The Relationship between Type II Diabetes and Alzheimer's Disease

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Abstract. Alzheimer's disease (AD) currently stands as a prominent focal point in contemporary research, ranking among the top ten causes of death worldwide. At the same time, diabetes has also secured its position as the third most prevalent ailment in developed countries. While more and more people are paying attention to these two diseases, it is worth noting that certain researchers have posited that type 2 diabetes (T2D) has a substantial influence on the development of AD. However, there is still a lack of unified explanation of underlying mechanics framework and extent of its influence remains elusive. This review will explore the risk factors, shared mechanisms, and convergent signaling pathways that contribute to AD and T2D, with an emphasis on the participation of mitochondrial dysfunction, abnormal glucose metabolism, inflammation, oxidative stress and insulin resistance. The relationship between AD and T2D is still unknown. Nonetheless, understanding the common mechanisms and signaling pathways of this harmful interchange between AD and T2D may offer new avenues for identifying potential therapeutic targets and devising effective treatment strategies.

1 Introduction

With the aging of the population, the currency of Alzheimer's disease (AD) and diabetes is rising gradually, which has raised serious public health concerns. The majority of dementia sufferers, approximately 60% to 80%, have AD, the most widespread sort of dementia [1, 2]. The average age of onset is about 60 years. And it is a chronic neurodegenerative disease, mainly defined by symptoms such as memory loss, cognitive decline, behavioral changes and more.

The primary pathological features of AD are the accumulation of amyloid plaques and neurofibrillary tangles (NFT) containing tau proteins [3]. However, numerous attempts to treat these two pathological indicators through pharmacological therapies have been unsuccessful. In 2019, there were approximately 52 million individuals afflicted with ADRD around the world, with China representing for close to 25.5% of the global population, equivalent to 13 million people [4]. It is projected that by 2050, the number of Chinese Alzheimer's disease patients will exceed 30 million, with patients aged 80 and above constituting roughly half of the total number of populations [5]. And 106.8 million people globally will have AD in total [2].

The elevated level of blood sugar is a hallmark of type 2 diabetes (T2D), a chronic metabolic disorder predominantly caused by β-cell malfunction or insulin resistance. And obesity caused by unhealthy living habits such as high calorie diet and lack of exercise is one of the biggest incentives for T2D. The main hallmarks of the disease include polydipsia, polyphagia, polyuria, thirst and fatigue. The onset of diabetes will have dementia as well.

According to a study, there will be about 529 million people with diabetes worldwide in 2021, with about 96% will having type 2 diabetes [6]. Predictive studies suggest that by 2050, the global diabetic population could double compare to 2021, reaching approximately 1.31 billion individuals [6]. Since the first Rotterdam study suggested that type 2 diabetes seemed to be related to Alzheimer's disease, more and more studies have substantiated the connection between AD and T2D [7]. This may be related to shared mechanisms and signaling pathways. AD and T2D are age-related conditions, with their incidence and prevalence rising as individuals age. Clinical and epidemiological investigations have underscored the significant part T2D as a risk factor for AD. The risk factors shared in developing AD and T2D are abnormal glucose metabolism, insulin resistance, inflammation, oxidative stress, and mitochondria impairment. In certain scientific circles, AD is also known as "type 3 diabetes" [8]. The proof from studying the patterns of diseases in populations shows that T2D significantly contributes to the advance of AD, increasing the likelihood of developing dementia by 2 to 5 times [9]. A direct link is generated between type 2 diabetes and specific subclass dementia, according to a comprehensive study done on all Danes 65 and older [10]. Nevertheless, the precise mechanisms underpinning this linkage between these two disorders remain incompletely elucidated. This study tries to give a summary of the most recent data supporting the link between AD and T2D.

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Table 1. 2019-2050 Number of Alzheimer's disease patients in China (million).

