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Review Article

Connection between Type 2 Diabetes and Alzheimer's disease: Insights from epidemiology to mechanisms and treatment approaches

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Abstract

This paper aspires to present an extensive exploration of the epidemiological data that connects Type 2 Diabetes Mellitus (T2DM) and its associated ailments, including obesity, hyperinsulinemia, and metabolic syndrome, to the onset of Alzheimer's disease (AD). Objective is to delve into the intricate workings, especially the nuances of insulin resistance and deficiency, that might illuminate the relationship linking T2DM and AD, and to evaluate the promise of anti-diabetic medications in the therapeutic landscape of AD. A comprehensive exploration was conducted to examine the research on the relationship between insulin resistance and deficiency with amyloid-β accumulation and tau protein phosphorylation, both of which are key factors in the onset and progression of Alzheimer's disease. The study focused on clinical investigations involving anti-diabetic medications such as thiazolidinediones, metformin, insulin, glucagon-like peptide-1 receptor agonists, and dipeptidyl peptidase-4 inhibitors, evaluating their potential use in Alzheimer's treatment. Epidemiological and foundational studies indicate that Alzheimer's Disease (AD) may be likened to "Type 3 Diabetes." Despite the mixed outcomes from clinical trials involving anti-diabetic therapies for AD, the potential remains intriguing. The effectiveness of these drugs, importantly, hinges on whether or not the apolipoprotein E (APOE)-ε4 variant is present, as individuals without the APOE-ε4 allele tend to have more favourable outcomes. The intricate connection linking T2DM and AD is bolstered by both epidemiological and mechanistic insights, yet the efficacy of anti-diabetic medications for addressing AD necessitates deeper exploration, especially considering genetic elements like the APOE-ε4 genotype.

Keywords: Type 2 diabetes mellitus, Alzheimer's disease, Insulin resistance, anti-diabetic agents, APOE-ε4 genotype, amyloid-β, tau protein, clinical trials.

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1. Introduction

Type 2 diabetes mellitus (T2DM) has surged in prevalence, driven by the escalating rates of obesity and an increasingly aging global citizenry. While notable strides have been achieved in thwarting and managing the traditional macro vascular and microvascular issues tied to diabetes, these innovations have inadvertently lengthened the lives of those affected, possibly ushering in new challenges like dementia.[1] Epidemiological research reveals that people with T2DM face a staggering 50%–150% heightened risk of developing dementia when compared to the broader population.[2-4] Prince and his associates projected a significant surge in the worldwide occurrence of dementia, escalating from 35.6 million in 2010 to an astonishing 115.4 million by the year 2050. Considering the anticipated surge in both diabetes and dementia, the future toll of dementia—especially Alzheimer's disease (AD) and vascular dementia may be significantly more severe than currently projected.[5] Among various types of dementia, AD reigns as the most prevalent, comprising 60%–80% of all instances.[6] Over the last thirty years, a wealth of research has illuminated a definitive connection between T2DM and an escalated risk of developing AD. Additionally, issues connected to T2DM, like obesity, hyperinsulinemia, and metabolic syndrome, are regarded as possible risk contributors for AD.[7,8]

While the definitive pathways connecting T2DM and AD are not completely known, numerous hypotheses have arisen, covering insulin resistance and deficiency, impaired signalling of insulin receptors, abnormal insulin-like growth factor (IGF) signalling, glucose toxicity, the accumulation of

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advanced glycation end products, damage to cerebrovascular networks, and inflammation of blood vessels. Given the limited efficacy of current AD treatments, which merely decelerate symptom progression for 6–12 months in about half of those treated,[11] and the disappointing results of various promising drugs during Phase III clinical trials,[12] there exists an urgent necessity to investigate novel therapeutic avenues. Grasping the influence of T2DM on AD progression could unveil vital insights for both prevention and intervention strategies. This piece of research emphasizes the prospective application of various anti-diabetic agents like insulin, metformin, thiazolidinediones, GLP-1R agonists, and DPP-4 inhibitors in the fight against Alzheimer's disease. Our objective is to assess the outcomes of clinical trials examining these agents, illuminating their potential and constraints in the quest to combat AD.

