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SYSTEMATIC REVIEW

Type II Diabetes: The New Risk Factor for Alzheimer's Disease

Diabetes tipo II: El nuevo factor de riesgo para Alzheimer

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ABSTRACT

Introduction: type 2 Diabetes Mellitus (T2DM) is a chronic disease prevalent in older adults, associated with cita microvascular and macrovascular complications. Recent studies suggest a link between T2DM and an increased risk of dementia, particularly Alzheimer's disease. The main hypothesis of this study suggests that inflammation and alterations in glucose metabolism, characteristics of T2DM, may contribute to the development of Alzheimer's pathology.
Method: a systematic review was conducted on studies investigating the relationship between T2DM and Alzheimer's disease. Observational studies examining patients with T2DM, and a confirmed diagnosis of cognitive impairment or Alzheimer's disease were included. Searches were performed in databases such as PubMed and Google Scholar, with articles published between 2000 and 2024.
Results: out of 29 studies found, 4 relevant articles were selected. The data reveals a significant association between T2DM and an increased risk of cognitive impairment in older adults, highlighting mechanisms such as microcirculatory damage, ß-amyloid accumulation, and cerebral insulin resistance. Additionally, it was found that systemic oxidative stress is lower when both diseases coexist, which may be related to a lower cognitive decline compared to patients suffering from only one of the two diseases.
Conclusion: the systematic review confirms a significant relationship between T2DM and Alzheimer's disease, supporting the hypothesis that metabolic processes and insulin resistance are key factors in the progression of cognitive decline. The findings suggest that when both diseases coexist, systemic oxidative stress is moderated, opening new areas of research on protective or modulatory mechanisms. However, additional studies are needed to confirm causality and explore specific interventions that reduce the risk of Alzheimer's in T2DM patients.

Keywords: Alzheimer's Disease; Type II Diabetes Mellitus; Insulin Resistance; Risk Factors; Type III Diabetes.

RESUMEN

Introducción: la Diabetes Mellitus tipo 2 (DM2) es una enfermedad crónica prevalente en adultos mayores, asociada con complicaciones microvasculares y macrovasculares. Estudios recientes sugieren un vínculo entre la DM2 y un mayor riesgo de demencia, particularmente la enfermedad de Alzheimer. La hipótesis principal de este estudio sugiere que la inflamación y las alteraciones en el metabolismo de la glucosa, características de la DM2, podrían contribuir al desarrollo de la patología de Alzheimer.
Método: se realizó una revisión sistemática de estudios que investigan la relación entre la DM2 y el Alzheimer. Se incluyeron estudios observacionales que examinaron a pacientes con DM2 y diagnóstico confirmado de deterioro cognitivo o Alzheimer. Las búsquedas se realizaron en bases de datos como PubMed y Google Académico, con artículos publicados entre 2000 y 2024.

Resultados: de los 29 estudios encontrados, se seleccionaron 4 artículos pertinentes. Los datos revelan una asociación significativa entre la DM2 y el riesgo aumentado de deterioro cognitivo en adultos mayores, destacando mecanismos como el daño microcirculatorio, la acumulación de ß-amiloide y la resistencia a la insulina cerebral. Además, se encontró que el estrés oxidativo sistémico es menor cuando ambas enfermedades coexisten, lo que podría estar relacionado con un menor deterioro cognitivo en comparación con los pacientes que padecen solo una de las dos enfermedades.
Conclusión: la revisión sistemática confirma una relación significativa entre la DM2 y el Alzheimer, apoyando la hipótesis de que los procesos metabólicos y la resistencia a la insulina son factores clave en la progresión del deterioro cognitivo. Los hallazgos sugieren que cuando ambas enfermedades coexisten, el estrés oxidativo sistémico se modera, abriendo nuevas áreas de investigación sobre mecanismos protectores o moduladores. Sin embargo, se requieren estudios adicionales para confirmar la causalidad y explorar intervenciones específicas que reduzcan el riesgo de Alzheimer en pacientes con DM2.

Palabras clave: Enfermedad de Alzheimer; Diabetes Mellitus, Tipo II; Resistencia a la Insulina; Factores de Riesgo, Diabetes Tipo III.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is one of the most common chronic diseases among older adults, characterized by insulin resistance and high blood glucose levels. In addition to its microvascular and macrovascular complications, recent research has suggested a possible link between T2DM and an increased risk of developing dementia, particularly Alzheimer's disease, which is the leading cause of cognitive decline in this population. This association suggests that the pathological mechanisms of T2DM may contribute to the development of Alzheimer's, giving rise to the concept of 'type 3 diabetes' to describe this possible connection.

