The Link Between Diabetes and Dementia:Is Alzheimer's Type 3 Diabetes?

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Key points:

- Introduction
- The relationship between diabetes and dementia, particularly Alzheimer's disease.
- Insulin resistance, chronic hyperglycemia, and inflammation as shared mechanisms.
- Common Risk factors
- Potential lifestyle and pharmacological interventions for prevention and management

Introduction

A progressive brain disease, Alzheimer's disease (AD) slowly deteriorates thinking, behavior, and memory. Researchers attribute it to aberrant protein accumulation, inflammation, and metabolic dysfunction, though the exact root cause is still unknown. Unexpectedly, one of the main risk factors for AD is Type 2 Diabetes (T2D). According to studies, the brain's insulin resistance speeds up neurodegeneration by causing memory loss, inadequate glucose metabolism, and the buildup of toxic proteins. As a result, Type 3 Diabetes (T3D), also known as "diabetes of the brain," was coined to describe the connection between Alzheimer's and insulin dysfunction.[1] Given the importance of metabolism to brain health, researchers hypothesize that certain anti-diabetic medications may enhance cognitive function in AD patients. Gaining insight into this relationship could lead to new approaches to managing and preventing Alzheimer's.[2]

Pathophysiological Link Between Diabetes and Dementia

Insulin Resistance and Brain Dysfunction

In addition to being essential for controlling blood sugar,insulin promote memory,synaptic plasticity and neuronal survival. Insulin resistance, on the other hand, interferes with glucose metabolism, resulting in

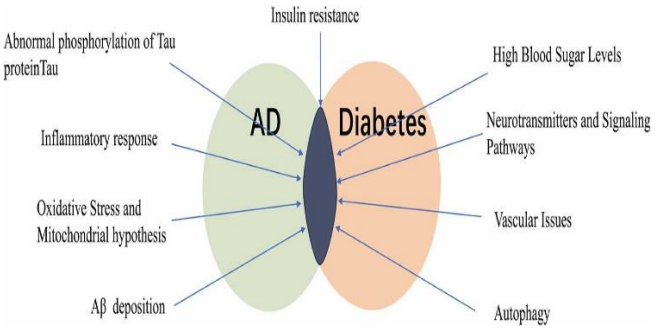

Figure 1: *The physiological and pathological basis of AD and diabetes.*[1]

beta-amyloid (Aβ) buildup, tau hyperphosphorylation, oxidative stress, and neuroinflammation. These factors all contribute to Alzheimer's Disease (AD), which is sometimes referred to as "diabetes of the brain." Cognitive decline and metabolic dysfunction is linked by insulin resistancemarkers found in brain and cerebrospinal fluid. Memory is further deteriorated by the aging-related decline of insulin-like growth factor-1 (IGF-1), which is necessary for brain function. Insulin resistance increases Aβ deposits by activating MAPK and BACE1, and tau tangles are promoted by GSK3β dysregulation. New treatments for AD prevention may result from an understanding of this connection.[1]

Chronic Hyperglycemia and Neurodegeneration

Persistent hyperglycemia contributes to oxidative stress, inflammation, and neuronal damage, all of which accelerate neurodegeneration3. High blood sugar levels promote the formation of advanced glycation end-products (AGEs), which trigger inflammation and exacerbate beta-amyloid (Aβ) plaque accumulation—one of the hallmarks of Alzheimer's disease.[3]

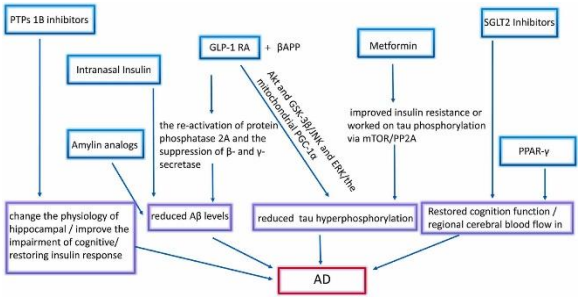

Figure 2: *Possible mechanism of major anti-diabetes drugs affected on AD.[1]*

Comparison of Type 2 Diabetes and Alzheimer's Disease Pathophysiology [4]