2. Alzheimer's disease

Clinically, Alzheimer's disease (AD) manifests as a complex interplay of progressive memory deficits and a gradual decline in cognitive function, ultimately resulting in premature mortality, which generally occurs 3–9 years following diagnosis.[13] The neuro pathological characteristics of AD exhibit appertaining to the occurrence of extracellular senile plaques that are rich in amyloidd-β (Aβ) protein, in conjunction with neurofibrillary tangles comprised of intracellular and aberrantly phosphorylated tau protein, along with a significant loss of neurons and synapses, particularly within the hippocampal and cortical regions.[14] In consideration of these pathological indicators, the "amyloid cascade hypothesis" is recognized as the predominant theoretical framework. This hypothesis asserts that the accumulation of Aβ, whether arising from increased synthesis or reduced clearance, triggers a sequence of subsequent phenomena associated with AD, ultimately directing the progression of the disease.[13,16,17] Despite exhibiting clinical manifestations akin to other dementia types, AD originates from two distinct etiological pathways. A small proportion of AD cases, referred to as familial early-onset AD, is founded upon genetic mutations. These situations arise from missense inconsistencies related to three vital genes: amyloid precursor protein (APP), presenilin-1 (PSEN1), and presenilin-2 (PSEN2).[18,19] Familial AD accounts for less than 5% of all cases and generally presents itself during middle adulthood.[20] Alternatively, the great bulk of AD occurrences are inconsistent, with factors like older age, female identity, vascular health issues, traumatic brain injury history, a lineage of dementia, and genetic susceptibilities most notably the apolipoprotein E (APOE) ε4 allele—acting as the main unchangeable risk factors.[21,22] In addition to these immutable risk factors, a variety of modifiable risk elements have been identified. Recent research emphasizes that over half of sporadic or late-onset AD cases are associated with seven adjustable risk factors: depression, diabetes, tobacco use and obesity during midlife, hypertension in middle age, a sedentary lifestyle, and low levels of educational attainment.[23] Addressing these amendable risk factors possesses the potential to profoundly impact the prevention and management of AD.

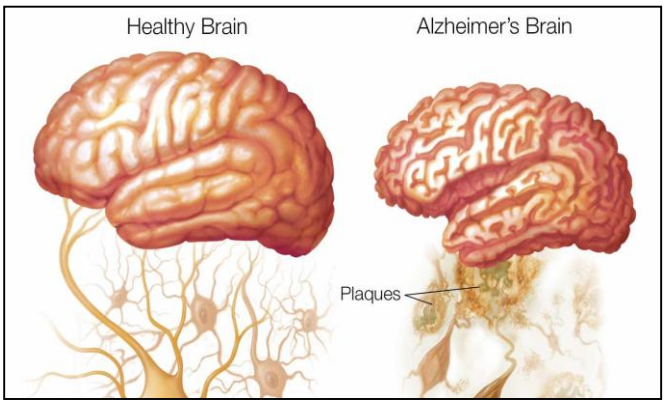

Figure 1: Healthy brain & Alzheimer's brain difference

2.1. T2DM and its related conditions

Engaging with the complex interplay between Type 2 Diabetes Mellitus (T2DM) and Alzheimer's disease (AD) entails reflecting on the natural evolution that leads to T2DM. Two fundamental mechanisms orchestrate the emergence of T2DM: insulin resistance paired with insufficient insulin production from the pancreatic β-cells.[1] In the early stages, Showing in **Figure 1** counteract insulin resistance, pancreatic β-cells ramp up insulin output, leading to a state of hyperinsulinemia that aids in keeping glucose levels harmoniously balanced. Yet, as the functionality of β-cells wanes over time, insulin synthesis falters in its ability to combat insulin resistance, resulting in escalated blood glucose levels and, ultimately, paving the way for prediabetes and T2DM.[2] Obesity, especially the accumulation of visceral fat, serves as a principal catalyst for insulin resistance, forging a connection between being overweight and the development of T2DM.[3] Also, this change is indicative of metabolic syndrome, distinguished by raised blood pressure, lipid discrepancies, and increased systemic inflammation.[4] From a scientific lens, it continues to be an unanswered question to clarify if the central tie between T2DM and AD is entrenched in hyperglycaemia, hypertension, insulin resistance, or variables uniquely related to the malfunction of adipose tissue. These elements are intricately woven together and frequently manifest simultaneously, complicating the task of isolating a singular primary cause. Nevertheless, unravelling this relationship is vital for further clarifying the contributions of adiposity, hyperinsulinemia, metabolic syndrome, and diabetes in the unfolding narrative of AD's pathogenesis.[5,6]

2.2. Epidemiological studies linkingT2DM, obesity, hyper insulinemia and metabolic syndrome to ADT2DM

A vast number of research efforts have conclusively shown the relationship between Alzheimer's disease (AD) and Type 2 Diabetes Mellitus (T2DM) in recent years. These investigations have consistently indicated that those afflicted

with T2DM face a significantly elevated risk of succumbing to AD when contrasted with the broader populace. For example, it is noted that individuals grappling with T2DM exhibit a staggering 50%–100% heightened risk of developing AD.[1,2] The detailed relationships are presented in **Figure 2** that fuse T2DM with AD are many and layered, covering chronic elevated blood sugar, insulin resistance, and the related metabolic disruptions like obesity, high insulin production, and metabolic syndrome.

