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IMPACTS OF LACK OF GLYCEMIC CONTROL IN CHILDHOOD ON COGNITIVE DEVELOPMENT: AN INTEGRATIVE REVIEW

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Abstract: Goal: To evaluate the effects of hyperglycemia and hypoglycemia during childhood on the cognitive performance of children with diabetes mellitus. **Method:** This is an integrative review of the literature, research was carried out using databases available in the Virtual Health Library (VHL), Medical Literature Analysis and Retrieval System Online (MEDLINE), National Library of Medicine/PubMed, SciELO. The descriptors used were: Diabetes Mellitus, Glycemic Control, Child, Glycemic Control, Child. Combined with each other with the boolean operators OR / AND.
Keywords: Diabetes Mellitus, Glycemic Control, Child, Glycemic Control, Child

INTRODUCTION

Diabetes is a condition resulting from insufficient production or poor absorption of insulin, a hormone responsible for regulating blood glucose. Lack of insulin can result in high glucose levels, which, if not properly controlled, can lead to serious complications in the heart, arteries, eyes, kidneys and nerves. Lack of proper diabetes care can, in extreme cases, be fatal. (BRAZIL, 2023). According to recent data, Brazil ranks 5th worldwide in incidence of diabetes, with approximately 16.8 million adults between 20 and 79 years old affected by the disease. This number is estimated to increase to 21.5 million by the year 2030. (INTERNATIONAL DIABETES FEDERATION, 2021)

Type 1 diabetes mellitus is characterized by the destruction of beta cells in the pancreas, resulting in impaired insulin secretion. Type 2 diabetes mellitus is a chronic disease that alters the processing of glucose in the blood, starting with insulin resistance, which prevents the hormone from acting effectively even when produced. (MOREIRA; CARVALHO, 2016).

According to (FERREIRA et al. 2013), when receiving the diagnosis of a chronic disease, where one realizes that one will live with the illness throughout one's life, it becomes crucial to understand the importance of self-care and adapting to new life methods to cope. the challenges that will arise.

A child's life is irreversibly transformed by the demands of treatment and the consequences of chronic illness. Both she and her family go through a variety of experiences, each impacting in different dimensions. Adaptation to these new circumstances varies depending on the family's stage of life, the specific role of the child within the family nucleus, and how each family member is affected and reorganizes their dynamics during this challenging period. (DAMIÃO; ANGELO, 2001).

Between 2010 and 2019, a total of 85,021 hospitalizations were observed in Brazil due to diabetes mellitus as the primary cause in children and adolescents aged between 0 and 19 years. During this period, the annual average number of hospitalizations was approximately 8,502.10 cases nationwide. Furthermore, the estimated average annual mortality rate in Brazil was 0.91 deaths per million inhabitants. In 2017, the highest rate was recorded during this period, with 1.06 deaths per million inhabitants (SOUSA et al., 2021).

According to Hermes et al. (2018), family actions are not always adequate when it comes to controlling the child's illness. When evaluating case studies in outpatient processes, it was observed that many children are not prepared to start and maintain treatment due to their parents' attitudes. This sometimes results in another family member taking on the role of guardian for the child. However, this change does not guarantee that care will be effective in controlling the disease.

In a cross-sectional study involving Chinese children, cognitive tests, including assessments of general intelligence, were

administered to pediatric patients with type 1 diabetes (T1D, n = 105) and healthy controls (HCs, n = 90). The study investigated the effects of specific variables related to diabetes, such as early onset of the disease (<7 years of age), severe episodes of hypoglycemia, chronic exposure to hyperglycemia and the occurrence of diabetic ketoacidosis (DKA), on children's cognitive outcomes. The results revealed that the DM1 group had lower IQ (P = 0.001) and attention (P = 0.018) scores compared to the HC group. Among patients with DM1, an earlier onset of diabetes correlated with lower performance on tests of visuospatial perception (P = 0.017) and logical memory (P = 0.012). Prolonged exposure to hyperglycemia over time was associated with worse visuospatial perception (P = 0.029), while DKA had a negative effect on IQ scores (P = 0.024). Compared to the subgroup with late severe hypoglycemia, the subgroup with early severe hypoglycemia (<7 years) showed lower performance in the immediate (P = 0.001) and delayed (P = 0.049) visual memory tests (HE et al., 2018).

Studies indicate that both hyperglycemia and hypoglycemia can negatively impact the development of cognitive functions in children, and these effects can persist into adulthood. Research has shown that children who experienced severe episodes of hypoglycemia performed worse on tests of memory and general cognition when compared to children who did not experience such episodes (SÁ et al., 2024).