Feature	Type 2 Diabetes (T2D)	Alzheimer's Disease (AD)
Insulin Resistance	Present in peripheral tissues (muscle, liver, adipose)	Present in the brain, affecting neuronal function
Glucose Metabolism	Impaired glucose uptake, leading to hyperglycemia	Decreased glucose metabolism in the brain
Inflammation	Chronic systemic inflammation	Neuroinflammation, contributing to neurodegeneration
Amyloid Deposition	Not a primary feature	Amyloid-β plaques are a hallmark pathology
Oxidative Stress	Increased oxidative damage	High levels of oxidative stress contribute to neuronal death
Mitochondrial Dysfunction	Contributes to insulin resistance	Leads to neuronal energy failure and cognitive decline
Therapeutic Response	Improved with insulin sensitizers (metformin, GLP-1 agonists)	Some improvement with anti-diabetic drugs (intranasal insulin, GLP-1 agonists)

Inflammation and Neuroinflammation

Diabetes is a pro-inflammatory condition that increases the levels of cytokines such as TNF-α and IL-6, which contribute to neuroinflammation and cognitive decline.[5] The inflammatory processes in diabetes parallel those observed in Alzheimer's disease, further supporting the connection between these conditions.

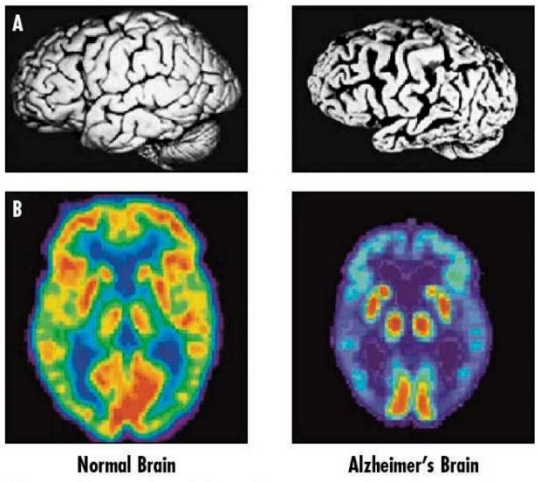

Figure 4: Brain *of Alzheimer patient.[7]*

Vascular Dysfunction and Cerebral Hypoperfusion

Diabetes is a significant risk factor for vascular dementia due to its impact on blood vessel health. Chronic hyperglycemia damages the cerebral microvasculature, leading to reduced blood flow and oxygen supply to the brain. This contributes to neuronal death and cognitive impairment, reinforcing the overlap between diabetes and dementia.[6]

Common Risk factors

- Aging
- Obesity
- Insulin resistance
- Elevated blood sugar levels
- High blood pressure
- Elevated cholesterol levels
- Genetic and oxidative stress.[1]

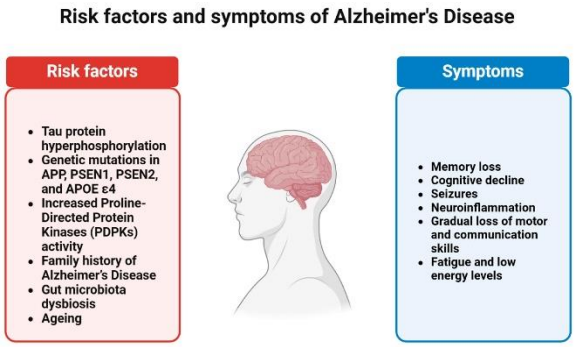

Figure 4: *The risk factors and symptoms associated with Alzheimer's Disease.*[1]

