Open access Journal of
Neurology & Neurosurgery
ISSN: 2476-0501

Juniper Publishers
key to the Researchers

Review Article
Volume 19 Issue 1 - July 2024
DOI: 10.19080/OAJNN.2024.19.556004

Open Access J Neurol Neurosurg

Impact of Diabetes Mellitus Type 2 on the Development of Alzheimer's Disease

Jubran Al Hooti[1], Nune Azaryan Dermenjian[2], Sahithya Ekasi[3], Chander Perkash Khatri[4], Vianka Vanessa Yánez Montalvo[5], Melanie Dayana Yánez Montalvo[6], Shanthanand sreekar chinthapally[3], Ileana Patricia Crespin Henriquez[7], Rishita Dave[8], Ruth Milena Machado[9], Juan C Pantoja[10], Viraj Shetty[11] and Maria Isabel Gomez-Coral[12]*

[1]*University College Dublin, Ireland*

[2]*Yerevan State Medical University, Armenia/USA*

[3]*Dr. Pinnamaneni Siddhartha Institute of Medical Sciences and Research Foundation, India*

[4]*Chandka Medical College, Pakistan*

[5]*Universidad de Guayaquil, Ecuador*

[6]*Facultad de Ciencias Medicas, Universidad de Guayaquil, Ecuador*

[7]*Universidad Evangélica de El Salvador, El Salvador*

[8]*University of Medicine and Health Sciences, St. Kitts*

[9]*Universidad Nacional Experimental Francisco de Miranda, Venezuela*

[10]*Universidad del Norte, Barranquilla, Colombia*

[11]*Bangalore Medical College and Research Institute, India*

[12]*Universidad del Valle, México*

Submission: July 08, 2024; **Published:** July 18, 2024

***Corresponding author:** Maria Isabel Gomez-Coral, Universidad del Valle de México, 154 Samson Lane, Frisco, TX, 76081, Mexico

Abstract

Diabetes Mellitus Type 2 (T2DM) and Alzheimer's Disease (AD) are prevalent chronic conditions in the aging population. T2DM is characterized by insulin resistance and chronic hyperglycemia, leading to long-term complications. AD, the most common form of dementia, is marked by progressive cognitive decline, amyloid-beta plaques, and neurofibrillary tangles. Epidemiological evidence suggests a significant correlation between T2DM and an increased risk of AD. This review explores the shared pathophysiological mechanisms linking T2DM and AD, including insulin resistance, oxidative stress, and inflammation. Insulin signaling in the brain is crucial for neuronal survival and cognitive function, and its disruption in T2DM contributes to AD pathology. Chronic hyperglycemia in T2DM induces oxidative stress and the formation of advanced glycation end products (AGEs), exacerbating neuronal damage and cognitive decline. Vascular complications in diabetes further impair cerebral blood flow, promoting neurodegeneration. Clinical implications highlight the necessity for integrated management strategies. Glycemic control, achieved through medications such as metformin and lifestyle interventions, can mitigate cognitive decline. Emerging therapies, including GLP-1 receptor agonists and intranasal insulin, show promise in addressing both metabolic and neurodegenerative aspects. Preventive measures, such as a balanced diet and regular physical activity, are crucial in reducing the risk of T2DM and AD. Future research should focus on understanding the precise mechanisms linking these diseases, optimizing therapeutic approaches, and exploring personalized medicine. This integrated perspective is essential for reducing the combined burden of T2DM and AD, ultimately improving patient outcomes.

Keywords: Type 2 Diabetes mellitus; Diabetes mellitus; Alzheimer's disease; Risk of hypoglycemia

Abbreviations: DM: Diabetes Mellitus; T2DM: Type 2 Diabetes Mellitus; AD: Alzheimer's Disease; DM: Diabetes Mellitus; APOE: Apolipoprotein E; GDM: Gestational Diabetes Mellitus; MODY: Maturity-Onset Diabetes of the Young; ROS: Reactive Oxygen Species; AGEs: Advanced Glycation End Products; MRI: Magnetic Resonance Imaging; PET: Positron Emission Tomography; CGM: Continuous Glucose Monitoring; APP: Amyloid Precursor Protein; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs; IL-1β: Interleukin-1 beta; IL-6: Interleukin-6; TNF-α: Tumor Necrosis Factor-alpha

Introduction

Two of the most common chronic conditions affecting the aging population are diabetes mellitus type 2 (T2DM) and Alzheimer's disease (AD). A hallmark of diabetes mellitus (DM), a long-term metabolic condition brought on by abnormalities in either insulin production, insulin action, or both, is hyperglycemia—that is, raised blood glucose levels. Two major forms are Type 1 Diabetes (T1DM) and Type 2 Diabetes (T2DM). T1DM, an autoimmune illness in which the immune system targets and kills the pancreatic

beta cells producing insulin, causes a total lack of insulin. Usually showing up in childhood or adolescence, this kind requires continuous insulin medication. Relative insulin insufficiency and insulin resistance define the more often occurring kind of diabetes, T2DM. It is usually connected to hereditary inclination, obesity, and inactive lives [1,2].

