IS ALZHEIMER'S DISEASE A TYPE 3 DIABETES? A REVIEW

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SUMMARY

Objectives: This is a review article that deals with the question of whether type 2 diabetes is a risk factor for the development of Alzheimer's disease.

Methods: We searched the PubMed database and relevant publications were selected for review. The introduction, which describes the possibilities of how type 2 diabetes can affect the development of Alzheimer's disease, is followed by other questions related to this issue: May on the contrary Alzheimer's disease induce type 2 diabetes? What is a relative risk for type 2 diabetes to induce dementia? How type 2 diabetes influence conversion of mild cognitive impairment to Alzheimer's disease? What is the role of antidiabetic medication? Proposition of term "type 3 diabetes" for Alzheimer's disease.

Results: Type 2 diabetes mellitus has been shown to increase the risk for cognitive decline and dementia, such as Alzheimer's disease and vascular dementia. Despite extensive research and numerous publications, the mechanisms underlying these associations remain unclear.

Conclusions: Because of similar molecular and cellular features among type 1 and type 2 diabetes and insulin resistance associated with memory deficit and cognitive decline, some researches proposed the term "type 3 diabetes" for Alzheimer's disease.

Key words: type 2 diabetes, dementia, Alzheimer's disease, type 3 diabetes

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INTRODUCTION

In the last decades, both diabetes mellitus and Alzheimer's disease (AD) are constantly increasing. Affected individuals, therefore, represent an enormous problem for the society, governments and global organizations. These diseases are usually considered as independent conditions, but increasing evidence shows that there are links between these two disorders. Some pathogenetic factors are shared by type 2 diabetes and Alzheimer's disease: chronic inflammation, oxidative stress, mitochondrial dysfunction, adiponectin deficiency, different expression of plasma cholinesterase activity and vascular damage could represent a possible explanation for the coexistence of these two conditions in many patients (1).

Cognitive dysfunction is increasingly recognized as an important comorbidity of diabetes mellitus. Different stages of diabetes-associated cognitive dysfunction can be discerned, with different cognitive features, affected age groups, prognosis, and likely also different underlying mechanisms. Relatively subtle, slowly progressive cognitive decrements occur in all age groups. More severe stages, particularly mild cognitive impairment (MCI) and dementia, with progressive deficits, occur primarily in older individuals. Evolving insights from studies on risk factors, brain imaging, and neuropathology provide important clues on mechanisms. Although both the risk of clinically diagnosed Alzheimer's disease and that of vascular dementia is increased in association with diabetes (2).

Type 2 diabetes has been consistently associated with an increased risk of dementia, including Alzheimer's disease and vascular dementia; mild cognitive impairment, which is a condition preceding dementia; and cognitive decline, which is the progressive clinical hallmark of dementia (1). Establishing whether type 2 diabetes is specifically associated with the biological features of Alzheimer's disease or other causes of dementia and ascertaining whether the mechanisms that link type 2 diabetes to dementia can suggest new approaches to dementia treatment have been fraught areas of research. The link between type 2 diabetes and cognitive dysfunction is largely consistent, and a large body of studies on animals and humans point toward biological mechanisms of type 2 diabetes that could be potentially actionable. Given this evidence and in light of the accelerating rates of type 2 diabetes worldwide, establishing the effect of type 2 diabetes on the brain and neurodegenerative diseases is necessary (3).

Type 2 diabetes mellitus and late-onset Alzheimer's disease – dementia are increasing in global prevalence and current predictions indicate they will only increase over the coming decades. These increases may be a result of the concurrent increases of obesity and aging. Type 2 diabetes mellitus is associated with cognitive impairments and metabolic factors, which increase the cellular vulnerability to develop an increased risk of age-related late-onset Alzheimer's disease. How type 2 diabetes mellitus increases the vulnerability of the brain's neurovascular unit (NVU), neuroglia and neurons are as follows: aging (chronic age-related

diseases), metabolic (hyperglycaemia advanced glycation end products and its receptor interactions, and hyperinsulinaemia – insulin resistance, oxidative stress, inflammation, vascular and microvascular NVU/neuroglial remodelling) with resulting impaired cerebral blood flow (4).

