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Investigating the Role of Glycemic Control in Cognitive Impairement Risk Among Elderly Individuals with Type 2 Diabetes: A Scoping Review

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INVESTIGATING THE ROLE OF GLYCEMIC CONTROL IN COGNITIVE IMPAIRMENT RISK AMONG ELDERLY INDIVIDUALS WITH TYPE 2 DIABETES: A SCOPING REVIEW

by

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ABSTRACT

Type 2 diabetes mellitus (T2DM), presents a significant health burden globally, affecting millions of individuals, especially in the elderly population. While its association with cardiovascular diseases and cognitive impairments is well-documented, further research on the precise influence of glucose control on cognitive outcomes in elderly T2DM patients is necessary. This scoping review aims to address this gap by investigating the impact of HbA1c levels representing glycemic control on the risk of developing cognitive impairments in elderly patients with T2DM. A literature search was conducted on MEDLINE and eligible studies involved T2DM patients aged 60 or older, with documented cognitive function and glycemic status. Screening and selection processes were conducted following PRISMA guidelines, and three relevant articles were selected for review. Most of the findings suggest a possible association between higher HbA1c levels and cognitive decline. Such results provide valuable insights regarding medical approaches focusing on glucose control that could be created to prevent and delay cognitive decline in T2DM patients.

DEDICATION

First and foremost, I dedicate this thesis to God, the one who was with me throughout the entire process since before I could imagine I would be able to accomplish such an important milestone in my academic career. This thesis is also dedicated to my amazing family and friends, who gracefully listened to me talking about type 2 diabetes and cognitive decline during many of our encounters and always motivated me to persist until this project was completed. Finally, a most special thank you to my loving parents and number one supporters. Mom and dad, I dedicate all my accomplishments to you; your faith in me continuously gives me the strength and inspiration I need to keep on pursuing my dreams. I wouldn't have been able to accomplish any of this without your love and endless encouragement.

ACKNOWLEDGMENTS

I would like to express my gratitude to Dr. Papa, who mentored me throughout this journey and made it possible for me to write this thesis. You listened to me talk about all the ideas I had for this project and gave me the chance to investigate a topic I am passionate about. I am beyond grateful for your mentorship. I would also like to thank Dr. Sugaya for your contribution to my committee and for offering your valuable advice. To Dr. Mouloua, thank you for being part of my committee and for your welcoming support during office hours; your encouragement has been a source of reassurance throughout my academic career. Finally, I would like to thank Mr. Todd for patiently guiding me through the search process for this review.

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CHAPTER ONE: INTRODUCTION

According to the Centers for Disease Control and Prevention (CDC), besides being one of the top ten causes of death, diabetes is a chronic disease that is present in the lives of around 38 million adults in the US (2023) and is expected to be more prevalent in adults older than 65 years (Wild et al., 2004). While both types of diabetes reflect the body's complete or partially compromised ability to produce insulin, in type 1 diabetes, this happens as an autoimmune response that destroys insulin-producing cells; on the other hand, type 2 diabetes mellitus (T2DM) is caused as a result of insulin resistance over time. It is estimated that out of all the people who have diabetes, around 90-95% of them present with the type 2 variant (CDC, 2023). Statistics like this highlight the importance of considering any possible health-compromising risks associated with T2DM. Certain factors such as advanced age, genetics, obesity, and lifestyle choices have been shown to increase the risk of developing the disease (Tinajero & Malik, 2021) (Ehtewish et al., 2022). T2DM is also a risk factor for cardiovascular diseases due to the symptoms associated with it (Beeri et al., 2009). For instance, hypertension and insulin resistance, symptoms of T2DM, can lead to increased chances of cardiovascular problems due to the strain on the heart and blood vessels (Fuchs & Whelton, 2020) (Kosmas et al., 2023). Moreover, other lifestyle factors that are usually seen in T2DM such as sedentarism and unhealthy diets with high concentrations of fats and sugars have been well-known to contribute to the development of cardiovascular concerns. Along with that, many studies have attributed T2DM to risks of developing cognitive impairments through either the onset of a cognitive disease itself or a compromised cognitive function (Ott et al., 1999) (Logroscino et al., 2004) (Kumari & Marmot, 2005) (Luchsinger et al., 2007) (Arntzen et al., 2011). As mentioned above, T2DM increases the likelihood of developing cardiovascular