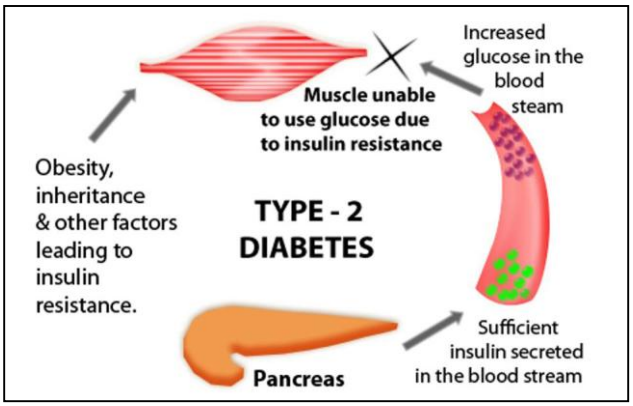

Figure 2: T2D follow

2.3. Obesity and AD risk

Excessive weight, particularly when it settles around the stomach, is significantly tied to the body's reduced ability to respond to insulin and the rise of type 2 diabetes mellitus (T2DM). Evidence suggests that being heavier in midlife creates a notable risk for the progression of Alzheimer's disease (AD) and several kinds of dementia.[3,5] Adults with an elevated body mass index (BMI) throughout their middle years could face a greater chance of encountering Alzheimer's disease as they age. The link between obesity and AD is somewhat elucidated by the impact of adipose tissue in fostering systemic inflammation and oxidative stress, both of which are important in the realm of neuro degeneration.

2.4. Hyper insulinemia and AD

The phenomenon of hyperinsulinemia, a critical marker of insulin resistance, has been tied to the risk of Alzheimer's disease (AD). Rising insulin levels within the brain could disrupt the clearance of amyloid-beta (Aβ), leading to its build up and the formation of amyloid plaques, a prominent pathological feature associated with Alzheimer's disease.[7] Epidemiological findings show that hyperinsulinemia not only leads to further cognitive decline in Type 2 Diabetes Mellitus (T2DM) individuals but also plays a crucial role in the advancement of Alzheimer's disease in the broader 5 demographic.

3. Type 3 Diabetes Mellitus a Detailed Overview

Type 3 Diabetes Mellitus (T3DM) is a term used to describe the proposed link between Type 2 Diabetes Mellitus (T2DM) and Alzheimer's disease (AD). Although not yet officially recognized as a separate type of diabetes by major medical organizations such as the American Diabetes Association or the World Health Organization, this term is increasingly accepted in scientific literature. It reflects the discovery that insulin resistance and impaired glucose metabolism in the brain are strongly associated with the onset and progression of Alzheimer's disease.[1]

3.1. Pathophysiology

The brain requires insulin not only for glucose metabolism but also for supporting neuronal growth, survival, and cognitive functions such as learning and memory. In Type 3 diabetes, insulin resistance occurs in the brain, resulting in decreased glucose uptake by neurons. This leads to energy deficiency, oxidative stress, inflammation, mitochondrial dysfunction, and synaptic failure—all contributing factors to neurodegeneration.[1]

Additionally, insulin plays a regulatory role in clearing amyloid-beta peptides, the abnormal protein deposits found in the brains of Alzheimer's patients. When insulin signalling is impaired, amyloid-beta accumulates, forming plaques that disrupt neural communication.[2] Similarly, tau proteins, which stabilize microtubules in neurons, become hyper phosphorylated under insulin-resistant conditions, forming neurofibrillary tangles another key hallmark of Alzheimer's disease.[2]

3.2. Link between T2DM and Alzheimer's disease

Multiple epidemiological studies have shown that patients with T2DM are at an increased risk—nearly twice as likely—of developing Alzheimer's disease compared to non-diabetic individuals.[2] This is due to shared pathophysiological mechanisms such as chronic hyperglycaemia, insulin resistance, micro vascular complications and inflammatory cytokine release.