Epidemiological studies have provided evidence for a link between diabetes and an increased risk to develop dementia. However, in spite of several proposed mechanisms for this association, it is not possible to make final conclusions with regard to what specific metabolic alterations could be responsible for this increased predisposition to dementia. The high heterogeneity between the different cases of AD and type 2 diabetes, and the effects of aging on the central nervous system and peripheral organs make it very complicated to dissect the specific mechanisms responsible for a general association observed in population-based cohort studies. Given the fact that both disorders are highly heterogeneous, it is likely that the link between the two is a consequence of a combination of different molecular, cellular and systemic factors which are difficult to unravel. Caution when proposing specific mechanisms or treatments seems indicated (5).

Recent epidemiological studies indicate that diabetes significantly increases the risk of developing AD, suggesting that diabetes may play a causative role in the development of AD pathogenesis. Therefore, elucidating the molecular interactions between diabetes and AD is of critical significance because it might offer a novel approach to identifying mechanisms that may modulate the onset and progression of sporadic AD cases (6).

Chronic exposure to hyperglycaemia can deteriorate cognitive function and other aspects of mental health. Hyperglycaemia is closely related to the development of cognitive impairment and dementia, suggesting that there may be a cause-effect relationship between hyperglycaemia and dementia. Glucotoxicity can result in structural damage and functional impairment of brain cells and nerves, haemorrhage of cerebral blood vessel, and increased accumulation of amyloid beta. These are potential mechanisms underlying diabetes-related dementia (7).

Type 2 diabetes and Alzheimer's disease are both highly prevalent diseases worldwide, and each is associated with high-morbidity and high-mortality. Numerous clinical studies have consistently shown that type 2 diabetes confers a two-fold increased risk for dementia, including dementia attributable to Alzheimer's disease. Cerebral vascular disease is likely to be playing a role. But increased Alzheimer's disease neuropathologic changes, specifically neuritic amyloid plaques and neurofibrillary tangles, are also posited mechanisms. The clinicopathological studies to date demonstrate type 2 diabetes to be consistently associated with infarcts, particularly subcortical lacunar infarcts, but not Alzheimer's disease neuropathologic changes, suggesting the association of type 2 diabetes with dementia may largely be mediated through cerebral vascular disease. Growing interest exists in insulin resistance (8).

May Alzheimer's Disease Induce Type 2 Diabetes?

A wealth of evidence indicates a strong link between type 2 diabetes and neurodegenerative diseases such as Alzheimer's disease. Brain atrophy, reduced cerebral glucose metabolism and central nervous system insulin resistance are features of both Alzheimer's disease and type 2 diabetes. Aβ and hyperphosphorylated tau may also have roles in pancreatic β-cell dysfunction and in reducing insulin sensitivity and glucose uptake by peripheral tissues such as liver, skeletal muscle, and adipose tissue. This suggests a role for these Alzheimer's disease-related proteins in promoting type 2 diabetes. Recent evidence also suggests that islet amyloid polypeptide (IAPP, or amylin) accumulates in the brain of Alzheimer's disease patients and may interact with Aβ to exacerbate the neurodegenerative process (9).

More recent evidence also provides new insights in exploring the contribution of the Alzheimer's disease pathogenic amyloid-β (Aβ) and tau proteins to type 2 diabetes. Uncertainty still remains concerning the degree of relative risk of type 2 diabetes to the development of cognitive impairment and dementia and other factors that should be taken into account when estimations of risk are made. There is a great deal of evidence from imaging studies of increased brain atrophy and greater impairment in brain function in type 2 diabetics compared to non-diabetics. Neuroimaging has provided insight into the relationship between type 2 diabetes, brain function and dementia and together with other biomarkers has provided potential associations with Alzheimer's disease-related pathology in particular determining associations with amyloid plaque deposition and tau accumulation. Testosterone levels may influence the metabolic abnormalities that have been associated with both type 2 diabetes and Alzheimer's disease, including insulin resistance, obesity, oxidative stress, and chronic inflammation. Testosterone also downregulates the enzyme BACE1 which is involved in the generation of Aβ. While BACE1 is well recognized for its role in Alzheimer's disease, it also plays an important role in type 2 diabetes in that it influences insulin sensitivity. Another link between Alzheimer's disease and diabetes is the fact that insulin degrading enzyme is also a major Aβ-degrading enzyme, and testosterone has been shown to modulate expression of insulin degrading enzyme. Dicarbonyl compounds react with amino acids to form advanced glycation end-products (AGEs), which have been implicated in the pathology and advancement of many chronic and degenerative diseases, including type 2 diabetes and Alzheimer's disease. In type 2 diabetes, AGEs are thought to contribute to retinopathy, neuropathy, nephropathy, and cognitive impairment; whereas in Alzheimer's disease, AGEs lead to oxidative stress, chronic inflammation and mitochondrial dysfunction, all of which are important factors in the pathogenesis of Alzheimer's disease. The links now understood to exist between type 2 diabetes and Alzheimer's disease consolidate the theory that there are common pathogenic mechanisms at play. Many of these pathogenic mechanisms are similar to those of cardiovascular disease (10). From the above it becomes clear that the mechanism of development of Alzheimer's disease and diabetes have a similar basis.