The most prevalent cause of dementia in older persons is Alzheimer's disease (AD). It is a progressive neurological condition. Behavioral and personality changes, memory loss, and a gradual reduction in cognitive function define it. Amyloid-beta plaques and neurofibrillary tangles made up of hyperphosphorylated tau protein that accumulate in the brain are two clinical hallmarks of Alzheimer's disease. These disorders destroy neurons, cause neuroinflammation, and disrupt neuronal transmission. As Alzheimer's disease progresses, mild cognitive impairment transforms into severe cognitive and functional decline, necessitating full-time care. Alzheimer's disease risk factors include age, genetic susceptibility (APOE gene mutations), and lifestyle decisions such as diet, physical exercise, and cardiovascular health. Although there is currently no cure for Alzheimer's disease, treatments try to improve the quality of life and manage symptoms [3,4].

For many different reasons, one must understand the interactions between various diseases-insulin resistance and chronic hyperglycemia-which have been shown to negatively affect brain function. In the brain, insulin resistance reduces neuronal activity and energy consumption, influencing the development and course of AD. Moreover, chronic hyperglycemia can lead to oxidative stress and advanced glycation end products (AGEs), which are important for AD pathologies, including amyloid-beta plaques and tau tangles [5,6].

The prevalence of metabolic illnesses, such as type 2 diabetes (T2D) and insulin resistance related to obesity, is rapidly rising on a global scale, primarily as a result of unhealthy lifestyle choices. Diabetes, for instance, is currently expected to impact 382 million individuals globally, and this alarming number is projected to increase to nearly 600 million people by 2035 [6,7]. Simultaneously, the occurrence of Alzheimer's disease (AD), the prevailing kind of cognitive decline in older individuals, also rises in tandem with the global aging population. It is estimated that there are already 35 million individuals globally who are affected by AD, and this figure is projected to double in the following decades [6,8].

Since the first Rotterdam research, a growing body of epidemiological and clinical data has emerged, demonstrating that people with diabetes are much more likely to have cognitive decline and dementia, especially Alzheimer's disease [8]. Understanding the relationship between T2DM and AD is necessary to develop comprehensive preventative and treatment plans. Early therapy for T2DM patients, which includes stringent glucose control and lifestyle adjustments, may lower the risk of AD or postpone its onset. It may be possible to create innovative therapeutic methods for treating insulin resistance and neurodegeneration in addition to understanding the shared routes and processes. Because it can significantly improve both the overall treatment of type 2 diabetes and the quality of life for those with AD or at risk for the condition, this integrated approach is crucial. Examining the relationship between these two conditions highlights the need for multidisciplinary research and treatment strategies intended to reduce the combined burden of type 2 diabetes and Alzheimer's disease [1-9].

Diabetes Mellitus Pathophysiology

Diabetes includes a group of metabolic disorders characterized by high blood sugar levels due to defects in insulin secretion, insulin action, or both. Chronic hyperglycemia in diabetes is linked to long-term damage, dysfunction, and failure of various organs. It can damage the eyes, kidneys, nerves, heart, and blood vessels. The development of diabetes involves several pathogenic processes. An autoimmune destruction of pancreatic β-cells leads to insulin deficiency and abnormalities causing insulin resistance. The root cause of the metabolic abnormalities in diabetes is insufficient insulin action on target tissues. This deficiency arises from inadequate insulin secretion or tissue response to insulin at various hormone action pathway stages. Impaired insulin secretion and defects in insulin action often coexist in the same patient, making it difficult to determine which abnormality primarily causes hyperglycemia. Most diabetes cases fall into two primary etiopathogenetic categories, Type 1 and Type 2. Type 1 diabetes is caused by an absolute insulin deficiency, often detectable by autoimmune markers and genetic background. Type 2 diabetes results from a combination of insulin resistance and an insufficient response to insulin secretion. In type 2 diabetes, hyperglycemia may be present long before diagnosis. The degree of hyperglycemia may vary over time, reflecting the progression of the underlying disease process [10].

Other types of diabetes include gestational diabetes mellitus (GDM), which is diabetes diagnosed in the second or third trimester of pregnancy. Monogenic diabetes syndromes such as neonatal diabetes and maturity-onset diabetes of the young [MODY], diseases of the exocrine pancreas such as cystic fibrosis, and drug-induced diabetes such as in the treatment of HIV/AIDS or after organ transplantation [11,12]. Schwartz et al. suggested a new "β-cell-centric" classification system for diabetes that focuses on the pancreatic β-cell as the common denominator and calls for a review of the current classification system to develop a more useful one [13].

Diabetes can lead to both microvascular, which includes neuropathy, nephropathy, and retinopathy, and macrovascular, which includes cardiovascular disease, stroke, and peripheral

How to cite this article: Jubran Al H, Nune Azaryan D, Sahithya E, Chander Perkash K, Vianka Vanessa YM, et al. Impact of Diabetes Mellitus Type 2 on the Development of Alzheimer's Disease. Open Access J Neurol Neurosurg 2024; 19(1): 556004. DOI: 10.19080/OAJNN.2024.19.556004

vascular disease complications through various mechanisms. Patients with type 2 diabetes have a substantially higher risk of fatal and non-fatal cardiovascular events compared to non-diabetic individuals [14]. Chronic hyperglycemia is a crucial driver of diabetic vascular complications, acting through various mechanisms like increased advanced glycation end products, protein kinase C activation, polyol pathway stimulation, and oxidative stress [15]. Understanding the pathways of reactive oxygen species (ROS) generation can provide the basis for new therapeutic strategies against vascular complications in diabetes. Despite intensive glycemic control and optimal multifactorial treatment, the cardiovascular risk burden in diabetes is not entirely eradicated. The development of mechanism-based therapeutic strategies is highly warranted [16].