These factors damage the brain's vascular system and impair cognitive function over time. The overlap in mechanisms supports the conceptualization of Alzheimer's disease as a metabolic condition akin to diabetes.[1]

3.3. Clinical features of type 3 diabetes

Although T3DM is not diagnosed through traditional blood glucose tests, its symptoms mimic those seen in Alzheimer's patient's gradual memory loss, difficulty with language and problem-solving, mood changes and confusion, impaired judgment and difficulty performing daily tasks. Cognitive assessments, neuroimaging (such as MRI or PET scans), and patient history are used to evaluate suspected cases. Biomarkers like amyloid-beta and tau levels in cerebrospinal fluid also help confirm the diagnosis.[3]

Table 1: Recent epidemiological studies linking type 2 diabetes mellitus, obesity, hyperinsulinemia, and metabolic syndrome to Alzheimer's disease

Author(s)	Country	Study name	Age (years)	Follow-up (years)	Sample size (Total/Cases)	RR (95% CI)	RR (Adjusted 95% CI)	Notes
Livingston *et al.*, 2020[27]	UK	Lancet dementia commission	>60	15 (2000–2015)	3,010/450	1.5 (1.2–2.1)	2.0 (1.3–3.1)	Association with modifiable factors
Xu *et al.*,2021[28]	Sweden	Kungsholmen project	>75	9 (1988–1997)	1,248/75	1.5 (1.0–2.1)	1.3 (0.9–2.1), 2.6 (1.2–6.1)	
Borenstein *et al.*, 2022[29]	USA	Kame project	>65	9 (1992–2001)	1,859/NR	NR	3.3 (1.4–8.1)	Focus on ethnic variability
Arnold *et al.*, 2020[30]	USA	Alzheimer's disease neuroimaging initiative	>65	10 (2010–2020)	1,950/450	1.5 (1.0–2.1)	1.7 (1.2–3.1)	Impact of insulin resistance

Table 1 are showing among the adult population, the alarming correlation between Alzheimer's disease (AD) and Type 2 diabetes mellitus (T2DM) has emerged as a notable observation, with risk estimates ranging from 50 percent to 100 percent. A thorough meta-analysis encompassing over 6,184 individuals diagnosed with diabetes and 38,530 individuals without diabetes yielded an aggregated relative risk (RR) of 1.5 (95% confidence interval [CI]: 1.2–1.8) for the incidence of AD among those with diabetes. Although there exists ongoing discourse regarding the relationship between diabetes and distinct subtypes of dementia, T2DM is conceptualized as a multifaceted metabolic enigma potentially comprising numerous other recognized risk factors for dementia, including atherosclerotic vascular disease, the presence of the apolipoprotein E (APOE)-ε4 allele, and particular attributes of T2DM, such as prolonged duration of the condition, elevated blood glucose levels, and the requirement for insulin therapy. Additional research indicates that these factors may further exacerbate the risk of developing dementia. Lauren C et al. have also conducted investigations concerning the association of diabetes in middle age with subsequent dementia risk in later life.[26]

Conversely, the Honolulu-Asia Aging Study revealed a relative risk of 1.8 for AD among older adults diagnosed with diabetes, including those who also carry the APOE-ε4 allele .A multitude of studies have indicated that the interplay between diabetes and the APOE-ε4 allele significantly enhances the risk of dementia.[13] The investigation examined the heightened risk of mild cognitive impairment and dementia in women who did not have T2DM, but it was observed that each 1% increase in glycosylated haemoglobin (HbA1c; a biomarker for glycaemic control) was associated with an augmented risk of this condition. A further study conducted in Sweden involving 1,301 elderly community residents aged 75 and older did not find a statistically significant correlation between diabetes and AD. Conversely, individuals with diabetes who underwent insulin therapy as a consequence of their condition demonstrated a strong association with diabetic vascular dementia.

This has been further validated by Meta analyses of these patterns. One particular study reported a relative risk of 1.6 (95% CI: 1.Among people with T2DM, AD was found to be 4–1.7) and a whopping 2.3 (95% CI: 2.0–2.7) for vascular dementia by others (10). Taken together, these outcomes suggest that while T2DM may be associated with a greater risk for both AD and vascular dementia, the relationship is most often stronger for vascular dementia. These associations are heavily modified by ethnic and APOE-ε4 status, as well as diabetes duration, glycaemic control, and insulin treatment.[10]

3.4. Treatment implications for Alzheimer's disease with or without type 2 diabetes

Identifying the sophisticated relationship between insulin resistance and Alzheimer’s disease (AD), pharmaceuticals created for type 2 diabetes mellitus (T2DM) could offer impressive therapeutic effects for AD.[10] The administration of insulin through the nasal route has demonstrated encouraging results in initial studies, offering a swift means to transport insulin to the central nervous system without the peril of hypoglycaemia.[19] In a research project focusing on individuals with cognitive impairments, intranasal insulin significantly enhanced memory, attention, and overall functional performance.[12] Also, a further analysis of

participants afflicted with mild cognitive impairment and Alzheimer's disease disclosed that the application of intranasal insulin positively affected cognitive capabilities, with remarkable differences in brain glucose metabolism identified using PET imaging.[26]

Besides, metformin, a popular choice for T2DM management, has been indicated to show neuroprotective traits. It effectively lowers blood sugar levels, alleviates insulin resistance, and mitigates inflammation. Initial investigations suggest that metformin usage correlates with a diminished risk of cognitive decline, yet further exploration is essential to fully unravel its potential advantages in AD.