What Is a Relative Risk for Type 2 Diabetes to Induce Dementia?

Out of 15 epidemiologic studies 14 studies reported positive associations, of which 9 were statistically significant. Risk estimates ranged from 0.83 to 2.45. The pooled adjusted risk ratio was 1.57 (95% confidence interval (CI): 1.41–1.75), with a population-attributable risk of 8%. Smoking and hypertension, when comorbid with type 2 diabetes, had odds of 14 and 3, respectively. Of the 5 studies that investigated the interaction

between type 2 diabetes and apolipoprotein E ε4, 4 showed positive associations, of which 3 were significant, with odds ranging from 2.4 to 4.99. The pooled adjusted risk ratio was 2.91 (95% CI: 1.51–5.61). Risk estimates were presented in the context of a key confounder – cerebral infarcts – which are more common in those with type 2 diabetes and might contribute to the manifestation of clinical Alzheimer's disease. There was evidence from clinico-neuropathological studies that demonstrates the following: first, cerebral infarcts are more common than Alzheimer's disease -type pathology in those with type 2 diabetes and dementia. Second, those with dementia at post-mortem are more likely to have both Alzheimer's disease type and cerebrovascular pathologies. Finally, cerebral infarcts reduce the number of Alzheimer's disease lesions required for the manifestation of clinical dementia, but they do not appear to interact synergistically with Alzheimer's disease type pathology. Therefore, the increased risk of clinically diagnosed Alzheimer's disease seems to be mediated through cerebrovascular pathology (11).

The study examined the association of diabetes with the onset of dementia (including Alzheimer's disease, vascular dementia and any dementia) and mild cognitive impairment by using a quantitative meta-analysis of longitudinal studies. All studies that examined the relationship between diabetes and the onset of dementia or mild cognitive impairment were included. Pooled relative risks were calculated using fixed and random effects models. Nineteen studies met inclusion criteria for this meta-analysis, and 6,184 subjects with diabetes and 38,530 subjects without diabetes were included. All subjects were without dementia or mild cognitive impairment at baseline. The quantitative meta-analysis showed that subjects with diabetes had higher risk for Alzheimer's disease (relative risk (RR): 1.46, 95% CI: 1.20–1.77), VD (RR: 2.48, 95% CI: 2.08–2.96), any dementia (RR: 1.51, 95% CI: 1.31–1.74), and MCI (RR: 1.21, 95% CI: 1.02–1.45) than those without. The quantitative meta-analysis showed that diabetes was a risk factor for incident dementia (including Alzheimer's disease, vascular dementia and any dementia) and mild cognitive impairment (12).

The aim of another study was to investigate the association between diabetes and the risk of all type dementia, Alzheimer's disease and vascular dementia. A total of 28 studies contributed to the analysis. Pooled RR of developing all type dementia (n = 20) was 1.73 (1.65–1.82, I (2) = 71.2%), Alzheimer's disease (n = 20) was 1.56 (1.41–1.73, I (2) = 9.8%) and vascular dementia (n = 13) was 2.27 (1.94–2.66, I (2) = 0%) in patients with diabetes mellitus. The results showed a 73% increased risk of all type dementia, 56% increase of Alzheimer's disease and 127% increase of vascular dementia in diabetes patients (13).

Several large longitudinal population-based studies have shown that the rate of cognitive decline is accelerated in elderly people with diabetes mellitus. But the relation between diabetes and Alzheimer's disease is still an area of controversy. A total of 17 studies involving 1,746,777 individuals were included in the meta-analysis. After pooling these 17 studies, subjects with diabetes had significant higher incidence of AD than those without diabetes (RR: 1.53, 95% CI: 1.42–1.63). Study concluded that the risk of AD is higher among people with diabetes than in the general population (14). The values presented in selected studies show that the relative risk for dementia in type 2 diabetes is quite serious.

