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THE ASSOCIATION BETWEEN TYPE 2 DIABETES AND DEMENTIA IN ELDERLY PATIENTS: SYSTEMATIC REVIEW

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Abstract:

Objectives: *To investigate the association between diabetes and dementia in elderly patients, with a focus on understanding the potential risk factors, pathophysiological mechanisms, and clinical implications of this relationship.*

Methods*: A thorough search was conducted for pertinent literature using PubMed, SCOPUS, Web of Science, Science Direct, and Wiley Library. Rayyan QRCI was used throughout this extensive procedure.*

Results: *Our results included eleven studies with a total of 5,758,607 patients. The follow-up duration ranged from 1 year to 12 years. It is common for older diabetic individuals to have cognitive impairment that is not diagnosed. There is a substantial correlation between glycated albumin, glycated albumin/HbA1c, IL-6, superoxide dismutase, poor diabetes self-management, decreased BMI, weight loss and the cognitive performance of senior T2D patients. One study found that metformin has a protective effect on dementia risk in T2D patients while the other reported that it has no effect. Old women with T2D showed higher rates of cognitive impairment as well as lower levels of executive and global cognitive function. One study reported that lower cognitive functioning is independently correlated with larger burdens of amyloid and small vessel disease.*

Conclusion: *There is strong evidence that individuals with diabetes have a higher risk of dementia, however comprehensive epidemiological data about risk factors are scarce. The potential link between diabetes and dementia is attracting more attention in the scientific community since it is a highly relevant topic from both a public health and scientific standpoint. Investigating this connection might make some new pathways leading to neurodegeneration clearer.*

Keywords: *dementia, diabetes, T2DM, cognitive function, geriatrics, elderly.*

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BACKGROUND:

Diabetes is a chronic metabolic disorder characterized by high levels of blood sugar due to body's inability to use insulin effectively (Type 2 diabetes). It is a well-known risk factor for various complications, including cardiovascular disease, kidney disease, and neuropathy [1]. Dementia, on the other hand, is a syndrome characterized by a decline in cognitive function that interferes with daily activities. Alzheimer's disease is the most common cause of dementia, followed by vascular dementia and other less common types [2]. Both diabetes and dementia are more prevalent in the elderly population, and as the global population continues to age, the burden of these conditions is expected to increase [3].

Recent studies have suggested that there is a potential association between diabetes and dementia, especially in elderly patients. Some research has shown that individuals with diabetes have a higher risk of developing dementia compared to those without diabetes [4]. The exact mechanisms underlying this association are not fully understood, but several hypotheses have been proposed. One potential mechanism is the impact of high blood sugar levels on the brain. Chronic hyperglycemia can lead to inflammation, oxidative stress, and damage to blood vessels, which may contribute to the development of dementia. Insulin resistance, a hallmark of Type 2 diabetes, has also been implicated in the pathogenesis of dementia, as insulin plays a crucial role in brain function and neuroprotection [5].

In addition to the potential biological mechanisms, there are also several common risk factors for both diabetes and dementia that may contribute to their association. These include obesity, physical inactivity, hypertension, and dyslipidemia. These risk factors are often present in individuals with diabetes and are also known to increase the risk of cognitive decline and dementia. Furthermore, diabetes-related complications such as cardiovascular disease and stroke can further increase the risk of developing dementia in elderly patients with diabetes [6].

The association between diabetes and dementia in elderly patients has important implications for clinical practice. Healthcare professionals need to be aware of this potential relationship and consider the increased risk of dementia in elderly patients with diabetes [7]. Regular cognitive screening and assessment should be incorporated into the routine care of individuals with diabetes, especially those with additional risk factors for dementia. Furthermore, the management of diabetes in elderly patients should take into account the potential impact on cognitive function. Optimal glycemic control, management of cardiovascular risk factors, and lifestyle interventions may not only help prevent diabetes-related complications but also reduce the risk of cognitive decline and dementia [8].

The potential mechanisms underlying this relationship, including the impact of high blood sugar levels and insulin resistance, as well as common risk factors for both conditions, highlight the need for a comprehensive approach to the care of elderly patients with diabetes. Healthcare professionals should be vigilant in assessing cognitive function and managing diabetes in order to mitigate the risk of dementia in this vulnerable population [9].

The association between diabetes and dementia in elderly patients is a topic of growing concern, as both conditions are prevalent among the aging population. Understanding the relationship between diabetes and dementia is crucial for developing effective prevention and management strategies for these two debilitating conditions.