Alzheimer's Disease: An Overview

Alzheimer's Disease (AD) is a progressive neurodegenerative condition involving the parts of the brain that control memory, thought, and language [17]. Dementia is characterized as a syndrome that causes a significant decline in cognitive ability that impairs an individual's activities of daily living [18]. AD is the most prevalent type of dementia, with two-thirds of cases above the age of 65 years attributed to AD [19]. It is a progressive disorder with an insidious onset that can present with mild memory loss and can lead to a complete loss of ability to have prolonged conversations and respond to environmental stimuli [17].

In 2020, the Centers for Disease Control and Prevention (CDC) reported that AD is the seventh leading cause of death in the United States [20]. The prevalence of AD has increased by 147.95% from 1990 to 2019 and is projected to affect a total of 150 million people by 2050 [21]. There are various methods to classify AD, including MRI findings, cognitive impairment, and age of onset [22,23]. AD is commonly classified into different stages: presymptomatic stage, mild cognitive impairment stage, and dementia stage, which is then further subdivided into mild, moderate, and severe [24]. Typically, AD presents after the age of 65, which is referred to as late-onset AD. The incidence of AD doubles every 5 years after the age of 65 [25]. However, in approximately 5% of AD cases, it manifests before the age of 65, and this is described as Early-onset AD, which exhibits atypical symptoms. Its diagnosis is often delayed, leading to a more severe progression of the disease before the initiation of treatment [26]. Currently, the management of AD is based on symptomatic relief as there is no curative treatment found as of yet [27].

AD is characterized by the pathological accumulation of abnormal neuritic plaques and neurofibrillary tangles in the brain [28]. This leads to neuronal cell death, specifically cholinergic neurons, which begins in the entorhinal cortex within the hippocampus [19]. Two main hypotheses have been proposed for the pathophysiological development of AD [28]. The cholinergic hypothesis is based on evidence of early loss of cholinergic neurons, beta-amyloid causing cholinergic synaptic loss, and anticholinergics adversely affecting memory retention [29]. Therefore, it suggests that reduced levels of acetylcholine in the brain primarily cause reduced cognitive function. The second is the amyloid hypothesis, which suggests that amyloid precursor peptide (APP) is cleaved by beta and then gamma-secretase, resulting in aggregation of a 42 amino acid peptide (AB42), leading to neuronal toxicity. AB42 forms aggregate fibrillary amyloid proteins rather than degrade, as APP typically does [30].

Various genetic associations have been identified to increase the risk of developing AD. The APP gene lies on chromosome 21, so individuals with trisomy 21 have an extra copy of the APP gene, leading to increased production of amyloid-beta peptides [31]. 100% of Down syndrome patients experience exhibit AD pathology. Various other genes have been identified to increase the risk of developing AD, such as Presenilin 1 on chromosome 14 and Presenilin 2 on chromosome 1 [32].

Histopathological studies have identified three core components in AD disease development. Neuritic Plaques are microscopic lesions with a core of extracellular AB42 that aggregate, form milliary structures, and deposit in gray matter [33]. Neurofibrillary tangles are fibrillary intracytoplasmic structures composed of tau protein, stabilizing axonal microtubules [34]. Microtubules are crucial for intracellular transport and run along neuronal axons. In AD, the toxic aggregation of AB amyloid leads to hyperphosphorylation of tau, which causes it to misfold and form aggregates within neurons in twisting shapes called neurofibrillary tangles. Finally, cognitive decline is primarily associated with granulovacuolar degeneration of hippocampal pyramidal neurons, specifically, the decrease in presynaptic boutons from pyramidal neurons from the laminae III and IV layers [35]. A mixture of these three core components has been observed in almost all AD cases, and extensive research has been invested in developing knowledge in these areas.

Diabetes Mellitus and Alzheimer's Disease

Epidemiological Evidence

Epidemiological research has consistently shown a significant correlation between diabetes mellitus (DM) and an increased risk of Alzheimer's disease (AD). For instance, studies such as the Rotterdam Study have demonstrated that individuals with DM have a 50-100% increased likelihood of developing AD compared to those without DM [36]. A meta-analysis of multiple cohort studies found that type 2 diabetes is associated with a 50% increased risk of AD [37]. Furthermore, longitudinal studies have emphasized that the risk of AD increases with the duration and severity of diabetes [38]. Those with poorly controlled blood glucose levels or long-standing diabetes are at a particularly heightened risk. These findings underline the critical need to understand the underlying mechanisms that link these two conditions.

How to cite this article: Jubran Al H, Nune Azaryan D, Sahithya E, Chander Perkash K, Vianka Vanessa YM, et al. Impact of Diabetes Mellitus Type 2 on the Development of Alzheimer's Disease. Open Access J Neurol Neurosurg 2024; 19(1): 556004. DOI: 10.19080/OAJNN.2024.19.556004

Biological Mechanisms

Insulin Signaling Pathways in the Brain

Insulin is crucial for peripheral glucose metabolism and plays an important role in the central nervous system. Insulin receptors are widely distributed in the brain, particularly in regions involved in cognitive functions, such as the hippocampus and cerebral cortex. In diabetes, insulin resistance extends to the brain, impairing insulin signaling pathways. This impairment disrupts neuronal survival, synaptic plasticity, and neurotransmitter release [39]. Moreover, insulin resistance in the brain is linked to increased amyloid-beta (Aβ) production and reduced clearance, contributing to amyloid plaque formation, a key feature of AD pathology [40].

