DOBOSZ, Maciej, RUDZIŃSKI, Gracjan, CHILIMONIUK, Zuzanna, WIĘSYK, Piotr, KUSAK, Natalia & CHAŁUPNIK, Aleksandra. Is Alzhezimer's disease a New Type Diabetes? Crosstalk between two serious disorders: review. Journal of Education, Health and Sport. 2023;13(3):119-127. eISSN 2391-8306. DOI http://dx.doi.org/10.12775/JEHS.2023.13.03.017
https://apcz.umk.pl/JEHS/article/view/41588
https://zenodo.org/record/7569172

The journal has had 40 points in Ministry of Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of December 21, 2021. No. 32343. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical Culture Sciences (Field of Medical sciences and health sciences); Health Sciences (Field of Medical Sciences and Health Sciences). Punkty Ministerialne z 2019 - aktualny rok 40 punktów. Załącznik do komunikatu Ministra Edukacji i Nauki z dnia 21 grudnia 2021 r. Lp. 32343. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).

Received: 29.12.2022. Revised: 17.01.2023. Accepted: 25.01.2023.

Is Alzhezimer's disease a New Type Diabetes? Crosstalk between two serious disorders: review

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Abstract:
Introduction and purpose: More and more reports suggest that diabetes plays an important role in the pathogenesis of Alzheimer's disease (AD). Understanding this link may provide a new approach to modulating the onset and progression of sporadic AD cases. The aim of the study is to present the current state of knowledge on the basic mechanisms and factors influencing the development of AD in patients with type 2 diabetes in the context of clinical practice.
State of knowledge: It is estimated that up to 80% of Alzheimer's patients have glucose intolerance or diabetes. Impaired insulin signaling can lead to abnormal processing and accumulation of beta-amyloid protein, which can result in memory deficits and cognitive decline. Insulin deficiency can also cause over-activity of the GSK3 enzyme, leading to tau hyperphosphorylation and senile plaque accumulation. Diabetes can also cause fibrotic changes in cerebral vessels, disrupting brain metabolism and potentially leading to hippocampus atrophy. The release of cytokines during the metabolic syndrome can also cause oxidative stress and neuroinflammation, which may contribute to neuronal atrophy. It has been reported that healthy diet, physical exercises and prevention of metabolic diseases may reduce the incidence of AD.
Conclusions: Epidemiological data and pathophysiological studies indicate a significant relationship between these diseases that AD is sometimes called Type 3 diabetes. Early detection of hyperglycemia and its proper management, may be crucial in the context of the clinical prevention of dementia diseases. It is essential to pay attention to the cognitive abilities of patients with metabolic diseases.

Key words: Diabetes, Alzheimer's disease, Oxidative stress, Metabolic disorders, Cognitive disorders, Dementia;

INTRODUCTION AND PURPOSE

Type 2 diabetes mellitus (T2DM) and Alzheimer's disease (AD) are two prevalent chronic conditions that significantly impact global morbidity and mortality. A growing body of evidence suggests that T2DM and AD may be linked through common pathophysiological pathways, including inflammation, oxidative stress, and insulin resistance.

Multiple epidemiological studies have demonstrated that individuals with T2DM are at increased risk for developing AD, and conversely, those with AD are at greater risk for developing T2DM. The relationship between these two conditions is complex and not fully understood, but understanding this link may have important implications for the prevention and treatment of both T2DM and AD.
This review aims to provide an overview of the current knowledge regarding the relationship between T2DM and AD. We will discuss the various mechanisms that may underlie this relationship, as well as the potential clinical and therapeutic implications of this association.