This systematic review aims to provide a comprehensive understanding of the association between diabetes and dementia in elderly patients. By synthesizing existing evidence, this study can help identify potential risk factors, mechanisms, and treatment implications for individuals with both diabetes and dementia. The findings of this review may also inform healthcare professionals, policy makers, and researchers in developing targeted interventions and improving the overall care for elderly patients at risk of developing these conditions.

The aim of this systematic review is to investigate the association between diabetes and dementia in elderly patients, with a focus on understanding the potential risk factors, pathophysiological mechanisms, and clinical implications of this relationship.

METHODS:

Study Design and Duration

PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were followed in the implementation of this systematic review [10]. January 2024 marked the start of this systematic review.

Search strategy

To discover the pertinent literature, a thorough search was conducted across four main databases: PubMed, MEDLINE, SCOPUS, Web of Science, and Inspec. We limited our search to English and considered each database's specific needs. The following keywords “dementia, diabetes, T2DM, cognitive function, geriatrics, elderly” were transformed into PubMed Mesh terms or subject terms in Scopus and used to locate the pertinent studies. The Boolean operators "OR" and "AND" matched the required keywords. Publications with full English text, available free articles, and human trials were among the search results.

Eligibility Criteria

Inclusion Criteria:

1. Studies involving elderly patients aged 60 years and above.
2. Studies that examine the association between diabetes (type 1 or type 2) and dementia.
3. Research articles published in English.
4. Studies with a clear diagnosis of diabetes and dementia.
5. Randomized controlled trials, cohort studies, case-control studies, or cross-sectional studies.

Exclusion Criteria:

1. Studies involving patients below 65 years of age.
2. Studies not focusing on the association between diabetes and dementia.
3. Non-English language publications.
4. Studies lacking a clear diagnosis of diabetes or dementia.
5. Animal studies, case reports, editorials, and commentaries.

Data extraction

Rayyan (QCRI) [11] was used twice to verify the search method's results. The researchers added inclusion/exclusion criteria to the combined search results in order to evaluate the relevance of the titles and abstracts. The reviewers gave each paper that met the inclusion criteria a thorough inspection. The authors talked about ways to resolve conflicts. A data extraction form that had already been prepared was used to upload the approved study. The authors extracted data about the study titles, authors, study year, city, participants, gender, follow-up duration, disorder, and main outcomes. A separate sheet was created for the risk of bias assessment.

Strategy for data synthesis

Utilizing information from relevant studies, summary tables were created to provide a qualitative assessment of the research findings and components. Once the data for the systematic review has been gathered, the most efficient way to use the data from the included study articles was chosen.

Risk of bias assessment

To assess the quality of the research, the Joanna Briggs Institute (JBI) [12] critical assessment criteria for studies providing prevalence data was used. Nine questions were used in this tool's assessment of studies. If the response was in the affirmative, the question received a score of 1. A score of 0 was given to any response that was no, ambiguous, or not applicable. Ratings of < 4, 5 to 7, and ≥ 8 for overall quality were considered low, moderate, and excellent quality in that order. Researchers evaluated the quality of the studies they conducted, and conflicts were resolved through debate.

RESULTS:

After a thorough search, 690 study articles were found; 322 duplicates were eliminated. After 368 studies had their titles and abstracts screened, 279 were not included. Only four items out of the four reports that were requested were not found. After screening 85 papers for full-text assessment, 59 were rejected due to incorrect study results, 13 were rejected due to incorrect population type, and 2 articles were editor's letters. This systematic review contained eleven acceptable research papers. An overview of the procedure used to choose studies is provided in **Figure 1.**

