Cognitive Impairments in Type 1 Diabetes Mellitus: Integrative Review

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Abstract

This review verified cognitive domains affected by type 1 diabetes mellitus (T1DM) and the instruments used for its assessment. We performed a search in three databases using the descriptors "type 1 diabetes" AND "cognitive dysfunction". Only six of the 120 articles found met the criteria for inclusion in the review. The analysis of these articles indicates that the main cognitive functions compromised by T1DM are attention, visual attention, verbal memory, immediate and late recovery, and psychomotor speed. Among the selected articles, we found that the most used instruments were the Montreal Cognitive Assessment (MoCA), the Wechsler scales (WMS-III and WMS-RC), the Trail Making Test, The Grooved Pegboard, and substitution (letter-symbol, digit-symbol). Due to the different impairments found, we suggest the importance of standardizing a battery of cognitive assessments and greater efforts to understand the functional impairments resulting from damage to cognition in individuals with T1DM.

Keywords: type 1 diabetes mellitus, cognitive dysfunction, neuropsychological assessment, cognitive functions, integrative review

COMPROMETIMENTOS COGNITIVOS NA DIABETES *MELLITUS* TIPO 1: REVISÃO INTEGRATIVA

Resumo

Esta revisão verificou os domínios cognitivos afetados pela diabetes *mellitus* tipo 1 (*type 1 diabetes* mellitus [T1DM]). Realizamos busca em três bases de dados, utilizando os descritores "type 1 diabetes" AND "cognitive dysfunction". Apenas seis dos 120 artigos encontrados cumpriram critérios para inclusão na revisão. A análise desses artigos indica que as principais funções cognitivas comprometidas pela T1DM são atenção, atenção visual, memória verbal, recuperação imediata e tardia e velocidade psicomotora. Nos artigos selecionados, verificamos que os instrumentos mais utilizados foram o *Montreal Cognitive Assessment* (MoCA), as escalas Wechsler (WMS-III e WMS-RC), o Teste de Trilhas, *The Grooved Pegboard* e substituição (letra-símbolo, dígito-símbolo). Em virtude dos diferentes comprometimentos encontrados, sugerimos a importância da padronização de uma bateria de avaliações cognitivas e maiores esforços na compreensão dos prejuízos funcionais decorrentes dos danos à cognição em indivíduos com T1DM.

Palavras-chave: diabetes *mellitus* tipo 1, disfunção cognitiva, avaliação neuropsicológica, funções cognitivas, revisão integrativa

DEFICIENCIAS COGNITIVAS EN LA DIABETES *MELLITUS* TIPO 1: REVISIÓN INTEGRADORA

Resumen

Esta revisión analizó los dominios cognitivos afectados por la diabetes *mellitus* tipo 1 (*type 1 diabetes* mellitus [T1DM]) y los instrumentos utilizados para su evaluación. Se realizó una búsqueda en tres bases de datos, utilizando los descriptores "type 1 diabetes" AND "cognitive dysfunction". Solo seis de los 120 artículos encontrados cumplieron los criterios para su inclusión en la revisión. El análisis de estos artículos indica que las principales funciones cognitivas comprometidas por la TDM1 son la atención, la atención visual, la memoria verbal, la recuperación inmediata y tardía y la velocidad psicomotora. Entre los artículos seleccionados, encontramos que los instrumentos más utilizados fueron la *Montreal Cognitive Assessment* (MoCA), las escalas Wechsler (WMS-III y WMS-RC), la Prueba de Rastro, *The Grooved Pegboard* y la sustitución (letra-símbolo, dígito-símbolo). Debido a las diferentes deficiencias encontradas, sugerimos la importancia de estandarizar una batería de evaluaciones cognitivas y mayores esfuerzos para comprender las deficiencias funcionales que resultan del daño a la cognición en personas con TDM1.

Palabras clave: diabetes *mellitus* tipo 1, disfunción cognitiva, evaluación neuropsicológica, funciones cognitivas, revisión integradora

Diabetes mellitus is one of the most prevalent chronic diseases worldwide (World Health Organization, 2016). Due to advances in treatment, individuals with diabetes have increased their life expectancy, and thus, they experience the most prevalent neurocognitive changes at advanced ages (Munshi, 2017; Ryan et al., 2016). Cognitive decline and dementia occur more frequently in individuals with diabetes and prediabetes (Xue et al., 2019). However, it is essential to highlight that diabetes mellitus itself does not imply cognitive impairment or dementia. Vascular damage, alcohol, and drug abuse, seizures, head trauma, and depression contribute to these changes (Saedi et al., 2016). In addition, the age of disease onset and the number of severe episodes of hypoglycemia, chronic hyperglycemia, and retinopathy are also associated with cognitive decline in these patients (Broadley et al., 2017; Kodl & Seaquist, 2008).