4. Metabolic Syndrome

Metabolic syndrome, a phenomenon first unveiled more than forty years ago, comprises a constellation of metabolic irregularities, featuring abdominal obesity, hypertension, dyslipidemia, and disrupted glucose and insulin processing.[10] Inquiries into how metabolic syndrome correlates with Alzheimer's disease (AD) have revealed differing conclusions. A project examining 2,632 older black and white individuals indicated that metabolic syndrome, evaluated per the standards of the National Cholesterol Education Program (NCEP), was related to a greater likelihood of cognitive decline, especially in participants with elevated inflammatory markers.[19] In contrast, a population-based study involving 980 older adults (aged 69–78 years) identified a significant association between metabolic syndrome and AD.[3] Yet, despite these conclusions, additional thorough longitudinal research, like the Honolulu-Asia Aging Study, the Three-City Study, the Italian Longitudinal Aging Study, and a varied senior demographic in the United States, did not affirm this relationship.[13]

The occurrence of metabolic syndrome shifts depending on the demographic group being examined and the diagnostic standards applied, like those defined by the National Cholesterol Education Program Adult Treatment Panel III or the latest criteria suggested by the National Heart, Lung, and Blood Institute (NHLBI) alongside the International Diabetes Federation (IDF).[14] It remains unclear whether one or two specific components of metabolic syndrome contribute to cognitive decline, or if the cumulative effect of these components intensifies the risk.[10] Therefore, it is imperative to examine these components collectively and explore their interactions over time.[13]

4.1. Potential pathways linking insulin resistance and deficiency to T2DM and Alzheimer's disease

The key features of type 2 diabetes mellitus (T2DM) include both insulin resistance and a shortage of insulin, which are now seen as important factors in the emergence of Alzheimer's disease (AD).[8] Evidence points to amyloid-β (Aβ) oligomers interacting with hippocampal neurons, which leads to a lower presence of insulin receptors (IRs) and further compounds insulin resistance in the central nervous system.[20] Lower amounts of insulin, insulin-like growth factor (IGF), and insulin receptors (IRs) have been noted in the neuro pathological processes linked to Alzheimer's disease, highlighting a more complicated connection between insulin resistance and the Alzheimer's disease pathology.[26] Additionally, insulin is vital for managing the transformation of amyloid precursor protein (APP) and the synthesis of Aβ, in which insulin and IGF-1 lessen Aβ build up by enhancing its release and breakdown outside the cell.[12]

In T2DM, an uptick in tumour necrosis factor-alpha (TNF-α) signalling triggers pathways that hinder insulin receptor signalling and foster peripheral insulin resistance.[7] Aβ oligomers likewise interfere with insulin signalling in neurons.[8] Insulin resistance might also obstruct the breakdown of Aβ through insulin-degrading enzymes, thus amplifying Aβ accumulation and its toxic effects. Furthermore, there exists a correlation between insulin resistance and tau hyper phosphorylation, driven by the stimulation of glycogen synthase kinase-3β (GSK-3β), which intensifies neurodegeneration in Alzheimer's disease.[9]

4.2. Treatment implications for Alzheimer's disease in the presence or absence of type 2 diabetes

The interesting relationship between insulin resistance and Alzheimer's disease (AD) indicates that medications developed for type 2 diabetes mellitus (T2DM) may also uncover therapeutic opportunities regarding AD.[1] Intranasal insulin delivery has revealed encouraging results in initial trials, as it swiftly channels insulin to the central nervous system while sidestepping the danger of hypoglycaemia.[13] In a research endeavour focused on individuals with cognitive impairments, intranasal insulin enhanced memory, attention, and overall functional capability. Another investigation involving patients with mild cognitive impairment and AD discovered that intranasal insulin not only bolstered cognitive function but also showcased impacts on brain glucose metabolism, observable through positron emission tomography (PET) imaging.[13]