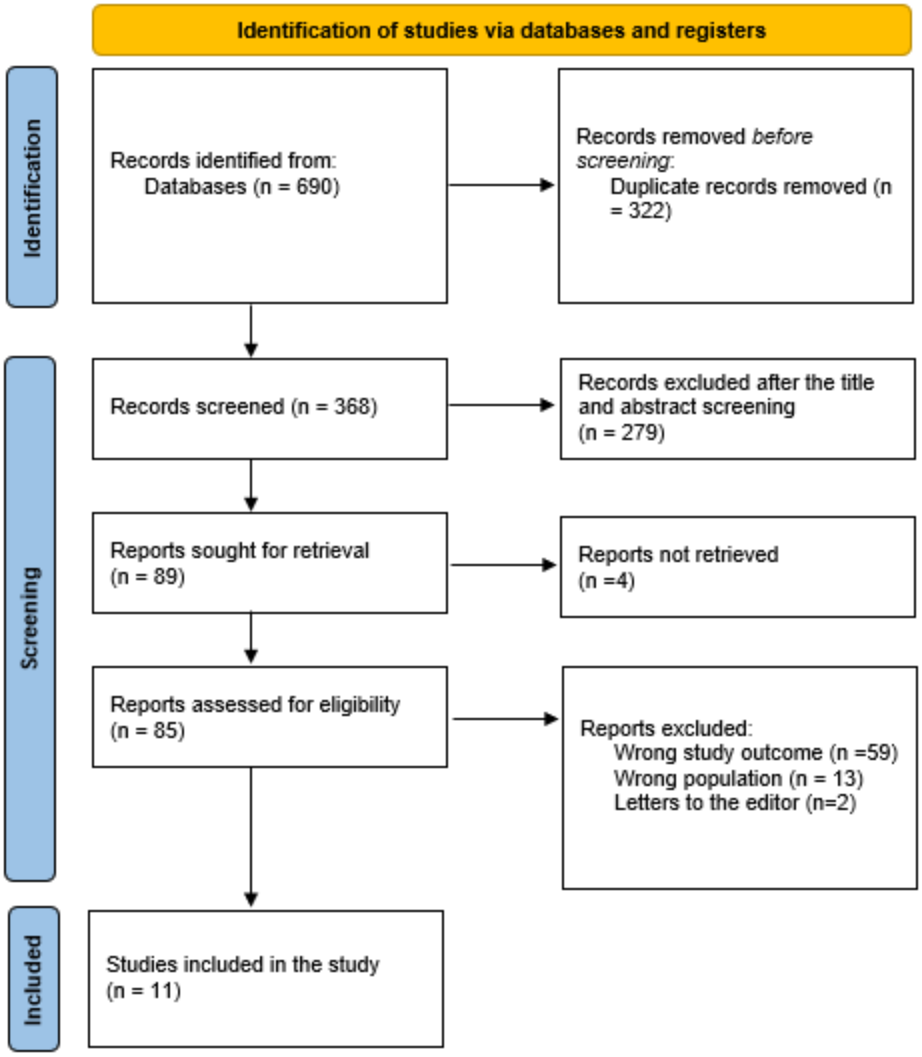

Figure (1): Study selection is summed up in a PRISMA flowchart.

Table (1) presents the sociodemographic characteristics of the included study articles. Our results included eleven studies with a total of 5,758,607 patients. Four were cross-sectional studies [13, 15, 16, 18], four were retrospective in nature [19, 20, 22, 23], and three were case-control studies [14, 17, 21]. Three studies were conducted in the USA [13, 16, 21], three in the UK [14, 17, 20], two in China [15, 23], one in Taiwan [18], one in Spain [19], and one in Korea [22].

Table (2) presents the clinical characteristics. The follow-up duration ranged from 1 year [14] to 12 years [23]. It is common for older diabetic individuals to have cognitive impairment that is not diagnosed [14-23]. There is a substantial correlation between glycated albumin, glycated albumin/HbA1c, IL-6, superoxide dismutase, poor diabetes self-management, decreased BMI, weight loss and the cognitive performance of senior T2D patients [15, 16, 20]. One study found that metformin's protective effect on dementia risk in T2D patients [17] while the other reported that it has no effect [21]. Old women with T2D showed higher rates of cognitive impairment as well as lower levels of executive and global cognitive function [18, 19]. One study reported that lower cognitive functioning is independently correlated with larger burdens of amyloid and small vessel disease [13].

Table (1): Sociodemographic characteristics of the included participants.

Study	Study design	Country	Participants	Mean age	Males (%)
Lesman et al., 2024 [13]	Cross-sectional	USA	47	77.9 ± 3.7	30 (63.83%)
Merzon et al., 2024 [14]	Case-control	C	350	73.8 ± 5.8	157 (44.9%)
Si et al., 2023 [15]	Cross-sectional	China	28	75	14 (50%)
Kim et al., 2022 [16]	Cross-sectional	USA	84	68.5 ± 5.4	38 (45.2%)
Zheng et al., 2023 [17]	Case-control	UK	210,237	68	114,678 (54.5%)
Chen et al., 2023 [18]	Cross-sectional	Taiwan	318	67.58±4.97	183 (57.5%)
Lopez-de-Andres et al., 2023 [19]	Retrospective cohort	Spain	5,250,810	≥60	NM
Chen et al., 2023 [20]	Retrospective cohort	UK	1064	69.4 ± 4	546 (51.3%)
Xue & Xie, 2023 [21]	Case-control	USA	1306	73.9 ± 7.9	630 (42.2%)
Cho et al., 2023 [22]	Retrospective cohort	Korea	20,487	71.7 ± 10.1	NM
Chau et al., 2023 [23]	Retrospective cohort	China	273,876	66.8–75.6	129,543 (47.3%)

Table (2): Clinical characteristics and outcomes of the included studies.

