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METABOLIC ASSOCIATION BETWEEN DIABETES MELLITUS AND ALZHEIMER'S DISEASE: NEUROPATHOLOGICAL INTERACTION?

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ABSTRACT

Diabetes Mellitus (DM) causes epidemiological dimensions of homeostasis imbalance in the population and the presence of Alzheimer's disease (AD) is becoming more prevalent worldwide. As AD is the most frequent neurodegeneration among the elderly, its relationship with DM has been increasingly discussed and investigated. We analyzed the relationship between AD and DM with its neurodegenerative disorders, metabolic correlations and neuropathological interaction in pharmacology. A narrative review was carried out, compiling articles published between 1996 and 2020 from the PubMed/MEDLINE, BVS/LILACS and Scielo databases in Portuguese, English and Spanish, using the keywords: "Diabetes Mellitus", "Alzheimer's Disease", "Type 3 Diabetes", "Insulin Resistance" and "Antidiabetics". A multifactorial correlation was observed, with insulin toxicity, hyperglycemia, presence of the Apoε 4 allele, and neurofibrillary tangle formation. The influence of pharmacology on therapy for these comorbidities was noted, highlighting the harmfulness of implemented medications. Prospective epidemiological studies should be conducted to analyze this correlation.

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INTRODUCTION

With the growing increase in the aging of the Brazilian population and changes in the age-gender-pyramid, there is a rise in the incidence of pathologies associated with senescence such as Diabetes Mellitus (DM) and dementias. According to Flor et. al, the population involvement by DM has been standing out with its increasing morbidity and mortality (1). Global epidemiological assessments indicate that 382 million individuals have DM, and may reach 592 million in 2035. Regarding mortality, it is estimated that by 2030, DM may become the seventh leading cause of death on the planet (1). In Brazil, according to data from the Epidemiological Bulletin, released by the Ministry of Health in 2020, the prevalence of DM went from 5.5% in 2006 to 7.4% in 2019, characterizing an increase of 34.5% in the period, which ratifies this disease as a major public health problem (2). According to the Alzheimer Brazil Institute, it is estimated that there are more than 45 million individuals living with dementia, and this number is expected to multiply in twenty years. Once it is known that Alzheimer's Disease (AD) is the most frequent type of neurodegeneration in Brazil, it is estimated that almost 2 million people have it, 40 to 60% of which are Alzheimer's type.

When analyzing the involvement of dementias in 195 countries, the Global Burden of Diseases, Injuries and Risk Factors, published in 2018, reported an increase of 117% between the years 1990 and 2016. In this study, the numbers rose from 20.2 million to 43.8 million, respectively, being this pathology, in general, the fifth leading cause of death in the world (3). The epidemic proportion of the prevalence of diabetes has been growing around the world in an ascending form, which has become an obstacle in the individual's homeostasis (4). The etiological mechanisms, genetics, environment and immunology, are the ones that cause the clinical, metabolic manifestations and possible complications of this chronicity. Furthermore, with regard to the pathophysiology of diabetes, there is hyperglycemia, hypoinsulinemia, hyperglucagonemia, protein glycation, variations in osmolarity, lipid changes and the level of systemic blood pressure. Conditions such as retinopathies, neuropathies and cardiovascular diseases are usually related to diabetes, however other causes have been shown to be accentuated, such as the metabolic correlation between DM and AD (5). The pioneering analysis study between these pathologies was elaborated through a control case by Hyamn