Furthermore, metformin, an extensively used treatment for T2DM, is believed to exhibit neuroprotective qualities.[14] It effectively lowers blood glucose levels, mitigates insulin resistance, and curtails inflammation.[25] Initial research has indicated that the use of metformin correlates with a diminished risk of cognitive decline, yet further exploration is essential to thoroughly grasp its potential advantages in AD.[9]

4.3. Potential mechanisms of insulin resistance and deficiency linking T2DM with Alzheimer's disease

The phenomena of insulin resistance and deficiency, which are quintessential characteristics of type 2 diabetes mellitus (T2DM), are increasingly recognized for their pivotal role in the etiology of Alzheimer's disease (AD).[1] Empirical investigations have demonstrated that amyloid-β (Aβ)

oligomers bind to hippocampal neurons, thereby initiating the internalization of insulin receptors (IRs) and consequently promoting insulin resistance within the central nervous system.[20] A documented reduction in insulin, insulin-like growth factor (IGF), and IR levels has been observed within the neuro pathological framework of AD, thereby reinforcing the association between insulin resistance and AD. Furthermore, insulin is instrumental in regulating the processing of amyloid precursor protein (APP) and the synthesis of Aβ, as both insulin and IGF-1 attenuate Aβ accumulation by promoting its extracellular release and degradation.

In the landscape of T2DM, heightened tumour necrosis factor-alpha (TNF-α) signalling ignites pathways that undermine insulin receptor signalling, ultimately resulting in peripheral insulin resistance.[7] Aβ oligomers mirror this disruption of insulin signalling within neurons.[8] Insulin resistance may also hinder the breakdown of Aβ through insulin-degrading enzymes, thus amplifying Aβ accumulation and its toxic effects. Furthermore, insulin resistance is linked to tau hyper phosphorylation via the activation of glycogen synthase kinase-3β (GSK-3β), further exacerbating neurodegeneration in AD.[9]

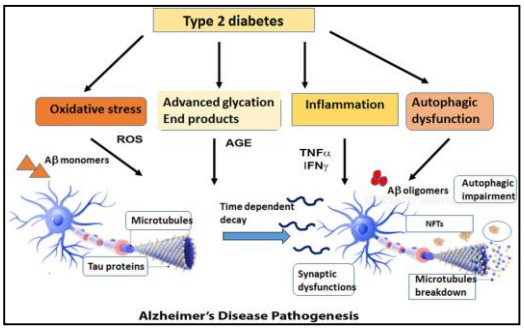

Figure 3: Mechanisms linking T2DM to AD

4.4. Given the link between insulin resistance and Alzheimer's disease (AD)

In light of the recognized connection between insulin that Showing in **Figure 3** resistance and Alzheimer's disease (AD), drugs utilized for type 2 diabetes mellitus (T2DM) could hold significant therapeutic promise for AD. The administration of intranasal insulin has shown substantial promise in initial investigations, as it enables the rapid transportation of insulin to the central nervous system while concurrently reducing the likelihood of hypoglycaemic events.[12] In a cohort of cognitively impaired individuals, the use of intranasal insulin resulted in enhancements in memory, attention, and overall functional status.[18] Furthermore, a trial involving participants with mild cognitive impairment and AD revealed that intranasal insulin not only improved cognitive function but also induced observable effects on brain glucose metabolism as evidenced by positron emission tomography (PET) imaging.

Moreover, metformin, a widely prescribed medication for T2DM, has been postulated to exhibit neuro protective effects. It functions by reducing blood glucose levels, alleviating insulin resistance, and diminishing inflammation.[22] Initial investigations have indicated that the administration of metformin correlates with a decreased risk of cognitive decline; however, further inquiry is warranted to comprehensively elucidate its potential advantages in the context of AD.[14]

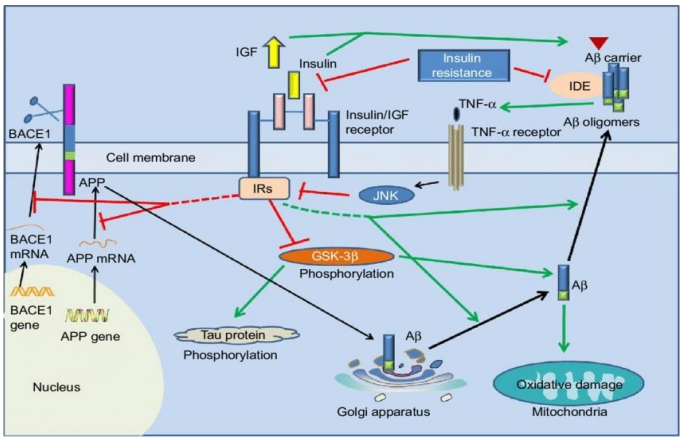

Figure 4: The Relationship between Type 2 diabetes mellitus and Alzheimer's disease (IGF-1: Insulin-like Growth Factor 1, APP: Amyloid Precursor Protein, IDe: Insulin-Degrading Enzyme, JNK: c-Jun N-terminal Kinase, Aβ: Amyloid-β, GSK-3β: Glycogen Synthase Kinase-3β, TNF-α: Tumour Necrosis Factor Alpha, BACe1: β-Site Amyloidogenic Cleavage of Precursor Protein-Cleaving Enzyme 1 and IRs: Insulin Receptor Substrates).