Most studies on cognitive impairment focus on type 2 diabetes mellitus, in which lower performances are evidenced in verbal memory, processing speed, and psychomotor speed (Kodl & Seaquist, 2008; Kumar et al., 2009). Executive functions, including mental flexibility, inhibitory control, and working memory are also compromised (Kodl & Seaquist, 2008; Vincent & Hall, 2015). However, few studies have examined the cognitive function of patients with type 1 diabetes mellitus (T1DM).

Existing studies indicate compromises in intelligence tests, processing speed, and sustained attention in individuals with T1DM compared to non-diabetics (Brands et al., 2005). Additionally, impairments in motor efficiency, attention, visuoconstruction, and mental flexibility are also observed (Kodl & Seaquist, 2008). However, the results are inconclusive, partly because of the heterogeneity of the instruments employed, which justifies the need to review the literature.

The lack of consensus in the literature on neuropsychological functioning in T1DM represents an issue for individuals diagnosed in childhood or adolescence, who live longer with the cognitive changes. It is also relevant to people in productive age, who may feel the effects of these changes in their search for academic accomplishments, better jobs, and increased income. This group of patients will also need full neuropsychological functioning to administer themselves a complex treatment that requires decision-making, attention, and inhibition of specific behaviors (Vloemans et al., 2018; Wasserman et al., 2015).

By determining which domains will be affected by T1DM, we can proceed with the indication of early neurorehabilitation interventions to reduce possible physical damage and functional losses to the individual (Chaytor et al., 2015).

This article aimed to evaluate cognitive impairments in T1DM, seeking a consensus on the neuropsychological alterations most found in this group of patients. We also included a survey on the primary assessment tools used.

To this end, the integrative review method was adopted. This review model has a defined search and analysis structure, which enables the visualization of the scenario of studies on a given topic, thus allowing the identification of contradictions and consistencies, as well as enabling the delimitation of future studies (Botelho et al., 2011). The response of this review to this question may contribute to the delimitation of future studies, as well as to the creation of neuropsychological rehabilitation programs.

Method

A search was performed in three databases (PubMed, Embase, and Cochrane) on February 5, 2022, using the descriptors "type 1 diabetes" AND "cognitive dysfunction". Only studies conducted on humans were included, which resulted in complete articles published in English from 2015 to 2022. Analysis of the selected articles was performed descriptively, following the data description table in the integrative review proposed by Souza et al. (2010). Duplicated articles, papers whose abstracts and titles were not in agreement with our objective, review/meta-analysis articles, and guidelines were excluded (Figure 1).

Figure 1

Flowchart of Search and Selection of Articles
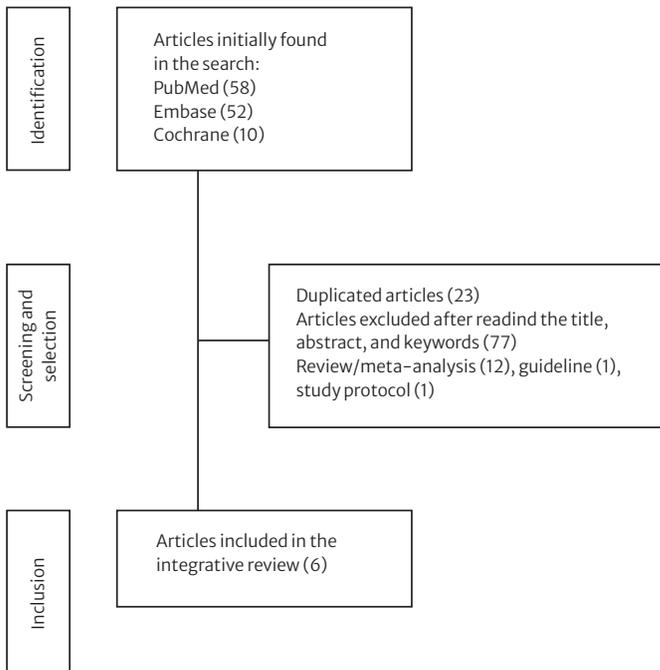
Results

Initially, 120 complete articles were found: 58 articles in PubMed, 52 in Embase, and ten in Cochrane. Of these, 23 articles were excluded because they were duplicated, 77 articles were excluded after reading the title, abstract, and keywords because they were not consistent with the objective of this review, and 12, because they were reviews or meta-analyses, one protocol, and one guideline. Finally, only six articles were selected for full reading.

