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Review Article

The Role of Type 3 Diabetes in Alzheimer's Disease: A Review of Current Evidence

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Abstract: **Background**: Type 2 Diabetes Mellitus (T2DM) and Alzheimer's Disease (AD) are increasingly linked through shared pathophysiological mechanisms, giving rise to the concept of Type 3 Diabetes Mellitus (T3DM). Brain insulin resistance, oxidative stress, and neuroinflammation are central to both conditions, contributing to cognitive decline and AD progression. **Aim:** This review aims to explore this emerging relationship and its implications for prevention and management. **Methods**: Using an integrative review, 21 studies were systematically analyzed. The review focused on identifying demographic, genetic, and lifestyle factors contributing to T2DM and AD and examined shared molecular pathways such as insulin dysregulation and amyloid-beta accumulation. **Results**: The findings reveal that T3DM shares key features with T2DM and AD, including insulin resistance and chronic inflammation. Lifestyle interventions, such as diet and exercise, alongside routine cognitive and metabolic screenings, are critical in mitigating progression. **Conclusions**: Further research into diagnostic biomarkers and targeted therapies is essential to manage T3DM and its impact on AD. The role of nursing professionals in early detection, education, and holistic management is emphasized as vital in addressing this dual disease burden. This review offers actionable insights into integrated strategies for addressing these interconnected conditions.

Keywords: Type 3 Diabetes Mellitus, Alzheimer's Disease, Brain Insulin Resistance, Neurodegeneration, Integrated Care Strategies

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1. Highlights

What is already known about this topic:

- Diabetes Mellitus and Alzheimer's Disease (AD) are interconnected through shared pathological mechanisms, including insulin resistance and chronic inflammation.
- Dysregulation of the brain's insulin signaling pathway contributes to cognitive impairments observed in both AD and Type 2 Diabetes Mellitus (T2DM).
- The molecular crosstalk between T2DM and AD is increasingly evident, with emerging studies identifying overlapping pathophysiological and pathogenic pathways.

What this paper adds:

- Early detection of cognitive decline in Type 2 Diabetes Mellitus (T2DM) through routine insulin resistance screenings and cognitive assessments can significantly delay the onset of Alzheimer's Disease (AD).

- Integrating lifestyle modifications, such as anti-inflammatory diets and structured physical activity programs, is crucial for managing the dual burden of T3DM and AD.
- Future research should prioritize developing personalized therapeutic interventions targeting shared pathways like insulin signaling and neuroinflammation to improve outcomes in at-risk populations.

2. Introduction

As the global population continues to age, the dual burden of metabolic and neurodegenerative diseases has become increasingly evident. Diabetes Mellitus, particularly Type 2 Diabetes Mellitus (T2DM), is now recognized not only for its systemic impact but also for its implications in cognitive decline and Alzheimer's Disease (AD). Research indicates that individuals with impaired glucose tolerance or diabetes are significantly more prone to developing AD compared to their healthy counterparts [1]. T2DM is characterized by persistent insulin resistance, which begins in a prediabetic state when the pancreas is unable to efficiently regulate glucose levels [2]. This resistance extends to insulin signaling in the brain, disrupting vital metabolic and neuronal processes and linking diabetes to the pathophysiology of AD [3–7]. Notably, studies highlight that impaired insulin signaling impacts glucose metabolism and exacerbates amyloid beta aggregation, a hallmark of Alzheimer's pathology [9,10]. This growing body of evidence underscores the urgent need to explore the complex interplay between metabolic dysfunction and neurodegenerative processes.

The metabolic and pathological overlap between T2DM and AD has led to the conceptualization of AD as "Type 3 Diabetes" [8]. Key mechanisms contributing to this overlap include oxidative stress, mitochondrial dysfunction, and abnormal protein processing, such as the aggregation of hyperphosphorylated tau proteins and amyloid-beta plaques [3,9,10]. Chronic inflammation, mediated by TLR4, exacerbates insulin resistance in both peripheral tissues and the brain, further fueling AD-related neurodegeneration [11,8]. Additionally, mitochondrial dysfunction caused by oxidative damage has been implicated in the early stages of neurodegeneration, suggesting that interventions aimed at preserving mitochondrial health could provide neuroprotective benefits [12,13]. Genetic factors, environmental exposures, and lifestyle habits also influence these processes, emphasizing the multifaceted nature of this disease intersection [6,12]. Given the central role of insulin resistance in these conditions, targeting the insulin signaling pathway has emerged as a promising therapeutic approach [3,7].

Emerging research has explored potential therapeutic interventions that target these shared pathways. Antidiabetic medications such as GLP-1 receptor agonists and metformin show promise in mitigating neuroinflammation, improving insulin sensitivity, and enhancing cognitive function in experimental models [3,7,13]. Notably, metformin, a widely used insulin-sensitizing drug, has shown potential benefits in improving cognitive performance and reducing AD-related biomarkers, although findings remain inconclusive [3]. Dietary and lifestyle modifications, such as incorporating antioxidant-rich foods and engaging in regular physical activity, may also reduce oxidative stress and improve metabolic health, potentially delaying AD onset [14,15]. Studies have demonstrated that regular exercise enhances insulin sensitivity and promotes neurogenesis, suggesting a synergistic effect when combined with dietary interventions [14]. Biomarkers, including tau proteins and advanced glycation end products (AGEs), have shown diagnostic potential, paving the way for early detection and intervention [2,6,7]. Despite these advances, there remains a pressing need for further research to establish the safety and efficacy of these strategies in clinical settings [3]. Innovative treatment approaches, such as intranasal insulin and fibroblast growth factor 21 (FGF21), are also being explored for their ability to bypass systemic barriers and directly target brain insulin resistance [15,16].

This study contributes to the growing body of evidence that identifies "Type 3 Diabetes" as a critical link between metabolic dysfunction and Alzheimer's Disease. By reviewing the existing literature, this research aims to address three key questions: (1) What is the current evidence supporting the relationship between Type 3 Diabetes and Alzheimer's Disease? (2) Why has Type 3 Diabetes not been formally recognized as a clinical diagnosis despite its significance? (3) What are the most compelling mechanistic links between Type 3 Diabetes and Alzheimer's Disease based on current understanding? This study provides a comprehensive analysis of the interconnected pathophysiological mechanisms, offering insights that may inform the development of diagnostic criteria and targeted therapies. The outcome of this research underscores the importance of integrating metabolic management into AD care regimens, potentially transforming clinical practice by emphasizing preventative strategies and personalized treatment approaches for at-risk populations. By bridging gaps in understanding and addressing the overlap of these two conditions, this research aims to contribute to more effective prevention, early detection, and treatment strategies, ultimately improving patient outcomes and quality of life.

3. Materials and Methods

3.1. Design

This study utilized an integrative review approach as proposed by Whittemore and Knafl [22]. The process involved five key steps: identifying the problem, conducting a systematic literature search, evaluating the quality and relevance of selected studies, analyzing the data to identify patterns, and synthesizing the findings. The integrative review was chosen because of its flexibility in evaluating diverse primary research using varying techniques and methodologies. As the sole method allowing the synthesis of multiple approaches, this review strategy offers significant potential to influence evidence-based healthcare practices. Although strategies for data extraction and collection within this method are well-developed, synthesis, analysis, and conclusion-drawing techniques remain inadequately standardized, presenting opportunities for further refinement in methodology [22].

