gastrointestinal glucose absorption and liver insulin production, but not blood glucose [93, 94].

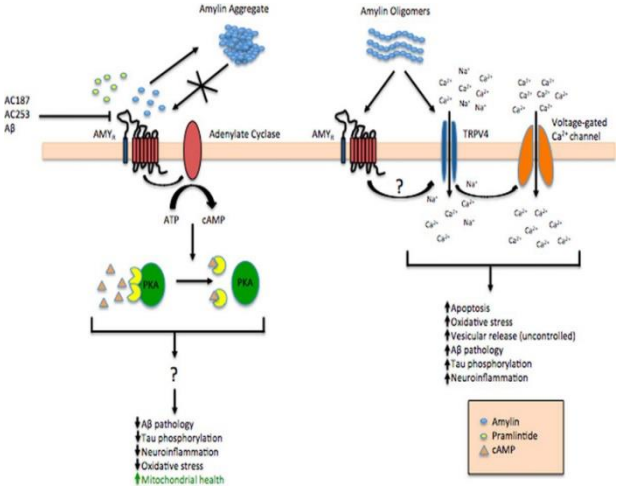


**Fig: 7 Soluble amylin and pramlintide activate AMYR, which recruits adenylate cyclase. Adenylate cyclase activation produces cAMP and activates PKA. This canonical amylin signalling route may explain its positive effects. At high quantities, amylin forms oligomers and plaques, eliminating signalling amylin. Amylin plaques cannot signal through endogenous AMYR, but amylin oligomers may interact with AMYR and/or TRPV4 to depolarize the membrane through Na+ and Ca2+ influx. This initial depolarization allows voltage-gated Ca2+ to approach threshold, causing Ca2+ inflow. Uncontrolled Ca2+ influx is also harmful in pancreatic -cells and causes late-stage -cell death in T2D.**

## IX. CONCLUSION

There has been a growing body of data that demonstrates that AD and T2DM share a common pathophysiology, and this review has attempted to summarise that information and explain the fundamental mechanisms at the intersection of these two diseases. Preclinical experiments employing animal models of A and tau are based almost solely on FTDP-17 cases, rather than those of more conventional Alzheimer's disease (AD) models. Despite the fact that AD and T2DM may have comparable genetic underpinnings, there may be major differences in the development and spread of the disease pathology between the familial and sporadic cases. Combinatorial therapies, in particular, call for consideration of this. Preclinical investigations have suggested several antidiabetic medicines to have a potential favourable influence on multiple aspects of neurodegeneration, suggesting these medications warrant deeper study in AD given the pathophysiological links between AD and diabetes mellitus. Multiple clinical trials on intranasal insulin administration in AD have given good results with no substantial adverse effects, making insulin an interesting therapy option for the illness. Several AD and MCI drug trials are currently under process, with findings expected in the next several years. Additional discoveries on how antidiabetic drugs alter the brain's chemical systems could lead to novel treatments in the future.

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