disease, which has led researchers to investigate whether such diabetes-related cardiovascular symptoms could predispose individuals to develop cognitive deficits. As it turns out, findings show that individuals who suffer from cardiovascular disease present with a higher risk of having dementia (Reijmer et al., 2011), suggesting that cardiovascular diseases could also be associated with other cognitive impairments besides dementia. Furthermore, hypertension has been found to negatively influence individuals' scores on cognitive assessments (Arntzen et al., 2011) (Sanchez et al., 2021), showing that T2DM-related cardiovascular symptoms can be associated with compromised cognitive function. These results point to a rationale that involves T2DM as an indirect factor that can become a risk for cognitive impairments through the cardiovascular symptoms it is associated with. However, considering that T2DM involves a wide array of factors besides its cardiovascular-related symptoms, other areas of focus have been studied to avoid faulty conclusions about the association of the disease with cognitive deficits. For instance, researchers have analyzed the duration of T2DM and medical therapies used for its treatment to check for possible interferences that those could cause on cognition (Cheng et al., 2012) (Campbell et al., 2018) (Pilipenko et al., 2020). According to the findings, pre-diabetes, early-stage T2DM, and recently diagnosed T2DM patients were more prone to having cognitive impairment (Cheng et al., 2012). Additionally, T2DM patients taking metformin, a common oral medication used in the treatment of the disease, had their cognitive function enhanced, suggesting that it could potentially lead to a decrease in the risk of developing cognitive diseases (Campbell et al., 2018) (Pilipenko et al., 2020). As it is noted, much research has focused on cardiovascular-related risk factors for the development of cognitive impairments in patients with T2DM, however, most of them have not considered the influence glucose control might have on this matter. This is especially important given the role metformin has been demonstrated to play in improving cognition in T2DM patients

considering it lowers blood sugar levels that the disease can cause. Also, other studies have investigated the role of diabetes duration and medical therapies on cognitive performance. Yet not much information is found in the literature about these factors being considered simultaneously. There is still a need to analyze the influence of glucose control through glycated hemoglobin (HbA1c) levels. Identifying the role of blood glucose concentrations in the risk of developing cognitive disorders could aid in finding ways to prevent diabetes-related cognitive impairments and disorders. More specifically, such findings could be a resource in the clinical setting by enabling neuropsychologists and neurologists to implement preventive measures and treatments that could stop or delay cognitive impairments in the diabetic population. Therefore, this scoping review will review literature available on the impact of glycemic control on the risk of developing cognitive impairments in elderly patients with T2DM and explore potential correlations and implications.

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CHAPTER TWO: METHODS

Eligibility Criteria

The eligibility criteria for study selection were based on a "PICO" question structure, which is specified below. Articles eligible for selection included case studies, clinical studies, clinical trials, controlled clinical trials, observational studies, and randomized controlled trials that involved human participants.

Population (P): ≥ 60 years old patients with T2DM;

Intervention (I): High glucose control levels demonstrated by measurements of glycated hemoglobin (HbA1c);

Comparison (C): The two comparison factors involved a well-controlled T2DM group and a poorly controlled T2DM group based on levels of glycemic control;

Outcome (O): Cognitive function;

Exclusion Criteria

For this study, the exclusion criteria involved review articles, meta-analysis articles, editorials, opinion articles, and animal studies.

Search Strategy

An extensive literature search was conducted through MEDLINE to search for potential articles written in the English language and published between the years 1996 and 2024. The search was conducted by using the main keywords "diabetes mellitus", "type 2 diabetes mellitus", "diabetic patients", "non-insulin-dependent diabetes mellitus", "diabetes NIDDM", "mild

cognitive impairment", "cognition disorders", "Alzheimer's disease", "dementia", "cognitive impairment", and synonyms. Additional details regarding the exact search terms used are included in Appendix A. No limitations were applied to the location from which the studies were conducted.