The articles differ in the objectives, age groups evaluated (children, adults, and elderly), instruments used, and domains evaluated (Table 1). This article will initially present data on

neuropsychological functioning and instruments used. Then, the association of clinical and demographic variables with cognition is examined, followed by the impact of these changes on an individual's functionality.

Table 1

Presentation of Results

Authors	Objective	Sample	Cognitive function investigated	Instruments	Results	Conclusion
He et al. (2018)	To verify whether there are differences in cognitive performance between children with type 1 diabetes and control group.	105 subjects with type 1 diabetes and 90 controls (M = 7–17 years).	General intelligence, attention, perceptual reasoning, visuospatial perception, processing speed, memory.	Wechsler Intelligence Scale for Children – Chinese Revision (WISC–RC), Wechsler Adult Intelligence Scale (WAIS–RC), digit span, similarities, picture completion, block design, symbol search subtests, Wechsler Memory Scale – Chinese Revision (WMS–RC).	Individuals with diabetes had lower scores in general intelligence tests, perceptual reasoning skills, and attention.	Early exposure to severe hypoglycemia seems to result in impaired memory. The study indicates the importance of minimizing exposure to deficient glycemic control, as it can lead to cognitive impairments.
Ding et al. (2019)	To compare the neurocognitive functioning of patients with type 1 diabetes and healthy adults.	70 subjects with type 1 diabetes (M = 32 years) and 48 adult controls, over 18 years old.	Attention, calculation, recall, language ability to follow simple commands, visuospatial skills, concentration, language, abstraction, calculation, and orientation.	Mini–Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA).	MMSE and MoCA scores were lower in the group of individuals with diabetes.	Some factors such as age, fasting C peptide level, educational level, diabetic peripheral neuropathy (DPN), and diabetes complications may be associated with cognitive impairments.

Table 1

Presentation of Results

Authors	Objective	Sample	Cognitive function investigated	Instruments	Results	Conclusion
Awad et al. (2017)	To analyze the cognitive functioning of long-term diabetes patients (> 30 years) who do not have clinical comorbidities related to diabetes.	43 individuals with type 1 diabetes and 86 controls (*M* = 57 years).	Episodic memory, semantic memory, short-term episodic memory, working memory, visual attention, psychomotor speed.	Free recall of sentences, fluency A, fluency B, fluency of profession, free recall of words, letter–symbol substitution.	Neuropsychological tests did not differ between groups for sentence–free recall. Performance in tests that evaluated short–term episodic memory, visual attention, and psychomotor speed was significantly worse in individuals with diabetes than in controls.	The authors indicate that diabetes seems to affect cognition even in the absence of comorbidities.
Ryan et al. (2016)	To verify whether there is a relationship between cognitive performance and episodes of severe hypoglycemia, retinal vessel diameter, and the presence of micro– and macrovascular complications.	198 subjects with type 1 diabetes (*M* = 56 years).	Mental efficiency, executive function, non–verbal and verbal memory.	Trail Making Test – Parts A and B, stroop of words, interference test, The Grooved Pegboard, Digit–Symbol Substitution Test (DSST), verbal fluency using the letters F, A, S, Rey's Complex Figure (copy, immediate and late recovery), and immediate and late recovery of history.	Recent episodes of severe hypoglycemia have been associated with worse performance in assessing mental efficiency and non–verbal memory.	Narrowing of the central retinal arteries is associated with poor mental efficiency measures.
Chaytor et al. (2015)	To analyze the functional implications of diabetes.	101 subjects with type 1 diabetes (with hypoglycemia) and 100 controls (without hypoglycemia) (*M* > 60 years).	Processing speed, visual search, mental flexibility, executive functions, verbal learning and memory, manual dexterity, and cognitive screening.	Symbol Digit Modalities Test, Trail Making Test, Hopkins Verbal Learning Test – Revised, The Grooved Pegboard Test, and MoCA.	Verbal memory and complex processing speed appear as predictors of the ability to accurately complete important calculations related to diabetes management.	Factors such as advanced age, low schooling, and symptoms of depression may be associated with difficulties in performing mathematical calculations, which are necessary for efficient diabetes control.