RESULTS

Insulin resistance and deficiency

Insulin receptors and insulin signaling affect glucose homeostasis, cognition and neuronal integrity through influencing several receptor-mediated mechanisms including neurotransmitter build-up calcium influx, and synaptic connections, neurogenesis and apoptosis [1]. It is estimated that up to 80% of Alzheimer's patients have glucose intolerance or diabetes [2,3]. Insulin insensitivity has been linked to memory deficits, cognitive decline and many of the characteristic symptoms shown in AD [4]. Cognitive decline process appears to start early in prediabetic stages of insulin resistance [5,6]. In which fasting blood glucose levels are inappropriately high, but below the threshold for diabetes, which referring to the mechanistic relationship between insulin sensitivity and dementia [7]. Significant reductions in insulin-like growth factor (IGF-1) and insulin levels have been demonstrated in post-mortem brain analysis of Alzhaimer's patients [8]. The imbalance in the production and elimination of amyloid-β (Aβ) leads to its over accumulation in the brain, which can be an inducing factor in the development of the disease [9]. Consequently, emerging clinical and animal model studies are indicating that diabetes is likely to be a contributing factor to the emergence of overt Aβ pathology in AD patients [10–12]. The group of Dr Holtzman discovered there is a possibility that hyperglycaemia modulates the levels of Aβ through the activity of neurons. By using in vivo glucose clamps and microdialysis techniques, they have shown that hyperglycaemia increases Aβ levels by modifying neuronal activity via KATP channels [13]. Some studies have demonstrated how insulin changes AβPP processing by increasing BACE-1 expression. The increase in BACE1 expression resulted from an increase in translation via the PERK-eIF2α phosphorylation pathway, rather than more identified alterations in lysosomal GGA3-dependent degradation or transcriptional mechanisms [14]. In addition, in a study in vitro, it has been demonstrated that insulin is able to raise Aβ extracellular concentrations by hastening AβPP/Aβ transport out of the endoplasmic reticulum and trans-Golgi network into the plasma membrane by suppressing its degradation mediated by an enzyme that degrades insulin, a metalloprotease responsible for the insulin degradation and an Aβ-degrading major soluble enzyme at neutral pH [15]. What is remarkable - there are several clinical studies showing that the brains of people with AD contain increased levels of saturated free fatty acids (FFAs) in comparison to the brains of healthy individuals and in patients with metabolic syndrome [16]. Consistent with some results, local IR and alterations in central glucose metabolism have the potential to be considered early markers of AD diagnosis [17]. Insulin resistance in AD and diabetes may result in hyperinsulinaemia, and hence the saturation of insulin enzymes enzymes (IDE) to degrade insulin and Aβ [18].

Chronic inflammation / oxidative stress

Lack of insulin responsiveness, insulin receptor upregulation, impaired insulin receptor binding or faulty activation of the insulin signalling cascade lead to defective insulin signalling in the brain in both AD and T2D. A key implication of this modified cascade is diminished neuronal glucose uptake, manifesting as compromised neuroplasticity, deficit neurotransmitters, breakdown of the bioenergetic pathway and ignition of the fatal cascade of inflammation [18]. While microglia show phenotypic plasticity in response to trauma, these changes are further modified in the presence of diabetes. By itself, hyperglycaemia is able to increase microglia proliferation and increase the expression of pro-inflammatory markers including CD16, TNF-α and inducible nitric oxide synthase (iNOS), resulting in microglia displaying an exaggerated response to a secondary stimulus of inflammation [19]. Reactive oxygen species (ROS) toxicity has been linked between Alzheimer's disease (AD) and type 2 diabetes mellitus (T2DM). Sufferers with both AD and T2DM have impaired, oxidised DNA, RNA, protein and lipid products, all of which may be used as likely markers of disease progression. Oxidative stress has been identified as a major cause of the development of both AD and T2DM, a number of pathways may be associated with the production of ROS production [20]. A disturbed gastrointestinal ecosystem (dysbiosis) seems to be a contributing factor in the progression and sustenance of many diseases, such as depression, type 2 diabetes and Alzheimer's disease [21]. Dysbiosis has been shown to exert regulatory functions on inflammation and oxidative stress [22].