Study Selection

The studies resulting from the search were transferred to JBI Sumari for the screening process, which was conducted by two reviewers. To be considered for selection, the articles had to include patients who were 60 years old or older and who had T2DM. Moreover, the participants had to have their cognitive function status stated by the study shown by cognitive assessment measurements. The study also had to include participants' glycated hemoglobin (HbA1c) levels, possible occurrence of glycemic episodes, and whether the patient's T2DM was well-controlled with the use of medications and/or diets and/or frequent monitoring or poorly controlled. While considering inclusion and exclusion criteria, screening for titles and abstracts was completed independently by two different reviewers before considering full-text reviews. Once that process was finalized, the two reviewers proceeded to evaluate whether the remaining articles met all inclusion criteria by completing full-text reviews. All results from both the search strategy and study selection are reported in the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) (Page et al., 2021) flow diagram (Fig.1).

Data Extraction

Once full-text screenings were completed by the two reviewers, some specific factors were extracted from each study. These were summarized into an evidence table (Table 1) and included authorship, publication year, publication type, sample size, sample characteristics, glucose control measurement, and cognitive function measurement.

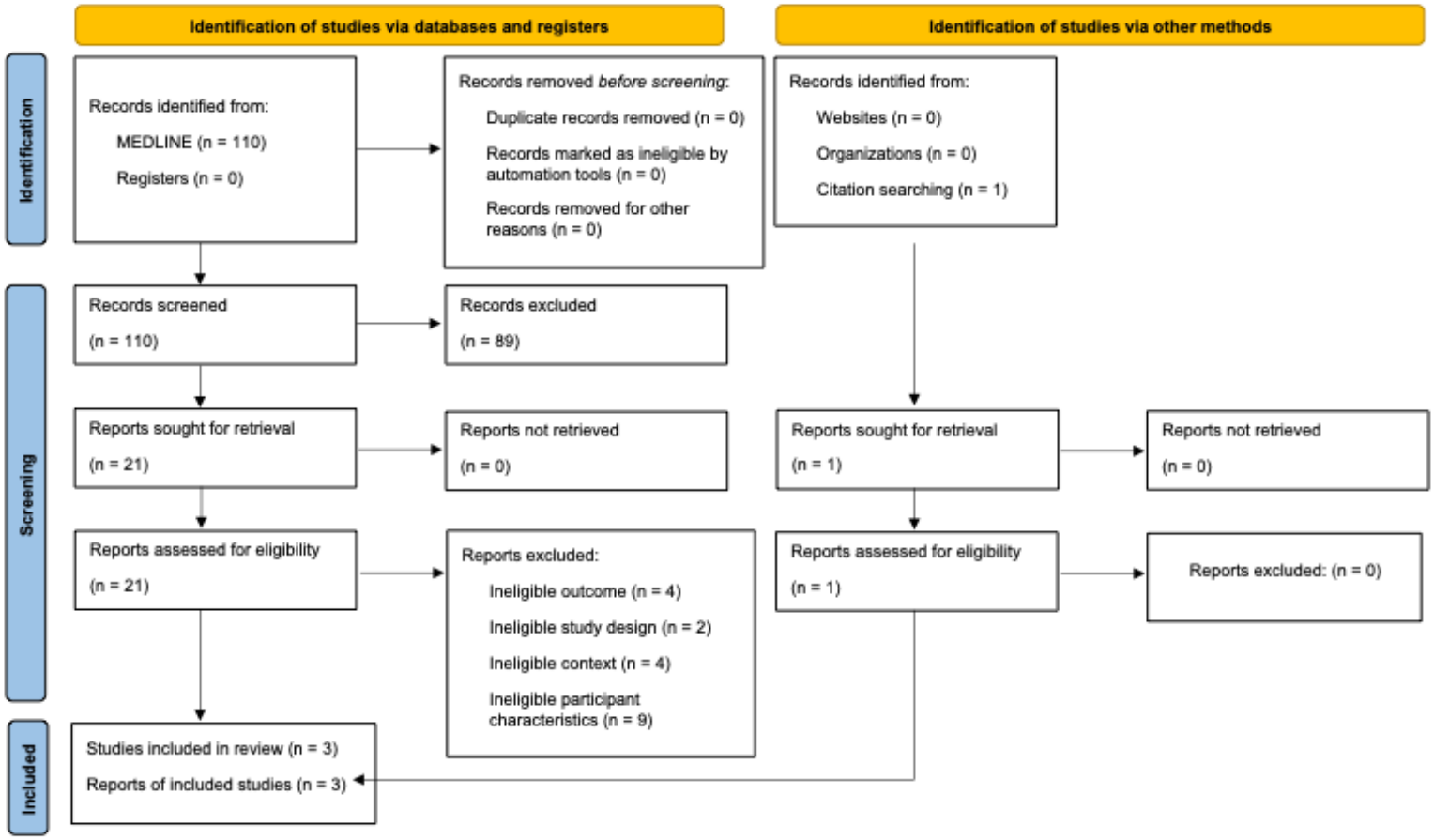

Figure 1 PRISMA Flow Diagram of Study Selection

Table 1 Evidence Table for Included Studies

Study	Study Design	Sample Size, Group 1 / Group 2 [a,b]	Sex (%), Males / Females	Inclusion Criteria	HbA1c levels (%) Group 1 / Group 2 [c]	Cognitive Assessment	Outcome Measures	Results
Verny 2015 [d]	Prospective	*n* = 987, 284 / 703	Non-decliners: 51.2% vs. 48.8% Decliners: 39.8% vs. 60.2%	T2DM, ≥ 70 years	7.5 ± 1.2 / 7.8 ± 1.5	MMSE	Diabetes duration, hypoglycemia, HbA1c, retinopathy, MDRD, peripheral neuropathy, foot sore, amputation, peripheral arterial disease, heart failure, coronary ischemia, cerebrovascular involvement	Higher HbA1c associated with cognitive impairment