3.2. Search Strategy

A comprehensive systematic search was conducted across multiple academic databases, including PubMed, Google Scholar, EBSCO/CINAHL, and ScienceDirect, to identify studies exploring the association between Type 3 Diabetes Mellitus (T3DM) and Alzheimer's Disease (AD). The search, carried out between May and July 2024, utilized a combination of relevant keywords and Boolean operators, such as "Type 3 Diabetes Mellitus," "T3DM," "Alzheimer's Disease," "AD," "Insulin Resistance," "Brain Insulin Resistance," "Cognitive Impairment," "Shared Mechanisms," and "Dysregulated Insulin Signaling." Boolean operators were applied to combine terms effectively (e.g., ("T3DM" OR "Type 3 Diabetes Mellitus") AND ("Alzheimer's Disease" OR "AD") AND ("Insulin Resistance" OR "Cognitive Impairment")). The search was limited to peer-reviewed articles published in English within the last 10 years.

The search identified a total of n=972 records, including n=937 from databases and n=35 from manual searches of references and other sources. After removing n=211 duplicates, n=761 unique records remained for screening. Of these, n=489 were excluded for being outside the 10-year publication window, leaving n=272 records for title and abstract screening. During this step, n=112 records were excluded for irrelevance or insufficient focus on the T3DM-AD relationship.

A total of n=160 full-text articles were retrieved and assessed for eligibility. Of these, n=138 were excluded for the following reasons: n=29 were in non-English languages, n=36 were not peer-reviewed, n=16 were editorials, letters, or commentaries, n=4 focused on

AD with other neurological deficits, n=12 addressed diabetes with severe comorbidities affecting cognition or glucose regulation, and n=41 were excluded for other reasons, such as insufficient data on the T3DM-AD relationship. Ultimately, n=21 studies met all inclusion criteria and were included in the qualitative synthesis.

This systematic process followed the PRISMA methodology to ensure rigorous identification, screening, eligibility assessment, and inclusion of relevant studies. The final selection provided robust insights into the shared pathophysiological mechanisms linking T3DM and AD, particularly the pivotal role of dysregulated insulin signaling in neurodegeneration.

These selected studies provided robust evidence of dysregulated insulin signaling's pivotal role in the pathogenesis of AD, a characteristic shared with Type 2 Diabetes [1,3,4,6].

Figure 1 illustrates the PRISMA Flow Diagram for the study, summarizing the process of identifying, screening, and selecting relevant literature.

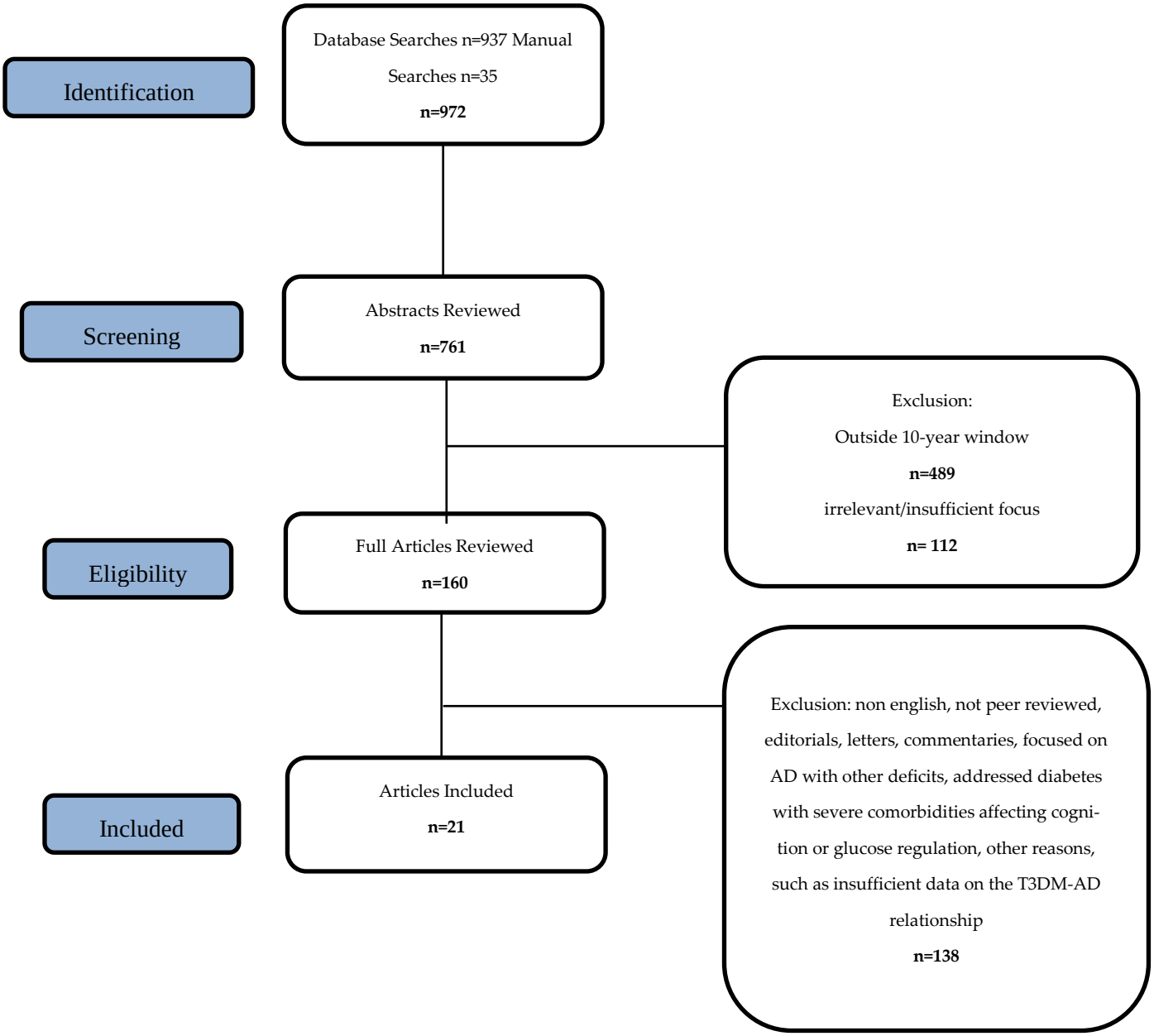

Figure 1. PRISMA flow diagram

3.3. Eligibility Criteria

The inclusion and exclusion criteria, summarized in Table 1, were designed to refine the literature to studies directly examining the association between diabetes and Alzheimer's Disease.

Table 1. Eligibility Criteria

Criteria	Inclusion	Exclusion
Language	All articles published in English.	Non-English articles and publications.
Publication Date	Articles published within the last 10 years (2014–2024).	Articles published more than 10 years ago.
Peer Review	Articles and publications that are peer-reviewed.	Articles and publications that are not peer-reviewed, news articles, editorials, letters, and commentaries.
Focus on Diabetes	Patients diagnosed with Diabetes.	Patients not diagnosed with Diabetes.
Focus on Alzheimer's Disease	Patients diagnosed with Alzheimer's Disease (AD).	Patients not diagnosed with Alzheimer's Disease (AD).
Age Range	Patients in age ranges typically associated with the onset and progression of T2DM and AD (middle-aged to elderly).	Not applicable or not meeting the age-related criteria for T2DM and AD.
Study Focus	Articles investigating the concept of "Type 3 Diabetes" in relation to AD.	Articles addressing AD with other neurological/psychiatric conditions (e.g., schizophrenia, bipolar, TBI).
Comorbidities	N/A	Patients with severe comorbidities (e.g., ESRD, CHF, active malignancies).
Medication Use	N/A	Patients using medications affecting cognition or glucose regulation (e.g., antidepressants, glucocorticoids).
General Criteria	Articles that meet all inclusion criteria.	Articles that do not meet the inclusion criteria.