How Type 2 Diabetes Influences Conversion of Mild Cognitive Impairment to Alzheimer's Disease?

There is an increased rate of mild cognitive impairment diagnosis, but little is known about how to treat or predict dementia outcomes in persons with the condition. There were 76 eligible articles in this study. Diabetes and prediabetes increased risk of conversion from amnestic mild cognitive impairment to Alzheimer's dementia. Diabetes was also associated with increased risk of conversion from any type or non-amnestic mild cognitive impairment to all-cause dementia. Metabolic syndrome and prediabetes predicted all-cause dementia in people with amnestic and any type mild cognitive impairment, respectively. Diabetes increased the risk of conversion to dementia (15).

Type 2 diabetes mellitus is associated with dementia. Mild cognitive impairment is a key determinant in this association. It is not clear whether type 2 diabetes mellitus increases the risk of conversion from MCI to dementia; 634 participants with type 2 diabetes mellitus – mild cognitive impairment, 261 type 2 diabetes mellitus participants who were cognitively intact, and 585 mild cognitive impairment participants without diabetes. During follow-up, 152 and 49 subjects developed dementia in the mild cognitive impairment and cognitively-intact cohorts, amounting to an adjusted hazard ratio of 1.66 (95% CI: 1.07–2.26). In a survival analysis of the cohorts, MCI accelerated the median progression to dementia by 2.74 years. In a multivariable analysis of the type 2 diabetes mellitus – mild cognitive impairment cohort, major risk factors for dementia were age > 75 years and longer durations of diabetes, while significantly reduced risks of dementia were associated with oral hypoglycaemic agents and HMG-CoA reductase inhibitors. Insulin was not associated with significantly changed risk. Type 2 diabetes mellitus – mild cognitive impairment may aggravate the clinical picture as a concomitant factor (16). It is not quite clear whether type 2 diabetes mellitus increases the risk of conversion from MCI to dementia.

What is the Role of Antidiabetic Medication?

Type 2 diabetes is characterized by accelerated cognitive decline and higher dementia risk. Controversy exists regarding the impact of metformin, which is associated with both increased and decreased dementia rates. A prospective observational study was conducted on 1,037 community-dwelling older participants without dementia aged 70–90 years at baseline (Sydney Memory and Ageing Study). Exclusion criteria were dementia, major neurological or psychiatric disease, or progressive malignancy. Neuropsychological testing measured cognitive function every 2 years; a battery of tests measured executive function, memory, attention/speed, language, and visuospatial function individually. These were used to determine the measure of global cognition. Incident dementia was ascertained by a multidisciplinary panel. Total brain, hippocampal, and parahippocampal volumes were measured by MRI at baseline and 2 years (n = 526). Of 1,037 participants, 123 had diabetes, 67 received metformin (DM+MF) and were demographically similar to those who did not (DM-noMF), and participants without diabetes (noDM). DM+MF had significantly slower global cognition and executive function decline compared with DM-noMF. Incident dementia was significantly higher in DM-noMF compared with DM+MF (OR = 5.29, 95% CI: 1.17–23.88, p = 0.05). It was concluded that older people

with diabetes receiving metformin have slower cognitive decline and lower dementia risk (17).

Diabetes is a risk factor for dementia, but whether antidiabetic medication decreases the risk is unclear. Study was performed as a nested case-control study within a cohort of all 176,250 patients registered with type 2 diabetes in the Danish National Diabetes Register between 1995 and 2012. This population was followed for dementia diagnosis or anti-dementia medication use until May 2018. Using risk-set sampling, each dementia case (n = 11,619) was matched on follow-up time and calendar year of dementia with four controls randomly selected among cohort members without dementia (n = 46,476). Ever use and mean daily defined dose of antidiabetic medication was categorized in types (insulin, metformin, sulfonylurea and glinides combined, glitazone, dipeptidyl peptidase 4 (DPP4) inhibitors, glucagon-like peptide 1 (GLP1) analogs, sodium-glucose transport protein 2 (SGLT2) inhibitors, and acarbose). Use of metformin, DPP4 inhibitors, GLP1 analogs, and SGLT2 inhibitors were associated with lower odds of dementia after multiple adjustments (ORs of 0.94 (95% CI: 0.89–0.99), 0.80 (95% CI: 0.74–0.88), 0.58 (95% CI: 0.50–0.67), and 0.58 (95% CI: 0.42–0.81), respectively, with a gradual decrease in odds of dementia for each increase in daily defined dose. Analyses of the most frequent treatment regimes did not show any synergistic effects of combined treatment. It was concluded that use of metformin, DPP4 inhibitors, GLP1 analogs and SGLT2 inhibitors was associated with lower risk of dementia in patients with diabetes (18).