Umegaki 2015 [e]	Prospective	*n* = 59, 17 / 42	Non-decliners: 35.7% vs 64.3%	T2DM, ≥ 65 years	7.3 ± 0.7 / 7.2 ± 0.7	MMSE, Stroop Color Word, Alzheimer's Disease Assessment Scale	DT, HbA1c, DBP, SBP, LDL-C, HDL-C, IRI, CRP, eGFR, Apo ε, SU, RAS, microangiopathy SCI, PVH, WMH, smoking [g]	No observed association between HbA1c levels and cognitive decline

Study	Study Design	Sample Size, Group 1 / Group 2 [a,b]	Sex (%), Males / Females	Inclusion Criteria	HbA1c levels (%) Group 1 / Group 2 [c]	Cognitive Assessment	Outcome Measures	Results
			Decliners: 52.9% vs. 47.1%					
Lehtisalo 2016 [f]	Randomized control trial (subgroup analysis)	*n* = 364, 171 (122) / 193	Non-diabetics: 31.1% vs. 68.9% Diabetics: 31.6% vs. 68.4%	Subgroup analysis of patients with T2DM, ≥ 60 years	<5.7 Vs. 5.7-6.5 vs. > 6.5	CERAD, Trail Making Test A (TMT)	Cognitive function, BMI, Blood Pressure, APO ε4, Diabetes duration	>6.5 HbA1c, longer T2DM linked to poorer cognition. >6.5 HbA1c linked to worse TMT scores.

[a] Total sample size (*n*), group 1 sample size / group 2 sample size.
[b] First two studies: group 1 = no cognitive decline / group 2 = cognitive decline. Third study: group 1 = T2DM (sample with losses in follow-up) / group 2 = control without T2DM.
[c] First two studies: group 1 = no cognitive decline / group 2 = cognitive decline. Third study: group 1 = non-diabetic / group 2 = pre-diabetic / group 3 = diabetic.
[d] Hba1c levels measured at baseline and 5-year follow-up (unclear when); cognitive function measured at baseline.
[e] Hba1c levels measured at baseline and every year of 6-year follow-up; cognitive function measured at baseline and at the end of 6-year observation.
[f] Hba1c levels measured once a year; cognitive function measured at baseline and 2 years after (on average).
[g] DU, diabetic treatment; CRP, C reactive protein; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; SU, statin use; RAS, renin–angiotensin system inhibitor use; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; IRI, immunoreactive insulin; LDL-C, low-density lipoprotein cholesterol; MMSE, Mini-Mental State Examination; PVH, paraventricular hyperintensities; SBP, systolic blood pressure; WMH, deep white matter hyperintensities.