et.al, in 1984, and in 1990 a positive association was found between DM and AD (6). From that decade onwards, several studies were started in search of proof of this association, as well as the metabolic correlations between both diseases (7–9). Alzheimer's is the most common neurodegenerative disease in humans and has, with the growing increase in the aging population, become more prevalent (10). When analyzing its histopathological structure, and the molecular and biochemical abnormalities, amyloid plaques, neurofibrillary tangles, dystrophic neuritis, impaired energy metabolism, mitochondrial dysfunction, oxidative stress, synaptic degeneration and the loss of hippocampal neurons can be found as triggering factors of this dementia (11). AD is the result of an oxidized and inflammatory lesion generated from the deposition of deformed proteins in aged brains, which causes the generators of clinical manifestations such as energy shortages and synaptic disorders. In addition, in the cohort study by Tomita N et al., an analysis is presented regarding the three main components that induce the relationship between type 2 DM and the development of AD, in addition to mentioning other components associated with this cognitive decline (12). The action of insulin and glucose metabolism are shown to be considerable elements in the correlation of the development of dementia, including AD (6–9). The main mechanisms presented are generated from glucose toxicity and insulin resistance, which are related to the deposition of beta-amyloid proteins in neural plaques. This accumulation generates neurodegeneration and reduced expression of TAU, a protein that controls the dynamics of microtubules during the maturation and growth of neurites (13), which is regulated by IGF-1 (Insulin-like growth factor) associating it also, in this way, to the development of AD (14), (15), (16). Pharmacotherapy for the control and halt the progression of DM, widely disseminated, had its effectiveness explored with regard to the therapy developed for these comorbidities, thus highlighting the harmfulness of some drugs implemented for such conditions. When analyzing the correlation between both pathologies, studies have made evident the coexistence of insulin/depletion of the IGF-1 and IGF-2 genes and their resistance in the brain. De la Monte et. al , in view of this association, introduced the term Type 3 Diabetes in several studies, indicating that AD represents a specific cerebral type of diabetes. (15,17–19). The aim of this study is to analyze the metabolic correlation between DM and AD and the most evident associations, seeking to remedy the gaps in the literature, given the scarce studies that compile the main correlations observed between both pathologies. In addition, it sought to evaluate the influence of pharmacology on the modulation of the pathways present in the neuropathological interaction. Therefore, this review seeks to demonstrate the most consistent and recent theories regarding these two pathologies that are extremely prevalent and important for public health.

MATERIALS AND METHODS

In this article, the information was compiled through a narrative review, produced between April 2019 and November 2020, from the PubMed/MEDLINE, BVS/LILACS and Scielo databases. The descriptors used were: "Diabetes Mellitus", "Alzheimer's Disease", "Type 3 Diabetes", "Insulin resistance" and "Antidiabetics". Among the inclusion factors, original clinical and experimental articles, systematic reviews and theses were selected, accounting for 144 articles from which 77 were selected. Articles about the themes of individual pathologies were used, their subthemes and the correlation between them, with publications in English, Portuguese and Spanish. The exclusion criteria were articles that were not adapted to the theme of development of this article. Studies and articles available from 1989 to 2020 were reviewed, suggesting an association between DM and AD.

Development

Insulin toxicity/hyperinsulinemia: Insulin resistance is a condition commonly seen in aging, as well as in conjunction with other comorbidities. It is characterized as the lowest response expected for a pre-determined amount of insulin. This resistance, characteristic of DM 2 (type 2 Diabetes Mellitus), impairs the ability of cells to maintain their metabolism in an essential balance. This condition is strongly linked to abnormalities in peripheral tissues, such as metabolic stress and neuroinflammation (20), (21). The upregulation of pro-inflammatory cytokines (IL-1, IL-6 and TNF-α) due to the mechanisms that cause DM (Diabetes Mellitus), can generate less sensitivity to insulin and consequently in systemic inflammation. The mechanisms related to the development of resistance are able to activate inflammatory proteins such as JNK (c-Jun amino-terminal kinase), resulting in responses such as neuroinflammation (22). Among them, there is the activation of the innate immune response pathway and the amyloidogenic pathway that promote the development of dysfunction and, consequently, neuronal death (23).
In relation to insulin toxicity, this refers to changes in the amounts of the components of its signaling pathway (For example, through IRS/PI-3 kinase/Akt, an important molecule in the transport of glucose by stimulating insulin) and decrease in this response (20),(24). Furthermore, when combined with hyperglycemia, it accelerates the formation of neuritic plaques when interacting with the presence of the ε4 allele of apolipoprotein E (APOε4) (25). Insulin deficiency can be shown to be a determining factor for the development of DM. Amid this irregularity, IGF growth factors are reduced, which depletion mediates cognitive impairment in AD (26). The coexistence of insulin/depletion of IGF gene and resistance in the brain, indicate that AD represents a specific cerebral type of diabetes, which share characteristics with both DM 1 and DM 2, considering a new nomenclature for such an association: Type 3 diabetes (11), (27,28).

***Hyperinsulinemia and alteration in the tau protein*:** Tau is a microtubule-associated protein that stabilizes neuronal microtubules in the central nervous system (CNS), which plays an important role in axonal transport and synaptic transmission. Thus, due to its connection with the microtubules, it allows this stabilization and, consequently, the transport of synaptic vesicles. When analyzing the TAU protein, it is observed that it is stimulated by insulin and IGF-1, the latter being characterized as growth promotion factors with a structure similar to that of insulin (29). Therefore, given the deficiency of this hormone, the TAU protein will be affected. As a result, this protein will change to an insoluble form, losing affinity for microtubules, impairing axonal transport and synaptic transmission, thus generating dementia in AD (10,13), (30). Finally, the activation of proinflammatory signaling pathways causes changes in neuronal insulin signaling, amplifying the evidence between peripheral resistance of DM2 and the correlation with the remodeling present in AD. In addition, this rearrangement in the neuronal signaling is associated with the deterioration of synapses that lead to memory loss (6).