Another study aims to review epidemiological, clinical and preclinical data that weigh on pathophysiological links, mechanisms of disease and associations between type 2 diabetes and dementia including therapeutic approaches in type 2 diabetes and its pathophysiological implications for dementia. Therapeutic approaches for type 2 diabetes have shown inconsistent results in relation to dementia prevention and delay of cognitive decline. Evaluation of the effect of antidiabetic medications and non-pharmacological interventions in dementia prevention in type 2 diabetes is promising but has thus far offered inconsistent results (19). Antidiabetic medications have currently inconsistent results.

Proposition of Term “Type 3 Diabetes” for Alzheimer’s Disease

Recently researchers proposed the term “type 3 diabetes” for Alzheimer’s disease because of the shared molecular and cellular features among type 1 diabetes, type 2 diabetes and insulin resistance associated with memory deficits and cognitive decline in elderly individuals. Recent clinical and basic studies on patients with diabetes and Alzheimer’s disease revealed previously unreported cellular and pathological findings among diabetes, insulin resistance and Alzheimer’s disease. These studies are also strengthened by various basic biological studies that decipher the effects of insulin in the pathology of Alzheimer’s disease through cellular and molecular mechanisms. For instance, insulin is involved in the activation of glycogen synthase kinase 3β, which in turn causes phosphorylation of tau, which involved in the formation of neurofibrillary tangles. Interestingly, insulin also plays a crucial role in the formation amyloid plaques (20).

Similar to dementia, the risk for developing type 2 diabetes mellitus increases with age, and type 2 diabetes mellitus also increases the risk for dementia, particularly Alzheimer’s disease. Although type 2 diabetes mellitus is primarily a peripheral disorder and Alzheimer’s disease is a central nervous system disease, both share some common features as they are chronic and complex diseases, and both show involvement of oxidative stress and inflammation in their progression. These characteristics suggest that type 2 diabetes mellitus may be associated with Alzheimer’s disease, which gave rise to a new term, type 3 diabetes. In this study peripheral proteomic biomarkers of Alzheimer’s disease and type 2 diabetes mellitus were searched based and identified 17 common biomarkers that were differentially expressed in both patients with Alzheimer’s disease or type 2 diabetes mellitus when compared with healthy controls (21). Currently, clinical and epidemiological and molecular knowledge justify the use of the term “type 3 diabetes” for Alzheimer’s disease.

CONCLUSION

Type 2 diabetes mellitus has been shown to increase the risk for cognitive decline and dementia, such as in Alzheimer’s disease and vascular dementia. Despite extensive research and numerous publications, the mechanisms underlying these associations remain unclear. Because of similar molecular and cellular features among type 1 and type 2 diabetes and insulin resistance associated with memory deficit and cognitive decline, some researches proposed the term “type 3 diabetes” for Alzheimer’s disease.

In this context, from the point of view of prevention of both of these diseases, it is important that reducing the incidence of one disease can result in a reduction in the incidence of the other. This is naturally significant from a public health point of view.

