Diabetes Mellitus, Alzheimer's Disease and Vascular Dementia

Subjects: Nursing

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Type 2 diabetes mellitus (T2D) is a metabolic disease reaching pandemic levels worldwide. In parallel, Alzheimer's disease (AD) and vascular dementia (VaD) are the two leading causes of dementia in an increasingly long-living Western society. Numerous epidemiological studies support the role of T2D as a risk factor for the development of dementia.

Keywords: Alzheimer's disease ; dementia ; vascular dementia ; diabetes ; insulin ; neurodegeneration ; neuron death ; neuroinflammation

1. Introduction

Diabetes mellitus (DM) is a chronic disease characterized by elevated blood glucose levels due to the body's inability to produce sufficient insulin or use it efficiently. Although there are different types of DM, the most common are type 1 diabetes (T1D) and type 2 diabetes (T2D) [1].

On the other hand, dementia is a syndrome that encompasses a heterogeneous group of diseases of the central nervous system (CNS), characterized by cognitive impairment [2]. In terms of incidence, the main types of dementia are Alzheimer's disease (AD), vascular dementia (VaD), dementia with Lewy bodies and frontotemporal lobar dementia [3]. According to a WHO report, dementia currently affects around 50 million people, mostly from low- and middle-income countries, and about 10 million cases are registered every year [4]. It is estimated that by 2030, 82 million people will have dementia [4], and this number will increase to 130 million by 2050 [5].

AD is a neurodegenerative disease of the central nervous system and is characterized by a progressive deterioration of higher brain functions, affecting the ability to make decisions and execute them [6][7]. AD patients survive an average of 7 years, and slightly less than 3% of those affected live more than 14 years after diagnosis [8]. In terms of epidemiology, AD is the leading cause of dementia and occurs most frequently in people over 65 years of age (with a 10% prevalence), representing between 60% and 75% of all dementia cases [9][10]. The major risk factor for AD is age, and as life expectancy progressively increases, so does the number of people affected by this disease. Currently, more than 50 million people worldwide suffer from AD, with an associated economic cost of 30,000 EUR/year/patient in developed countries [11]. Projections for 2050 suggest that the number of people affected could exceed 107 million [9]. These rates represent an unbearable economic and social drain.

2. Link between Diabetes Mellitus, Alzheimer's Disease and Vascular Dementia

Over the last 15 years, the relationship between T2D, AD and VaD has been extensively studied. Based on published studies, the data suggest that T2D, among other metabolic pathologies, could contribute to the development of a neurodegenerative process that would be a precursor to the development of dementia. Following this idea, DM seems to play a role at this level. The bibliography shows that the incidence of both pathologies increases with age, and it is common to find them coexisting. In fact, some authors claim that 45% of people with T2D suffer from mild cognitive impairment [12], raising the chance of developing dementia by 1.5–2.5 times [13]. In contrast, people with established dementia show insulin disturbances, with altered fasting glucose levels [14].

It also appears that the risk of dementia increases as patients develop other risk factors, including heart disease, hyperlipidemia, hypercholesterolemia or smoking, although T2D is important for its synergistic capacity [13][15][16]. In this relationship, insulin levels and insulin resistance are best correlated with the severity and progression of VaD [17][18].

Furthermore, it seems that DM promotes vascular damage caused by high levels of glucose in the blood, which is accentuated if it coexists with other pathologies that affect blood vessels, such as arteriosclerosis and hypertension [19][20].

The relationship between T2D and VaD can be based on processes that converge between the two pathologies, described below.

2.1. Insulin Receptors in Central Nervous System

Insulin receptors at the central level are located in astrocytes and neuronal synapses and are very abundant in regions of the basal forebrain, such as the septum (origin of cortical and hippocampal cholinergic innervation) [21], and areas particularly relevant for learning and memory processes, such as the cortex and the hippocampus [22]. This wide distribution of insulin receptors explains the involvement of insulin in cognitive processes [23], probably mediated by relevant neurotransmitters in AD, such as norepinephrine and acetylcholine [24][25]. Insulin also contributes to synaptic plasticity mediated by insulin receptors [26]. Similarly, insulin regulates glucose metabolism as the main nutrient of the CNS, directly involved in learning and memory processes [27][28]. In fact, the acute administration of insulin to humans and rodents produces an improvement in cognitive processes and memory [29][30][31][32][33] as well as an increase in the expression of insulin receptors in the dentate gyrus, leading to better performance in spatial memory tests [32][34]. Indeed, some authors have postulated that insulin could counterbalance AD pathology [35].