Table 1

Presentation of Results

Authors	Objective	Sample	Cognitive function investigated	Instruments	Results	Conclusion
Musen et al. (2018)	To understand the cognitive long-term interfer-ences of type 1 diabetes.	82 subjects with type 1 diabetes, 31 subjects with type 2 diabetes, and 30 controls.	General intelligence, executive function, working memory, long-term memory, and psychomotor speed.	Wechsler Abbreviated Scale of Intelligence (WASI), Trail Making Test, Delis-Kaplan Executive Function System (D-KEFS), The Letter-Number Sequencing Subtest from the Wechsler Memory Scale III, Rey's Verbal Auditory Learning Test, Learning Test, and The Grooved Pegboard.	Individuals with type 1 and type 2 diabetes performed worse than controls in tests that evaluated executive function, working memory, and psychomotor speed, although diabetics presented a score within the normal standard in the evaluation.	The study highlights that the worse performance of individuals with diabetes does not necessarily indicate that they are more prone to dementia.

Neuropsychological changes and assessment instruments used

Most studies showed that people with type 1 diabetes performed worse in neuropsycholog-ical tests when compared to controls matched by age and schooling. However, neuropsychological alterations varied widely between studies, so that general intelligence tests, perceptual reasoning skills, and attention demonstrated inferior performance in children and adolescents with diabetes (He et al., 2018). Global cognitive functioning measures, such as the Montreal Cognitive Assessment (MoCA) and the Mini-Mental State Examination (MMSE), showed impairments in adults with T1DM (Ding et al., 2019).

Short-term episodic memory, visual attention, and psychomotor speed tests showed worse results for diabetics with more than 30 years of diagnosis, even with scores within the normal range (Awad et al., 2017). The long-term cognitive consequences of diabetes mellitus were also investi-gated in individuals with T1DM who had the disease for more than 50 years, individuals who had type 2 diabetes mellitus, and non-diabetic controls (Musen et al., 2018). The results showed lower memory performance (immediate and delayed recall) in individuals with types 1 and 2 diabetes mellitus, although the scores were still within normal limits.

Regardless of age and other variables, the most cited neuropsychological changes were at-tention – visual attention (Awad et al., 2017; Ding et al., 2019; He et al., 2018), verbal memory –, with immediate and delayed retrieval (Chaytor et al., 2015; Musen et al., 2018), and psychomotor speed (Awad et al., 2017; Musen et al., 2018).

The heterogeneity of the neuropsychological profiles is due, in part, to the different instru-ments used in the evaluation of these patients. The most used neuropsychological instruments were the following: MoCA, Wechsler's scales (Wechsler Memory Scale III – WMS-III – and Wechsler

Memory Scale – Chinese Revised – WMS–RC), Trail Making Test, The Grooved Pegboard, and substitution (letter–symbol, digit–symbol) (Figure 2). The instruments used in the analyzed studies with lower recurrence were: MMSE, sentence–free recall, Fluency A, Fluency B, Verbal Fluency (F, A, S), Fluency Professions, free word recall, Stroop Word, Interference Test, Rey's Complex Figure (copy, immediate, and posterior recall), the recall part of the number–symbol pairs (Digit–Symbol Substitution [DSST] recall), immediate and late recall of a short story, and Rey's Auditory–Verbal Learning Test. Only one study reported that Wechsler Intelligence Scale for Children (WISC), Wechsler Adult Intelligence Scale (WAIS), and WMS were adapted for the target population (He et al., 2018).

