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Relationship Between Children's Cognitive Function and Type 1 Diabetes Mellitus (T1DM): A Systematic Review

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Abstract
Background: Type 1 diabetes mellitus (T1DM) is the most common type of diabetes in children and is caused by various factors, including immune system abnormalities, genetic factors, and environmental influences. T1DM usually occurs in early to mid-childhood when an autoimmune process damages the pancreas's beta cells, producing insufficient insulin. Purpose: Review several studies on T1DM associated with cognitive decline in children. Methods: The study systematically reviews five articles from randomized controlled trials, focusing on the cognitive function of children with T1DM. It specifically explored the relationship between T1DM, cognitive deficits, and the impact of diabetic ketoacidosis on cognitive function in children. Results: This review included five articles from randomized controlled trials between 1999 and 2023, distributed across two nations. The studies included 1.579 children with T1DM or with Ketoacidosis diabetic. Sample testing with cognitive function measurements in each article. Discussion: Type 1 diabetes patients had milder to moderate cognitive deficits on a variety of neuropsychological tests compared with nondiabetic control subjects. These cognitive deficits are primarily related to mental processing speed, executive function, and memory. Summary: Children with T1DM, especially those with a history of diabetic ketoacidosis, exhibited mild to moderate cognitive deficits, particularly

in mental processing speed, executive function, and memory. The review emphasized the potential impact of T1DM on children's cognitive development and academic performance, underscoring the need for early diagnosis and appropriate management to mitigate cognitive decline.

Keywords: Type 1 Diabetes Mellitus (T1DM), Cognitive Function, Children

1. Introduction

Type 1 diabetes mellitus (T1DM) is an autoimmune disorder involving multiple factors. It is characterized by T cell-induced destruction of β-cells in the pancreas, resulting in insulin production and release deficiencies. This condition has the potential to be severe and life-threatening (Akil et al., 2021). Type 1 diabetes mellitus, which is also referred to as insulin-dependent diabetes mellitus or juvenile-onset diabetes, accounts for about 5-10% of all diabetes cases (Banday et al., 2020). In studies conducted in the United States, 80% of diabetes cases were T1DM at ages <9 years and 6-76% between 10 and 19 years (Saraswathi et al., 2019). In 2021, the estimated global total of new cases of T1DM in children and adolescents is 355,900 diagnosed cases. This figure is predicted to increase to 476,700 cases by 2050 (Ward et al., 2022).

Type 1 diabetes mellitus is the most common type of diabetes in children and is triggered by factors such as immune system disorders, genetic factors, and environmental influences. T1DM usually begins to appear in early to mid-childhood, when the beta cells of the pancreas are damaged by an autoimmune process, leading to a lack of insulin production (Pasi & Ravi, 2022). The disruption in insulin production starts with the formation of auto-antibodies against pancreatic β-cells, eventually resulting in β-cell damage. When β-cells are damaged, insulin production is impaired. In the early stages of clinical symptoms, some functioning β-cells may take over, producing insulin, resulting in a temporary period of normalcy. Over time, T1DM patients will experience disease progression or may develop complications due to diabetes (Ward et al., 2022). Insulin deficiency leads to uncontrolled lipolysis and increased plasma levels of free fatty acids, thus suppressing glucose metabolism (Ozougwu, 2013). This is because insulin can restrain the use of fat as an energy source by inhibiting the hormone glucagon (Raghupathy, 2015). The hormonal changes that occur will increase glucose production from glycogenolysis and gluconeogenesis, causing an increase in acetoacetic and β-hydroxybutyric acids (ketones) that exceed the capacity of the equilibrium system in the blood. This complication is metabolic acidosis, referred to as diabetic ketoacidosis (DKA). It can progress to hyperglycemia, hyperketonemia, osmotic diuresis, severe vomiting, dehydration, electrolyte deficiency, and more severe insulin resistance (Wolfsdorf et al., 2006).