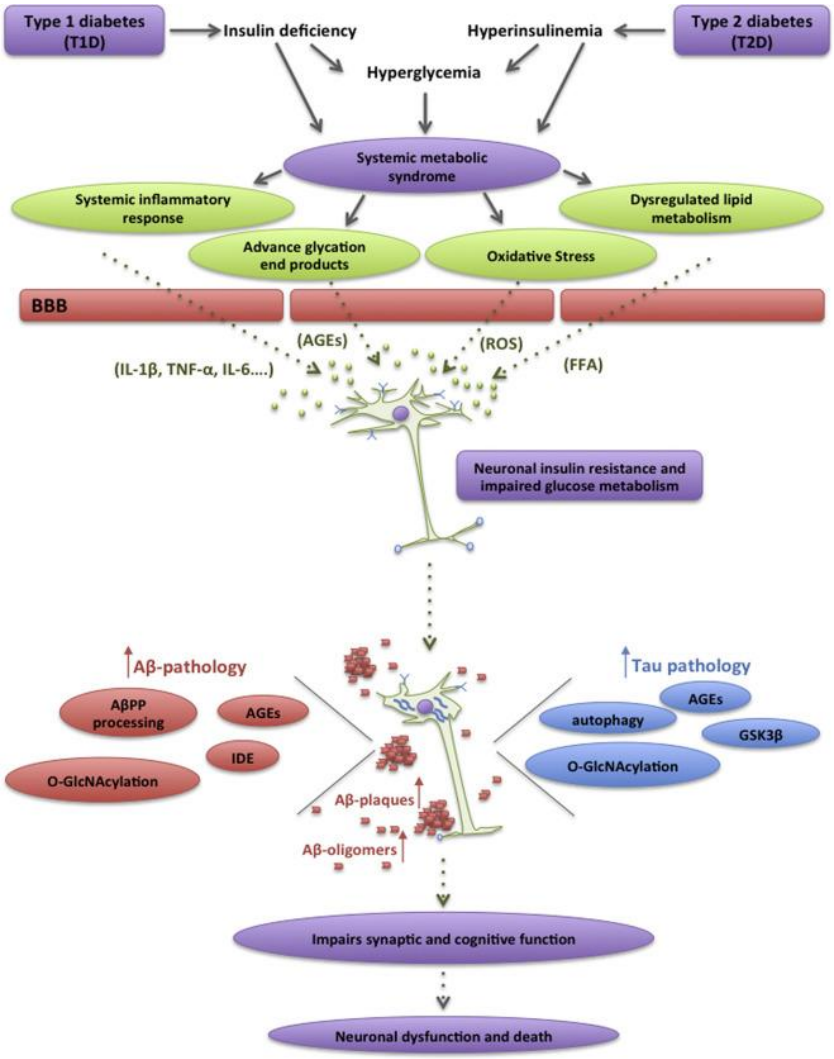

Fig. 1. Factors determining the pathophysiology of dementia in diabetes [23]

Cerebrovascular dysfunction

Simultaneous vascular changes are seen more often in the brains of diabetic and AD patients than in those with AD without diabetes [24]. High levels of glucose or advanced glycation end products up-regulate the production of vascular cell adhesion molecule-1 (VCAM- 1) in endothelial cells and following endothelial inflammation, and decrease NO generation, thereby enhancing atherosclerosis [25,26].

The production of pro-inflammatory signalling molecules like cytokines, chemokines and adhesion molecules by glial cells, neurons and endothelial cells conditions the Blood–Brain Barrier's integrity and the immune cell migration into the brain. Indeed, processes of inflammation foster changes in capillaries structurally, such as segmentation, thickening, pericyte atrophy, laminin accumulation in the basement membrane and elevated permeability of blood vessels to plasma proteins. These processes have been suspected in various diseases, which include Alzheimer's disease (AD), vascular dementia (vascular stroke), Parkinson's disease and diabetes [27].

Insulin resistance decreases nitric oxide production resulting in a change in the reflex of blood vessels and higher levels of adhesion molecules which recruit to the vessel wall by monocytes. Monocytes invade deeply into the vascular wall and induce inflammation, resulting in arteriosclerosis [28].

Lately, ganglioside GM1, one of the membrane-localized glycolipids, has been mediating vascular insulin resistance by promoting inflammatory stimulation and/or senescence. Aging-associated GM1 levels are known to promote insulin resistance in human aortic endothelial cells (HAECs) [29].

Glial pathology

A number of chronic systemic inflammatory conditions, such as obesity, type 2 diabetes and periodontitis, can trigger immunological priming or unfavourable glial activation, increasing neuroinflammation and thus raising the risk or facilitating AD progression. Therefore, reducing peripheral inflammation is a possibly successful strategy to reduce the incidence of AD [30].

Insulin is key involved in the expansion and maintenance of excitatory synapses [31] and formation of dendritic spines by activating Ras-related pathways and AKT-mTOR pathways [32], that are integral to the signaling of insulin [33]. Insulin also affects cell survival by modulating apoptotic pathways and intermediates involved in the apoptotic cascade [34].
Reduced glucose transporters have been shown to correlate with abnormal tau hyperphosphorylation in neurodegenerative diseases [35].
Clinical research has suggested a potential link between post-stroke cognitive impairment and AD. Present evidence suggest that bradykinin is likely to be one of the crucial players, particularly in diabetes, where the pro-inflammatory and pro-obesity effects of bradykinin appear to explain the elevated mortality and size of ischaemic lesions in the acute phase of stroke. In diabetes, chronic inflammatory imbalances essentially alter not only the intracellular microglia signalling environment, and also the endothelial vasculature, all of that contributing to the cognitive impairment observed in PSCI [36].