Study		Follow-up duration (years)	Main outcomes	JBI
Lesman et al., 2024 [13]	AD	NM	After accounting for diabetic management, lower cognitive functioning is independently correlated with larger burdens of amyloid and small vessel disease. A multimodal and tailored strategy is necessary for the prevention, diagnosis, and treatment of cognitive decline in non-demented older persons with T2D. This is because several factors may independently trigger cognitive decline in this population.	Moderate
Merzon et al., 2024 [14]	Cognitive function	1	This study emphasizes how common it is for older diabetic individuals to have cognitive impairment that is not recognized. It also emphasizes how critical it is to recognize cognitive impairment as a risk factor for subpar outpatient care and higher inpatient service utilization.	Moderate
Si et al., 2023 [15]	Cognitive function	NM	There is a substantial correlation between glycated albumin, glycated albumin/HbA1c, IL-6, and superoxide dismutase and the cognitive performance of senior T2D patients. Cognitive impairment is associated with inflammation and oxidative stress.	High
Kim et al., 2022 [16]	Cognitive function	NM	Poor diabetes self-management practices and cognitive impairment are risks for older persons with T2D. There is a pressing need to comprehend how cognitive function impacts DSMB in the older adult population because a growing number of older persons are predicted to experience both T2D and cognitive impairment in the near future.	Moderate
Zheng et al., 2023 [17]	Dementia	5	Beyond its glycemic effect, this population-based cohort study offers compelling epidemiological evidence of metformin's protective effect on dementia risk in T2D patients.	Moderate
Chen et al., 2023 [18]	Cognitive function	NM	In comparison to men, women showed higher rates of cognitive impairment as well as lower levels of executive and global cognitive function. Age, years of education, depressive symptoms, HbA1c, and length of diabetes were found to be connected with cognitive performance in female patients, whereas age, years of education, sleep quality, and HbA1c were found to be significant factors in male patients' cognitive performances.	Moderate
Lopez-de-Andres et al., 2023 [19]	VaD and AD	NM	Between 2011 and 2020, the incidence of dementia in men and women with T2DM increased, along with the prevalence of VaD and AD. The incidence of all-cause dementia is 1.34 times greater in women than in men, according to our statistics, which also show notable sex differences. The numbers for VaD and AD are similar.	High
Chen et al., 2023 [20]	Dementia	4	For older adults with type 2 diabetes, a decreased BMI and weight loss over time are both suggestive of an increased risk of dementia; changes in waist circumference may not be as useful.	Moderate
Xue & Xie, 2023 [21]	Dementia	3.6	The administration of metformin to AD patients with T2D did not significantly lower their chance of acquiring severe dementia.	Moderate
Cho et al., 2023 [22]	Dementia	5 - 10	A greater likelihood of dementia development is directly linked to poorly controlled diabetes based on long-term glycemic exposure; in other words, a shorter time to dementia onset corresponds to higher glycemic exposure.	Moderate
Chau et al., 2023 [23]	Dementia	12	During a 12-year follow-up period, 25% of patients with T2D had a new onset of dementia. While older age, ischemic stroke, fasting blood glucose, antiplatelet agent usage, and calcium channel blocker usage were indicators of risk for incident vascular dementia, advancing age and antiplatelet agent use were risk factors for the incidence dementia.	Moderate

*NM=Not mentioned

DISCUSSION:

This comprehensive review demonstrated evidence that it is common for older diabetic individuals to have cognitive impairment that is not diagnosed [14-23]. One study reported that lower cognitive functioning is independently correlated with larger burdens of amyloid and small vessel disease [13]. Similarly, a systematic review by **Biessels *et al.*** reported that mechanistic investigations indicate that the pathophysiology is caused by changes in glucose, insulin, and amyloid metabolism as well as vascular disease; however, it is not evident which of these pathways is clinically significant [24]. Diabetes may have a variety of pathophysiological effects on the development and progression of the numerous underlying diseases linked to dementia [25]. These mechanisms include aging itself and those shared by vascular dementia and Alzheimer's disease. It is becoming more widely acknowledged that individuals suffering from dementia, especially those who are extremely old, are likely to exhibit a variety of diseases in their brains, including Alzheimer-type dementia and vascular abnormalities [26].