Type 1 diabetes mellitus is usually detected in childhood and adolescence, which is a period of rapid development of the central nervous system. Elevated blood glucose levels in non-diabetic and pre-diabetic patients have been associated with cognitive impairment. Diabetes is characterized by persistent elevation of blood glucose levels. Thus, hyperglycemia becomes a possible causative agent of cognitive impairment in diabetic patients (Feinkohl et al., 2015). There is concern that the developing brain may be more susceptible to extreme blood sugar fluctuations (Moheet et al., 2015). Some studies also suggest that complications of DKA may cause neurologic damage that subsequently affects cognitive function (Diabetes.co.uk, 2019; Lacy et al., 2020). Children with impaired cognitive development due to the rapid onset of T1DM can have a negative impact on their academic performance (Moheet et al., 2015). This article focuses on the association between T1DM and cognitive function in children with T1DM. We have conducted a literature search to provide a summary database on cognitive function in T1DM pediatric patients and added the latest literature to update the previous systematic review.

2. Methods

2. 1. Selection Method

We conducted this *systematic review* and meta-analysis by PRISMA (*Preferred Reporting Items for Systematic Reviews and Meta-Analyses)* guidelines and the *Cochrane Handbook for Systematic Reviews of Interventions*, version 6.3,2022.

2. 2. Reference Standard

Research with a *Randomized Controlled Trial* design shows the prognosis of the effect of a history of diabetes mellitus on cognitive function.

2.3. Search Strategy

In the literature search effort, independent researchers (AA et al.) conducted a comprehensive search in several leading databases, such as Cochrane and PubMed. The literature search process was completed from October 12, 2023, to October 31, 2023, using terminology according to the MeSH (*Medical Subject Heading*) browser. Specific keywords were used by following the *boolean operator keywords* guidelines, i.e. : *((diabetic[Title/Abstract] OR diabetic OR hyperglycemia OR hyperglycemic) AND ((children[MeSH Terms]) OR (child))) AND (cognitive OR cognitive impairment OR cognitive behavior)*. The full description is available in Appendix 1.

2.4. Eligibility Criteria

Before starting the literature search, we formulated strict inclusion and exclusion criteria to identify relevant studies.

Inclusion criteria:

a. study with *Randomized Controlled Trials* design and prospective cohort,
b. The patients included in the population were patients with type 1 diabetes mellitus or mild diabetic ketoacidosis,
c. measuring IQ scores before DM diagnosis and after DM diagnosis, and
d. have a control group in a healthy population. On the other hand,

Exclusion criteria:

a. Not using English or not using a compatible language, and
b. Does not provide access to full text. Three independent researchers (AA, SLR, KRR) conducted the entire paper selection process, with joint consultation with another researcher (MRK) to resolve disagreements.

2.5. Study Selection

From all the databases we used, we managed to collect 40 articles. We collected all the articles in evidence. After reviewing, we found eight duplicate articles, three unsuitable for studies because they were *eBooks* and *books*, and irrelevant articles. Furthermore, from the selection by reading the entire article, we excluded 24 articles because 17 of them did not use a history of diabetes as an intervention, two did not see the effect on cognitive function, and 5 of them did not have access to the full text. The final result of the literature selection was that we found five articles that can be used for qualitative analysis and two articles that can be used for quantitative analysis. The flow of our literature selection can be seen in Figure 1.