To evaluate the effects of hyperglycemia and hypoglycemia during childhood on the cognitive performance of children with diabetes mellitus.

METHOD

This is an integrative review of the literature on the impacts of lack of glycemic control in childhood on cognitive development.

For its elaboration, the steps proposed by Mendes, Silveira and Galvão were followed: formulation of the theme, establishment of criteria for inclusion and exclusion of studies, definition of information to be extracted from selected studies, evaluation of studies, interpretation of results and synthesis of the knowledge.

In formulating the present study, the following guiding question was developed: How lack of glycemic control in childhood influences cognitive development? For elaboration of the guiding question, it was used the PICo strategy, an acronym for P: Problem or target population; I: Intervention or phenomenon of interest; Co: Context.

ACRONYM	DESCRIPTORS
P	Infancy
I	Cognitive
Co	Glycemic Control/Childhood

Searches were carried out using databases available in the Virtual Health Library (VHL), Medical Literature Analysis and Retrieval System Online (MEDLINE), National Library of Medicine/PubMed, SciELO.

The descriptors used were: Diabetes Mellitus, Glycemic Control, Child, Glycemic Control, Child. Combined with boolean operators: OR / AND. To establish criteria for inclusion and exclusion of studies, articles that did not meet the topic discussed were discarded, as well as course completion works, theses and dissertations. To select the articles, articles were read through the databases and selected4articles for study. At the end of the study, the knowledge synthesis stage was carried out, in which the main results of the analysis of the articles included in the study were studied.

IDENTIFICATION	ARTICLE	AUTHOR	YEAR	OBJECTIVE
E1	A Longitudinal Investigation of Cognitive Function in Children and Adolescents with Type 1 Diabetes Mellitus	Brenda A. Kirchhoff, Dustin K. Jundt, Tasha Doty, Tamara Hershey,	2016	To explore longitudinal change in cognitive function in youth with T1D compared to non-diabetic sibling controls, and how glycemic control and age of onset influence cognitive performance over time.
E2	Serum brain-derived neurotrophic factor and neurocognitive function in children with type 1 diabetes	Hui-Ju Chen, Yann Jinn Lee, Chao Ching Huang, Yuh Feng Lin, Sung Tse Li	2018	To investigate the association between serum BDNF concentrations and neurocognitive function in children with type 1 diabetes. We also explored differences in serum BDNF expression and neurocognitive function in children with type 1 diabetes with and without GAD65-Ab.
E3	The effect of poor glycemic control on cognitive function in children and adolescents with type 1 diabetes mellitus: a single-center cross-sectional study	Safiah M Al-Shehaili, Seham S Al-Johani, Nora T Al-Sarhan, Aisha A Al-Anazi, Faten F Al-Mijmaj, Wadha N Al-Qhatani, Lama M Al-Nasser, Dania R Al-Yami, Amal S Al-Razooq	2020	To investigate the effect of chronic hyperglycemia, hypoglycemia and diabetic ketoacidosis (DKA) on cognitive function in children and adolescents with type 1 diabetes mellitus (T1D) and explore whether early onset of the disease is correlated with cognitive impairment.
E4	Glycemic extremes are related to cognitive dysfunction in children with type 1 diabetes: a meta-analysis	Jing He, Andrew G Ryder, Shichen Li, Wanting Liu, Xiongzhao Zhu	2016	To investigate the pattern and magnitude of cognitive dysfunction in children with type 1 diabetes compared with non-diabetic controls.

Table 1: Synthesis of information extracted from selected articles

IDENTIFICATION	PREVALENCE IN THE SAMPLE
E1	Young people with diabetes performed worse than controls on visual-spatial ability and memory tasks over time, and did not improve as much on processing speed.
E2	45 children with type 1 diabetes and 50 normal controls Mean full-scale IQ, verbal comprehension, perceptual reasoning, and working memory scores in the diabetes group were significantly lower than in controls.
E3	Higher mean HbA1c levels were associated with cognitive dysfunction in three verbal domains: fluid reasoning, quantitative reasoning, and working memory
E4	1,355 participants with type 1 diabetes and 696 controls. Compared to nondiabetic controls, children with type 1 diabetes showed significantly poorer general cognitive performance as well as specific deficits in total intelligence, attention, and psychomotor speed.

Table 2: Synthesis of information extracted from selected articles

Source: The author

RESULTS

Records identified in Databases/ Libraries/ Search Engines (n=50 publications)

Registration after removing duplicates and reading titles and abstracts (n=21 publications)

Full articles assessed for eligibility (n=14 publications)

Studies Included (n=4)

Source: Written by the author

Figure 1: Process of identification, selection, eligibility and inclusion of articles

DISCUSSION

In the results of the selected studies, the significant impact of the lack of glycemic control in childhood on cognitive development is clearly evident. Research reveals that a lack of glycemic control has a substantial influence on the cognitive functions of affected children, highlighting the urgent need for effective strategies to improve diabetes management from an early age, aiming to mitigate potential negative impacts on long-term cognitive development.