3.4. Data Evaluation and Quality Appraisal

The selected studies were meticulously evaluated using a matrix table based on Sparbel and Anderson's tool [23]. Table 2 was categorized each article by author, year, study design, methodology, aims and objectives, level of evidence, and significant findings related to T3DM and AD (Table 4). Researchers independently appraised the methodological quality of all selected articles, ensuring adherence to the inclusion and exclusion criteria. Disagreements in the assessment were resolved through consensus in multiple collaborative meetings. To further assess study quality, the Levels of Evidence framework proposed by Melnyk [24] was applied. Three experts in systematic review were consulted for peer-review.

The final set of articles provided comprehensive insights into the intersection of insulin resistance, glucose dysregulation, and AD pathology, reinforcing the hypothesis that AD, characterized as T3DM, shares critical mechanistic pathways with T2DM [8,13]. These insights support the broader aim of advancing diagnostic criteria and identifying targeted therapeutic interventions for T3DM and AD.

Table 2. Characteristics of Included Studies

Year & Author, Country	Design	Aim	Findings	Level of Evi

				den ce
Aljanabi et al. (2020, USA) [2]	Review Paper	1. To investigate the association between insulin resistance and cognitive impairment, with a focus on Alzheimer's disease (AD). 2. Identify the most effective therapy regimen for reducing AD development in people with impaired glucose metabolism.	A link between Alzheimer's disease (AD) and impaired insulin signaling, where insulin resistance leads to the hyperphosphorylation of tau proteins, contributing to neurofibrillary tangles, oxidative stress, and cognitive decline. Insulin influences cognition in a bidirectional way: peripheral insulin increases dementia risk, while controlled intranasal or intravenous insulin shows potential for improving cognitive function. Therapeutic options like Metformin and GLP-1 agonists have shown mixed results, with some studies suggesting neuroprotective benefits. Intranasal insulin holds promise, but further research is needed to confirm the effectiveness and safety of these treatments in preventing or slowing AD progression.	V
Baglietto-Vargas et al. (2016, USA) [13]	Review Paper	To tackle new results in animal model and clinical research including the use of anti-diabetic drugs as promising therapies for AD, as well as highlight the participation of numerous novel pathogenic molecular processes caused by DM that contribute to AD pathogenesis.	A strong link between diabetes and Alzheimer's disease. In people with diabetes, the brain has trouble using insulin, which may lead to memory loss and cognitive decline. High blood sugar can make this worse by increasing harmful proteins in the brain that cause damage. Diabetes also causes inflammation and stress on brain cells, making them weaker over time. Some diabetes medications, like insulin taken through the nose, have shown promise in improving memory and brain function. However, other treatments, like Metformin, may need to be used carefully, as they could increase the risk of Alzheimer's in certain cases.	V
Burillo et al. (2021, Spain) [1]	Review Paper	To examine the primary molecular pathways implicated in the link between type 2 diabetes and neurodegeneration, specifically Alzheimer's disease.	This research highlights the connection between type 2 diabetes (T2DM) and Alzheimer's disease (AD), focusing on shared mechanisms like insulin resistance, inflammation, and oxidative stress. Impaired insulin signaling disrupts glucose metabolism and increases the risk of brain damage, including amyloid-beta (Aβ) plaque buildup and tau protein dysfunction, both key contributors to AD. Endoplasmic reticulum (ER) stress and autophagy dysfunction also play a role, leading to cell death and further cognitive decline. Chronic inflammation and the buildup of advanced glycation end-products (AGEs) worsen insulin resistance and contribute to neurodegeneration. Treatments targeting these pathways, such as autophagy enhancers and insulin therapies, show potential, but more research is needed to fully understand their therapeutic effects on AD progression in T2DM patients.	V
Čater & Hölter (2022, Germany) [3]	Review Paper	To provide an overview of the existing animal models that are used to study the overlap between diabetes and Alzheimer's disease, and to discuss the potential mechanisms linking the two conditions.	Recent research has shed light on the complex connection between diabetes and Alzheimer's disease, revealing that both conditions share key physiological pathways, including impaired insulin signaling, disrupted glucose transport, and cholesterol dysfunction, which primarily impact brain regions like the hypothalamus and hippocampus. These shared mechanisms lead to overlapping symptoms such as metabolic dysregulation, neurodegeneration, and cognitive decline. Core pathological processes include inflammation, oxidative stress, mitochondrial dysfunction, and amyloid plaque formation. While animal models, especially rodents, have been essential in advancing research, their physiological differences from humans pose challenges for translating findings into human treatments. Transgenic models, which more accurately reflect human	V

			disease, are helping researchers better understand these diseases and test potential therapies. Further research is needed to refine these models and pinpoint precise therapeutic targets for both diabetes and Alzheimer's.	
Chatterjee & Mudher (2018, United Kingdom) [4]	Review Paper	To explore how insulin resistance in T2DM worsens Aβ and tau diseases and identify similar pathological features.	Insulin resistance (IR) in Type 2 diabetes mellitus (T2DM) worsens Alzheimer's disease (AD) pathology by impairing glucose uptake in the brain and disrupting key signaling pathways, such as PI3K/AKT and MAPK. This leads to increased GSK-3β activity, which results in the hyperphosphorylation of tau proteins, forming neurofibrillary tangles (NFTs) that contribute to synaptic dysfunction and neuronal death. Additionally, insulin resistance affects the brain's ability to manage amyloid-beta (Aβ) proteins, which accumulate as plaques in AD. Studies using animal models have shown that both insulin resistance and hyperglycemia accelerate these neurodegenerative processes, linking T2DM with increased tau phosphorylation and impaired amyloid-beta clearance. Impaired lipid metabolism further exacerbates these effects, highlighting the critical role of metabolic dysfunction in the progression of AD.	V
Fiore et al. (2019, Italy) [9]	Review Paper	To demonstrate the strong correlation between AD and DM.	Alzheimer's disease (AD) risk is heightened by hyperinsulinemia and insulin resistance, which promote the buildup of amyloid plaques and increased tau protein synthesis, leading to neurodegeneration. Impaired insulin signaling contributes to decreased brain glucose metabolism, resembling an AD-like pattern. Hyperinsulinemia also accelerates the formation of neurofibrillary tangles and senile plaques, further exacerbating insulin resistance. Additionally, both T2DM and AD are associated with vascular damage, although the precise mechanism connecting vasculopathy in T2DM to AD remains unclear. Effective diabetes management—through exercise, a low-fat diet, and medication for glycemic control—can help prevent hyperglycemia and hypoglycemia, potentially reducing the risk of cognitive decline and AD.	V
Huang et al. (2017, China) [7]	Review Paper	To draw awareness to the connection between diabetes mellitus and Alzheimer's disease, as well as the function that TLR4 activation plays in insulin resistance.	Toll-like receptor 4 (TLR4) plays a crucial role in both diabetes mellitus (DM) and Alzheimer's disease (AD). TLR4 is strongly linked to insulin resistance, influenced by gut microbiota changes and free fatty acids from adipose tissue, contributing to persistent insulin resistance. Chronic TLR4 activation leads to inflammation, impacting both the body's internal environment and the brain, causing complications such as diabetic retinopathy, neuropathy, and nephropathy. In Alzheimer's disease, TLR4-mediated neuroinflammation is present at all stages, contributing to amyloid-beta (Aβ) buildup and brain damage. The activation of TLR4 is a key factor connecting DM and AD, as it contributes to both insulin resistance and neuroinflammation, potentially linking the progression of these two diseases.	V
Kimura (2016, Japan) [12]	Review Paper	To summarize histological evidence indicating diabetes mellitus (DM) causes Alzheimer's disease (AD) pathology in animal models and examine the notion that	Type II diabetes significantly increases the risk of developing Alzheimer's disease (AD), primarily due to abnormal insulin signaling. Both type I and type II diabetes worsen AD pathology, as shown in animal models, where disrupted insulin signaling accelerates the formation of amyloid-beta (Aβ) plaques and tau neurofibrillary tangles (NFTs). Diabetes exacerbates Aβ pathology by increasing its production and decreasing its clearance, due to the	V