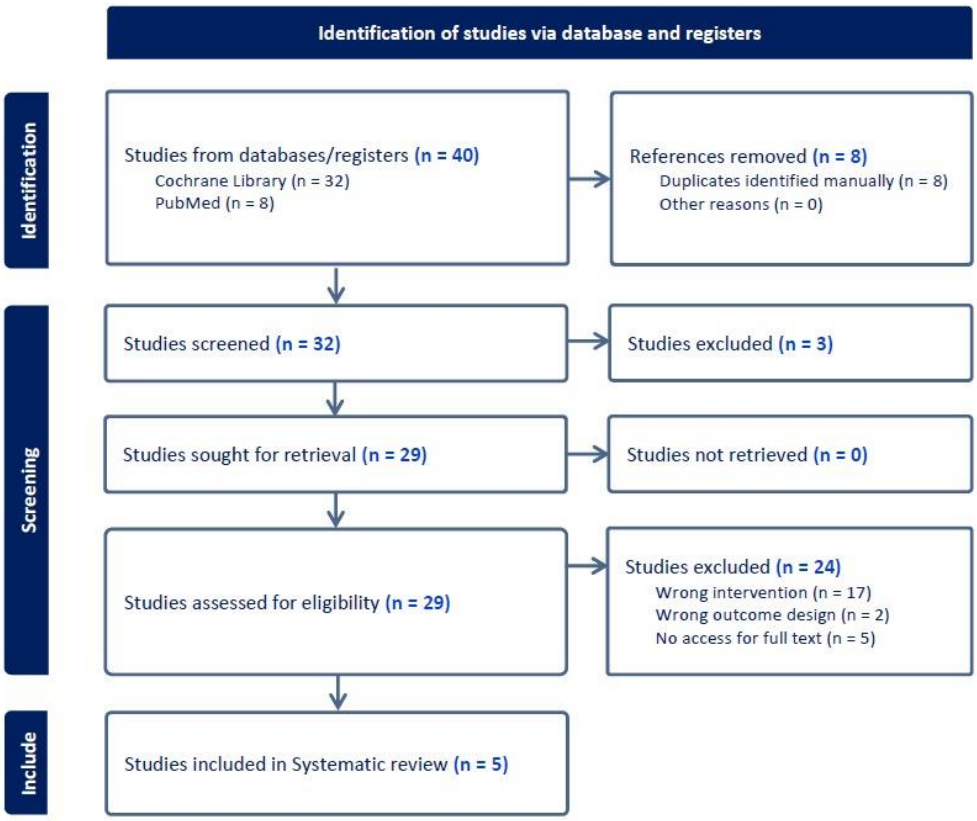
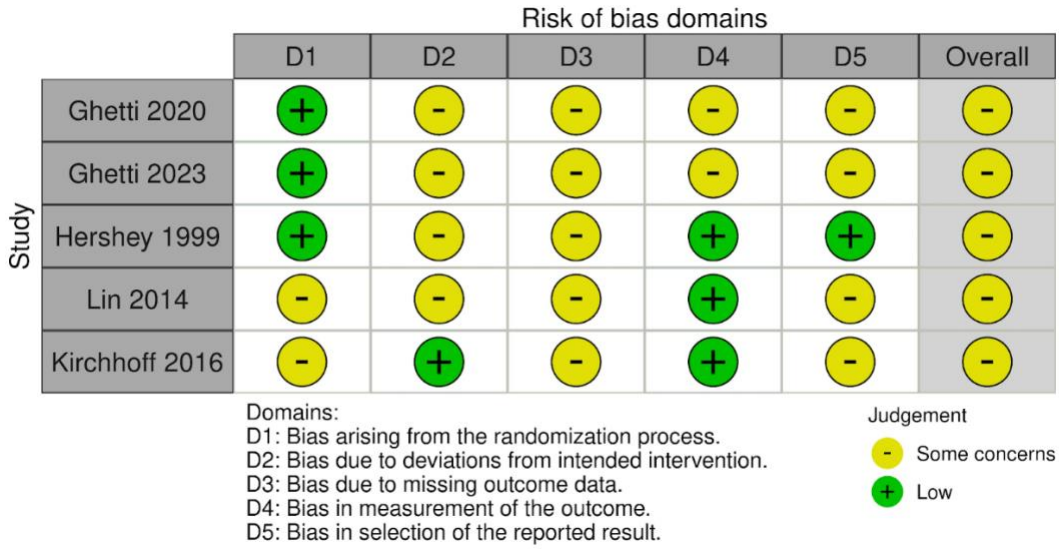


Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram

2.6. Risk of Bias in Individual Studies (Qualitative Synthesis)

The quality of the selected studies was assessed using the *Risk of Bias for Randomized Trials* (RoB2). RoB2 consists of five domains and 28 questions to be evaluated. These questions refer to the randomization process, intervention, outcome data, and reported results. The choices made were yes, probably yes, probably no, no, and not included, which, when summed up, can be seen whether the researcher tends toward the practical, tends toward the comparator, moves away from uncertainty, tends toward the unpredictable, and chooses not to answer. Quality ratings were analyzed by one independent reviewer (AA). Scores were presented based on the RoB 2 algorithm, such as low risk, some concern, and high risk. The results of the bias assessment found that the two journals we used had results with some concerns. Indications of study quality are shown in table 1.