Hippocampus atrophy

According to some opinions, the hippocampus is a structure in some way protected against the changes induced by diabetes [18]. However, it has unfortunately been proven that the hippocampus of patients with diabetes atrophies to nearly the same degree as during regular Alzheimer's disease [37]. This atrophy is more pronounced in women than in men, even despite better glycaemic control in women [38]. A number of recent studies have suggested that impaired insulin signalling in the hippocampus impairs memory and other executive functions, blaming a decline in insulin signalling and the simultaneous development of insulin resistance [11,39,40]. The effect of type 2 diabetes on the thickness of the cerebral cortex was investigated. There were 124 people with T2DM and and 693 without T2DM. The study involved 124 people with T2DM and and 693 without T2DM. The researchers found no direct effect of T2DM on cortical thickness or the decline in cognitive function, but there was, an indirect pathway connecting T2DM and cognitive decline via baseline cortical thickness[41]. However, another study in 2014 found that diabetes reduces brain volume[42], including a decrease in hippocampal volume[43].

Genes present in diabetes that predispose to amyloidogenesis - IDE, GSK3B, IAPP

Diabetes and impaired insulin signalling in the brain are associated with the pathogenesis of Alzheimer's disease (AD). The relationship of diabetes and AD-related amyloid pathology is found to be stronger among those carrying the apolipoprotein E (APOE) ε4 gene allele, the strongest genetic risk factor for late AD. APOE4 gene mice were shown to have compromised insulin action, particularly in old age. The researchers found that the APOE4 protein, produced by the gene, was able to bind more aggressively to insulin receptors on the neuronal surface than its regular counterpart, APOE3. Once the receptor is blocked, the sticky APOE4 protein starts to clump together and becomes toxic. Insulin signal processing becomes increasingly impaired, starving brain cells [44].
Lately, there has been increasing evidence that glycogen synthase kinase-3β (GSK-3β) could be a possible link connecting DM and AD. In DM, GSK-3β is a key enzyme for glycogen synthesis, which has a crucial role in regulating blood glucose levels. In AD, GSK-3β has an important function in the hyperphosphorylation of the microtubule-associated protein tau (tau), another pathological feature in AD. Furthermore, insulin resistance in DM is likely to cause β-amyloid (Aβ) accumulation, that will be removed by tau, yet the excessive phosphorylation of tau exacerbates the neurotoxicity even further [45].
During another study, injection of islet amyloid polypeptide (IAPP) was followed by an increase in its production in the pancreas. Following colocalisation experiments between IAPP and Aβ using islet amyloid from patients with type 2 diabetes and the brains of AD subjects, IAPP was identified to be localized in brain deposits of Aβ [46].

Ways of prevention

As long as there is not any appropriate treatment for diabetes that can prevent from dementia, most scientists suggest to focus on prevention. Jin-Tai Yu et al. identified numerous factors that increase the risk of developing Alzheimer's disease. These factors include: poor education, high body mass index in late life, poor cognitive activity, depression, hyperhomocysteinemia, stress, midlife hypertension, head trauma, and orthostatic hypotension (strong evidence, Level A), as well as mid-life obesity, late-life weight loss, lack of exercise, sleep disorders, smoking, cerebrovascular disease, frailty, and atrial fibrillation (poorer evidence, Level B). It has been proven that fighting with those risk factors can have a huge impact on slowing down the progression of Alzheimer's disease. [47].

Healthy diet plays crucial role in slowering cognitive decline. A range of different nutrients and foods have been investigated that correlated with reduced risk of cognitive impairment, dementia and AD, for example, omega-3 polyunsaturated fatty acids and vitamins such as the B complex (vitamins B6 and B12 and folate), antioxidants (vitamins A, C and E) and vitamin D [48]. Most studies showed significant improvements in cognitive outcomes (memory and executive functions or global cognition) with ketone supplementation or a ketogenic diet. [49] Another study showed that green tea intake substantially decreased body weight, body fat (BF) and body mass