Figure 2

Frequency of Use of the Most Popular Tests
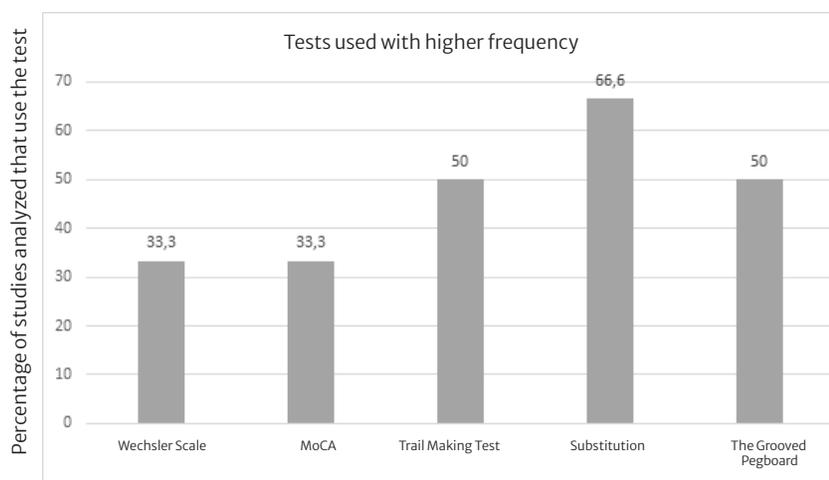
Impact of neuropsychological changes on functionality

Most studies have not explored the impact of neuropsychological changes on the functional abilities of people with diabetes. Only one of them mentioned that neuropsychological changes could affect the treatment of these individuals, which highlights the importance of this evaluation in the diagnosis and care for these patients (Chaytor et al., 2015). Chaytor et al. (2015) indicate that impaired performance in verbal memory and speed of attention processing would be predictors of difficulties in essential calculations, which are necessary for the management of treatment in diabetes. The authors also highlight the importance of a neuropsychological assessment of these patients and suggest that low schooling and depressive symptoms may also interfere with treatment outcomes.

Clinical variables associated with neuropsychological changes

The literature indicates that some clinical variables are important elements in the emergence of cognitive impairment in individuals with diabetes. He et al. (2018) verified the relationship between glycemic control and cognitive impairment, demonstrating that severe hypoglycemia, chronic hyperglycemia, and diabetic ketoacidosis may impair the cognitive domains evaluated in their study. A high level of peptide C and the presence of diabetic neuropathy may also be risk factors for cognitive dysfunction in T1DM (Ding et al., 2019). Other authors have also mentioned the presence of vascular complications and the diameter of retinal vessels as variables that interfere with cognitive functioning (Ryan et al., 2016).

The early onset of the disease (before the age of seven), as well as disease time (Awad et al., 2017), may increase the odds of cognitive impairment (He et al., 2018). Even in the absence of co-morbidities, a period longer than 30 years of living with diabetes was sufficient to affect cognition in people with diabetes in comparison to controls (Awad et al., 2017). Moreover, regarding clinical variables, Musen et al. (2018) indicated that long-term hyperglycemia could be an important factor in brain damage.

Demographic variables associated with neuropsychological changes

Cognitive impairments related to diabetes have been explored more in older adults (Ryan et al., 2016; Awad et al., 2017; Musen et al., 2018; Chaytor et al., 2015) than in children, young people, or adults (He et al., 2018; Ding et al., 2019; Ryan et al., 2016).

Ding et al. (2019) highlight that age and educational level along with clinical variables may interfere with the onset of cognitive dysfunction. Chaytor et al. (2015) pointed that the high educational level of participants should be considered when expanding the data to the general population.

<div align="center">

Discussion

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Every review plays the role of gathering specific knowledge on a given subject to contribute to significant studies in the area (Souza et al., 2010). This integrative review aimed to evaluate cognitive impairments in T1DM, seeking a consensus on the neuropsychological alterations most found in individuals with this type of diabetes. In conducting the review, it was possible to survey the main instruments used in the evaluation of this group. In addition, from the data obtained, it was possible to verify the demographic and clinical variables of the disease most commonly associated with cognitive decline. Moreover, we noticed a significant gap in our investigation of the impact of cognitive changes on the functionality of these patients.

Cognitive impairments were verified in T1DM in different age groups. However, studies with older adults predominate (Ryan et al., 2016; Awad et al., 2017; Musen et al., 2018; Chaytor et al., 2015) probably because of the higher frequency of cognitive alterations in this age group than in the other ones.

All studies showed that patients with T1DM had lower cognitive performance than controls, especially in general and visual attention constructs, verbal memory, immediate and late evocation,

and psychomotor speed. However, the results are not conclusive given the heterogeneity of the methods employed. The differences range from the selection of participants according to the clinical variables of the disease to the selection of neuropsychological assessment instruments. The heterogeneity of the battery of evaluations presented in this review makes it difficult to establish a consensus regarding the affected functions. Furthermore, the reviewed studies did not describe the strengths or areas of preservation of participants, which is one of the evaluation objectives and is necessary for neuropsychological rehabilitation programs.