2.2. Type 2 Diabetes Progression Correlated with Pancreatic Amilin Deposition as Brain Aβ Deposition Correlated with Alzheimer's Disease Progression

The progression of T2D is correlated with pancreatic amylin deposition, which is similar to that of brain Aβ. In addition, insulin, amylin and Aβ are degraded peripherally by the insulin-degrading enzyme (IDE) [36]. This suggests that these substrates may compete at this level [37]. It has been postulated that substrate imbalance may influence the pathogenesis of AD and T2D [38].

From another point of view, insulin resistance detected in AD patients could be mediated by a decrease in the activity of the enzymes responsible for its degradation. Both the insulin-degrading enzyme (IDE) and neprelisine (NEP) are involved in insulin degradation as well as Aβ and amylin degradation [39]. Accordingly, it has been postulated that an imbalance of substrates can affect the degradation rate of other substrates and possibly influence the pathogenesis of T2D and AD [38][40][41][42]. A decrease in IDE expression may result in reduced insulin and Aβ degradation in the brain [41][43]. Consequently, it is conceivable that actions promoted by elevated insulin levels, or its deficiency, may also be a link between T2D and AD.

2.3. Insulin-Like Growth Factor

Insulin and the insulin-like growth factor (IGF) have similar structures and play a significant role in the regulation of aging. IGF acts as a cellular growth factor but also plays a hormonal role in regulating growth and metabolism at the systemic level [44]. IGF is the main prenatal and postnatal growth factor. This is why low levels of insulin during gestation can lead to slower growth and low height and weight of the offspring [33][45]. In contrast, an increase in insulin levels at an early stage, as occurs in maternal T2D, leads to large and overweight children, among other complications [46].

In this context, insulin plays a crucial role in the development of neuronal complexity, as well as in neurogenesis in early neonatal development. In this sense, insulin deprivation during early life may result in reduced neural network development, whereas exogenous administration of insulin may promote increased neural development and complexity [33][47]. A more complex neural network is a protective factor against the development of dementia [48]. Based on the aforementioned, a gestational environment with altered insulin levels could condition the possible development of dementia in the later stages of life [49][50].

Additionally, plasma inulin can cross the BBB in a soluble form and gain access to neurons, microvasculature and even immature neuronal bodies [51]. Insulin plays a key role as a growth-regulating hormone during the early stages of life. In animal models, it has been shown that an imbalance in insulin levels also impairs neurogenesis in early life [33], as well as in more mature and long-lived phases [52]. In addition, the coexistence of T2D with AD pathology reduces neurogenesis and thus neuronal replacement from stages prior to cognitive decline [53]. Insulin is also involved in the regulation of neuronal and synaptic functions in the hippocampus, cortex and cerebellum, protecting neurons from neurodegeneration and cell death [54][55][56][57].

2.4. Insulin Promotes Typical Features of Alzheimer's Disease

Tau pathology is one of the main features of AD, and many studies have reported the impact of insulin dysfunction and diabetes on it [58][59][60]. Indeed, high insulin levels in the brain, induced by prediabetes or T2D, may increase the hyperphosphorylation of tau protein [61]. It is feasible that higher levels of phosphorylated tau observed in hyperinsulinemia and T2D states could be mediated by insulin receptors at the central level [59]. Additionally, T1D hypoinsulinemia may increase tau hyperphosphorylation [62]. In this regard, a clinical phase I study with the drug SCR-1693 showed a reduction in tau protein phosphorylation levels associated with an improvement in cognitive and central insulin resistance [63].

Inflammation of the CNS is increasingly regarded to play a role in cognitive disorders such as dementia [64]. Insulin promotes the expression of proinflammatory cytokines such as α-TNF and IL6 [65], which are the most important proinflammatory cytokines. Moreover, these cytokines negatively affect the metabolism of Aβ oligomers [66].

On the other hand, one of the mechanisms proposed to link insulin to cognitive impairment is its role in Aβ metabolism [37][41]. In this regard, insulin promotes the amyloidogenic pathway by modulating β and γ-secretases [40][67][68]. Additionally, insulin inhibits or hinders the passage of Aβ through the BBB [69]. Following this idea, insulin would prevent the clearance of Aβ and promote its accumulation in the brain [70]. In return, Aβ interferes with insulin signaling in the CNS; in fact, soluble Aβ oligomers may disrupt insulin signaling in hippocampus neuronal cultures [71].

2.5. Role of Prediabetes and Diabetes Mechanism in the Neurodegenerative Process of Alzheimer's Disease and Vascular Dementia

Previous epidemiological and clinical studies support a close relationship between T2D and AD [72][73]; however, the underlying linking mechanisms are not yet fully understood. It also remains unclear whether hyperinsulinemia and insulin resistance, indicative of a prediabetic state prior to T2D, may induce or accelerate central pathology in AD, in a similar manner to that induced by T2D. Indeed, glucose and insulin play a crucial role in maintaining normal brain activity, and alterations of insulin-dependent functions could be associated with central pathological conditions observed in AD [66][72][74].