In study E1young people with diabetes performed worse than controls on tests of visual-spatial ability and memory over time, without significant improvements in processing speed. Higher levels of hyperglycemia were related to reduced crystallized intelligence and slower processing, but better performance on memory tasks across all time periods assessed. A more pronounced negative relationship was observed between hyperglycemia and visual-spatial capacity in young people with early-onset diabetes compared to those with late-onset diabetes. It is important to highlight that the reduction in hyperglycemia over time was associated with an improvement in visual-spatial capacity and faster processing.

In article E2, forty-five children with type 1 diabetes (mean age 14.0 ± 2.6 years, 42% male) and 50 normal controls (mean age 13.2 ± 2.3 years) were studied., 54% male) were recruited. Serum BDNF level was significantly lower in the diabetes group than in controls (15.92 ± 7.2 vs. 18.5 ± 5.1 ng/mL, respectively, t = -2.03, p = 0.045) and much lower in the subgroup with GAD65-Ab positive type 1 diabetes. Mean full-scale IQ, verbal comprehension, perceptual reasoning, and working memory scores in the diabetes group were significantly lower than in controls (all p < 0. 05). Among children with type 1 diabetes, the worst glycemic control was related to lower general cognitive abilities (r = -0.34, p < 0.02), lower verbal comprehension (r = -0.305, p< 0.05) and lower perceptual reasoning scores (r = −0.346,*P*= 0.02).

In study E3, higher mean HbA1c levels were associated with cognitive dysfunction in multiple verbal domains, including fluid reasoning, quantitative reasoning, and working memory. The frequent occurrence of hypoglycemia showed a negative impact on verbal knowledge. In contrast, significant episodes of hypoglycemia affected both verbal and nonverbal domains of cognition, especially verbal and nonverbal fluid reasoning, as well as knowledge and working memory.

Children with a recurrent history of diabetic ketoacidosis (DKA) performed below average on nonverbal fluid reasoning tasks. Furthermore, the occurrence of moderate or severe DKA, regardless of its frequency, negatively impacted children's general intelligence quotient.

In a meta-analysis study, highlighted in E4, a total of 19 studies were included in our analysis, involving 1,355 participants with type 1 diabetes and 696 individuals in the control group. Compared to non-diabetic controls, children with type 1 diabetes demonstrated significantly lower general cognitive performance (g = -0.46), also presenting specific deficits in total intelligence (g = -1.06), attention (g = -0. 60) and psychomotor speed (g = -0.46). Extremes of blood glucose were associated with global

cognitive impairment (g = -0.18), in addition to slightly lower performance in memory tests (g = -0.27).

The studies reviewed on the impacts of lack of glycemic control in childhood on cognitive development revealed significant and worrying results. Children with type 1 diabetes have consistently been found to have lower cognitive performance compared to non-diabetic controls, showing specific deficits in areas such as overall intelligence, attention, and psychomotor speed. Furthermore, extreme blood glucose levels were associated with a global impairment of cognition, with adverse effects also observed on memory. Frequent hypoglycemia negatively affected verbal knowledge, whereas significant episodes of hypoglycemia affected both verbal and nonverbal domains of cognition, including fluid reasoning. Children with a recurrent history of diabetic ketoacidosis performed below average on nonverbal reasoning tasks, and moderate or severe occurrence of ketoacidosis negatively impacted general intelligence quotient. These results highlight the critical importance of adequate glycemic control from infancy to mitigate adverse effects on long-term cognitive development in children with type 1 diabetes mellitus.

FINAL CONSIDERATIONS

In conclusion, the studies reviewed clearly and consistently demonstrate the negative impact of a lack of glycemic control in childhood on cognitive development. Children with type 1 diabetes have lower cognitive performance in several areas, such as total intelligence, attention and psychomotor speed, when compared to non-diabetic controls.

Elevated levels of hyperglycemia are associated with deficits in fluid reasoning, quantitative reasoning, and working memory, while frequent episodes of hypoglycemia negatively affect verbal knowledge and other cognitive domains.

Furthermore, diabetic ketoacidosis, especially when recurrent or severe, significantly impacts the general intelligence quotient of affected children. These findings highlight the urgent need for effective strategies to improve early diabetes management, aiming to mitigate potential negative impacts on long-term cognitive development.

Therefore, professional performance that is based on the principles of humanization and comprehensive care is necessary.

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