Table 1: Quality of Inclusion Articles



3. Results

Titles and abstracts were comprehensively scrutinized to verify their compliance with the established inclusion and exclusion criteria. The systematic search results yielded five articles by independent researchers (SLR, MRK). The search result extraction table will then describe the search results, starting from the author, country, year, study design, population and sample size, a method for measuring cognitive function, and findings in each article. The research description table can be seen in Table 2.

Table 2: Research description

Author (Year)	Country	Title	Study design	Population and Sample Size	Methods for Measuring Cognitive Function	Results
Ghetti et al. (2023).	United States of America	Cognitive Function Following Diabetic Ketoacidosis in Young Children with Type 1 Diabetes	RCT	Seventy-three children aged 3-5 years with newly diagnosed type 1 diabetes mellitus from 12 pediatric emergency centers.	This study measured IQ using the Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III). Children aged 3 years received the WPPSI test with four subtests: block design, arithmetic, vocabulary, and comprehension. For 4–5-year-olds, the WPPSI test includes block design, information, matrix reasoning, vocabulary, picture concepts, word comprehension, and coding.	It was found that 22 children (30.1%) had moderate-severe diabetes mellitus and had IQs up to <105, and 24 children (32.87%) had medium-severity diabetes with IQs >105. While there were 27 (37.3%) children who were not diagnosed with diabetes had IQ >110
Ghetti et al. (2020).	United States of America	Cognitive Function Following Diabetic Ketoacidosis in Children With New-Onset or Previously Diagnosed Type 1 Diabetes	RCT	A total of 1,249 children were studied. Several children with type 1 DM aged 6-18 years were taken from the Pediatric Emergency Care Applied Research Network (PECARN). There were also some children with type 1 DM but no history of diabetic ketoacidosis also taken from PECARN.	Cognitive tests included spatial and color memory tasks, Wechsler Abbreviated Scale of Intelligence (IQ measured 65-160), forward number span, and backward tasks (numbers: 0-18).	The study found that patients with moderate/severe DKA had a lower adjusted mean IQ score of 100.6 (SD 1.34) compared to those with mild DKA (adjusted mean IQ score of 101.8, SD 1.14) and those with no DKA history (adjusted mean IQ score of 103.0, SD 1.46). Additionally, patients with mild DKA had a lower adjusted mean forward digit span recall score of 8.3 (SD 0.14) compared to those with no DKA history (adjusted mean forward digit span recall score of 8.5, SD 0.20). Furthermore, patients with moderate/severe DKA had a lower adjusted mean forward digit span recall score of 8.0