Despite these advances, there are still many unanswered questions about the precise origin of this relationship. This lack of clarity highlights the need for more detailed and specific studies to understand how DM2 could influence the progression of Alzheimer's disease and vice versa. The central hypothesis of this study suggests that inflammatory processes and alterations in glucose metabolism, characteristic of DM2, could play a fundamental role in the development of Alzheimer's pathology.[1,2,3]

The objective is to explore in depth the relationship between the clinical and pathophysiological characteristics of type II diabetes and its influence on the development of Alzheimer's disease in order to identify connections that contribute to a better understanding and management of both conditions. It will also focus on analyzing how diabetes treatments may influence the development or progression of Alzheimer's disease. The aim is to determine whether these treatments have a protective effect or whether they could accelerate the pathological processes related to cognitive impairment in patients with type II diabetes.[4]

METHOD

The study is a systematic review based on the collection and analysis of data from previous research exploring the relationship between type 2 diabetes mellitus (DM2) and Alzheimer's disease.

The study's target population included articles published in English and Spanish that investigated the relationship between T2DM and Alzheimer's disease in older adults. The inclusion criteria consisted of studies that examined patients with T2DM and a diagnosis of Alzheimer's disease or related cognitive impairment confirmed through specific tests. Studies in populations with other types of diabetes, narrative reviews without primary data, and articles that did not address the direct relationship between the two conditions were excluded.

The research was conducted through searches of electronic databases such as PubMed and Google Scholar, covering publications from 2000 to the date of the study. The searches were conducted in an academic setting, using the digital and bibliographic resources available in the aforementioned databases.[5,6]

A systematic protocol was used for the search and selection of articles, including key terms such as "type 2 diabetes mellitus," "Alzheimer's," "cognitive impairment," "risk," "relationship," "epidemiology," and "type 3 diabetes." The selection of studies was carried out meticulously and in detail to ensure the quality of the information. To reduce bias, the studies were reviewed thoroughly. Data were collected on study characteristics, outcome measures, and definitions of key variables, such as blood glucose levels, indicators of insulin resistance, and clinical diagnoses of Alzheimer's disease.

As this was a systematic review, data analysis was performed using a qualitative and descriptive approach, integrating and evaluating the information obtained from the selected observational studies. Relevant information was meticulously extracted, including details on study design, participant characteristics, and main results related to type II diabetes and Alzheimer's disease. This approach allows us to understand the

relationship between the two diseases without the need for statistical analysis, focusing instead on the integration and evaluation of the available evidence.[7,8]

This approach allows us to gain a detailed understanding of the relationship between the two diseases. Due to the heterogeneity of the studies or the nature of the results, statistical analysis was not considered necessary, focusing instead on evaluating and integrating the available evidence.

RESULTS

This section presents the results obtained from an exhaustive search of research conducted through Google Scholar and PubMed, where 29 articles were found that met the inclusion and exclusion criteria. Of these, four were selected because they were considered the most relevant, as they answered the research question on the relationship between type 2 diabetes mellitus (T2DM) and cognitive impairment, including its possible link to Alzheimer's disease.

The data reviewed show that T2DM is significantly associated with an increased risk of cognitive impairment in older adults. In observational studies, a higher prevalence of cognitive impairment was reported in individuals with T2DM compared to those without the disease (see table 1). Several hypotheses have been proposed for this relationship, including microcirculatory lesions and metabolic changes that favor the formation of neurofibrillary tangles and ß-amyloid protein deposits in the brain. Alterations in insulin signaling, specifically resistance and abnormal signaling, and an imbalance between oxidizing and antioxidant species have also been observed. Although both diseases converge on free radical-mediated systemic oxidative stress, the metabolic pathways are distinct.

Table 1. Categories

Older adults	In Diabetics	Diabetic
60-65 years	1,00 (ref)	1,00 (ref)
66-70 years	1,73 (0,68;4,44)	2,16 (0,49; 9,61)
71-76 years	2,95 (1,20; 7,27)	1,61 (0,30; 8,59)
76-80 years	4,24 (1,76; 10,2)	5,83 (1,41; 24,2)
> 80 years	11,5 (5,04; 26,4)	36,8 (8,08; 167,4)
OR Trend	1,83 (1,53;2,19)	2,37 (1,68; 3,35)
p value	< 0,0001	<0,001

(Table 1) Ref.: The reference group was assigned to people aged between 60 and 65. Therefore, a value greater than 1 indicates a higher risk of cognitive impairment (MMSE < 13) in people with and without T2DM. A MMSE (Mini-Mental State Examination) score of < 13 would indicate cognitive impairment. The OR (odds ratio) for the trend indicates the probability of developing cognitive impairment for every 5 years of age increase.