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Conflict of interests

None declared

REFERENCES

1. Fiore V, De Rosa A, Falasca P, Marci M, Guastamacchia E, Licchelli B, et al. Focus on the correlations between Alzheimer's Disease and Type 2 Diabetes. Endocr Metab Immune Disord Drug Targets. 2019;19(5):571-9.
2. Biessels GJ, Despa F. Cognitive decline and dementia in diabetes mellitus: mechanisms and clinical implications. Nat Rev Endocrinol. 2018 Oct;14(10):591-604.
3. Beeri MS, Bendlin BB. The link between type 2 diabetes and dementia: from biomarkers to treatment. Lancet Diabetes Endocrinol. 2020 Sep;8(9):736-8.
4. Hayden MR. Type 2 Diabetes Mellitus increases the risk of late-onset Alzheimer's Disease: ultrastructural remodeling of the neurovascular unit and diabetic gliopathy. Brain Sci. 2019 Sep 29;9(10):262. doi: 10.3390/brainsci9100262.
5. Salas IH, De Strooper B. Diabetes and Alzheimer's Disease: a link not as simple as it seems. Neurochem Res. 2019 Jun;44(6):1271-8.
6. Baglietto-Vargas D, Shi J, Yaeger DM, Ager R, LaFerla FM. Diabetes and Alzheimer's disease crosstalk. Neurosci Biobehav Rev. 2016 May;64:272-87.
7. Lee HJ, Seo HI, Cha HY, Yang YJ, Kwon SH, Yang SJ. Diabetes and Alzheimer's Disease: mechanisms and nutritional aspects. Clin Nutr Res. 2018 Oct;7(4):229-40.

8. Pruzin JJ, Nelson PT, Abner EL, Arvanitakis Z. Review: relationship of type 2 diabetes to human brain pathology. Neuropathol Appl Neurobiol. 2018 Jun;44(4):347-62.
9. Bharadwaj P, Wijesekara N, Liyanapathirana M, Newsholme P, Ittner L, Fraser P, et al. The link between Type 2 Diabetes and neurodegeneration: roles for amyloid-β, amylin, and tau proteins. J Alzheimers Dis. 2017;59(2):421-32.
10. Martins RN. Understanding the link between dementia and diabetes. J Alzheimers Dis. 2017;59(2):389-92.
11. Vagelatos NT, Eslick GD. Type 2 diabetes as a risk factor for Alzheimer's disease: the confounders, interactions, and neuropathology associated with this relationship. Epidemiol Rev. 2013;35:152-60.
12. Cheng G, Huang C, Deng H, Wang H. Diabetes as a risk factor for dementia and mild cognitive impairment: a meta-analysis of longitudinal studies. Intern Med J. 2012 May;42(5):484-91.
13. Gudala K, Bansal D, Schifano F, Bhansali A. Diabetes mellitus and risk of dementia: a meta-analysis of prospective observational studies. J Diabetes Investig. 2013 Nov 27;4(6):640-50.
14. Zhang J, Chen C, Hua S, Liao H, Wang M, Xiong Y, et al. An updated meta-analysis of cohort studies: Diabetes and risk of Alzheimer's disease. Diabetes Res Clin Pract. 2017 Feb;124:41-7.
15. Cooper C, Sommerlad A, Lyketsos CG, Livingston G. Modifiable predictors of dementia in mild cognitive impairment: a systematic review and meta-analysis. Am J Psychiatry. 2015 Apr;172(4):323-34.
16. Ma F, Wu T, Miao R, Xiao YY, Zhang W, Huang G. Conversion of mild cognitive impairment to dementia among subjects with diabetes: a population-based study of incidence and risk factors with five years of follow-up. J Alzheimers Dis. 2015;43(4):1441-9.
17. Samaras K, Makkar S, Crawford JD, Kochan NA, Wen W, Draper B, et al. Metformin use is associated with slowed cognitive decline and reduced incident dementia in older adults with Type 2 Diabetes: The Sydney memory and ageing study. Diabetes Care. 2020 Nov;43(11):2691-701.
18. Wium-Andersen IK, Osler M, Jørgensen MB, Rungby J, Wium-Andersen MK. Antidiabetic medication and risk of dementia in patients with type 2 diabetes: a nested case-control study. Eur J Endocrinol. 2019 Nov;181(5):499-507.
19. Bello-Chavolla OY, Antonio-Villa NE, Vargas-Vázquez A, Ávila-Funes JA, Aguilar-Salinas CA. Pathophysiological mechanisms linking Type 2 Diabetes and dementia: review of evidence from clinical, translational and epidemiological research. Curr Diabetes Rev. 2019;15(6):456-70.
20. Kandimalla R, Thirumala V, Reddy PH. Is Alzheimer's disease a Type 3 Diabetes? A critical appraisal. Biochim Biophys Acta Mol Basis Dis. 2017 May;1863(5):1078-89.
21. Diniz Pereira J, Gomes Fraga V, Morais Santos AL, Carvalho MDG, Caramelli P, Braga Gomes K. Alzheimer's disease and type 2 diabetes mellitus: a systematic review of proteomic studies. J Neurochem. 2021 Mar;156(6):753-76.

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