Role of Oxidative Stress and Inflammation

Chronic hyperglycemia in DM leads to the excessive production of reactive oxygen species (ROS) and advanced glycation end products (AGEs), both of which induce oxidative stress and inflammation. These processes are detrimental to neuronal health. AGEs accumulate in neurons and glial cells, triggering inflammatory pathways and exacerbating neuronal damage [41]. In addition, oxidative stress damages lipids, proteins, and DNA within the body, resulting in neuronal apoptosis and cognitive impairment [42]. Inflammation further accelerates this process, creating a vicious cycle that promotes neurodegeneration and the progression of AD [43].

Vascular Contributions to Cognitive Impairment

Diabetes significantly increases the risk of vascular complications, including both microvascular (small vessel) and macrovascular (large vessel) damage. In the brain, microvascular damage leads to reduced cerebral blood flow, chronic hypoperfusion, and blood-brain barrier disruption. These vascular issues impair nutrient delivery and waste removal, which are essential for maintaining neuronal health. Furthermore, diabetes-related macrovascular complications, such as atherosclerosis, can lead to strokes and white matter lesions, contributing to cognitive impairment. The combination of vascular dysfunction and AD-related pathologies such as amyloid plaques and tau tangles synergistically accelerates cognitive decline [44].

Clinical Implications

Diabetes Mellitus (DM) is increasingly recognized as a significant risk factor for Alzheimer's Disease (AD). The pathophysiological links between DM and AD involve insulin resistance, hyperglycemia, and inflammation, contributing to neuronal damage and cognitive decline. Insulin resistance, a hallmark of Type 2 DM, affects brain function and structure. Insulin signaling is crucial for neuronal survival, synaptic plasticity, and memory formation. In DM, impaired insulin signaling can exacerbate amyloid-beta (Aβ) accumulation and tau phosphorylation, key pathological features of AD. Chronic hyperglycemia leads to advanced glycation end products (AGEs) and oxidative stress, further damaging neuronal tissues and contributing to cognitive decline [45,46].

DM is associated with systemic inflammation, impacting the central nervous system. Pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α are elevated in both DM and AD, suggesting a common inflammatory pathway that accelerates neurodegeneration. Microglial activation, a response to inflammation, also contributes to the progression of AD pathology [47,48]. The interplay between DM and AD complicates the diagnosis and monitoring of AD. Patients with DM are at higher risk of cognitive impairment, and the presence of hyperglycemia can exacerbate these symptoms. Monitoring glucose levels and maintaining glycemic control are crucial in patients with DM to mitigate the risk of cognitive decline. Additionally, biomarkers such as insulin levels, Aβ, and tau proteins can aid in the early detection and monitoring of AD progression in diabetic patients [49].

DM in The Diagnosis and Monitoring of AD

Diabetes mellitus significantly impacts the diagnosis and monitoring of AD. Epidemiological studies have established that individuals with DM are at a higher risk of developing AD, with diabetes increasing the likelihood of AD by 50-100% compared to those without diabetes [36]. This relationship underscores the importance of routine cognitive assessments for diabetic patients, particularly those with poorly controlled blood glucose levels or long-standing diabetes [37]. Insulin resistance, a hallmark of type 2 diabetes, is also observed in the brains of AD patients, indicating that metabolic dysfunctions may contribute to neurodegenerative processes [39]. The use of advanced imaging techniques, such as positron emission tomography (PET) and magnetic resonance imaging (MRI), helps detect early AD-related changes in diabetic patients, facilitating timely intervention [40].

Moreover, continuous glucose monitoring (CGM) plays a crucial role in managing diabetic patients at risk of AD. By maintaining stable glucose levels, CGM reduces the incidence of hypoglycemia, which is associated with acute cognitive impairment and increased AD pathology [42]. Biomarkers such as amyloid-beta and tau proteins, typically elevated in AD, can also be measured in diabetic patients to aid in early diagnosis and monitor disease progression [38]. Combining these diagnostic tools with regular cognitive testing and vigilant metabolic control offers a comprehensive approach to managing the dual burden of DM and AD, ultimately improving patient outcomes.

Management Strategies: Glycemic Control and Neuroprotective Approaches for Patients with DM and AD

Managing patients with both DM and AD requires a multifaceted approach that addresses both metabolic and neurological aspects. The primary goals are to achieve optimal glycemic control and to

How to cite this article: Jubran Al H, Nune Azaryan D, Sahithya E, Chander Perkash K, Vianka Vanessa YM, et al. Impact of Diabetes Mellitus Type 2 on the Development of Alzheimer's Disease. Open Access J Neurol Neurosurg 2024; 19(1): 556004. DOI: 10.19080/OAJNN.2024.19.556004

protect against neurodegeneration. Maintaining tight glycemic control is essential to reduce the risk of cognitive decline. Several studies suggest that intensive glycemic management can delay the onset and progression of cognitive impairment in patients with DM. Medications such as insulin sensitizers, including metformin and thiazolidinediones (e.g., pioglitazone), have shown promise in improving cognitive function and reducing AD pathology in diabetic patients [50,51]. A balanced diet with low glycemic index foods and regular physical activity can improve insulin sensitivity and overall metabolic health. Exercise also promotes neurogenesis and synaptic plasticity, which benefit cognitive function [52,53]. Continuous glucose monitoring (CGM) helps maintain stable glucose levels, reducing the risk of hypoglycemia and its associated cognitive complications [54].