We found a substantial correlation between glycated albumin, glycated albumin/HbA1c, IL-6, superoxide dismutase, poor diabetes self-management, decreased BMI, weight loss, and the cognitive performance of senior T2D patients [15, 16, 20]. **Geijselaers *et al.*** included 86 publications and demonstrated that in individuals with type 2 diabetes who do not have dementia, glycemia—specifically, high HbA1c concentration and glucose variability—is inversely correlated with cognitive performance. Nevertheless, this correlation is not very strong, with HbA1c often explaining less than 10% of the variation in cognitive function. Significantly, very few studies have examined the effects of glucose-lowering medication on long-term cerebral outcomes, such as dementia and structural brain abnormalities on MRI [27].

There is evidence to support the "toxic" effects of hyperglycemia, which may cause the brain's structural and functional problems to gradually advance [25]. Thus, one factor that may influence cognitive alterations in diabetics is chronic hyperglycemia [28]. Chronically hyperglycemic rats display aberrant synaptic plasticity as well as cognitive deficits [29]. Increased glucose flux via the polyol and hexosamine pathways, disruptions of intracellular second messenger pathways, a discrepancy in the generation and collecting of reactive oxygen species, and advanced glycation of significant structural and functional proteins are the mechanisms through which high glucose concentrations can have toxic effects [30]. In addition to having a direct impact on brain tissue, these processes may also cause microvascular alterations [25]. Therefore, diabetes may induce broader and generalized microvascular changes in the brain by this pathway, leading to microinfarcts and likely resulting in changes to white matter and generalized atrophy, as opposed to creating circumscript vascular lesions.

One could call these impacts on cognition and brain structure that are mediated by global-glucose "accelerated brain ageing." Notwithstanding its lack of specificity, this phrase may be significant conceptually. Numerous processes, including oxidative stress, the build-up of advanced glycation end products, and microvascular disease, that mediate the harmful effects of hyperglycemia are also linked to the aging process of the brain [31, 32]. Actually, persons with diabetes who do not have dementia exhibit a pattern of cognitive decline and brain atrophy that resembles some features of brain aging [31, 33].
We found that old women with T2D showed higher rates of cognitive impairment as well as lower levels of executive and global cognitive function [18, 19]. **Chen *et al.* [18]** reported that women in their study had significantly lower average levels of education than males, which could be explained by the fact that education plays a significant role in women's cognitive and brain reserve.

In addition, the majority of the elderly female participants in this research were postmenopausal, and since estrous hormone has been shown to protect cognitive performance [34], the decline in cognitive function in older women may potentially be related to low estrogen levels.

We also found that the effect of metformin use was controversial as one study found metformin's protective effect on dementia risk in T2D patients [17] while the other reported that it has no effect [21].

The recommendations for all dementia risk variables have been made public by the Lancet Commission on dementia prevention, intervention, and care [35, 36]. People with diabetes can follow a healthy diet and exercise regimen; at the moment, the Mediterranean diet is advised, but no specific sort of exercise is suggested [35]. Research on the impact of anti-diabetic medications on dementia risk is still lacking.
Obesity sufferers can also start exercising and eating well. There is a dearth of data on the long-term advantages of weight loss on the risk of dementia, despite reports of its short-term benefits [35].

Research aims to close existing knowledge gaps to enhance patient outcomes. To obtain the essential data, prospective, carefully designed, long-term trials will be required for diabetic patients at risk of dementia. It is also important to determine early alterations in brain biomarkers in individuals with diabetes and prediabetes who have a higher risk of dementia. Determining the early brain alterations linked to the impending onset of dementia and connecting these alterations to hereditary and/or clinical factors is also crucial.

CONCLUSION:

There is strong evidence that individuals with diabetes have a higher risk of dementia, however comprehensive epidemiological data about risk factors are scarce. The potential link between diabetes and dementia is attracting more attention in the scientific community since it is a highly relevant topic from both a public health and scientific standpoint. Actually, investigating this connection might make some new pathways leading to neurodegeneration more clear.

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