CHAPTER THREE: RESULTS

Study Selection

During the search process, 111 articles were found before the two reviewers went through screening for both title and abstracts and full-text reviews. While considering the eligibility criteria and PICO guidelines, 89 studies were excluded during the first screening analysis, and 19 studies were excluded after full-text reviews due to ineligible outcomes (n= 4), study design (n=2), context (n=4), or participant characteristics (n=9) (Fig.1). Therefore, only three articles met the established eligibility criteria and were included in this scoping review.

Study Characteristics

All three articles incorporated into the analysis were in the English language, two of them being prospective cohort studies, and one being an ancillary study to a randomized controlled trial. These studies were from 2015 and 2016 and represented data from: France, Japan, and Finland. Moreover, all three studies included T2DM elderly patients ≥ 60 years old who had their cognitive function assessed, resulting in data from more than 1,000 patients (Verny et al., 2015) (Umegaki et al., 2015) (Lehtisalo et. Al., 2016).

Appraisals

To critically evaluate the studies' reliability and validity, appraisal assessments were conducted through the Joanna Briggs Institute (JBI) software program for all three articles (See Appendix B) (Joanna Briggs Institute, 2017).

Article One

The first article included was a prospective cohort based on the French GERODIAB study parameters which measured morbidity, mortality, and glucose control throughout five years (Verny et al., 2015). Participants (n = 987) were ≥ 70 years old, had T2DM, and had their cognition assessed using the Mini-Mental State Examination (MMSE). Patients were divided into two groups according to the presence (n = 284) or absence (n = 703) of cognitive decline determined by the MMSE scores and/or previous diagnostic. HbA1c levels were measured at baseline and throughout the follow-up. Results indicated that, even though duration of diabetes didn't show a significant difference between the groups (17.6 ± 11.1 vs. 17.9 ± 10.7 years; P = .651), there was a significant difference in age (78.4 ± 5 vs. 76.5 ± 4.8 years; P < .001), and sex with a higher incidence of women in the cognitive decline group (60.2 vs. 48.8%; P < .001). Higher HbA1c levels were also found in the cognitive decline group (7.8 ± 1.5 vs. 7.5 ± 1.2%; P = .002), which also included more patients receiving insulin treatment (65.1% vs. 54.3%; P = .002) compared to metformin treatment (40.1% vs. 52.3%; P < .001). Such findings imply that older T2DM patients with higher HbA1c levels may be at increased risk of experiencing cognitive decline.

Article Two

The second article incorporated into the review was also a prospective cohort study, which was conducted over six years and included ≥ 65 years old T2DM patients (n = 59) in Japan (Umegaki et al., 2015). Clinical indicators such as HbA1c levels were measured at baseline and every year of the study, and cognitive assessments were administered at baseline and at the end of the 6-year period. Neuropsychological assessments used included the MMSE, an Alzheimer's Disease Assessment Scale subtest, Stropp Color Word test, and the Digit Symbol Substitution

(DSS) test for psychomotor skills. Cognitive function scores were measured by the difference of scores obtained in the end and beginning of the study and transformed into z-scores so a composite score could be generated to assess the rate of cognitive decline. Participants with a z-score ≥ 0 were assigned to the group without cognitive decline (n = 42), while participants with a z-score < 0 were assigned to the cognitive decline group (n = 17). Results showed that there was a significant difference in age between the two groups (77.7 ± 5.4 vs. 83.3 ± 5.2 years; P <0.001) but no significant difference was found regarding the duration of T2DM (20.20 ± 9.7 vs. 23.6 ± 7.1 years; P = 0.148). Moreover, the statistical analysis did not indicate a significant difference of HbA1c levels between the groups (7.3 ± 0.7 vs. 7.2 ± 0.7; P = 0.391).