In addition to glycemic control, several neuroprotective strategies are being explored. Anti-inflammatory agents, such as non-steroidal anti-inflammatory drugs (NSAIDs) and cytokine inhibitors, are being investigated for their potential to reduce neuroinflammation and slow disease progression [55,56]. Since oxidative stress is a critical factor in both DM and AD, antioxidants such as vitamin E, coenzyme Q10, and polyphenols have shown neuroprotective effects in preclinical studies [57]. Cognitive training and rehabilitation programs can help maintain cognitive function and slow AD progression in diabetic patients. These interventions focus on improving memory, executive function, and daily living activities [58,59].

Combining pharmacological treatments with lifestyle interventions offers a holistic approach to managing patients with DM and AD. This integrated strategy controls blood sugar levels, reduces neuroinflammation, and enhances cognitive function. The bidirectional relationship between DM and AD necessitates comprehensive diagnostic and management strategies. Early diagnosis through biomarkers and stringent glycemic control, coupled with neuroprotective therapies, can significantly improve the quality of life for patients suffering from both conditions.

Therapeutic Interventions

Current Treatments for DM and AD and their Potential Interactions

Current treatments for DM and AD often have overlapping considerations due to shared pathophysiological mechanisms. For DM, treatments primarily focus on glycemic control through medications such as metformin, insulin, and thiazolidinediones [36]. Metformin has shown neuroprotective effects, potentially reducing AD pathology through its impact on insulin sensitivity and inflammatory processes [37]. Thiazolidinediones, such as pioglitazone, also demonstrate benefits in reducing cognitive decline by improving insulin signaling in the brain [39]. For AD, current treatments include cholinesterase inhibitors (donepezil, rivastigmine) and NMDA receptor antagonists (memantine), which aim to manage symptoms rather than alter disease progression [40].

However, these medications must be carefully managed due to potential interactions. For instance, antidiabetic drugs that lower blood glucose levels can increase the risk of hypoglycemia, which is associated with acute cognitive impairment and may exacerbate AD symptoms [42]. Therefore, it is crucial to balance glycemic control with the risk of hypoglycemia to optimize cognitive outcomes in patients with both DM and AD.

Emerging therapies targeting the shared pathophysiological mechanisms of DM and AD

Emerging therapies are increasingly targeting the shared pathophysiological mechanisms of DM and AD. One promising area of research involves using incretin-based therapies, such as GLP-1 receptor agonists (e.g., liraglutide), which have shown the potential to enhance cognitive function and reduce AD pathology through their neuroprotective and anti-inflammatory properties [38]. Another novel approach is insulin delivered intranasally, which bypasses the blood-brain barrier and directly affects brain insulin signaling, potentially mitigating cognitive decline in AD patients [41].

Furthermore, therapies targeting oxidative stress and inflammation, such as antioxidants (vitamin E, coenzyme Q10) and anti-inflammatory agents (NSAIDs, cytokine inhibitors), are under investigation for their dual benefits in managing both DM and AD [43]. Advances in gene therapy and the use of stem cells also offer potential future treatments by addressing the underlying genetic and cellular dysfunctions common to both diseases [44]. These innovative approaches underscore the importance of integrated treatment strategies considering the complex interplay between DM and AD, aiming to improve overall patient outcomes.

Preventive Measures

Lifestyle Interventions

Lifestyle changes play a crucial role in preventing diabetes mellitus (DM) and potentially reducing the risk of Alzheimer's disease (AD). Diet and exercise are two primary components of these lifestyle interventions. A balanced diet with low glycemic index foods, healthy fats, and lean proteins can help maintain stable blood glucose levels and improve insulin sensitivity [38]. The Mediterranean diet, rich in fruits, vegetables, whole grains, and healthy fats, has been associated with a reduced risk of DM and AD [36].

Regular physical activity, an equally crucial component, plays a significant role in preventing diabetes and reducing the risk of Alzheimer's disease. Exercise not only enhances insulin sensitivity and aids in weight management but also boosts cardiovascular health, all of which are critical in the fight against DM. Moreover, exercise has been found to stimulate neurogenesis and synaptic plasticity, both of which are beneficial for cognitive function and may lower the risk of AD [37]. Engaging in a variety of exercises, including aerobic activities like walking and swimming, as well as strength training, can provide comprehensive health benefits.

How to cite this article: Jubran Al H, Nune Azaryan D, Sahithya E, Chander Perkash K, Vianka Vanessa YM, et al. Impact of Diabetes Mellitus Type 2 on the Development of Alzheimer's Disease. Open Access J Neurol Neurosurg 2024; 19(1): 556004. DOI: 10.19080/OAJNN.2024.19.556004

Research indicates that even moderate physical activity can substantially reduce the risk of cognitive decline in individuals with or at risk for DM [39].

Pharmacological Interventions

A vital part of the puzzle, are instrumental in managing DM and mitigating the risk of AD. Antidiabetic medications, such as metformin and thiazolidinediones, effectively control blood glucose levels and show potential neuroprotective effects. Metformin, for instance, has been associated with improved cognitive function and reduced AD pathology, likely due to its effects on insulin sensitivity and inflammatory pathways [40]. Similarly, thiazolidinediones like pioglitazone have shown promise in enhancing insulin signaling in the brain and reducing cognitive decline [41].