		abnormal insulin signaling is a critical factor in AD pathology.	heightened activity of enzymes responsible for Aβ accumulation. It also aggravates tau pathology by overactivating GSK3β, an enzyme that promotes tau phosphorylation. Normally, insulin signaling inhibits GSK3β, but insulin resistance in diabetes leads to its abnormal activation, resulting in more tau tangles and neuronal damage. Studies have shown that insulin treatment improves AD pathology in animal models, highlighting the link between diabetes and AD progression.	
Kubis-Kubiak et al. (2020, Poland) [5]	Review Paper	The main goal is to investigate and identify potential biomarkers for Alzheimer's disease that could aid in early diagnosis and track disease progression, especially in the context of diabetes mellitus.	Alzheimer's disease (AD) and type 2 diabetes mellitus (T2DM) share several pathophysiological characteristics, such as insulin resistance, disrupted glucose metabolism, and the buildup of toxic proteins like amyloid-beta (Aβ) and tau. Impaired insulin signaling in the brain is central to both conditions, affecting memory, cognitive function, and neuronal survival. Abnormal glucose metabolism not only contributes to T2DM but also exacerbates AD by increasing the production and accumulation of amyloid plaques and promoting tau hyperphosphorylation. Metabolic disturbances are key contributors to the progression of AD, emphasizing the importance of biomarkers related to glucose and insulin metabolism for early diagnosis. Biomarkers like Aβ42, total tau, and phosphorylated tau, though promising, still have limitations in preclinical detection, underscoring the need for more reliable diagnostic tools. The use of diabetic medications, such as insulin therapy, shows potential in improving cognitive function in AD patients, with some studies indicating that intranasal insulin may slow cognitive decline. However, the effectiveness of such treatments remains a topic of debate, highlighting the need for further research.	V
Lynn et al. (2022, USA) [18]	Review Paper	To highlight shared mechanisms between diabetes mellitus (DM) and Alzheimer's disease	Type 2 Diabetes Mellitus (T2DM) increases the risk of developing Alzheimer's disease (AD) through shared mechanisms like insulin signaling failure, inflammation, oxidative stress, and mitochondrial dysfunction. Insulin resistance in T2DM worsens neurodegeneration and cognitive decline, linking T2DM to AD, often referred to as "type 3 diabetes." Oxidative stress further damages cells by mutating mitochondrial DNA and impairing mitophagy, leading to insulin dysfunction and neurodegeneration. Potential therapies include antidiabetic medications like Metformin and GLP-1 receptor agonists, which improve insulin signaling and reduce inflammation, and intranasal insulin, which targets the brain directly. Dietary interventions and lifestyle changes that focus on antioxidant and anti-inflammatory approaches also show promise in managing both conditions.	
Madhusudhanan et al. (2020, India) [10]	Review Paper	- to examine the pathophysiology of AD from the standpoints of the more recent T2DM-dependent pathways that are backed by data from T2DM patients, as well as the traditional protein accumulation theory. - to examine the various mechanisms by which hyperglycemia exacerbates	The understanding of Alzheimer's disease (AD) is expanding beyond its traditional view as a neurodegenerative disorder, with growing research linking it to Type 2 Diabetes Mellitus (T2DM). Studies suggest that insulin resistance, common in T2DM, may contribute to cognitive decline and memory issues, supporting the theory that diabetic individuals are at higher risk of developing AD. Animal models have shown that diet-induced insulin resistance worsens AD pathology. Amylin, a neuropeptide from the pancreas, is also implicated in AD progression, with its accumulation exacerbating symptoms in T2DM patients. Elevated tau hyperphosphorylation, a hallmark of AD, is linked to insulin	V

		neurodegeneration, using AD as a case study. - to discuss some of the most recent improvements in the understanding of how metabolic problems cause neurodegeneration and how this has led to advancements in the treatment of AD.	signaling disruptions in the brain. Inflammation, particularly through toll-like receptor 4 (TLR4) activation, plays a role in both diseases, contributing to insulin resistance and neuroinflammation. Therapeutic options like Metformin, Thiazolidinediones (TZDs), and amylin analogues show potential in improving cognitive function for both conditions, while fibroblast growth factor 21 (FGF21) has demonstrated similar benefits in preclinical studies.	
Michailidis et al. (2022, Greece) [8]	Review Paper	To discuss the shared pathophysiological connections between AD and T2DM	Alzheimer's disease (AD) and type 2 diabetes mellitus (T2DM) share several common pathological processes. Insulin resistance, a hallmark of T2DM, impairs glucose regulation and is linked to hyperglycemia, while also contributing to neuroinflammation and disease progression in AD. Neuroinflammation, driven by insulin and IGF-1 resistance, worsens both conditions. Oxidative stress, caused by an imbalance in reactive oxygen species (ROS), leads to neuronal damage, amyloid plaques, tau tangles in AD, and impaired insulin signaling in T2DM. Advanced Glycosylation End Products (AGEs) further contribute to amyloid aggregation and neurotoxicity in AD. Mitochondrial dysfunction exacerbates oxidative stress and insulin resistance, leading to neurodegeneration. Metabolic syndrome, characterized by high blood pressure, high blood sugar, and abnormal cholesterol, increases the risk of both AD and T2DM by promoting these shared pathological mechanisms.	V
Nguyen et al. (2020a, Vietnam) [11]	Review Paper	To demonstrate the basic mechanisms of insulin resistance mediates dysregulation of bioenergetics and its progress to Alzheimer's Disease (AD).	The findings highlight a strong connection between insulin resistance and cognitive decline, indicating that insulin-sensitizing drugs could potentially alleviate Alzheimer's disease (AD) symptoms. Insulin signaling in the brain is crucial for maintaining glucose metabolism, and insulin resistance is a common feature in both diabetes and AD. Therapeutic approaches aimed at improving insulin sensitivity, such as the use of anti-diabetic drugs, lifestyle changes, and nutraceuticals, show promise in slowing AD progression by enhancing glucose metabolism, reducing amyloid-beta buildup, and mitigating neuroinflammation. Research on rodents also suggests that vegetables and fruits rich in bioactive components like carotenoids, antioxidants, polyphenols, and flavonoids may protect against cognitive decline and brain damage caused by oxidative stress. Curcumin and other nutraceuticals offer further potential as therapeutic options for enhancing cognitive function in AD.	V
Nguyen et al. (2020b, Vietnam) [27]	Review Paper	- to illustrates how the basic processes of insulin resistance promote dysregulation of bioenergetics and advance to AD. - to establish a viable and promising zone for improved hypometabolism and changed insulin signalling, which could lead to the development of therapeutics for AD.	To fully understand insulin's role in both healthy and diseased brains, more data on the relationship between Alzheimer's disease (AD) severity and age-matched controls is needed. Lower central nervous system (CNS) insulin levels are linked to increased amyloid-beta (Aβ) accumulation and reduced clearance, worsening AD pathology. Several mouse models of AD exhibit impaired insulin signaling, but more research is required to understand how AD affects the diabetes phenotype. Insulin receptors are most abundant in the olfactory bulb, cerebral cortex, and hippocampus, and insulin plays a vital role in cell survival by influencing apoptotic pathways. Insulin resistance is a shared feature of diabetes, obesity, and AD, with excess insulin leading to disrupted neuronal processes and	V

