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REVIEW

Alzheimer's disease as a neurodegenerative manifestation of type 2 diabetes

La enfermedad de Alzheimer como manifestación neurodegenerativa de la diabetes tipo 2

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ABSTRACT

The research addressed the relationship between Type 2 Diabetes Mellitus (DM2) and Alzheimer's disease, two pathologies of high prevalence and impact. Although traditionally considered independent diseases, they were shown to share common pathophysiological mechanisms such as insulin resistance, oxidative stress and chronic inflammation. Scientific evidence allowed the hypothesis of Alzheimer's as a possible 'type 3 diabetes' to be proposed, highlighting the implication of genetic factors, such as the ε4 allele of the APOE gene. In addition, antidiabetic therapies with neuroprotective potential, such as intranasal insulin and metformin, were analysed. This complex and multifactorial relationship offered new therapeutic and preventive perspectives for both diseases, especially in older adults.

Keywords: Diabetes Mellitus; Alzheimer's; Neurodegeneration; Insulin Resistance; Treatment.

RESUMEN

La investigación abordó la relación entre la Diabetes Mellitus Tipo 2 (DM2) y la enfermedad de Alzheimer, dos patologías de alta prevalencia e impacto. Aunque tradicionalmente se consideraron enfermedades independientes, se demostró que comparten mecanismos fisiopatológicos comunes como la resistencia a la insulina, el estrés oxidativo y la inflamación crónica. La evidencia científica permitió proponer la hipótesis del Alzheimer como una posible "diabetes tipo 3", resaltando la implicancia de factores genéticos, como el alelo ε4 del gen APOE. Asimismo, se analizaron terapias antidiabéticas con potencial neuroprotector, como la insulina intranasal y la metformina. Esta relación compleja y multifactorial ofreció nuevas perspectivas terapéuticas y de prevención para ambas enfermedades, especialmente en adultos mayores.

Palabras clave: Diabetes Mellitus; Alzheimer; Neurodegeneración; Resistencia a la Insulina; Tratamiento.

INTRODUCTION

Type 2 Diabetes Mellitus (DM2) and Alzheimer's disease represent two of the most significant challenges for public health worldwide due to both their high prevalence and their impact on patients' quality of life. Traditionally studied as independent pathologies -one of a metabolic nature and the other neurodegenerative- in recent years, growing evidence suggests a close connection between the two.[1] This relationship has given rise to new pathophysiological hypotheses, such as the proposal to consider Alzheimer's disease as a form of "type 3 diabetes". Understanding the mechanisms linking DM2 with cognitive impairment and neurodegeneration has become crucial for the development of more comprehensive and practical therapeutic approaches.

DEVELOPMENT

Type 2 diabetes mellitus (DM2) is a chronic metabolic disease characterized by elevated blood glucose levels due to insulin resistance or insufficient insulin production. Its prevalence has increased considerably in recent decades, especially in older adults, and it is considered one of the main threats to global public health.[2,3] In addition to its classic complications, such as retinopathy, nephropathy, and cardiovascular disease, recent studies have begun to link it to neurodegenerative diseases such as Alzheimer's disease.

Alzheimer's disease is the most common cause of dementia and represents one of the leading causes of disability in the elderly. It is characterized by the abnormal accumulation of β-amyloid plaques and neurofibrillary tangles of hyperphosphorylated tau protein, which produce progressive neuronal deterioration and loss of cognitive functions.[4,5]

In recent years, evidence has emerged suggesting a pathophysiological connection between DM2 and Alzheimer's disease. This relationship has been so significant that some researchers have proposed the term "type 3 diabetes" to refer to Alzheimer's disease as a manifestation of metabolic syndrome in the brain.[6,7] This hypothesis is based on the fact that insulin resistance and chronic hyperglycemia affect critical brain functions, such as synaptic plasticity, neuronal energy metabolism, and neuroprotection.

One of the most studied mechanisms in this relationship is brain insulin resistance, which impedes the proper use of glucose by neurons, leading to synaptic dysfunction and cell death. This resistance also interferes with the elimination of β-amyloid, promoting its accumulation in the brain.[8] In parallel, chronic inflammation and systemic oxidative stress present in DM2 contribute to neuronal damage, favoring a neurodegenerative environment similar to that observed in patients with Alzheimer's disease.[9]

In addition, hyperglycemia favors the formation of advanced glycation products (AGEs), which alter the structure and function of essential proteins, including enzymes and neuronal receptors. These molecules also induce inflammatory responses in the central nervous system, promoting neurotoxicity.[10]

On the other hand, genetic factors also play an important role. For example, the presence of the ε4 allele of the APOE gene has been related to an increased risk of both Alzheimer's disease and complications in patients with DM2, which reinforces the hypothesis of a common genetic component between both pathologies.[11]

Regarding treatment, some studies have suggested that certain antidiabetic drugs could influence the development or progression of cognitive impairment. Intranasal insulin, for example, has been shown to improve cognitive performance without causing hypoglycemia by acting directly on brain receptors.[7,12] Therapies with metformin and GLP-1 analogs are also being evaluated due to their neuroprotective effects observed in preclinical and clinical studies.

Along these lines, research such as the Chilean study on "type 2 diabetes mellitus, family history of diabetes and cognitive impairment in older adults" has shown that patients with DM2 and family history have a higher probability of developing dementia compared to those without these factors.[13]

Finally, evidence suggests that when DM2 and Alzheimer's coexist, a reduction in systemic oxidative stress may be observed compared to patients with only one of the two diseases. This finding raises the possibility of protective or modulatory mechanisms that have not yet been fully understood and opens a new avenue for clinical research.[7,9,14]

In summary, the relationship between DM2 and Alzheimer's disease is complex and multifactorial. It involves standard metabolic, inflammatory, and genetic processes that could act in synergy to promote neurodegeneration. Identifying and understanding these mechanisms is essential to designing more effective prevention and treatment strategies for both pathologies.

CONCLUSIONS

In conclusion, the association between Type 2 Diabetes Mellitus and Alzheimer's disease transcends a simple epidemiological coincidence, revealing a complex interrelationship based on standard mechanisms such as insulin resistance, chronic inflammation, oxidative stress, and shared genetic factors. These findings not only broaden our understanding of the pathophysiology of both diseases but also open the door to new prevention and treatment strategies, especially those that address metabolic impairment in the central nervous system. Progress in this line of research is essential to address the growing number of people affected by these conditions, particularly in aging populations

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FINANCING

None.

CONFLICT OF INTEREST

None.

AUTHORSHIP CONTRIBUTION

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