index (BMI). A favorable effect of green tea drinking was observed at lower doses of green tea (dose ≤800 mg/day) and in obese subjects in long-term intake (> 8 weeks) [50]. Rohith N Thota redesigned a study in which they tested whether curcumin supplementation has an effect on reducing peptides associated with insulin resistance. Curcumin supplementation significantly reduced circulating levels of IAPP and GSK-3 in comparison to the placebo group. This could potentially confound insulin resistance and contribute to a reduction in the production of Tau protein and amyloid B which will translate into a reduced risk of Alzhaimer's disease [51]. There is a considerable correlation between Metabolic syndrome and AD [52]. Several epidemiological studies have shown that middle-aged obesity, as assessed by means of anthropometric parameters like BMI and/or waist-to-hip circumference ratio, is related to an elevated late-life risk of dementia, independently of any other cardiovascular or socio-economic background risk factors [53–55]. Nonetheless, some studies have agreed that a reverse causality effect exists, according to which BMI decreases in the years before the development of dementia. There has been a suggestion that this 'obesity paradox' or weight loss directly prior to and throughout the clinical phase of dementia is connected to heightened caloric expenditure and hypothalamic dysregulation[56]. In the Baltimore Longitudinal Study of Aging (BLSA), obesity in middle age was related to earlier age of disease occurrence, greater amyloid load on PET imaging and greater Braak's NFT grade at autopsy, but not to higher CERAD scores of neuritic plaques [57]. Insulin resistance in AD and diabetes has the potential to lead to hyperinsulinaemia, thereby saturating enzymes of insulin-degradation (IDE) to degrade insulin and Aβ [18]. A number of recent investigations suggest that the frequency of AD is greater in T2D subjects and obese individuals, suggesting shared underlying mechanisms driving these conditions [56,58]. It has been proven that regular physical exercise has a favourable impact on the conventional cardiovascular risk factors (e.g. decreased vascular flow, diabetes) implicated in the pathogenesis of Alzheimer's disease. The exercise is also conducive to neurogenesis by increasing metabolic agents (e.g. ketone bodies, lactate) and muscle-derived myokines (cathepsin-B, irisin), both of which stimulate in turn the release of neurotrophins such as cerebral-derived neurotrophic agent. In addition , regular exercise has an anti-inflammatory impact and improves the redox state of the brain, thus reducing the underlying pathophysiological features of Alzheimer's disease (e.g. amyloid-β deposition) [59]. Increased levels of physical exercise have been shown to be protective against AD dementia and inversely, lower levels of physical activity are known to be linked to a greater risk of developing AD [60,61]. Exercise has the potential to foster neuronal plasticity and AβPP non-amyloidogenic processing by augmenting brain-derived neurotrophic factor (BDNF) signalization [62]. The protective relationship between physical activity in leisure time and AD risk is dose-dependent, based on a recent meta-analysis of prospective studies [63].

Intermittent fasting was assessed for its impact on metabolic dysfunction and cognitive function in a rat model of Alzheimer's disease and menopause. Intermittent fasting decreased skin temperature and fat mass and had enhanced tolerance of glucose with reduced food intake. Intermittent fasting further protected memory loss: short-term and special memory. Accordingly, intermittent fasting has the potential to counteract certain metabolic pathologies associated with menopause and protect from age-related memory deterioration [64].

There is a significant relationship between sleep disturbances and the development of dementia, particularly Alzheimer's disease (AD). According to a meta-analysis, individuals with insomnia have an increased risk of developing AD, while those with respiratory sleep disorders have an increased risk of all types of dementia, including AD and vascular dementia. Poor sleep habits and sleep disorders, such as short sleep duration, shift work, obstructive sleep apnea, and insomnia, are common among adults with type 2 diabetes and may predict worse outcomes in individuals with existing diabetes. Impaired sleep and dysregulation of circadian rhythms can lead to an imbalance of the parasympathetic and sympathetic nervous systems, as well as elevated blood insulin and glucose levels, which may make the brain more vulnerable to the consequences of diabetes and dementia [65–68].

Smoking-related brain oxidative stress has been identified as a possible promoting mechanism for pathology and increased AD risk [69]. There was a linear dose-response correlation observed between cigarette smoking and T2DM risk; a 16% higher risk of T2DM for every increment of 10 cigarettes smoked per day. They found that 5.4% of T2DM cases in women and 18.8% of T2DM cases in men and may be attributed to cigarette smoking [70].

CONCLUSIONS

It is well established that there is a significant correlation between diabetes and the development of Alzheimer's disease (AD). Multiple studies have demonstrated that individuals with diabetes, particularly type 2 diabetes, have a higher risk of developing AD compared to those without diabetes. This increased risk may be due to various mechanisms, including hyperinsulinemia, insulin resistance, and inflammation. Additionally, diabetes has been shown to exacerbate the pathological features of AD, such as amyloid beta plaque accumulation and tau protein phosphorylation. Effective management of diabetes, including blood glucose control and lifestyle modifications, may potentially reduce the risk of developing AD and slow its progression. Further research is

needed to fully understand the underlying mechanisms and identify potential interventions for preventing or mitigating the impact of diabetes on AD.

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