			cognitive decline. Hypometabolism in AD is driven by reduced glucose availability, affecting synapse function and contributing to neurodegeneration. Therapeutic approaches that target insulin resistance and aim to improve energy metabolism are crucial, as no specific treatments have yet proven effective in preventing cognitive decline or AD progression.	
Nisar et al. (2020, Pakistan) [19]	Literature review	Explore the genetic link between the two illnesses (DM and AD).	The pathophysiology of both diabetes mellitus (T2DM) and Alzheimer's disease (AD) involves a combination of genetic and environmental factors. Insulin resistance is a key mechanism that impairs brain function, linking T2DM directly to cognitive decline and AD progression. Uncontrolled inflammatory stress in neurons promotes the buildup of amyloid and tau proteins, which worsen AD. Genetic mutations in the amyloid precursor protein (APP) contribute to amyloid-beta aggregation, with APP present in both brain and pancreatic tissues, suggesting shared pathways between AD and T2DM. Research has identified around 759 genes linked to both conditions, with pathways like CREBBP, MAPK, and PI3K-AKT playing crucial roles in insulin signaling and memory processes. Both genetic predispositions and environmental factors, such as diet and lifestyle, accelerate brain atrophy, making these shared mechanisms critical to understanding and treating both diseases.	V
Rorbach-Dolata & Piwowar (2019, Poland) [20]	Review Paper	To present the most recent and significant data related to the phenomena of Type 3 Diabetes. From a pharmacological standpoint, it also addresses the possible gaps in diabetes prevention and diagnosis that could lead to neurometabolic problems.	The relationship between Alzheimer's disease (AD) and diabetes, particularly Type 2 diabetes mellitus (T2DM), is increasingly understood through mechanisms such as poor insulin signaling, brain insulin resistance, and hyperglycemia-induced excitotoxicity. Glutamate, an excitatory neurotransmitter, plays a significant role in neurodegeneration through overstimulation, leading to neuronal death. Studies in diabetic mouse models have shown that hyperglycemia and insulin abnormalities increase tau protein phosphorylation and cleavage, contributing to AD pathology. Amyloid-beta (Aβ) deposits, common in both AD and T2DM, along with advanced glycation end products (AGEs), further aggravate these conditions. Impaired brain glucose metabolism, particularly in individuals carrying the APOE4 gene mutation, is considered a valuable marker for AD, often presenting years before cognitive impairment. Insulin resistance in the brain disrupts synaptic plasticity and contributes to neurodegeneration. Amylin, an amyloid polypeptide, is also implicated, with higher levels observed in insulin-dependent T2DM patients. Experimental treatments for Type 3 diabetes (T3D), such as the drug T3D-959, are showing promise. This PPAR agonist improves insulin signaling, reduces neuroinflammation, and normalizes neuropathology in clinical trials, highlighting the potential of treating AD as a neurometabolic disorder linked to hyperglycemia and insulin signaling dysfunction.	V

Salas & De Strooper (2019, Belgium) [17]	Review Paper	Critically examine and understand the connection between Alzheimer's disease (AD) and metabolic disorders such as type 2 diabetes mellitus (T2DM), and review significant clinical and preclinical findings to determine how these metabolic conditions may elevate the risk of developing AD, particularly in the aging population.	Epidemiological studies indicate a link between diabetes, particularly Type 2 diabetes mellitus (T2DM), and an increased risk of developing dementia, though the exact metabolic alterations responsible remain unclear. Cognitive impairments are more common in individuals with diabetes, with deficits noted in areas such as attention and cognitive flexibility. Population-based studies, like the Rotterdam study, suggest a nearly two-fold increase in dementia risk for T2DM patients, particularly for Alzheimer's and vascular dementia. T2DM is associated with decreased brain glucose metabolism, observed through reduced [18F]-fluorodeoxyglucose (FDG) uptake, which correlates with a higher risk of Alzheimer's disease. Structural brain abnormalities, including hippocampal volume loss and white matter dysfunction, are linked to cognitive decline in T2DM patients. Impaired insulin signaling, a hallmark of T2DM, contributes to amyloid buildup and tau hyperphosphorylation, both key processes in Alzheimer's pathology. Moreover, T2DM-related oxidative stress, mitochondrial dysfunction, and chronic neuroinflammation further exacerbate Alzheimer's disease progression. Obesity, a common comorbidity with T2DM, adds to this risk by promoting systemic inflammation, which may lead to brain inflammation and increased dementia susceptibility.	V
Shieh et al. (2020, Taiwan) [6]	Review Paper	To be able to obtain existing research studies on key proteins involved or link between neurodegenerative conditions and Diabetes Mellitus.	Evidence showed that lifestyle choices are becoming significant contributors for accelerating onset of AD and Diabetes Mellitus (DM) is a major risk for neurodegeneration. Statistics: 1. 29% of Type II DM patients will eventually suffer severe decline in cognition and degeneration. 2. Vascular degeneration secondary to DM disrupts blood flow to the brain resulting in neuronal inflammation and further degeneration. Mitochondrial dysfunction has a significant impact in accelerating dementia onset especially AD.	V
Schilling (2016, USA) [16]	Review Paper	Research has shown a significant correlation between diabetes and Alzheimer's disease, but the exact nature of this relationship is still unknown. To address this, this study will evaluate the data for each pathway and determine any important therapeutic implications.	The findings suggest that maintaining healthy insulin-degrading enzyme (IDE) levels and avoiding excessive insulin may help prevent or reduce the effects of Alzheimer's disease (AD). Insufficient IDE activity, linked to severe insulin insufficiency, can contribute to amyloid-beta buildup, a hallmark of AD. Reduced IDE synthesis is also associated with the Apolipoprotein E4 (ApoE4) allele, a significant genetic risk factor for AD. Excess insulin or amylin can inhibit the breakdown of amyloid-beta, as IDE's ability to degrade amyloid-beta diminishes at higher insulin levels, a common issue in early-stage type 2 diabetes. The use of pramlintide, an amylin analogue, has shown promise in alleviating memory problems in AD mouse models. Further research is needed to confirm these findings and their implications for AD treatment strategies.	V

Sun et al. (2020, China) [14]	Review Paper	To further discuss about the metabolic connections between AD and DM should shed light on the origins and dynamics of both conditions and, at the very least, partially explain their etiology.	Impaired insulin signaling in diabetes mellitus is linked to several metabolic problems, including oxidative stress, mitochondrial dysfunction, and disruptions in glucose and lipid metabolism. These factors contribute to protein alterations that may increase the risk of Alzheimer's disease (AD) in individuals with diabetes. Evidence suggests that amyloid-beta (Aβ) pathology disrupts insulin signaling, making it a potential target for AD treatment. Individuals with diabetes, due to abnormal glucose levels and metabolism, are more susceptible to cognitive dysfunction and AD. Mitochondrial dysfunction, characterized by imbalances in oxidation and antioxidant capacity, further exacerbates oxidative stress and impairs brain energy supply, leading to memory impairments. Lipid metabolism also plays a crucial role in the development of both diabetes and AD, suggesting that therapeutic approaches focusing on glycemic control and improved glucose metabolism may help reduce the risk of AD in diabetic individuals.	V
Vieira et al. (2018, Brazil) [15]	Review Paper	To review literatures on few key pathways that both DM and AD have in common and discuss about how finding these pathways could result in new treatment options for AD.	Recent research has established a clear connection between insulin resistance in Alzheimer's disease (AD) neurons and memory deficits, highlighting the role of impaired insulin signaling in AD pathology. Defective insulin signaling has been linked to the accumulation of amyloid-beta (Aβ) peptides, which disrupt neuronal function. Post-mortem studies of AD brains confirm these signaling defects, while animal models show that boosting insulin signaling protects neurons and synapses from Aβ toxicity. Anti-diabetic drugs, particularly Glucagon-like peptide-1 (GLP-1) analogues, have shown promise in improving cognitive function and neurogenesis, suggesting they could be effective in AD treatment. Insulin resistance in AD appears to share similar mechanisms with diabetes, involving chronic inflammation driven by proinflammatory cytokines like TNF-**α**. Emerging therapeutic targets include the mTOR pathway and protein tyrosine phosphatase 1B (PTP1B), both of which are crucial in regulating insulin signaling. Inhibiting PTP1B offers potential for treating both AD and diabetes, indicating that future therapies may focus on shared pathways between these two conditions.	V