4.5. Linking insulin resistance to Alzheimer's disease

The phenomenon of insulin resistance compromises the catabolic process of amyloid-β (Aβ) mediated by insulin-degrading enzyme (IDe) and disrupts the insulin signalling pathway, which typically functions to suppress the production of Aβ and the phosphorylation of tau protein. Under normative physiological conditions, that relationship between insulin resistance and Alzheimer's is shown in **Figure 4** signalling.[12]

1. Inhibits the β-site amyloidogenic cleavage of the amyloid precursor protein (APP) and its corresponding substrate.[10]

2. Facilitates the standard transport of Aβ from the Golgi apparatus and the trans-Golgi network to the plasma membrane, consequently augmenting extracellular secretion.[17]

3. Reduces the phosphorylation of glycogen synthase kinase-3β (GSK-3β).

The presence of insulin resistance and deficiency results in aberrant insulin signal transduction, culminating in heightened production and accumulation of Aβ within the

cerebral context. Aβ monomers undergo aggregation to form oligomers, which:

1. Elicit an abnormal activation of the TNF-α/c-Jun N-terminal kinase (JNK) pathway, thereby exacerbating further insulin resistance.[13]
2. Diminish Aβ-binding carrier proteins, thereby facilitating additional Aβ accumulation.
3. Induce oxidative injury to mitochondrial structures.

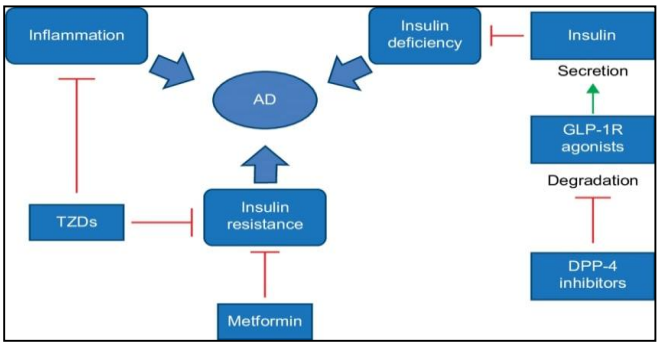

Figure 5: Potential mechanisms of anti-diabetic drugs in alzheimer's treatment, GLP-1R:- Glucagon-like peptide-1 receptor, AD:- Alzheimer's disease, DPP-4:- Dipeptidyl peptidase-4, TZDs:- Thiazolidinediones, Green line represents promotion and Red line represents inhibition.

4.6. Effect of antidiabetic drugs on cognitive impairment and AD

The mechanism of diabetes linked to Alzheimer their significant are compounded in **Figure 5** Even though the detailed mechanisms at play in metformin's pharmacological action are not yet fully clarified, investigations have revealed that diabetes medications, including metformin, could lessen cognitive decline in individuals diagnosed with type 2 diabetes mellitus (T2DM) and Alzheimer's disease (AD).[12]

1. Individuals with a T2DM diagnosis receiving anti-diabetic treatment, like metformin, show a slower progression of cognitive decline compared to their untreated counterparts.
2. A thorough epidemiological inquiry revealed that, over an eight-year timeframe, the administration of metformin and sulfonylureas was connected to a 35% lower risk of dementia development among individuals afflicted by T2DM.[19]

5. Key findings from studies

5.1. Rosiglitazone

Preliminary research has shown that daily administration of 4 mg of rosiglitazone led to improvements in cognitive functions, specifically in memory and selective attention. In a more comprehensive study involving over 500 participants with mild to moderate Alzheimer's disease, those without the APOE-ε4 allele experienced significant cognitive improvements, as measured by the Alzheimer's Disease Assessment Scale (ADAS-cog), after receiving an 8 mg dose of rosiglitazone. However, individuals carrying the APOE-ε4 allele did not show any noticeable cognitive benefits. Despite these initial positive outcomes, larger Phase III clinical trial (NCT00428090) involving patients with mild to moderate Alzheimer's disease found no statistically significant benefits from rosiglitazone treatment. This discrepancy between the early and later findings underscores the complexity of the disease and suggests that the effectiveness of rosiglitazone may depend on genetic factors, such as the presence of the APOE-ε4 allele.