APOε 4: A possible correlation: Apoε is a glycoprotein found in the brain and where, in plasma, it is a component of lipoproteins, VLDL and HDL, which are responsible for the redistribution of triglycerides and cholesterol in tissues (31). When relating AD to the presence of the Apoε allele, the ε4 variant of this gene was identified, suggesting that cholesterol may be decisive in the appearance of this pathogenesis (31). Epidemiological studies suggest that this allele is present in 15% of the population, and is also observed significantly in Alzheimer's patients (32). A study by Corder et al. (33) demonstrated a biological gradient, that is, the presence of a dose-response curve. Within this perspective, the mechanisms of association are still not well understood, however in the study by Bales et al. performed in mice, demonstrated that the interruption of the Apoε gene made it impossible to deposit β-amyloid protein (34). The presence of Apoε strengthens the association of hyperinsulinemia with AD, since the increase in insulin levels was responsible for a decline in neuropsychiatric tests related to memory (35), in addition to accelerating the formation of neuritic plaques (25). Furthermore, it should be noted that individuals with DM2 and carriers of the Apoε allele, have comparatively more neuritic plaques in the hippocampus

and neurofibrillary tangles (36), showing a possible correlation between DM and AD (37). In relation to a positive evidence linking DM and cerebrovascular neuropathology, AD, a greater association is found in those with the Apoε4 allele (38). However, such an association is neither necessary nor sufficient to cause neuropathology, it only contributes to its increased risk (31). In contrast, Borestein et. al, expresses that the lack of this allele generates an association between AD and DM, questioning the analyzed above (39).

Neurofibrillary tangles: Neurofibrillary tangles are sets of proteins composed from the deposition of β-amyloid peptide. These are formed by the accumulation of proteins in the neural plaques of the brain parenchyma that occur as a consequence of circulating insulin levels (14), (20),(35). This deposition triggers dystrophic neuritis that affects neural cell death and neurodegeneration (14), (40), (41). Recently published studies elucidate the theory that, with the advancement of AD pathology, there is a progressive increase in precursors of β-amiolide protein (42), (43). Neurofibrillary tangles are repeatedly mentioned as possible causes of AD when related to insulin levels (14). Referring to this factor, a study carried out by the University of Oxford, showed that individuals with diabetes have, comparatively, a greater amount of neurofibrillary tangles when related to those without diabetes (36).

Energy dysfunctions

Mitochondria have an important energy supply function to the body. In the face of aging, its function becomes limited due to injuries resulting from its own metabolism, caused by oxidative stress (44), (45). Derived from free radicals of oxygen and nitrogen atoms that, in excess, are associated with cell damage, oxidative stress causes DNA damage and generates anomalous proteins due to amino acid changes. These structural and functional modifications of proteins alter the conformation of amino acids that will result in atypical proteins. Thus, during the course of life, there is less degradation of defective proteins, leading to storage that will induce cell degeneration and diseases, such as AD (44). The imbalance of inflammatory components has a deleterious characteristic, that causes lesions in the peripheral tissues, which can result in neurodegenerative and metabolic diseases (20), (46). DM2 generates this inflammatory dysregulation, so that by raising the levels of IL-6 (interleukin-6) they damage the components of the CNS causing brain inflammation. Likewise in AD, the association between this imbalance and oxidative stress causes a reduction in anti-oxidative capacity, expanding the association between these comorbidities (36,45). Through micro-immune analysis, it is possible to observe the presence of components of the immune system in the inflammatory response in patients with AD. Among these elements are the overproduction of pro-inflammatory cytokines, such as TNF-α (tumor necrosis factor α) and the activation of macrophages in adipose tissue (20). The inflammation is related to the inhibition of the insulin receptor substrate (IRS-1, Insulin receptor substrate -1), which emphasizes the role of the connection of peripheral resistance with decreased cerebral insulin signaling, present in AD (20).

The metabolic triad formed by: mitochondria, insulin and JNK signaling – an inflammatory protein, which, when activated, alters insulin signaling by reducing the entry of glucose into cells (47) – causes neuronal dysfunction and a mitochondrial energy disorder, present in both pathogens (20,48,49).