Year	60s		70s		80s and above		Total
	Population	Proportion %	Population	Proportion %	Population	Proportion %	
2015	4.1	32.3	4.2	33.1	4.4	34.6	12.7
2019	4.2	32.1	4.1	31.3	4.8	36.6	13.1
2030	6.2	30.0	7.2	34.8	7.3	35.2	20.7
2040	5.7	21.2	10.2	37.9	11.0	40.9	26.9
2050	6.1	20.3	9.1	30.3	14.8	49.3	30.0

Note: The author was unable to find the specific number of patients with Alzheimer's disease in various age groups in 2019, so the data from 2015 was used for extrapolation, as it was official. (Referred from [5].)

2 Risk factors in developing AD and T2D

2.1 Abnormal glucose metabolism

In terms of the adult brain, glucose is a vital energy source, with about 25% of consumed glucose going toward basic brain functions [11]. It is essential for the generation of ATP and the regulation of oxidative damage. Studies have shown that brain tissue affected by AD exhibits higher glucose concentrations compared to age matched control groups, and the severity of AD correlates with these alterations. Longitudinal investigations have further illuminated a relationship between the progressive increase in fasting blood glucose levels over time and heightened glucose levels within brain tissue, bolstering the connection between AD and diabetes [12]. Abnormal glucose metabolism leads to a decrease in ATP synthesis, a process intricately involved in various cellular functions and neuronal signaling. As glucose metabolism provides cells with the energy required for their proper functioning, including signaling in neural cells, it is important for cellular survival and normal neuronal function.

2.2 Insulin resistance

Historically, insulin resistance was used to describe the suboptimal response of obese diabetic patients to exogenous insulin. However, in recent years, insulin resistance is described as a compromised biological reaction to insulin, which covers all of the biological reactions to insulin and is not limited to aspects of glucose metabolism. Insulin resistance is one of the characteristics of type 2 diabetes. Additionally, it has been suggested that Alzheimer's disease may also be influenced by impaired insulin processing. The levels of neurotransmitters are impacted by the harmful consequences of insulin resistance on the brain. Sugar processing becomes hampered as insulin resistance increases in the brain, which raises blood pressure in the brain. At the same time, reports of alterations in insulin and insulin receptors in AD have led to the classification of AD as "type 3 diabetes" [8].

2.3 Inflammation

Inflammation is a physiological process initiated by injured cells or tissues that release chemical signals, triggering blood vessel dilation and immune cells infiltration from the bloodstream to protect against pathogens such as bacteria and viruses. Linked to inflammatory diseases like AD, most neurodegenerative diseases are contributed to chronic neuroinflammation, characterized by heightened cytokines and activated immunocyte. The intrinsic myeloid cells of the brain, known as microglia, are the primary source of neuroinflammation in AD, which intensifies as the illness progresses [13]. T2D is characterized by chronic inflammation of tissues, which has been seen in insulin-targeted organs such the liver and pancreatic islets [14]. Particularly in obesity, where it is a very early event in the onset of adipose tissue inflammation, chronic hypoxia, a characteristic of AD, also serves as a stimulus of inflammation [14]. These cytokines provoke the generation of amyloid precursor protein (APP), result in an increased abundance of APP and subsequently heightened Aβ peptide production, contributing to its accumulation [15].

2.4 Oxidative stress

The pathogenic condition called oxidative stress is well-established in a number of neurovascular illnesses and is a substantial contributor to aging, age-related

neurodegenerative disease, and metabolic syndrome. It is described as cellular damage brought on by an imbalance between the body's ability to neutralize free radicals' detrimental effects through antioxidants and the creation of free radicals itself. The process by which free radicals, in their pursuit of electrons, can harm biological components such cell membranes, proteins, and DNA is referred to oxidative stress. This process is known as oxidation. Oxidative damage has a gravely impact on the human brain. Excitotoxicity and lipid peroxidation are two of the factors that cause oxidative damage in the brain. It was reported that the hippocampus is greatly sensitive to oxidative stress, leading to dysfunction that impairs remodeling ability, which is the ability of the hippocampus [16].