In addition to antidiabetic medications, other pharmacological agents are being explored for their potential to prevent or delay cognitive impairment. For example, GLP-1 receptor agonists, used primarily for glycemic control, have demonstrated neuroprotective properties and are being investigated for their ability to reduce AD pathology and improve cognitive outcomes [42]. Furthermore, anti-inflammatory drugs and antioxidants are being studied for their dual benefits in managing DM and AD. These agents aim to reduce oxidative stress and inflammation, which are common underlying mechanisms in the pathogenesis of both conditions [43].

Future Directions and Research Gaps

Diabetes mellitus (DM) and Alzheimer's disease (AD) are significant health challenges, with emerging evidence suggesting intricate connections between them. However, several critical gaps in understanding and therapeutic implications remain based on current literature. One critical gap is the mechanistic understanding of the DM-AD interaction. While insulin resistance, typical in type 2 diabetes, is implicated in AD pathology, including tau hyperphosphorylation and amyloid-beta (Aβ) accumulation, the precise molecular mechanisms linking insulin signaling dysfunction to neuroinflammation and oxidative stress in AD remain unclear. Furthermore, the differential effects of type 1 versus type 2 diabetes on AD risk and progression need more exploration. While type 2 diabetes is associated with insulin resistance, its specific impacts on synaptic loss and cognitive decline in AD require further clarification. Another significant research gap is evaluating the efficacy of anti-diabetic treatments, such as GLP-1 receptor agonists, in mitigating AD pathology [60-62].

Additionally, understanding the temporal relationship between insulin resistance onset, DM development, and AD pathogenesis is essential. Longitudinal studies are needed to determine whether insulin resistance precedes AD or develops concurrently, which could inform early intervention strategies. Reliable biomarkers for detecting early DM-related complications and AD pathology are also lacking. Identifying biomarkers that predict AD progression in DM patients could enhance timely interventions. Despite extensive investments, many clinical trials targeting AD pathways have failed, particularly in DM populations. Understanding these trial failures and optimizing designs considering patient heterogeneity and comorbidities like DM is critical. Personalized medicine approaches, such as tailoring treatments based on genetic profiles and disease characteristics, hold promise, yet understanding how genetic factors and sex differences influence insulin resistance and AD risk is lacking. Exploring combination therapies that synergize anti-diabetic and AD treatments shows potential but requires rigorous evaluation in clinical trials to optimize efficacy and safety. Finally, improving preclinical models to reflect better insulin resistance mechanisms and their impact on AD neurodegeneration is crucial for developing effective interventions [60-62].

Conclusion

The intricate relationship between diabetes mellitus type 2 (T2DM) and Alzheimer's disease (AD) necessitates a comprehensive understanding to develop effective prevention and treatment strategies. Both conditions share common pathophysiological mechanisms, such as insulin resistance, chronic hyperglycemia, oxidative stress, and inflammation, contributing to neuronal damage and cognitive decline. Epidemiological evidence supports a significant correlation between T2DM and an increased risk of AD, highlighting the importance of early diagnosis and intervention. Managing patients with both T2DM and AD involves a multifaceted approach that includes tight glycemic control, lifestyle interventions, and neuroprotective strategies. Medications that improve insulin sensitivity, reduce inflammation, continuous glucose monitoring, and regular physical activity can mitigate the cognitive decline associated with these conditions. Emerging therapies targeting shared mechanisms, such as incretin-based therapies and antioxidants, offer promising avenues for reducing the dual burden of T2DM and AD. Future research should focus on elucidating the precise molecular mechanisms linking T2DM to AD, developing reliable biomarkers for early detection, and optimizing therapeutic approaches through personalized medicine. Addressing these research gaps can enhance the quality of life for individuals affected by T2DM and AD, ultimately reducing the global burden of these interconnected chronic conditions.

References

1. American Diabetes Association (2014) Diagnosis and classification of diabetes mellitus. Diabetes Care 37(Suppl 1): S81-S90.
2. DeFronzo RA, Ferrannini E, Groop L, Henry RR, Herman WH, et al. (2015) Type 2 diabetes mellitus. Nature Reviews Disease Primers 1: 15019.
3. Alzheimer's Association (2020) 2020 Alzheimer's disease facts and figures. Alzheimer's & Dementia 16(3): 391-460.

How to cite this article: Jubran Al H, Nune Azaryan D, Sahithya E, Chander Perkash K, Vianka Vanessa YM, et al. Impact of Diabetes Mellitus Type 2 on the Development of Alzheimer's Disease. Open Access J Neurol Neurosurg 2024; 19(1): 556004. DOI: 10.19080/OAJNN.2024.19.556004