						(SD 0.17) than those without DKA history.
Kirchhoff et al. (2016)	United States of America	A longitudinal investigation of cognitive function in children and adolescents with type 1 diabetes mellitus	Prospective cohort	One hundred nineteen children aged 4-16 years with type 1 diabetes mellitus and 59 controls. The distance between the first and second data collection was 2 years, and between the second and third data collection was 3 years.	IQ (Wechsler Intelligence Scale Children-III), visual-spatial ability (Woodcock-Johnson III), and memory (Delayed Recall Trial of the Word Lists, which is a subtest of the Children Memory Scale). Reaction speed: Go-No-Go	Spatial relations: scores were 2.95 lower than controls (p = 0.006). Spatial Delayed Response (SDR): 4.42 mm less accurate than control (p=0.046). IQ data not shown. Reaction speed: 5.38 milliseconds slower (p=0.037)
Lin et al. (2014).	Australia	Risk Factor for Decline in IQ in Youth With Type 1 Diabetes Over the 12 Years From Diagnosis/Illness Onset	Prospective cohort	One hundred thirty-three children with type 1 diabetes and 126 controls. Twelve years later, the population size was 106 patients and 75 controls (HC).	IQ was assessed using the Wechsler Preschool and Primary Scale of Intelligence Revised (WPPSI-R) and Wechsler Intelligence Scale for Children-Revised (WISC-R) and at follow-up using the Weschler Abbreviated Scale of Intelligence (WASI).	VIQ baseline (107.06 HC; 103.65 patients), VIQ follow-up (100.60 HC; 95.81 patients, p=0.01), FSIQ baseline (110.76 HC; 107.05 patients), FSIQ follow-up(105.18 HC; 100.94 patients, p=0.02).
Hershey et al. (1999).	United States of America	Conventional Versus Intensive Diabetes Therapy in Children With Type 1 Diabetes	RCT	Sixteen non-diabetic children and 25 children with DM 1 with an age range of 9-18 years. Taken from St.Louis Children's Hospital. Divided into 3 groups: control group, CT group: Conventional diabetic, and IT group: Intensive diabetic	To compare the memory of non-diabetic children and children who received conventional and intensive therapy in this study, a single-trained experimenter assessed it, including a memory test, Delayed Match to Sample List. Presentation task. Word recognition task, paragraph recall task, spatial and memory object task, grooved pegboard task, response inhibition task, vocabulary and block design task,	Memory: Spatial Delayed Response significant difference between IT and CT against control with 60 seconds delay (p=0.05). Accuracy is not significant. Median response time of task: IT had a delay compared to CT and control (p=0.03) Paragraph recall task: The recall performance of each subject was slowed down, there was no significance. Spatial and Object Memory task: immediate response slowed in all subjects, no significance Motor Speed and Inhibition: There is a significant difference between CT and IT against the non-diabetic group using the right hand where there is a delay (P=0.03). Inhibitory response (accuracy task): no significant difference between the 3 groups, but more accurate in the non-diabetic group. Inhibition response (Median Reaction Time Ask): no significant difference, all subjects experienced slowing down. Vocabulary and Block Design task: no difference from control, CT, and IT groups. For tests that did not produce significant results in all three groups with (P<0.001)

3.1. Diabetes and risk of IQ reduction

From the evidence we have gathered that there is a risk of IQ reduction in one of the few studies conducted using children aged 3 to 5 years from various races and ethnicities, it was found that children with moderate to severe diabetes mellitus had significantly lower IQ scores than children with mild diabetes mellitus and without a history of diabetes, which was about 5-10 points from children who were not affected by diabetes (P=0.03). In addition, the study also included ethnicity but did not significantly affect the development of children's IQ. Diabetes mellitus and ketoacidosis are indeed related and affect IQ in children, especially if they have a history and have been

affected in the toddler age. In this study, family economic status also influenced the worsening of diabetes in children (p=0.01) (Ghetti et al., 2023).

The risk of decreased IQ and FISQ was also found in a study by Lin et al. (2014). The comparison between FISQ of diabetic and non-diabetic children was significantly different when followed up to see the second result. The examination in the study used the *Wechsler Preschool and Primary Scale of Intelligence Revised* (WPPSI-R) and the *Wechsler Intelligence Scale for Children-Revised* (WISC-R), where the scale was considered valid to determine the IQ level of a child (Lin et al., 2015).

3.2. Diabetes and other risks of reduced cognitive function

A study by Hershey et al. (1999) found other evidence of decreased cognitive function, including counting, memorization, and writing skills involving 41 children aged 9-18. In addition, these subjects also received conventional and intensive therapy. The results showed that in some tests, diabetic children were delayed in deciding something or finding answers; in this case, there was a significant delay of 40-60 seconds (P = 0.03). However, some tests do not show significance in the delay between the non-diabetes group and the IT and CT groups (95% CI P = <0.001) (Hershey et al., 1999).

Another study showed a significant change in IQ scores in patients with type 1 diabetes who experienced DKA. In patients with new-onset diabetes, the difference in IQ score was -0.08 (95% CI -0.16, -0.00). Also, in this study, the change in IQ score in patients without DKA was 0.08 (95% CI -0.16, -0.00). Based on the data provided, the change in FSIQ score was -6.11 (1.76) in *mean* (sd), and from the data provided, the change in FSIQ score was -5.58 (1.76) in *mean* (sd) (Ghetti et al., 2020).