2.5 Mitochondrial dysfunction

Through oxidative phosphorylation, mitochondria produce ATP and the creation of reactive oxygen species (ROS), immunological responses, and programmed cell death are other biological mechanisms that mitochondria participate in. Metabolic illnesses like T2D and obesity are linked to impaired mitochondrial function. Mitochondria dysfunction leads to ATP depletion and subsequent activation of AMPK, which stimulates MFF [11]. This stimulation results in mitochondrial fragmentation and eventually clearance via mitophagy. Impaired mitophagy causes damaged mitochondria to accumulate, which leads to energy depletion, inflammation, and oxidative stress. These effects eventually cause neuronal loss and cognitive decline, which are all defining characteristics of AD [12]. Compared to age-matched controls, AD-affected neurons have a higher incidence of mitochondria with damaged inner membrane. Mitochondrial abnormalities have been linked to cardiovascular disease in people with diabetes. The suppression of mitophagy speeds up cell death when there is mitochondrial damage [17]. Furthermore, as symptoms deteriorate, so does the decline in glucose metabolism, which happens before the manifestation of mitochondrial dysfunction [18].

3 Mechanism of shared by type 2 diabetes and Alzheimer's disease

Obesity is linked to persistent, systemic inflammation, which can cause insulin resistance, dysfunction of β-cells, and finally type 2 diabetes (T2D) [14]. Hyperglycemia, which is a hallmark of T2D and results from a confluence of β-cell dysfunction and insulin resistance, is present. ROS are frequently connected to mitochondrial dysfunction and impaired mitophagy. An imbalance in ROS production brought on by mitochondrial malfunction causes an excessive buildup of ROS, which aids in advanced age-related neurodegenerative disorders [19]. This excess of ROS causes oxidative stress, which is exacerbated by compromised DNA repair pathways and a reduced antioxidant response. The oxidation of mitochondrial DNA, protein, and lipids can result from increased ROS production, further altering mitochondrial dynamics and impeding mitophagy [20]. Consequently, this perpetuates a cycle wherein dysfunctional mitochondria generate more ROS, exacerbating mitochondrial damage and hindering biogenesis [20].

In AD, mitochondrial dysfunction and oxidative stress are closely contributed to the presence of Aβ peptides and phosphorylated tau protein. β-cell dysfunction and insulin resistance are connected to inflammation and endoplasmic reticulum (ER) stress. Persistent low-level inflammation is important to the emergence of T2D and obesity-induced insulin resistance [14]. Increased levels of oxidative damage are important in inducing insulin resistance in the brain resulting from AD. T2D is more prevalent among patients in older age groups and is characterized by cellular insulin resistance, numerous metabolic dysfunctions, and persistent inflammation. T2D has also been linked to accelerated aging in a number of organ systems [21]. In addition, neuroinflammation, which is a hallmark of AD and is fueled by microglia, becomes more pronounced as the condition worsens. Inflammation that persists over time is essential for AD development. Insulin resistance, characterized by a diminished response to insulin, can stem from both genetic and environmental factors. central insulin resistance and inflammation can cause reduced insulin sensitivity in human brain, which eventually induces the buildup of β-amyloid and the onset of AD. The cytokine TNF-α, which mediates tissue inflammation, has been shown to reduce insulin sensitivity [14]. Insulin resistance and the accompanying hyperinsulinemia are hypothesized to be responsible for the elevated risk of AD in people with diabetes. It is clear that AD has metabolic anomalies similar to those seen in T2D, such as energy metabolism and impaired glucose usage. Given that the brain predominantly uses glucose as its primary energy source, abnormal glucose metabolism is particularly noticeable in AD. Brain function is impacted directly by a reduction in glucose metabolism. Neuronal glucose consumption is primarily regulated by glucose transporter 3 (GLUT3) and insulin, with insulin-regulated glucose transporter 4 (GLUT4) playing a significant role during activities that require high energy demand and glucose metabolism [22]. Insulin resistance is a fundamental underlying cause of T2D. Compensatory hyperinsulinemia is seen before the disease manifests, but it gradually lowers as a result of advancing β-cell dysfunction, impairing glucose homeostasis, and eventually developing into diabetes [14].