6. Pioglitazone

The effects of pioglitazone on cognitive function in Alzheimer's disease have yielded mixed results. Some studies reported cognitive benefits in patients who had both Type 2 Diabetes Mellitus (T2DM) and Alzheimer's Disease (AD), suggesting that pioglitazone might have a role in improving cognition in these dual-diagnosed individuals. However, other studies failed to observe any significant cognitive enhancement from pioglitazone treatment. One of the main limitations of using thiazolidinediones (TZDs), like pioglitazone and rosiglitazone, for dementia prevention lies in their adverse side effects, which include fluid retention and an increased risk of congestive heart failure. These significant safety concerns have led to restrictions or even prohibitions on the use of rosiglitazone for T2DM management in both the United States and Europe. To enable the potential use of TZDs in Alzheimer's disease therapy, it is crucial to address and mitigate these safety issues. The risk-benefit ratio of TZDs needs to be thoroughly evaluated to determine their suitability for use in Alzheimer's patients, particularly in light of their potential side effects.

7. Summary

Type 2 diabetes mellitus (T2DM) alongside Alzheimer's disease (AD) has typically been thought of as two separate health issues. Nonetheless, comprehensive investigations have revealed epidemiological correlations and analogous pathophysiological mechanisms linking the two conditions. These revelations imply that analogous therapeutic interventions may yield beneficial effects for both disorders.[20] In light of this possibility, it is imperative to commence clinical trials to evaluate the efficacy of anti-diabetic pharmacotherapies in patients diagnosed with AD. The results derived from such studies will be critical not only for the advancement of effective therapeutic strategies for AD but also for deepening our comprehension of the intricate relationship between these ostensibly disparate yet interrelated diseases.[4,5]

8. Discussion

The literature assessed demonstrates a noteworthy relationship in terms of epidemiology and mechanisms linking Type 2 Diabetes Mellitus (T2DM) with Alzheimer's disease (AD). The notion of "Type 3 Diabetes" has emerged as a result of the intersecting pathological characteristics and common mechanisms such as insulin resistance, hyperinsulinemia, and metabolic syndrome that are implicated in both disorders. In light of the significant epidemiological data showing a greater risk of AD among T2DM patients, the clinical investigations into the therapeutic value of anti-diabetic agents concerning AD have shown mixed results. A pivotal observation is that the therapeutic efficacy of anti-diabetic agents is seemingly influenced by genetic determinants, notably the presence of the APOE-ε4 allele. Patients devoid of this allele appear to derive greater benefit from such treatments, thereby suggesting that tailored medical strategies could potentially augment treatment outcomes. The erratic results from clinical investigations underscore the intricate nature of AD pathogenesis and the necessity for more focused research to delineate the specific circumstances under which anti-diabetic therapies may exert their efficacy. The encouraging findings associated with the administration of intranasal insulin and metformin indicate that these pharmacological agents may confer advantageous effects on cognitive performance and cerebral metabolism. Nonetheless, the potential adverse effects and long-term safety profiles of these interventions warrant comprehensive evaluation. Thiazolidinediones (TZDs), despite their anti-inflammatory attributes and initial favourable findings in certain investigations, present considerable risks such as edema and heart failure, thereby constraining their clinical applicability in AD patients. The complicated dynamics between T2DM and AD emphasize the necessity of controlling metabolic risk elements, including obesity, hyperinsulinemia, and metabolic syndrome, to lessen the risk of developing AD. Strategies aimed at enhancing insulin sensitivity and diminishing systemic inflammation may hold promise in postponing or averting the onset of AD in populations identified as at-risk.

9. Conclusion

The reviewed literature underscores a significant epidemiological and mechanistic link between Type 2 Diabetes Mellitus (T2DM) and Alzheimer's Disease (AD), supporting the conceptualization of AD as "Type 3 Diabetes." While anti-diabetic agents offer promising therapeutic avenues, variability in clinical outcomes highlights the need for more robust and targeted research particularly in relation to genetic factors such as the APOE-ε4 allele. Personalized treatment strategies, along with comprehensive management of metabolic risk factors, are crucial for addressing the complex interplay between T2DM and AD. Future studies should focus on elucidating the precise molecular pathways by which T2DM contributes to AD progression and optimizing the clinical application of anti-diabetic therapies to enhance both efficacy and safety in the context of neurodegenerative disease.

10. Source of Funding

None.

11. Conflict of Interest

None.

12. Reference

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