Article 3

The last article selected for the review was an ancillary study of a Finnish randomized controlled trial that investigated diabetes prevention (Lehtisalo et. Al., 2016). The original study had an intervention period of four years on average and a follow-up period of nine years on average and had some of its parameters and data extracted to be used by the ancillary article. Participants in the subgroup analysis (n = 364) were ≥ 60 years old and had T2DM (n = 171) or not (n = 193). Participants who had diabetes for < 7.5 years were placed into the short-duration diabetes group (n = 86) and the ones who had diabetes for ≥ 7.5 years were assigned to the long-duration diabetes group (n = 85). HbA1c levels were measured once a year and were used to separate participants into non-diabetic (HbA1c <5.7), pre-diabetic (5.7-6.5), and diabetic (> 6.5) groups. Neuropsychological assessments used included the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) battery and the Trail Making Test A. These were administered at baseline and two years later. Results indicated that permanently elevated HbA1c (> 6.5) levels

predicted poorer cognitive function. Moreover, a longer duration of T2DM was linked to a decline in cognitive performance over time. Participants who underperformed in TMT had diabetic glucose concentrations detected by either HbA1c or 2-h glucose.

Summary of Results

The articles included in this review investigate the association between T2DM and cognitive decline in the elderly population while also considering glucose control represented by HbA1c levels. While the two first articles observed a significant association between older age and cognitive decline, they showed diverging findings regarding HbA1c levels and its association with cognitive impairment patients (Verny et al., 2015) (Umegaki et al., 2015). The French study found higher HbA1c levels in the group of participants with cognitive decline compared to the group without cognitive decline; it also revealed differences in sex ratio and T2DM treatment in the cognitive decline group (Verny et al., 2015). Conversely, the Japanese study did not observe a significant difference in HbA1c levels between the two groups; however, it also detected the association of older age and cognitive impairment (Umegaki et al., 2015). Similarly to the first article, the results of the Finnish study pointed to an association of elevated HbA1c levels and longer duration of T2DM to poorer cognitive function (Lehtisalo et. Al., 2016).

Table 2 Summary of Results of Included Articles

Study	Age (years)	Diabetes duration (years)	HbA1c (%) [a]	Cognitive Assessments
Verny 2015	76.5 ± 4.8 vs. 78.4 ± 5.0	17.9 ± 10.7 vs. 17.6 ± 11.1	7.5 ± 1.2 vs. 7.8 ± 1.5	MMSE
Umegaki 2015	77.7 ± 5.4 vs. 83.3 ± 5.2	20.20 ± 9.7 vs. 23.6 ± 7.1	7.3 ± 0.7 vs. 7.2 ± 0.7	MMSE, Stroop Color Word, Alzheimer's Disease Assessment Scale (verbal memory subtest)
Lehtisalo 2016	66.9 ± 6.8 vs. 69.6 ± 6.3	7.2 ± 3.6	5.7 ± 0.6 vs. 5.5 ± 0.5	CERAD, Trail Making Test A (TMT)

[a] First two studies: group 1 = no cognitive decline / group 2 = cognitive decline. Third study: group 1 = non -diabetic / group 2 = pre-diabetic / group 3 = diabetic

CHAPTER FOUR: DISCUSSION

Health challenges among the elderly population have been escalating globally and have been affected by the prevalence of T2DM, which has been linked to an increased risk of cardiovascular disease as well as cognitive impairments that could eventually lead to neurocognitive disorders (Ott et al., 1999) (Logroscino et al., 2004) (Kumari & Marmot, 2005) (Luchsinger et al., 2007) (Beeri et al., 2009) (Arntzen et al., 2011) (Fuchs & Whelton, 2020) (Kosmas et al., 2023). Research has focused on diabetes duration, treatment, and cardiovascular factors that could be associated with the development of cognitive decline; still, it's relevant to investigate glucose control levels in T2DM patients and how they might influence cognitive function over the years. This is especially important given glucose's role in providing energy to the brain. Because of the high demand for energy in the brain, glucose must be readily available and provide a continuous supply to maintain brain homeostasis and metabolic activity (Rao et al., 2006). This could imply that impaired glucose levels might compromise cognitive function as well as other brain processes.