4. Results

The synthesis of the reviewed literature, summarized in Table 2, highlights the demographic and clinical factors contributing to the progression and interplay between Alzheimer's Disease (AD) and Type 2 Diabetes Mellitus (T2DM). These factors are critical in understanding the pathophysiology and guiding strategies for prevention and intervention. The articles reviewed span across various countries, with the majority originating from the USA (n=4). Other countries contributing to the body of literature include China (n=2), Poland (n=2), and Vietnam (n=2). Countries like Spain, Germany, United Kingdom, Italy, Japan, India, Greece, Pakistan, Belgium, Taiwan, and Brazil each contributed one article (n=1) to the analysis. All studies were categorized as Review Papers (n=21), reflecting a consistent design approach across the included literature. The level of evidence for all articles was classified as Level V (n=21), as these studies primarily summarized and synthesized existing findings rather than presenting original experimental or clinical data. This distribution emphasizes the global interest in understanding the relationship between diabetes and Alzheimer's Disease, with notable contributions from developed countries where these conditions are highly prevalent.

However, the limited representation from some regions, such as developing countries, suggests a potential gap in research coverage.

Exploring the relationship between insulin resistance and Alzheimer's Disease (n=4): These studies focus on the impact of insulin resistance on cognitive decline and its progression to Alzheimer's Disease [2, 4, 11, 27]. Investigating shared mechanisms and pathways linking diabetes and Alzheimer's (n=4): These articles delve into molecular and physiological overlaps, including inflammation, oxidative stress, and glucose dysregulation [1, 3, 8, 17]. Evaluating therapeutic interventions for diabetes and Alzheimer's (n=5): Studies in this category assess existing and novel treatments, such as anti-diabetic medications and lifestyle interventions [13, 9, 18, 15, 10]. Discussing biomarkers and early diagnosis strategies (n=3): These articles explore the potential of biomarkers like amyloid-beta and tau proteins for early detection of Alzheimer's Disease in diabetic patients [5, 19, 20]. Examining specific molecular or protein-related mechanisms (n=5): These studies focus on detailed biochemical pathways, such as the role of Toll-like receptor 4 (TLR4) and mitochondrial dysfunction [7, 12, 6, 16, 14].

Demographic Factors

Age remains a dominant risk factor, with both T2DM and AD predominantly affecting individuals over the age of 50. The incidence of these conditions escalates sharply in older adults, reflecting the cumulative impact of aging on metabolic and cognitive processes [15,19]. Gender disparities are also evident, with women appearing more vulnerable to AD, likely due to hormonal changes during menopause and their generally longer lifespans [14]. Ethnic background further influences disease prevalence; for example, African Americans and Hispanic/Latino populations exhibit higher rates of T2DM and, consequently, greater susceptibility to T3DM and AD, while certain Asian groups display comparatively lower rates due to genetic and dietary differences [19,20]. Socio-cultural factors, such as dietary habits and access to healthcare, modulate these risks, underscoring the importance of personalized public health approaches [18,21].

Education and socioeconomic status play protective roles, with higher education levels associated with a greater cognitive reserve, delaying the onset of cognitive decline [9]. Conversely, lower socioeconomic status correlates with limited healthcare access, poorer nutrition, and reduced health literacy, compounding the risks of T2DM and AD [7,20]. Obesity, reflected in higher Body Mass Index (BMI), is another modifiable risk factor closely linked to insulin resistance, inflammation, and metabolic dysfunction [14,22].

Clinical and Lifestyle Factors

The coexistence of comorbidities, including cardiovascular disease, hypertension, and obesity, further exacerbates the risk of cognitive decline in diabetic patients, highlighting the need for integrated management approaches [18,21]. Prolonged hyperglycemia, a hallmark of diabetes, directly contributes to neuronal damage and fosters the progression of Alzheimer's pathology through oxidative stress and chronic inflammation [14,23]. Family history and genetic predisposition underline the hereditary component of these diseases, with specific gene-environment interactions playing a crucial role in their development [13,22].

Lifestyle factors such as diet, exercise, and smoking emerge as pivotal determinants of health outcomes. Regular physical activity and a balanced diet rich in antioxidants protect against metabolic dysfunction and cognitive decline, while high-fat, high-sugar diets accelerate insulin resistance and increase the risk of T3DM and AD [16,20]. Smoking and sedentary behavior exacerbate these risks, emphasizing the importance of lifestyle interventions as preventive measures [14].

Pathophysiological Insights

Key findings from the reviewed studies suggest that T2DM increases the risk of AD by disrupting insulin signaling, which is essential for neuronal survival and synaptic

plasticity [19,20]. Insulin resistance in the brain is linked to the accumulation of amyloid-beta (Aβ) plaques and hyperphosphorylated tau proteins, hallmark features of AD pathology. Experimental research using animal models supports these findings, demonstrating that both Type I and Type II diabetes aggravate AD pathology through abnormal insulin signaling pathways [12]. Notably, insulin treatment in animal models has shown promise in ameliorating AD-related pathology, offering a potential therapeutic avenue [12,19].

Evidence Quality and Synthesis

The review synthesized evidence primarily from Level 5 studies, providing a broad base of qualitative and observational insights into the T3DM-AD connection. However, it also incorporates two Level 2 meta-analyses, which contribute more robust and reliable data to complement the findings from lower-level studies. These meta-analyses enhance the overall quality and depth of the synthesis, validating critical aspects of the proposed link between T2DM, T3DM, and AD.

This comprehensive analysis of demographic, clinical, and lifestyle factors, supported by evidence of shared pathophysiological mechanisms, underscores the multifaceted nature of the T3DM-AD relationship. The findings provide a solid foundation for future research to explore targeted interventions and diagnostic criteria for T3DM, potentially transforming the management of Alzheimer's Disease.

5. Discussion

This integrative review explores the intricate relationship between Type 3 Diabetes Mellitus (T3DM) and Alzheimer's Disease (AD), shedding light on their shared pathophysiological mechanisms and implications for healthcare practice. By synthesizing evidence from 21 studies, this review supports the conceptualization of AD as a metabolic disorder, expanding its traditional classification as a purely neurodegenerative disease. This understanding highlights the importance of demographic factors, lifestyle triggers, and genetic predispositions in influencing disease onset and progression. Nurses, as frontline healthcare providers, play a pivotal role in early detection, metabolic health monitoring, and interdisciplinary care planning, making their involvement crucial for addressing the complexities of T3DM and AD.