4. Discussion

Type 1 diabetes mellitus (T1DM) is an autoimmune disease in which the body's immune system destroys the pancreatic beta cells that produce insulin. A wide range of metabolic, genetic, and immunogenetic characteristics of T1DM and age-related differences require a tailored approach for each individual (Speight & Pouwer, 2023). This insulin deficit can increase glucose levels, which can harm the body. Excessive glucose levels should be treated with exogenous insulin injections several times a day (Kahanovitz et al., 2017a)

The brain is the most complex and command center of the human body. This three-pound organ serves as the seat of intelligence, translator of senses, originator of movement, and regulator of behavior (*Brain Basics: Know Your Brain | National Institute of Neurological Disorders and Stroke*, n.d.) (CDC, 2022). During childhood, the human brain undergoes dynamic and unique structural and functional changes, requiring continuous glucose feeding for brain growth and function.

Children with T1DM are at risk of neurocognitive function deficits compared to their non-diabetic peers, particularly in memory skills, learning, and executive function (e.g., working memory, distraction, and response inhibition) (Broadley et al., 2017; Jaser & Jordan, 2021).T1DM has been associated with reduced amounts of total brain matter (gray and white matter), particularly in the parieto-occipital and temporal regions. Differences in affected brain regions depend on severe hypoglycemia, greater HbA1c, disease duration, and severity of microangiopathy (Ferguson et al., 2005; Mauras et al., 2021; Musen et al., 2006; Wessels et al., 2006).

In children, the number of T1DM cases with diabetic ketoacidosis (DKA) is high, with 71% in Indonesia in 2017 (Speight & Pouwer, 2023). DKA is a complication of T1DM caused by insulin deficiency and is a significant cause of morbidity and mortality in children (Kahanovitz et al., 2017b).

Several studies were conducted to look at the relationship between cognitive type 1 diabetes in children. Research conducted by Lin et al. It was found that at the beginning of the study, the IQ of children with type 1 diabetes was the same as that of controls, but when a follow-up examination was carried out, children with type 1 diabetes had

lower VIQ and FSIQ scores than controls. Younger age at diagnosis and more frequent hypoglycemic seizures showed a significant decrease in PIQ and FSIQ in children with type 1 diabetes.

Another study conducted by Kirchhoff et al. found that exposure to hyperglycemic and hypoglycemic conditions, as well as early onset of type 1 diabetes, was associated with decreased intelligence, visual-spatial ability, memory performance, and information processing speed in children with type 1 diabetes.

In children, the number of T1DM cases with diabetic ketoacidosis (DKA) is high, with 71% in Indonesia in 2017 (Pulungan et al., 2021). DKA is a complication of T1DM caused by insulin deficiency and is a significant cause of morbidity and mortality in children (Hadgu et al., 2019; Hanifah et al., 2022; Tonoli, 2013).

Children, especially young ones, have body systems that are still developing, including their central nervous system (Handryastuti et al., 2022; Hanifah et al., 2022). As such, the impact of a severe medical condition such as DKA can have more significant consequences on their cognitive function. The decline in cognitive function associated with DKA can have substantial long-term implications on children's cognitive development (Kostopoulou et al., 2023).

Studies show that children with DKA, regardless of severity, have lower IQ scores compared to children without DKA. This is evident from the statistical test results of Ghetti et al. 2023, which showed that children with DKA had significantly lower IQ scores than children without DKA. This effect remained even after considering socioeconomic and ethnic factors. From the results of this study, it can be concluded that a single episode of DKA is associated with a decrease in IQ scores in children that occurs within a short period after exposure to DKA (Ghetti et al., 2023).