Antidiabetic drugs in Alzheimer's Disease therapy

*A*nother fundamental tenet that supports the mechanisms shared between DM and AD is based on the analysis that drugs used for one disease may be a risk factor for the onset or progression of the other. In this sense, several studies were found relating the modulation of AD to the implementation of drugs for another designation (20),(49),(50)(51),(52).

The ways of controlling or stabilizing AD would be by recomposing the damaged brain insulin signaling, which can be provided with its activation and/or even with the glucagon receptor protein (GLP-1, Glucagon-like peptide -1) (20). Because it is a chronic disease with a great impact on global public health, DM has a wide range of drugs and therapies for its treatment. Among the articles analyzed, the most discussed drugs in the literature, which sought treatment for both pathologies, were: Metformin, Intranasal Insulin, Pioglitazone, Rosiglitazone and GLP-1 inhibitor.

a. **Biguanides – Metformin**

Metformin (dimethylbiguanide) is an antihyperglycemic agent of the biguanide class, used for treating DM2. It was initially reported by the French physician Jean Sterne, in 1957, as a good therapeutic drug in the treatment of DM, being approved by the FDA (Food and Drug Administration) for commercialization in the United States of America in 1994 (50,53). Its function is to reduce blood glucose levels, its hepatic formation, absorption by the gastrointestinal tract and improves insulin sensitivity, thus increasing the use of glucose by the body (49).

Beeri et. al, in a study published in 2008, addressed the use of metformin in the treatment of these comorbidities, pointing out a positive relationship between the use of oral antidiabetics associated with insulin in the treatment of DM. A substantial reduction in the density of neuritic plaques and β-amyloid deposition has been documented. This aspect delays the development of the mechanisms of severity and progression of AD and DM2 in the modulation of the neurobiological response, which is associated with insulin (54).

In a comparative analysis study, carried out by Karki et. al, the benefits of using metformin in the treatment of AD was based on the insulin resistance present in this comorbidity. Thus, the use of this medication would lead to improved sensitivity to this hormone in patients with AD. This beneficial effect is also seen in the reduction of neuronal damage that share pathways resulting in its survival. In addition, they inhibit advanced glycation end products (AGEs), JNK cascade and phosphorylation of the MAPT (microtubule-associated protein tau) gene, maintaining impaired synaptic transmission in AD. However, this study observed that the use of Metformin in the context of AD leads to the development of apoptosis, neuroinflammation, formation of neurofibrillary tangles and the aggregation of β-amyloid (49).

b. ***Thiazolidinediones - Pioglitazone and Rosiglitazone***

Insulin resistance, present in DM, is a risk factor for the development of AD. Thus, studies and clinical trials have sought to analyze drugs that have therapeutic effects in controlling the insulin pathway for AD (51, 52, 55–57). Pharmacological treatment with the class of antidiabetics called thiazolidinediones (TZD), having as its main representatives Rosiglitazone and Pioglitazone, act as agonists of the peroxisome proliferator-activated receptors gamma (PPARγ). As a result, they increase insulin sensitivity and cause glial anti-inflammatory effects (58),(21). Due to their potential for reducing peripheral insulin and increasing sensitivity to insulin, studies have raised the therapeutic role of these drugs in the treatment of AD (51). In a prospective, randomized and controlled study by Hanyu et al., an improvement in cognitive function was noticed in AD patients using Pioglitazone and Rosiglitazone. These agonists reduced β-amyloid formation and inflammatory products, which leads to neuroprotective effects (59). Yan et al., in a study using animal models of AD, analyzed that Pioglitazone presented only a small reduction in the levels of β-amyloid, not affecting the deposition of amyloid plaque or the activation of the microglia, indicating low efficacy of this PPARγ agonist (60). In a study carried out with 693 patients, double-blind, randomized and placebo-controlled, the use of monotherapy with Rosiglitazone in AD was analyzed by means of the allele stratification of Apoε4. The results have not shown significant efficacy in cognition with these allele carriers (55). However,

Pedersen et.al and Nicolakakis et. al, in experimental studies in AD mice, demonstrated a reduction in the deposition of amyloid plaques and vascular inflammation, as well as an improvement in the formation of synapses and, consequently, of memory and cognition (61,62).