4 Signaling pathways shared by T2D and AD

4.1 Shared blood transcriptomic signatures between AD and T2D

The analysis of blood transcriptomics, which involves profiling the abundance of transcripts in the bloodstream

on a genome-wide scale [23], has provided valuable insights into the immune system's status. In recent research, the blood transcriptomes in MCI, AD, and advanced AD patients were compared to patients suffered from T2D. The results showed the common molecular mechanisms between MCI and T2D were mainly signaling pathways for infection and inflammation. Atherosclerosis pathways and the PI3K-AKT signaling pathway and, on the other hand, were dysfunctional pathways in the advanced AD and T2D common network [24]. PI3K-AKT signaling pathway, is crucial in mediating the effects of insulin on the organism. Its activation makes it easier for peripheral tissues to absorb glucose. For the brain to remain healthy, synaptic flexible, and neuroprotective, insulin actions and the PI3K-AKT signaling pathway are crucial [25]. Additionally, the activation and operation of microglia are also linked to the PI3K-AKT signaling pathway [25]. Furthermore, the utilization of meta-analysis as a method proves to be valuable in selecting representative data from blood transcriptomics for AD and T2D.

4.2 Temporal cortex transcriptome signatures between AD and T2D

The initiation and development of neurodegenerative illnesses are intimately correlated with the temporal cortex, which is in charge of processes including memory, verbal fluency, language processing, and speech production [26]. The frontotemporal cortex's progressive loss in glucose usage throughout the early phase of dementia shows the beginning of these disorders [19]. The temporal lobe is essential for the memory section and its impairment considerably speeds up the development of AD. Reduced regional grey matter volume (GMV) and changed internal activity, particularly in the temporal cortex, were found in a meta-analysis of T2D patients, suggesting a possible connection between temporal cortex dysfunction and cognitive impairment in T2D [24]. Furthermore, research has shown elevated levels of malondialdehyde, both basally and upon iron/ascorbate stimulation, in the inferior temporal cortex of individuals with AD compared to controls, while other regions remain unaffected [27]. Longitudinal investigations have repeatedly shown that the development of NFT in the inner temporal lobe during the early phase of the disorder is accompanied by the decline in episodic memory function, a defining feature of AD [28]. The importance of the temporal cortex for memory and cognitive functions, as well as its role in the etiology of neurodegenerative diseases, are highlighted by these studies.

4.3 Insulin IGF-1 signaling

T2D is a metabolic disorder, which symptoms are high blood sugar levels brought on by faulty insulin signaling in the body. This impairment can occur due to insufficient insulin production (type I) or defects in insulin in target cells (type II). T2D and AD may be related through the complex molecular mechanisms involving IGF-1 signaling pathways and insulin. Research suggests that altered IGF-1 signaling in brain cells could be responsible for the accumulation of amyloid-beta (Aβ) in AD. Furthermore, insulin affects brain activity and cognitive functioning in independent ways. Problems with insulin/IGF signaling may cause amyloid-beta precursor protein (APP) increasingly expresses and Aβ accumulates consequently [29]. Additionally, these impairments link to oxidative stress, energy metabolism deficits, and the activation of neurodegenerative cascades mediated by pro-AβPP-Aβ [29]. Reduced levels of acetylcholine (ACh), a critical neurotransmitter involved in memory and learning processes, are another consequence of inadequate insulin signaling [30]. In patients with AD, both the concentration and function of ACh are decreased [30]. In addition, insulin resistance and poor insulin sensitivity in target cells are caused by down-regulated expression of the insulin IGF-1 receptor [31].