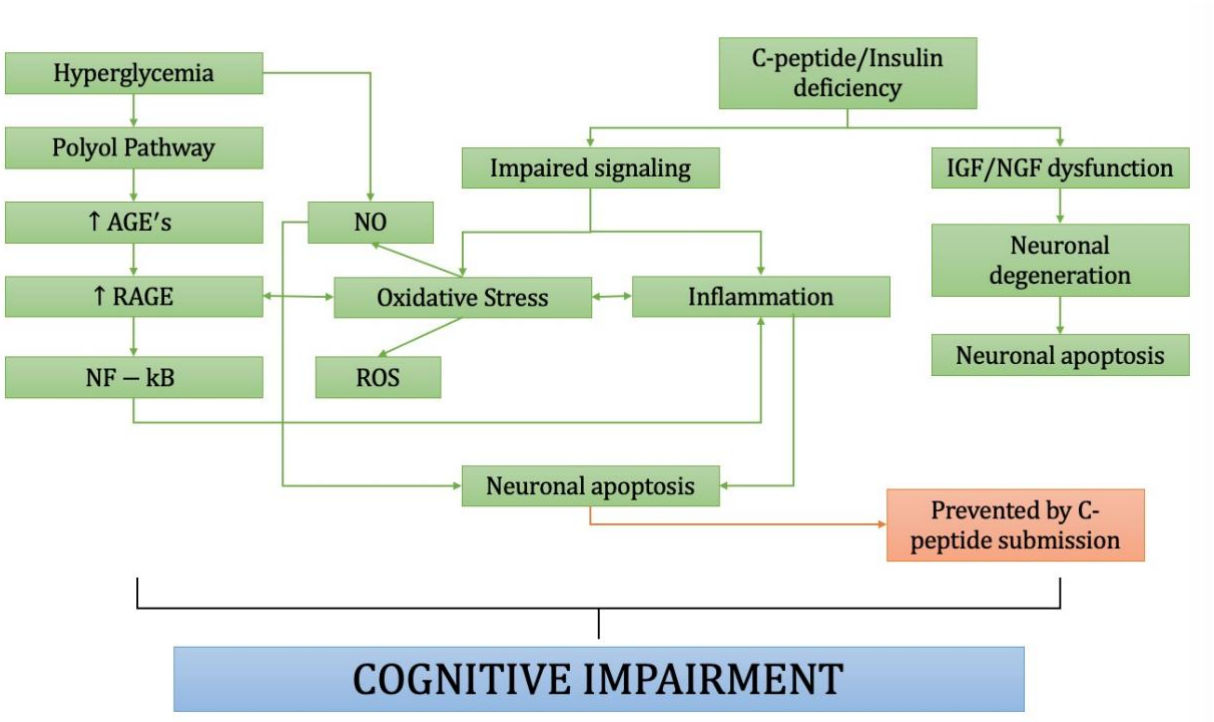


Figure 2: Mechanism of *cognitive decline* in T1DM

Severe hypoglycemia and the age of onset of type 1 diabetes are two of the most frequently studied variables associated with cognitive impairment (Chaytor, 2016). Severe hypoglycemia in children may impair cognitive abilities related to medial temporal functions, such as explicitly recalling past events (delayed declarative memory). The Hershey et al. study showed that severe hypoglycemia in children can impair cognitive abilities related to medial temporal function, such as explicitly recalling past events (delayed declarative memory) (Pourabbasi et al., 2016; Pulungan et al., 2021). In addition, caution should be exercised in imposing strict glucose control standards in pediatric patients with type 1 diabetes due to the higher risk of hypoglycemia associated with

intensive diabetes therapy (IT) (Hershey et al., 1999). Patients with type 1 diabetes have milder to moderate cognitive deficits on various neuropsychological tests compared to control subjects without diabetes. These cognitive deficits mainly relate to mental processing speed, executive function, and memory (Shalimova et al., 2019). Please have a look at Figure 2.

5. Conclusions

Type 1 diabetes mellitus in children, both those without DKA complications and those with DKA complications, can reduce children's cognition. Some of the influencing factors are the age at diagnosis of DKA, severe hypoglycemic and hyperglycemic conditions, and high Hba1c results. These factors can worsen the child's cognition as assessed by IQ, decreased intelligence, visual-spatial ability, memory performance, and information processing speed. Therefore, early diagnosis and appropriate management are necessary to reduce cognitive decline in children.

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