4. Selkoe DJ, Hardy J (2016) The amyloid hypothesis of Alzheimer's disease at 25 years. EMBO Mol Med 8(6): 595-608.
5. Arnold SE, Arvanitakis Z, Macauley-RSL, Koenig AM, Wang HY, et al. (2018) Brain insulin resistance in type 2 diabetes and Alzheimer disease: Concepts and conundrums. Nature Rev Neurol 14(3): 168-181.
6. De Felice FG, Ferreira ST (2014) Inflammation, defective insulin signaling, and mitochondrial dysfunction as common molecular denominators connecting Type 2 diabetes to Alzheimer disease. Diabetes 63(7): 2262-2272.
7. International Diabetes Federation (2013) IDF Diabetes Atlas (6th edn.). Brussels, International Diabetes Federation.
8. Alzheimer's Association (2013) 2013 Alzheimer's disease facts and figures. Alzheimer's & Dementia 9(2): 208-245.
9. Ott A, Stolk RP, Van Harskamp F, Pols HAP, Hofman A, Breteler MMB (1999) Diabetes mellitus and the risk of dementia: The Rotterdam Study. Neurol 53(9): 1937-1942.
10. American Diabetes Association (2014) Diagnosis and classification of diabetes mellitus. Diabetes Care 37(Supplement_1): S81-S90.
11. Boulin (1953) [Classification and diagnosis of diabetes]. Concours Méd 75(18): 1649-1650.
12. American Diabetes Association (2016) Classification and Diagnosis of Diabetes. Diabetes Care 40: S11-S24.
13. Schwartz SS, Epstein S, Corkey BE, Grant SF, Gavin J, et al. (2016) The time is right for a new classification system for diabetes: Rationale and implications of the β-cell–centric classification schema. Diabetes Care 39(2): 179-86.
14. Ahmed KA, Muniandy S, Ismail IS (2010) Type 2 diabetes and vascular complications: A pathophysiologic view. Biomed Res Tokyo 210.
15. Yamagishi S, Imaizumi T (2005) Diabetic vascular complications: Pathophysiology, biochemical basis and potential therapeutic strategy. Curr Pharma Design 11(18): 2279-2299.
16. Paneni F, Beckman JA, Creager MA, Cosentino F (2013) Diabetes and vascular disease: Pathophysiology, clinical consequences, and medical therapy: Part I. European Heart J 34: 2436-2443.
17. Centers for Disease Control and Prevention (2020) What is Alzheimer's disease?.
18. Gale SA, Acar D, Daffner KR (2018) Dementia. Am J Med 131(10): 1161-1169.
19. Kumar A, Tsao JW, Sidhu J, Goyal A (2022) Alzheimer disease.
20. Ahmad FB (2023) Provisional mortality data - United States, 2022. MMWR Morbidity and Mortality Weekly Report 72(18): 488-492.
21. Li X, Feng X, Sun X, Hou N, Han F, Liu Y (2022) Global, regional, and national burden of Alzheimer's disease and other dementias, 1990-2019. Front Aging Neurosci 14(1): 937486.
22. Zhang Q, Yang X, Sun Z (2022) Classification of Alzheimer's disease progression based on sMRI using gray matter volume and lateralization index. In Liu M (Ed.), Plos One 17(3): e0262722.
23. Adarsh V, Gangadharan GR, Fiore U, Zanetti P (2024) Multimodal classification of Alzheimer's disease and mild cognitive impairment using custom MKSCDDL kernel over CNN with transparent decision-making for explainable diagnosis. Sci Rep 14(1): 1774.
24. Porsteinsson AP, Isaacson RS, Knox S, Sabbagh MN, Rubino I (2021) Diagnosis of early Alzheimer's disease: Clinical practice in 2021. J Prevent Alzheimer's Dis 8(3): 371-386.
25. Qiu C, Kivipelto M, Von Strauss E (2009) Epidemiology of Alzheimer's disease: Occurrence, determinants, and strategies toward intervention. Dialogues Clin Neurosci 11(2): 111-128.
26. Mendez MF (2017) Early-onset Alzheimer disease. Neurologic Clin 35(2): 263-281.
27. Cummings J (2021) New approaches to symptomatic treatments for Alzheimer's disease. Molecular Neurodegeneration 16(1): 2.
28. Breijyeh Z, Karaman R (2020) Comprehensive review on Alzheimer's disease: Causes and treatment. Molecules 25(24): 5789.
29. Hampel H, Mesulam MM, Cuello AC, Martin RF, Ezio G, et al. (2018) The cholinergic system in the pathophysiology and treatment of Alzheimer's disease. Brain 141(7): 1917-1933.
30. Paroni G, Bisceglia P, Seripa D (2019) Understanding the amyloid hypothesis in Alzheimer's disease. In Solfrizzi V (Ed.), J Alzheimer's Dis 68(2): 493-510.
31. Salehi A, Wesson Ashford J, Mufson EJ (2015) The link between Alzheimer's disease and Down syndrome. A historical perspective. Curr Alzheimer Res 13(1): 2-6.
32. Hoogmartens J, Cacace R, Van Broeckhoven C (2021) Insight into the genetic etiology of Alzheimer's disease: A comprehensive review of the role of rare variants. Alzheimer's & Dementia: Diagnosis, Assessment & Dis Monitor 13(1): 12155.
33. Nelson PT, Jicha GA, Schmitt FA, et al. (2007) Clinicopathologic correlations in a large Alzheimer disease center autopsy cohort. Journal of Neuropathology and Experimental Neurol 66(12): 1136-1146.
34. National Institute on Aging (2024) What happens to the brain in Alzheimer's disease?.
35. Bell K, Bennett DA, Cuello AC (2007) Paradoxical upregulation of glutamatergic presynaptic boutons during mild cognitive impairment. J Neurosci 27(40): 10810-10817.
36. Ott A, Stolk RP, Hofman A, Van Harskamp F, Grobbee DE, Breteler MM (1996) Association of diabetes mellitus and dementia: The Rotterdam Study. Diabetologia 39(11): 1392-1397.
37. Janson J, Laedtke T, Parisi JE, O'Brien P, Petersen RC, et al. (2004) Increased risk of type 2 diabetes in Alzheimer disease. Diabetes 53(2): 474-481.
38. Biessels GJ, Staekenborg S, Brunner E, Brayne C, Scheltens P (2006) Risk of dementia in diabetes mellitus: a systematic review. Lancet Neurol 5(1): 64-74.
39. Craft S, Watson GS (2004) Insulin and neurodegenerative disease: shared and specific mechanisms. Lancet Neurol 3(3): 169-178.
40. Talbot K, Wang HY, Kazi H, Han LY, Bakshi KP, et al. (2012) Demonstrated brain insulin resistance in Alzheimer's disease patients is associated with IGF-1 resistance, IRS-1 dysregulation, and cognitive decline. J Clin Invest 122(4): 1316-1338.
41. Reddy PH (2006) Amyloid precursor protein-mediated free radicals and oxidative damage: implications for the development and progression of Alzheimer's disease. J Neurochem 96(1): 1-13.
42. Vlassara H, Uribarri J (2004) Advanced glycation end products (AGE) and diabetes: cause, effect, or both? Curr Diabet Rep 4(5): 351-356.
43. Iadecola C (2013) The pathobiology of vascular dementia. Neuron 80(4): 844-866.