Here, a scoping review was completed to assess the longitudinal impact of glycemic control, measured by HbA1c levels, on cognitive function. Even though one of the included studies did not find a significant difference in HbA1c levels of T2DM participants with and without cognitive decline, the other two studies showed that poorer cognitive function was associated with elevated levels of HbA1c. This is consistent with what has been shown in previous research, including a study in which patients were followed for ten years and higher HbA1c was significantly associated with cognitive decline (Ganguli et al., 2020). Altogether, these findings suggest that elevated levels of glucose detrimentally affect cognitive function over time. However, low levels

of glucose have also been associated with poorer cognition and oxidative stress (Languren et al., 2013)(Ebadi et al., 2018). Therefore, this highlights the importance of maintaining balanced blood glucose concentrations to protect cognitive health in T2DM individuals. The results from the included studies also revealed conflicting findings relating to the duration of T2DM and cognitive decline, with two of them demonstrating that the duration of the disease was not significantly associated with cognitive impairment, and one of them demonstrating that longer-duration T2DM worsened cognitive performance over time. However, previous findings have suggested that pre-diabetes and early-stage diabetes individuals present with an increased chance of experiencing cognitive decline (Yaffe et al., 2004) (Ruis et al., 2009). An interesting finding from article one was that the cognitively impaired participants were being treated with insulin more often than metformin, which prompts questioning regarding the influence of certain drug treatments on the prevention and improvement of cognitive function. In fact, it has been demonstrated that metformin helped improve cognitive function of T2DM patients (Campbell et al., 2018) (Pilipenko et al., 2020). Discoveries like this allow further questioning regarding the mechanisms through which certain drugs can positively interfere with decline in cognition. In turn, this could lead to a deeper understanding of the underlying factors involved in cognitive health and its decline in the context of patients who have T2DM. Additionally, these investigations could create opportunities for the development of targeted therapies that could preserve cognition, especially in T2DM patients.

Limitations and Future Directions

Certain limitations to the overall findings of this review should be acknowledged. For instance, it's important to recognize that each included study was conducted in a different country

This could affect results due to cultural differences potentially introducing confounding factors that might influence the participants' cognitive function. Nevertheless, having a diverse population sample can be beneficial due to a greater external validity attributed to it. Still, it is crucial that future studies consider genetic background differences when comparing data from individuals of different countries given that genetic variations may influence how HbA1c levels relate to cognitive decline. Besides this, it is important to consider that one of the studies included was an ancillary study to a randomized trial that conducted a subgroup analysis, which is a different study design to the other two prospective studies, and this could affect the interpretation of results. Finally, because of the restricted number of studies incorporating this review, there was insufficient data to perform subgroup analyses or meta-regression, which would allow to investigate potential confounding factors and the relationship between them.

Despite these limitations, this scoping review reveals the importance of glucose control in T2DM. The association between higher levels of HbA1c and cognitive decline emphasizes the need for updated strategies to manage T2DM symptoms in attempts to prevent diabetes-related cognitive impairment. Further longitudinal research with larger samples is needed to better understand how that could be achieved. If this was accomplished, future findings could benefit the elderly population with T2DM in diverse areas of life, such as driving ability. Considering that cognitive decline was associated with higher levels of HbA1c in T2DM patients, ≥ 60 years old individuals who have T2DM could be continuously screened to assess cognitive function while also receiving adequate care concerning glycemic control. Therefore, keeping healthy HbA1c levels and managing cognitive activity might mitigate the risk of cognitive decline, which could improve driving safety and prevent possible accidents caused by impaired cognition. Overall, investigating HbA1c levels and its association with cognitive decline in the elderly T2DM

population has the potential to improve patient's quality of life and could hopefully lead to a reality in which diabetes-related cognitive impairment is prevented.