The available scientific evidence on this relationship supports that the first pathological event in the DM disorder, as a promoter of dementia, is insulin resistance in the CNS [17][51][75]. Insulin plays an important role in cell growth and differentiation, as well as in protein synthesis [51][76]. Additionally, insulin inhibits catabolic processes such as glycolysis, lipolysis and proteolysis [76]. The wide distribution of insulin receptors throughout the CNS underscores its importance in central glucose homeostasis processes and its role in cognitive processes and neuronal development [51]. In this sense, it has been described that alterations in insulin balance in the CNS accelerate the brain aging process, increasing vascular damage and primarily affecting synaptic plasticity [76][77][78]. Vascular damage is often one of the first central events in diabetes [79], even in the prediabetic stages, and compensatory high insulin levels are sufficient to cause this damage [80]. Simultaneously with vascular damage, brain aging occurs, which is translated into reduced neuronal arborization and synaptic density. The loss of neuronal and synaptic density has been proposed as one of the best pathological markers for the assessment of AD. There is ample scientific evidence that different states of Aβ aggregation, from the most soluble forms to the formation of senile plaques, are neurotoxic [81][82][83]. It has been reported that synaptic loss promotes cell dedifferentiation and ultimately neuronal death [84].

In the second stage, scholars propose that the sequence of events involves the inflammatory process and glial activation. It has been suggested that the insulin resistance typical of prediabetes and T2D may exacerbate the inflammatory process when it interacts with the presence of Aβ [66]. Previous studies report that the presence of Aβ is sufficient to promote microglial activation and the inflammatory process [85][86]. Vascular damage and the T2D-induced imbalance of Aβ pathology toward more soluble forms have been shown to induce an increase in cytotoxic and pro-inflammatory cytokines and increase microglial activity [87][88]. This inflammatory process would increase oxidative molecular species, generating a harmful environment that would promote neurodegenerative processes [89]. Microglial cells, faced with vascular damage and the accumulation of toxic substances such as Aβ, begin to produce proinflammatory cytokines (IL-1β, IL-6, IL-18 and tumor necrosis factor-α (TNF-α)), chemokines (CCL1, CCL5, CXCL1), small messenger molecules (prostaglandins, NO) and ROS [90]. Although most cells involved in this process of neuroinflammation are microglia and astrocytes, capillary endothelial cells are also involved, as well as some infiltrating blood cells, which are more frequent when there is tissue damage in the BBB [90][91]. This pro-inflammatory ecosystem could lead to synaptic dysfunction, neuronal death and inhibition of neurogenesis [53][87][92].

3. Conclusions

Growing evidence suggests that T2D may increase the risk of developing AD. Several studies have found that insulin resistance and metabolic dysfunction associated with T2D negatively affect the brain and increase the accumulation of Aβ. Also, T2D promotes chronic inflammation, oxidative stress and vascular dysfunction in the brain which links T2D with AD and VaD.

Understanding the relationship between DM and AD is essential to prevent the development of AD through metabolic control. Likewise, knowledge of the involvement of DM in the progress and development of AD can help us address new therapeutic strategies for its treatment. In this sense, treatment to control T2D, such as metformin, has shown a beneficial effect, like neuroprotective, anti-inflammatory and antioxidant action in animal models [93][94][95]. However, limited studies in humans have shown a more discrete positive relationship with the use of metformin as a treatment for AD [96]. The possible beneficial effects of metformin as a treatment for Alzheimer's disease are still being studied and are a hot topic (for a review, see [97]).

Another emerging candidate for a therapeutic approach to AD an VaD is the application of intranasal insulin. This treatment has been shown to have beneficial effects in reducing inflammation and improving immune function. In addition, intranasal insulin improves cognitive status and helps to maintain cognitive abilities [98][99]. Other studies have shown that intranasal insulin as a treatment for AD has neuroprotective effects, and its use can maintain the insulin brain signaling to improve cognitive health [100] by reducing the P-tau/Aβ42 ratio [101] and preserving the white matter volume in deep and frontal regions, which correlates with AD progression [102]. However, recent long-term studies in humans have shown limited efficacy of intranasal insulin as a treatment for AD [101][103]. The current disagreement in the literature shows the need to carry out studies that demonstrate the usefulness of this treatment in the control of AD.

Finally, as the understanding of the relationship between T2D, AD and VaD increases, there are new opportunities for prevention and treatment. Improving glycemic control and promoting healthy lifestyles should be explored further. Thus, early attention to risk factors associated with dementia, such as T2D, may play a crucial role in preventing or delaying dementia.

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