The results in table 1 highlight a significant trend toward a higher risk of cognitive impairment with advancing age, both in individuals with T2DM and in those without diabetes. The OR (odds ratio) values show a steady increase in risk in both groups, with a more pronounced trend in people with T2DM, especially in those over 80 years of age.

Furthermore, when both diseases coexist, systemic oxidative stress appears to be reduced compared to the levels observed in each disease, which is associated with less cognitive decline.

This study also highlights that older adults with T2DM and/or a family history of the disease have a higher susceptibility to cognitive decline and, therefore, a higher risk of developing dementia compared to those without diabetes or a family history.

The relationship between T2DM and Alzheimer's becomes even more relevant when considering the metabolic pathways triggered by hyperglycemia and insulin resistance. These include decreased insulin signaling, inflammation, oxidative stress, and the formation of advanced glycation end products, processes that are also implicated in Alzheimer's disease.

Intranasal insulin administration, without systemic effects, has significantly improved cognitive performance in healthy adults and patients with early Alzheimer's disease. Clinical trials are currently underway to evaluate the usefulness of this form of insulin in preventing the conversion of mild cognitive impairment to Alzheimer's disease.

DISCUSSION

This systematic review provides a comprehensive overview of the significant relationship between type 2 diabetes mellitus (T2DM) and increased risk of cognitive impairment in older adults, specifically Alzheimer's disease. The studies reviewed highlight a significant association between the two.

This increased risk is in line with previous studies that have also reported a higher prevalence of cognitive impairment among patients with T2DM compared to those without the disease, supporting the hypothesis that T2DM may be a significant risk factor for cognitive impairment.

Proposed mechanisms to explain this relationship include metabolic and microcirculatory alterations, which contribute to the formation of neurofibrillary tangles and ß-amyloid protein deposits, distinctive features of Alzheimer's disease. These results are consistent with previous studies, which suggest that insulin resistance and alterations in insulin signaling in the brain play an important role in the progression of neurodegeneration.[9,10]

Other studies, such as "Association between type 2 diabetes mellitus, family history of diabetes, and cognitive impairment in older Chilean adults", reveal that patients with T2DM have a significantly higher prevalence of cognitive impairment compared to those without diabetes-supporting the hypothesis that T2DM is a key modifiable risk factor for cognitive impairment.

A novel finding in this review is the observation that when T2DM and Alzheimer's disease coexist, systemic oxidative stress is lower compared to levels observed in patients with each disease in isolation, which correlates with a lower degree of cognitive impairment.[11,12] This new finding opens up a new area of research, as it indicates a complex interaction between the two conditions that could provide clues about possible protective or modulatory mechanisms.

It is important to note that the interpretation of these findings may be subject to certain limitations. Most of the studies included in this review are observational in design, which prevents the establishment of a direct causal relationship between T2DM and cognitive impairment. In addition, heterogeneity in diagnostic criteria and cognitive function assessment tools may introduce biases that affect the generalizability of the findings.[13,14] To understand this relationship, studies are needed to examine the causality and effectiveness of specific interventions to reduce the risk of Alzheimer's disease in patients with T2DM. Genetic and environmental factors that may influence susceptibility to both diseases and how interventions targeting T2DM might affect the risk of cognitive decline should also be explored.

CONCLUSIONS

This systematic review highlights the important connection between type 2 diabetes mellitus (T2DM) and cognitive impairment, especially in the context of Alzheimer's disease. The studies reviewed show that T2DM increases the risk of memory and thinking problems in older adults and is associated with metabolic changes and damage to the brain that may worsen this process. The theories presented suggest that factors such as insulin resistance and oxidative stress may be involved in the development of Alzheimer's, making this relationship complex and suggesting that both conditions may influence each other.

In addition, it has been found that when T2DM and Alzheimer's coexist, oxidative stress in the body appears to be lower, which could indicate the presence of protective mechanisms that are worth investigating further. However, it is important to note that many of the studies reviewed are observational and have variations in the methods used, which may limit the interpretation of the results.

Interest in how diabetes treatments might affect cognitive decline opens up new opportunities for research and treatment of these problems. Future studies should focus on determining how these diseases are related to each other and evaluating new therapies and preventive strategies that could improve cognitive health in older adults at risk. In summary, understanding and addressing the relationship between T2DM and Alzheimer's disease is crucial for developing effective treatments that improve the quality of life of older adults facing these conditions.

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CONFLICT OF INTEREST
The authors declare that there is no conflict of interest.

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