4.4 The signaling pathways involving astrocytes

By sensing and transferring glucose and insulin, astrocytes play a crucial part in controlling [32]. These processes have a significant impact on synaptic plasticity and cognitive function [33]. Additionally, astrocytes are involved in the regulation of neurotransmitters and calcium homeostasis, relying on glycolysis for energy production [34]. The high expression of 6-phosphofructose-2-kinase/fructose-2,6-bisphosphatase-3 (Pkfkb3), which enhances glycolysis flow while decreases the stream of the pentose phosphate pathway (PPP), is one of the processes underlying astrocytic energy metabolism [35]. It's interesting to note that overexpression of Pkfkb3 can induce cell death and oxidative stress in addition to activating glycolysis in neurons [35]. An AD disease modifier has been hypothesized as inflammatory signaling within astrocytes. While Aβ plaques can induce the reactivity of astrocyte, astrocyte reactivity can also lead to increased Aβ plaque generation [36]. Brain insulin resistance, Aβ deposition, disrupted insulin signaling pathways, mitochondrial impairment, metabolic abnormalities, oxidative stress, and neuroinflammation are only a few of the pathological features of AD that are linked to astrocyte dysfunction. Astrocytes use the glucose transporter GLUT1 to take up glucose from blood vessels, which is then transformed into pyruvate [9]. In astrocytes, the remaining glucose is kept as glycogen. It has been acknowledged that GLUT1 targeting perhaps is a useful therapy for diabetes. For instance, decreased GLUT1 expression has demonstrated promise in treating diabetic retinopathy [9].

5 Conclusion

Type 2 diabetes and Alzheimer's disease, as the

widespread diseases in contemporary society, have attracted more and more attention. Numerous studies have highlighted a correlation between the onset of AD and T2D, with individuals afflicted by T2D exhibiting a higher susceptibility to developing AD. This may be explained by several factors. Firstly, there exist common risk factors shared by conditions, encompassing oxidative damage, mitochondrial impairment, abnormal glucose metabolism, neuroinflammation, and insulin resistance all of which may contribute to cognitive decline in both T2D and AD. These have been repeatedly stated, but not innovated. These findings suggest that there are common molecular mechanisms at play in both conditions, including not only the risk factors, but also mitochondrial autophagy, cell apoptosis, ER stress, etc. Additionally, there are four signaling pathways that intersect in AD and T2D. Moreover, blood transcriptomic signatures show its different symptoms in different stages of Alzheimer's disease. Temporal cortex transcriptome signatures mainly show changes in the volume of gray matter and cognitive dysfunction. Insulin IGF-1 signatures, and astrocytes signatures are both contributed to insulin resistance and glucose metabolism. These also once again demonstrate the viewpoint that AD can be regarded as a metabolic disorder, sometimes referred to as T3D. This review provides a scientific assessment of the tangible impact that T2D has on AD, and aims to clarify any misconceptions regarding their relationship. While there is evidence suggesting that T2D may influence the development of AD, the exact nature of this relationship is still unclear. Furthermore, future research can focus on refining the operation of the aforementioned related variables to facilitate a more in-depth understanding of this topic. As the evidence is multifarious, other aspects of AD are equally required to investigate. Such research has the potential to reveal new information on the pathogenesis and management of T2D and AD.