How to cite this article: Jubran Al H, Nune Azaryan D, Sahithya E, Chander Perkash K, Vianka Vanessa YM, et al. Impact of Diabetes Mellitus Type 2 on the Development of Alzheimer's Disease. Open Access J Neurol Neurosurg 2024; 19(1): 556004. DOI: 10.19080/OAJNN.2024.19.556004

44. Biessels GJ, Reagan LP (2015) Hippocampal insulin resistance and cognitive dysfunction. Nature Reviews Neurosci 16(11): 660-671.

45. Arnold SE, Arvanitakis Z, Macauley-Rambach SL, et al. (2018) Brain insulin resistance in type 2 diabetes and Alzheimer disease: concepts and conundrums. Nat Rev Neurol 14(3): 168-181.

46. Biessels GJ, Strachan MW, Visseren FL, Kappelle LJ, Whitmer RA (2014) Dementia and cognitive decline in type 2 diabetes and prediabetic stages: towards targeted interventions. Lancet Diabetes Endocrinol 2(3): 246-255.

47. Heneka MT, Golenbock DT, Latz E (2015) Innate immunity in Alzheimer's disease. Nat Immunol 16(3): 229-236.

48. De Felice FG, Ferreira ST (2014) Inflammation, defective insulin signaling, and mitochondrial dysfunction as common molecular denominators connecting type 2 diabetes to Alzheimer disease. Diabetes 63(7): 2262-2272.

49. Kent SA, Spires-Jones TL, Durrant CS (2020) The physiological roles of tau and Aβ: implications for Alzheimer's disease pathology and therapeutics. Acta Neuropathol 140(4): 417-447.

50. Chin-Hsiao T (2019) Metformin and the Risk of Dementia in Type 2 Diabetes Patients. Aging Dis 10(1): 37-48.

51. Cheng D, Noble J, Tang MX, Schupf N, Mayeux R, et al. (2011) Type 2 diabetes and late-onset Alzheimer's disease. Dement Geriatr Cogn Disord 31(6): 424-430.

52. Reusch JE, Bridenstine M, Regensteiner JG (2013) Type 2 diabetes mellitus and exercise impairment. Rev Endocr Metab Disord 14(1): 77-86.

53. Mattson MP (2005) Energy intake, meal frequency, and health: a neurobiological perspective. Annu Rev Nutr 25: 237-260.

54. Munshi MN (2017) Cognitive Dysfunction in Older Adults With Diabetes: What a Clinician Needs to Know. Diabetes Care. 40(4): 461-467.

55. Heneka MT, Carson MJ, El Khoury J, et al. (2015) Neuroinflammation in Alzheimer's disease. Lancet Neurol 14(4): 388-405.

56. Brosseron F, Krauthausen M, Kummer M, Heneka MT (2014) Body fluid cytokine levels in mild cognitive impairment and Alzheimer's disease: a comparative overview. Mol Neurobiol 50(2): 534-544.

57. Zuo L, Motherwell MS (2013) The impact of reactive oxygen species and genetic mitochondrial mutations in Parkinson's disease. Gene 532(1): 18-23.

58. Clare L, Woods RT (2004) Cognitive training and cognitive rehabilitation for people with early-stage Alzheimer's disease: A review. Neuropsychol Rehabil 14(4): 385-401.

59. Jean L, Bergeron ME, Thivierge S, Simard M (2010) Cognitive intervention programs for individuals with mild cognitive impairment: systematic review of the literature. Am J Geriatr Psychiatr 18(4): 281-296.

60. Nowell J, Blunt E, Edison P (2023) Incretin and insulin signaling as novel therapeutic targets for Alzheimer's and Parkinson's disease. Mol Psychiatr 28(1): 217-229.

61. Folch J, Ettcheto M, Busquets O, Elena SL, Ruben DC, et al. (2018) The Implication of the Brain Insulin Receptor in Late Onset Alzheimer's Disease Dementia. Pharmaceuticals (Basel) 11(1): 11.

62. Athar T, Al Balushi K, Khan SA (2021) Recent advances on drug development and emerging therapeutic agents for Alzheimer's disease. Mol Biol Rep 48(7): 5629-5645.

DOI: 10.19080/OAJNN.2024.19.556004

How to cite this article: Jubran Al H, Nune Azaryan D, Sahithya E, Chander Perkash K, Vianka Vanessa YM, et al. Impact of Diabetes Mellitus Type 2 on the Development of Alzheimer's Disease. Open Access J Neurol Neurosurg 2024; 19(1): 556004. DOI: 10.19080/OAJNN.2024.19.556004