APPENDIX A: SEARCH HISTORY

Table 3 Search History for Selection of Studies

Search ID#	Search Terms	Search Options	Last Run Via	Results
S7	S1 AND S2 AND S3 AND S5	Limiters - Age Related: Aged: 65+ years; Publication Type: Case Study, Clinical Study, Clinical Trial, Controlled Clinical Trial, Observational Study, Randomized Controlled Trial; Language: English Expanders - Apply equivalent subjects Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE	110
S6	S1 AND S2 AND S3 AND S4 AND S5	Expanders - Apply equivalent subjects Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE	110
S5	(MH "Prevalence") OR (MH "Incidence") OR (MH "Epidemiological Research") or TI ("Case Control" or Cohort or observational or epidem* or incidence or prevelan*) or MW epidem* or AB (epidem* or incidence or prevelan*)	Expanders - Apply equivalent subjects Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE	3,305,302
S4	((MH "Mild Cognitive Impairment") OR (MH "Cognition Disorders") OR (MH "Alzheimer's Disease") OR (MH "Dementia") or Cogniti* N3	Expanders - Apply equivalent subjects Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE	201

Search ID#	Search Terms	Search Options	Last Run Via	Results
	Impair* or cogniti* W3 disorder* or dementia* or alzheimer*) AND (S1 AND S2 AND S3)			
S3	(MH "Mild Cognitive Impairment") OR (MH "Cognition Disorders") OR (MH "Alzheimer's Disease") OR (MH "Dementia") or Cogniti* N3 Impair* or cogniti* W3 disorder* or dementia* or alzheimer*	Limiters - English Language; Age Related: Aged: 65+ years; Publication Type: Case Study, Clinical Study, Clinical Trial, Controlled Clinical Trial, Observational Study, Randomized Controlled Trial; Language: English Expanders - Apply equivalent subjects Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE	12,595
S2	(MH "Case Control Studies") OR (MH "Prospective Studies") OR (MH "Concurrent Prospective Studies") OR (MH "Experimental Studies+") OR (MH "Clinical Trials+") OR (MH "Observational Methods") OR TI ("Case Control" or trial or RCT or observational or cohort or quasi-experimental or experimental or prospective or retrospective or "case series" or randomi* or "control group") OR AB ("Case Control" or trial or RCT or observ* or cohort or	Limiters - English Language; Age Related: Aged: 65+ years; Publication Type: Case Study, Clinical Study, Clinical Trial, Controlled Clinical Trial, Observational Study, Randomized Controlled Trial; Language: English Expanders - Apply equivalent subjects Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE	281,341

Search ID#	Search Terms	Search Options	Last Run Via	Results
	quasi-experimental or experimental or prospective or retrospective or "case series" or randomi* or "control group")			
S1	(MH "Diabetes Mellitus, Type 2") OR (MH "Diabetes Mellitus") OR (MH "Diabetic Patients") or TI diabet* or AB Diabet* "Type 2" or AB Diabet* "Type II" or AB Diabet* non-insulin or AB Diabet* NIDDM or AB diabet* "adult onset"	Limiters - English Language; Age Related: Aged: 65+ years; Publication Type: Case Study, Clinical Study, Clinical Trial, Controlled Clinical Trial, Observational Study, Randomized Controlled Trial; Language: English Expanders - Apply equivalent subjects Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE	17,440

APPENDIX B: APPRAISALS

Table 4 Critical Appraisal of Eligible Studies

Citation	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11
Lehtisalo 2016.	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Umegaki 2015.	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Verny 2015.	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y
%	100.0	100.0	100.0	100.0	100.0	66.66	100.0	100.0	100.0	100.0	100.0

Question 1: Were the two groups similar and recruited from the same population?

Question 2: Were the exposures measured similarly to assign people to both exposed and unexposed groups?

Question 3: Was the exposure measured in a valid and reliable way?

Question 4: Were confounding factors identified?

Question 5: Were strategies to deal with confounding factors stated?

Question 6: Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?

Question 7: Were the outcomes measured in a valid and reliable way?

Question 8: Was the follow up time reported and sufficient to be long enough for outcomes to occur?

Question 9: Was follow-up complete, and if not, were the reasons to loss to follow-up described and explored?

Question 10: Were strategies to address incomplete follow-up utilized?

Question 11: Was appropriate statistical analysis used?

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