Potential Therapeutic Approaches Lifestyle Modifications

• Diet: A Mediterranean or ketogenic diet, rich in healthy fats and low in refined sugars, has been shown to improve insulin sensitivity and cognitive function. [7]

• Exercise: Regular physical activity enhances glucose metabolism, reduces inflammation, and supports neurogenesis, thereby lowering the risk of both diabetes and dementia.[8]

Pharmacological Interventions

• Metformin: A common anti-diabetic drug that has demonstrated neuroprotective effects in preclinical and clinical studies.[9]

• Intranasal Insulin Therapy: Designed to enhance insulin signaling in the brain, this therapy has shown promising results in improving cognitive outcomes in early Alzheimer's trials.[10]

• GLP-1 Receptor Agonists: Medications like liraglutide and semaglutide, commonly used in diabetes treatment, have exhibited potential benefits in reducing neuroinflammation and cognitive decline.[11]

Final Thoughts

The growing body of evidence supports a strong link between diabetes and dementia, with Alzheimer's disease exhibiting striking similarities to Type 2 diabetes. While the classification of Alzheimer's as Type 3 diabetes remains a topic of debate, the shared pathological mechanisms and promising response to anti-diabetic treatments highlight the metabolic component of neurodegeneration. Future research and targeted interventions may pave the way for novel therapeutic strategies that bridge the gap between endocrinology and neurology.

References

1. Peng Y, Yao SY, Chen Q, Jin H, Du MQ, Xue YH,Liu S. True or False? Alzheimer's disease is Type 3 Diabetes: Evidences from Bench to Bedside. Ageing research reviews. 2024 Jun 30:102383.
2. De Felice FG, Ferreira ST. Inflammation, defective insulin signaling, and mitochondrial dysfunction as common molecular denominators connecting type 2 diabetes to Alzheimer disease. Diabetes. 2014 Jul 1;63(7):2262-72.
3. Kale MB, Bhondge HM, Wankhede NL, Shende PV, Thanekaer RP, Aglawe MM, Rahangdale SR, Taksande BG, Pandit SB, Upaganlawar AB, Umekar MJ. Navigating the Intersection: Diabetes and Alzheimer's Intertwined Relationship. Ageing Research Reviews. 2024 Jul 14:102415.
4. de la Monte SM. Insulin Resistance and Neurodegeneration: Progress Towards the Development of New Therapeutics for Alzheimer's Disease. Drugs. 2016 Dec 17;77(1):47–65.
5. Zhao WQ, Townsend M. Insulin resistance and Alzheimer's disease: Mechanisms and therapeutic implications. Biol Psychiatry. 2023;65(12):918–28.
6. Barbagallo M, Dominguez LJ. Type 2 diabetes mellitus and Alzheimer's disease. World journal of diabetes. 2014 Dec 15;5(6):889.
7. Crane PK, Walker R, Hubbard RA, Li G, Nathan DM, Zheng H, Haneuse S, Craft S, Montine TJ, Kahn SE, McCormick W. Glucose levels and risk of dementia. New England Journal of Medicine. 2013 Aug 8;369(6):540-8.

8. Cholerton BR, Baker LD, Craft SU. Insulin resistance and pathological brain ageing. Diabetic Medicine. 2011 Dec;28(12):1463-75.
9. Morris JK, Vidoni ED, Perea RD, Rada R, Johnson DK, Lyons K, Pahwa R, Burns JM, Honea RA. Insulin resistance and gray matter volume in neurodegenerative disease. Neuroscience. 2014 Jun 13;270:139-47.
10. Biessels GJ, Despa F. Cognitive decline and dementia in diabetes mellitus: mechanisms and clinical implications. Nature Reviews Endocrinology [Internet]. 2018 Jul 18;14(10):591–604.
11. Scarmeas N, Stern Y, Mayeux R, Luchsinger JA. Mediterranean Diet, Alzheimer Disease, and Vascular Mediation. Archives of Neurology. 2006 Dec 1;63(12):1709.