References

1. http://www.infoplease.com/ipa/A0005110.html
2. P. Amiri, Z. Niazkhani, H. Pirnejad, K. Bahaadinbeigy, M.S. Baghini. Health Policy and Technology, **12** (2023)
3. Y. Zhang, R. Geng, M. Liu, S. Deng, J. Ding, H. Zhong, Q. Tu. Heliyon, **9** (2023)
4. R. Ren, J. Qi, S. Lin, et al. The China Alzheimer Report 2022. General Psychiatry 2022, **35** (2022)
5. Y. Wang, J. Liang, R. Jia, Y. Xu. Chinese Journal of Alzheimer's Disease and Related Disorders, **2** (2019)
6. Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the Global Burden of Disease Study 2021. GBD 2021 Diabetes Collaborators, **402**: 203-234 (2023)
7. M.N.N. Vieira, R.A.S. Lima-Filho, F.G.D. Felice. Neuropharmacology, **136**: 160-171 (2018)
8. S. Terzo, A. Amato, F. Mulè. Journal of Diabetes and its Complications. **35** (2021)
9. Z. Shen, Z. Li, M. Yu, K. Tan, S. Chen. Biomedicine & Pharmacotherapy, **158** (2023)
10. J.Q. Thomassen, J.S. Tolstrup, M. Benn, R. Frikke-Schmidt. Epidemiology and Psychiatric Sciences, **29** (2020)
11. E. Barone, F.D. Domenico, M. Perluigi, D.A. Butterfield. Free Radical Biology and Medicine, **176**: 16-33 (2021)
12. C. Carvalho, P.I. Moreira. Current Opinion in Neurobiology, **79** (2023)
13. F.L. Heppner, R.M. Ransohoff, B. Becher. Nat Rev Neurosci, **16**: 358–372 (2015)
14. T.V. Rohm, D.T. Meier, J.M. Olefsky, M.Y. Donath. Immunity, **55**: 31-55 (2022)
15. T. Ozben, S. Ozben. Clinical Biochemistry,**72**: 87-89 (2019)
16. S. Briyal, A.K. Ranjan, A. Gulati. Neurochemistry International, **165** (2023)
17. M. Bostancıklıoğlu. Gene, **705**: 157-166 (2019)
18. P.F. Pavlov, C.H. Petersen, E. Glaser, M. Ankarcrona. Journal of Cellular and Molecular Medicine, **13**: 4137-4145 (2009)
19. S. Dewanjee, P. Chakraborty, H. Bhattacharya, L. Chacko, B. Singh, A. Chaudhary, K. Javvaji, S.R. Pradhan, J. Vallamkondu, A. Dey, R.S. Kalra, N.K. Jha, S.K. Jha, P.H. Reddy, R.Kandimalla. Free Radical Biology and Medicine, **193**: 134-157 (2022)
20. R. Richard, S. Mousa. Biomedicine & Pharmacotherapy, **152** (2022)
21. G. Verdile, S.J. Fuller, R.N. Martins. Neurobiology of Disease, **84**: 22-38 (2015)
22. W. Peng, C. Tan, L. Mo, J. Jiang, W. Zhou, J. Du, X. Zhou, X. Liu, L. Chen. Metabolism, **123** (2021)
23. D. Chaussabel. Seminars in Immunology, **27**: 58-66 (2015)
24. J. Shu, N. Li, W. Wei, L. Zhang. Gene, **810** (2022)
25. S.J. A., B. Virginie, P.J. A. Frontiers in Neuroscience, **13** (2019)
26. W. Xia, Y. Chen, J. Ma. Frontiers in Aging Neuroscience, **9** (2017)
27. A.M. Palmer, M.A. Burns. Brain Research, **645**: 338-342 (1994)
28. Z. Papadatos, N.A. Phillips. Neurobiology of Aging, **128**: 33-42 (2023)
29. S.M. de la Monte. Drugs, **72**: 49–66 (2012)
30. P.T. Francis. CNS Spectrums, **10**: 6-9 (2005)
31. D.A. Butterfield, F.D. Domenico, E.Barone. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease, **1842**: 1693-1706 (2014)
32. S. Treviño, A. Díaz, G. González-López, J. Guevara. Differential biochemical-inflammatory patterns in the astrocyte-neuron axis of the hippocampus and frontal cortex in Wistar rats with metabolic

syndrome induced by high fat or carbohydrate diets, Journal of Chemical Neuroanatomy, **126** (2022)

33. J.E. Simpson, P.G. Ince, P.J. Shaw, P.R. Heath, R. Raman, C.J. Garwood, C. Gelsthorpe, L. Baxter, G. Forster, F.E. Matthews, C. Brayne, S.B. Wharton. Neurobiology of Aging, **32**: 1795-1807 (2011)
34. W. Bi, T. Lei, S. Cai, X. Zhang, Y. Yang, Z. Xiao, L. Wang, H. Du. International Immunopharmacology, **113** (2022)
35. C. Dai, C. Tan, L. Zhao, Y. Liang, G. Liu, H. Liu, Y. Zhong, Z. Liu, L. Mo, X. Liu, L. Chen. Brain Research Bulletin, **199** (2023)
36. S.C. Correia, R.X. Santos, C. Carvalho, S. Cardoso, E. Candeias, M.S. Santos, C.R. Oliveira, P.I. Moreira. Brain Research, **1441**: 64-78 (2012)