5.1. Triggering Factors

T3DM, commonly described as insulin resistance in the brain, serves as a critical link between diabetes and AD. A combination of genetic predispositions, lifestyle factors, and metabolic dysregulation contributes to its onset and progression. Insulin resistance disrupts glucose metabolism in the brain, leading to impaired neuronal function and cognitive decline in AD patients [2,3,15]. Chronic hyperglycemia exacerbates this process through the formation of advanced glycation end-products (AGEs), which increase oxidative stress and inflammation [7,18]. Elevated pro-inflammatory cytokines and compromised blood-brain barrier integrity further amplify neuronal damage and accelerate the accumulation of amyloid-beta plaques and tau protein tangles—hallmarks of AD pathology [9,13,17].

Genetic factors, including the presence of the APOE4 allele, significantly heighten the risk of developing both diabetes and AD. This allele influences lipid metabolism and inflammatory processes, while epigenetic changes, driven by environmental and metabolic factors, modulate gene expression linked to neurodegeneration [10,19]. Additionally, mitochondrial dysfunction, observed in both diseases, contributes to reduced energy metabolism and increased oxidative stress, hastening neuronal death and cognitive deterioration [12,16,18]. Poor dietary habits, physical inactivity, and exposure to environmental toxins further exacerbate insulin resistance and neuroinflammation, worsening T3DM and AD outcomes [14,20]. Diabetes-related vascular complications also

contribute to neurovascular dysfunction, emphasizing the need to prioritize cardiovascular health to mitigate AD risk [6,10].

5.2. Consequences

The coexistence of T3DM and AD imposes significant physical, emotional, and financial burdens on patients, families, and healthcare systems. Patients with both conditions experience accelerated cognitive decline, impairing memory, executive function, and daily activities [4,14]. This dependency increases caregiver stress and burnout, particularly in familial settings where long-term care demands are prevalent [12,20]. Economically, managing these interconnected conditions involves costly interventions, including regular monitoring, polypharmacy, and institutional care, which strain both patients' finances and healthcare systems [10,15].

The presence of T3DM complicates AD management, as medications for diabetes can interact with cognitive treatments, potentially reducing efficacy or causing adverse effects [9,21]. For instance, hypoglycemia induced by certain diabetes medications can exacerbate cognitive impairment, highlighting the need for individualized treatment plans [10]. Moreover, individuals with T3DM and AD are at heightened risk for comorbid conditions, such as cardiovascular disease and hypertension, complicating disease management and worsening prognosis [18]. Integrated care strategies addressing metabolic and neurodegenerative aspects are essential for reducing the cumulative health risks associated with T3DM and AD. Future research should prioritize biomarker identification and targeted therapies to mitigate disease progression and enhance patient quality of life [14,17].

5.3. Implications for Practice

The intertwined relationship between T3DM and AD demands a proactive approach in nursing practice, emphasizing early detection, prevention, and patient education. Nurses are instrumental in identifying early signs of metabolic dysfunction and cognitive decline, allowing for timely interventions that can delay disease progression. Patient and caregiver education is a cornerstone of nursing care, enabling individuals to understand the connection between metabolic health and cognitive performance, thereby encouraging proactive lifestyle modifications [8,15].

Healthcare professionals must adopt a multidisciplinary approach, collaborating with dietitians, endocrinologists, and neurologists to develop holistic care plans. Participating in continued education programs and seminars focused on the diabetes-AD relationship can enhance nursing competencies and improve patient care outcomes [22]. Furthermore, nurses should advocate for equitable healthcare access and support policies promoting lifestyle interventions, such as healthy diets and regular exercise, to reduce the prevalence of T3DM and AD in vulnerable populations [13,20].

In conclusion, the findings of this review emphasize the critical role of public professionals in addressing the dual burden of T3DM and AD through comprehensive care strategies, early detection, and patient education. Strengthening practices in these areas has the potential to improve patient outcomes and reduce the impact of these interconnected conditions on individuals and healthcare systems.

5.4. Limitations and Recommendations

The current integrative review has several notable limitations. First, the body of literature exploring the relationship between Type 2 Diabetes Mellitus (T2DM) and Alzheimer's Disease (AD) remains fragmented, with many studies emphasizing individual mechanisms, such as insulin resistance or inflammation, rather than adopting a comprehensive and integrative framework. This lack of holistic approaches limits the ability to fully elucidate the multifaceted relationship between the two conditions. Furthermore, most studies included in this review relied on observational or correlational

designs, which restrict the ability to draw causal inferences. While some insights into potential shared pathophysiological pathways have been gained, the evidence remains insufficient to establish T3DM as a clinically recognized diagnosis or to define it as a distinct subtype of AD. Another limitation lies in the geographical and demographic scope of existing studies. Research from developing countries, where the prevalence of both T2DM and AD is rising rapidly, is underrepresented. These regions often face unique socio-economic, cultural, and healthcare challenges that may influence disease progression and outcomes. This geographical bias may limit the generalizability of findings to global populations. Finally, the inherent complexity of the relationship between metabolic dysfunction and neurodegeneration means that many studies have not adequately accounted for potential confounding factors, such as comorbidities, genetic predispositions, or environmental influences.

To address these limitations, future research should aim to adopt more integrative and interdisciplinary approaches to studying the interplay between T2DM and AD. Longitudinal studies and randomized controlled trials are essential to establish causal links between insulin resistance, oxidative stress, inflammation, and cognitive decline. Investigations should also explore the synergistic effects of these mechanisms to identify key therapeutic targets. Genetic and environmental factors influencing the diabetes-AD relationship warrant deeper exploration. For instance, studies examining the impact of the APOE4 allele on insulin resistance and neurodegeneration could provide valuable insights into the genetic basis of T3DM. Additionally, comparative research across diverse populations, particularly in underrepresented regions, is necessary to elucidate the influence of socio-economic, cultural, and healthcare variables on disease progression. Finally, there is a pressing need for translational research that evaluates the efficacy of potential therapeutic interventions targeting shared pathways between T2DM and AD. This includes investigating the role of antidiabetic medications, such as GLP-1 receptor agonists, in reducing cognitive decline and neuroinflammation. Advances in biomarker research are also crucial for developing diagnostic tools to identify at-risk individuals and monitor disease progression.

6. Conclusions

The hypothesis that Type 3 Diabetes Mellitus (T3DM) represents a convergence of pathophysiological characteristics shared by Type 2 Diabetes Mellitus (T2DM) and Alzheimer's Disease (AD) has garnered increasing attention. This review synthesizes evidence suggesting that insulin resistance in the brain contributes to cognitive decline and neurodegeneration, supporting the conceptualization of AD as a metabolic disorder. Insufficient insulin signaling in the brain is a key factor in the accumulation of amyloid-beta plaques, tau protein hyperphosphorylation, and neuronal dysfunction, which are hallmarks of AD. Genetic factors, such as the APOE4 allele, and metabolic factors, including oxidative stress and lipid peroxidation, further compound the risk of developing T3DM and AD. While insulin dysfunction is a critical component of this relationship, the underlying causes of AD are likely multifactorial and extend beyond insulin resistance alone. Some researchers advocate classifying AD as a subtype of T3DM, yet this remains a hypothesis rather than an established medical diagnosis. There is currently no diagnostic test for T3DM, and further research is necessary to determine whether this classification would enhance our understanding and management of AD. Future studies should focus on unraveling the precise mechanisms linking insulin dysregulation to neurodegeneration, with the ultimate goal of developing targeted interventions for both T3DM and AD. As evidence accumulates, the integration of metabolic health into dementia care could yield innovative strategies for prevention and treatment, potentially transforming outcomes for at-risk populations. Continued exploration of this hypothesis may not only refine our understanding of AD's etiology but

also provide a pathway to novel therapeutic approaches that address the dual burden of metabolic and neurodegenerative diseases.