c. New route of administration - intranasal insulin

Insulin for daily use is preferably administered subcutaneously due to its chemical and pharmacological characteristics. Considering the need for a drug with rapid absorption and action, it became a choice as an alternative route of administration for inhaled insulin. (63). Through intranasal administration, the hormone passes directly through the olfactory epithelium composed of sensory neurons that allow this substance to reach the blood-brain barrier (BBB) quickly, contributing to its central action (64). Reger *et. al*, in a double-blind observational study with 25 participants, analyzed the use of intranasal insulin and its benefits in patients with AD. The groups were separated, with one receiving placebo and the other receiving intranasal insulin. Thus, they obtained positive results in relation to plasma protein, β-amyloid peptide, in addition to improving functional status and attention in patients receiving the drug, demonstrating a possible new approach in the treatment of neurodegenerative pathologies (65). Similarly, Claxton *et. al*, in an exploratory study, showed that the use of inhaled insulin has beneficial effects on the development of β-amyloid and on cognitive functionality in the prodromal stage of AD (66). Plastino *et. al*, in an observational study with insulin administration, analyzed cognitive loss in relation to the development of AD in diabetics (67). The patients were separated into 2 groups, with DM2 and mild to moderate AD. Thus, one used oral antidiabetic and the other used it in conjunction with insulin therapy. It was evident, therefore, that the group who used the treatment with both practices showed improvements in cognitive deficit, assessed by the Mini-Metal State Examination (MMSE) and Clinical Global Impression (68).

d. Incretinomimetics – GLP-1

GLP-1 (glucagon-like peptide-1) is derived from the class of incretin hormones, which is responsible for the regulation of insulin secretion depends on glucose. This peptide is produced by enteroendocrine L cells in the distal portion of the gastrointestinal tract. Its primary function is to reduce glucagon secretion and stimulate insulin secretion, thus reducing circulating glucose levels (69). GLP-1, through its receptor coupled to G protein (GLP-1R), exerts its insulinotropic action, present not only in pancreatic cells, but also in the CNS (dendrites and cell bodies of hippocampal and neocortical neurons) (70,71). Examples of drugs that uses GLP-1 agonists as possible therapeutic approaches are: exenatide, liraglutide and lixisenatide (70,72). The mechanism of incretinomimetics is due to their agonist interaction with the receptors and their signaling pathway similar to their endogenous form (72). In pre-clinical trials, the correlation of beneficial use of AD therapy in patients with DM2 was analyzed. Li et. al, in a genetic study with mice using exenatide, showed neuroprotection in order to reduce β-amyloid peptides and phosphorylation of the TAU protein (73). Accordingly, other experimental studies have shown that the administration of this drug has prevented and reversed TAU hyperphosphorylation by restoring the insulin signaling pathway leading to the increase of PI3K/Akt activation (74,75). In the midst of these metabolic changes, such models formulate that the administration of this agonist has cognitive benefits and provide integrity of the hippocampal nerve cells. In addition, the reduction of local inflammatory response and increase in physiological cholinergic activity was demonstrated (76). Xiong et. al in a studying animal models with AD showed that the use of liraglutide minimized neurodegeneration, thus preserving a neurophysiological process. This conservation occurs through the O-glycosylation of the TAU protein, leading to reducing in its hypophosphorylation, generating activation of the signaling pathway of JNK and ERK insulin (77), which increase the intracellular glucose transport through the IRS-1 receptor (22). The development and drug research for the treatment of DM is still ongoing and with constant discoveries and innovations. To that end, it is necessary to analyze the interactions of pharmacological groups and the correlations that lead to the pathological development between AD and DM. Thus, with scientific commitment, progress towards the determination of new drugs and therapies that provide beneficial outcomes for those patients with these diseases will be possible.

FINAL CONSIDERATIONS

The metabolic correlation between DM and AD has been verified as the studies are carried out. Several underlying pathophysiological mechanisms are shared between these pathologies, which helped in the formation of evidence of causal factors. The presence of this correlation was shown by the development of insulin toxicity, hyperglycemia, presence of Apoε4 allele and formation of neurofibrillary tangles. The influence of pharmacological therapeutics applied to these comorbidities, shed light on an unsatisfactory response of some drugs administered for such conditions. However, the pharmacology of usual medications such as those of the classes of biguanides, thiazolidinediones, intranasal insulin and incretinomimetics, had their uses in the treatment of DM presenting positive results, as cognitive benefit by modulating pathways, entailing stagnation or the delay of the evolution of both diseases. Thus, they appear as possible target choices in DM therapy and concomitantly in AD. In the light of this literature review, consistent sources of information were found that demonstrate a strong relationship between AD and DM. The high population prevalence of these both diseases causes an important public health problem, turning the correlation extremely relevant. In this concern, scientific commitment is necessary for further research on the subject, especially with regard to the issue of pharmacology of antidiabetics in the treatment of Alzheimer Disease.

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