The cause of cognitive impairment in these patients varies widely among studies. The age of disease onset, number of severe episodes of hypoglycemia, chronic hyperglycemia, diabetic neuropathy, retinal vessel diameter, diabetic ketoacidosis, and micro- or macrovascular complications may favor the onset of neuropsychological changes in this group of patients (Musen et al., 2018; He et al., 2018). Therefore, future studies should control for these variables so that they do not interfere with neuropsychological outcomes.

According to Awad et al. (2018), even with the exclusion of comorbidities, people with diabetes had worse performance in some cognitive tasks than controls, which could be explained as a detrimental effect of long-term contact with excessive glucose. Biessels et al. (2008) suggest that diabetes impairments free of disease-related comorbidities are established in two critical periods of life – in childhood and late adulthood –, phases in which the nervous system undergoes transformations, development, and neurodegeneration, respectively. Outside these periods, cognitive damage could be due to comorbidities related to diabetes.

Regarding functionality, according to Ribeiro (2011), the integrative model of this construct indicates that factors related to body structure affected by the disease, bodily and psychological functions, the presence of limitations in the performance of activities or actions, and the participation of the individual in the community, family life, and leisure time should be taken into account when analyzing the functionality of individuals with chronic disease. Therefore, the impacts of T1DM on the individual's life cover aspects beyond those mentioned by Chaytor et al. (2015). Besides the difficulties in the management of the disease (calculations to adjust the amount of insulin to the diet performed and the selection of food according to the prescribed diet), intentional and mnemonic impairments have consequences on school achievements, work performance, interaction with peers, in addition to impacts on traffic, leisure activities, such as reading a book or watching a movie. The impairment of psychomotor speed affects the execution of actions in response to the demands of the environment and the performance of various activities in daily life.

Pereira (2020) analyzed the repercussions of the diagnosis of diabetes mellitus on functionality. Participants reported negative repercussions of the diagnosis, such as increased anxiety, pessimism, and a greater sense of fatigue. In addition, they reported lower performance capacity at work and in the establishment of interpersonal relationships with friends or family members, which implies several limitations to the lifestyle of these individuals.

The integration of the data found in this review indicates that neuropsychological dysfunction in people with T1DM can be explained by different etiologies, including clinical complications of

the disease. However, there is no consensus on the most affected cognitive domains, probably because the studies included different age groups and the heterogeneity of the battery of tests. It should also be noted that the presence of diabetes mellitus was not verified in the control group, and the sample selection criteria differed between studies.

Another limitation of the evaluated articles was the predominance of cross-sectional studies, which prevented us from establishing a cause-effect relationship. Nevertheless, most studies point to the impact of diabetes on cognition, whether mild (worse performance than the control group, even if within the normal standard for the age) or significant impairments. Future studies should standardize the tests used for evaluation, analyze the impact of cognition resulting from each comorbidity, and verify the negative impact of cognitive impairment on the functionality of individuals with long-term diabetes. Only in this way will it be possible to establish a neuropsychological rehabilitation program that addresses the needs of these patients.

During the reading of the titles and articles for the selection of studies that would compose the present study, we noticed that the most recent studies, especially those published after 2020, do not focus on the cognitive evaluation of people with diabetes but, instead, on the search for possible biomarkers that are predictors of cognitive impairments. The search for biomarkers is helpful since it can help identify how to handle the treatment of these patients so as to reduce damage to cognition. In turn, biological measures do not seem to replace the behavioral and psychological findings that are still controversial and the highlights of this review. Future studies should consider the associations between biomarkers and cognitive impairment in T1DM, which can be seen as a limitation of this integrative review.

Final considerations

This review aimed to verify the cognitive damage in individuals with T1DM. To this end, we searched for "type 1 diabetes" AND "cognitive dysfunction" on the PubMed, Embase, and Cochrane databases, and identified six articles. The selected studies indicated that individuals with T1DM had worse performance than those without diabetes on neuropsychological testing. The main cognitive domains that were affected were attention, visual attention, verbal memory, immediate and late recovery, and psychomotor speed. The battery of tests is heterogeneous, and there is a gap in these studies regarding the impact of these impairments on the routine of individuals.

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