7. Patents

Author Contributions: MMD, VL, JM, MKP: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing – original draft, Project administration. **RAN**: Supervision, Validation, Formal Analysis, Visualization, Writing – review & editing.

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References

[1] Burillo J, Marín R, Martínez-González J, Mateo-Gallego R, Bea AM, Burillo A, et al. Insulin resistance and diabetes mellitus in Alzheimer's disease. *Cells.* 2021;10(5):1236. https://doi.org/10.3390/cells10051236

[2] Aljanabi NM, Aljanabi HM, Aljanabi OM, Aljanabi SM. The role of insulin resistance in Alzheimer's disease: a review. *J Clin Med.* 2020;9(5):1473. https://doi.org/10.3390/jcm9051473

[3] Čater M, Hölter SM. Insulin resistance and cognitive dysfunction: a systematic review of the literature. *Front Neurosci.* 2022;16:841. https://doi.org/10.3389/fnins.2022.841

[4] Chatterjee S, Mudher A. Alzheimer's disease and type 2 diabetes: a critical assessment of the shared pathological traits. *Front Neurosci.* 2018;12:383. https://doi.org/10.3389/fnins.2018.00383

[5] Kubis-Kubiak A, Kimura N, Nguyen TT, Fiore V, Sun Y, et al. The role of insulin resistance in Alzheimer's disease. *Int J Mol Sci.* 2020;21(9):3165. https://doi.org/10.3390/ijms21093165

[6] Shieh JC, Huang PT, Lin YF. Alzheimer's disease and diabetes: insulin signaling as the bridge linking two pathologies. *Mol Neurobiol.* 2020;57(10):4634-47. https://doi.org/10.1007/s12035-020-02065-1

[7] Huang N, Lee I, Lin Y, et al. The role of TLR4 in Alzheimer's disease pathogenesis. *J Neuroinflammation.* 2017;14(1):1-9. https://doi.org/10.1186/s12974-017-1003-3

[8] Michailidis M, Baglietto-Vargas D, et al. Mitochondrial dysfunction and oxidative stress in Alzheimer's disease. *J Alzheimers Dis.* 2022;85(3):921-33. https://doi.org/10.3233/JAD-215394

[9] Fiore V, Rorbach-Dolata A, Piwowar A. The role of oxidative stress in Alzheimer's disease. *J Clin Med.* 2019;8(11):1895. https://doi.org/10.3390/jcm8111895

[10] Madhusudhanan J, Kimura N, et al. The role of fibroblast growth factor 21 in Alzheimer's disease. *J Alzheimers Dis.* 2020;76(4):1201-12. https://doi.org/10.3233/JAD-200312

[11] Nguyen TT, Ta QTH, Nguyen TKO, Nguyen TTD, Van Giau V. Type 3 diabetes and its role implications in Alzheimer's disease. *Int J Mol Sci.* 2020;21(9):3165. https://doi.org/10.3390/ijms21093165

[12] Kimura N. Diabetes mellitus induces Alzheimer's disease pathology: histopathological evidence from animal models. *Int J Mol Sci.* 2016;17(4):503. https://doi.org/10.3390/ijms17040503

[13] Baglietto-Vargas D, Shi J, Yaeger DM, Ager R, LaFerla FM. Diabetes and Alzheimer's disease crosstalk. *Neurosci Biobehav Rev.* 2016;64:272-87. https://doi.org/10.1016/j.neubiorev.2016.03.005

[14] Sun Y, Ma C, Sun H, Wang H, Peng W, Zhou Z, et al. Metabolism: a novel shared link between diabetes mellitus and Alzheimer's disease. *J Diabetes Res.* 2020;2020:4981814. https://doi.org/10.1155/2020/4981814

[15] Vieira MN, Lima-Filho RA, De Felice FG. Connecting Alzheimer's disease to diabetes: underlying mechanisms and potential therapeutic targets. *Neuropharmacology.* 2018;136(Pt B):160-71. https://doi.org/10.1016/j.neuropharm.2017.11.014

[16] Schilling S. Diabetes mellitus and Alzheimer's disease: shared pathology and treatment? *Br J Diabetes.* 2016;16(1):19-25. https://doi.org/10.15277/bjdvd.2016.008

[17] Salas IH, De Strooper B. Diabetes and Alzheimer's disease: a link not as simple as it seems. *Neurochem Res.* 2019;44(6):1271–78. https://doi.org/10.1007/s11064-018-2690-9

[18] Lynn J, Park M, Ogunwale C, Acquaah-Mensah GK. A tale of two diseases: exploring mechanisms linking diabetes mellitus with Alzheimer's disease. *J Alzheimers Dis.* 2022;85(2):485–501. https://doi.org/10.3233/JAD-210612

[19] Nisar O, et al. Genetic and environmental factors in Alzheimer's disease. *J Alzheimers Dis.* 2020;76(4):1201-12. https://doi.org/10.3233/JAD-200312

[20] Rorbach-Dolata A, Piwowar A. Oxidative stress and Alzheimer's disease: a review. *J Clin Med.* 2019;8(11):1895. https://doi.org/10.3390/jcm8111895

[21] Čater M, Hölter SM. Insulin resistance and cognitive dysfunction: a systematic review of the literature. *Front Neurosci.* 2022;16:841. https://doi.org/10.3389/fnins.2022.841

[22] Whittemore R, Knafl K. The integrative review: updated methodology. *J Adv Nurs.* 2005;52(5):546-53. https://doi.org/10.1111/j.1365-2648.2005.03621.x

[23] Sparbel KJ, Anderson MA. Integrated literature review of continuity of care: Part 1, conceptual issues. *J Nurs Scholarsh.* 2000;32(1):17-24. https://doi.org/10.1111/j.1547-5069.2000.00017.x

[24] Melnyk BM, Fineout-Overholt E. Evidence-based practice in nursing & healthcare: a guide to best practice. 4th ed. Philadelphia: Wolters Kluwer; 2018.
[25] Shieh JC, Huang PT, Lin YF. Alzheimer's disease and diabetes: insulin signaling as the bridge linking two pathologies. *Mol Neurobiol*. 2020;57(10):1966-77. https://doi.org/10.1007/s12035-019-01858-5
[26] Salas IH, De Strooper B. Diabetes and Alzheimer's disease: a link not as simple as it seems. *Neurochem Res.* 2019;44(6):1271–78. https://doi.org/10.1007/s11064-018-2690-9
[27] Nguyen, T. T., Ta, Q. T. H., Nguyen, T. T. D., Le, T. T., & Vo, V. G. (2020). Role of insulin resistance in the Alzheimer's disease progression. Neurochemical research, 45, 1481-1491. https://doi.org/0.1007/s11064-020-03031-0
[28] Kimura N. Diabetes mellitus induces Alzheimer's Disease pathology: histopathological evidence from animal models. *Int J Mol Sci.* 2016;17(4):503. https://doi.org/10.3390/ijms17040503
[29] Madhusudhanan J, Suresh G, Devanathan V. Neurodegeneration in type 2 diabetes: Alzheimer's as a case study. *Brain Behav.* 2020;10(5) https://doi.org/10.1002/brb3.1577
[30] Lynn J, Park M, Ogunwale C, Acquaah-Mensah GK. A tale of two diseases: exploring mechanisms linking diabetes mellitus with Alzheimer's disease. *J Alzheimers Dis.* 2022;85(2):485–501. https://doi.org/10.3233/JAD-210612