Original Article

# The effect of poor glycemic control on cognitive function in children and adolescents with type 1 diabetes mellitus

## *A single-center cross-sectional study (2019–2020)*

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## ABSTRACT

**الأهداف**: تبحث هذه الدراسة تأثير ضعف التحكم في نسبة السكر في الدم المتمثل بارتفاع سكر الدم المزمن، انخفاض سكر الدم، والحماض الكيتوني السكري على الوظيفة الادراكية للأطفال والمراهقين المصابين بداء السكري من النوع الأول، ودراسة ما إذا كانت الإصابة المبكرة مرتبطة بضعف الإدراك.

**المنهجية**: شارك في الدراسة الأطفال والمراهقون المصابون بداء السكري من النوع الأول الذين حضروا عيادة داء السكري للأطفال من يناير 2019 إلى يناير 2020، ووافقوا على المشاركة، وتراوحت أعمارهم بين 5–14 عامًا، و لديهم متوسط ثلاث قراءات للهيموجلوبين السكري ≥7% خلال فترة الدراسة التي تعكس حالة للإرتفاع المزمن لسكر الدم. تمت مقابلتهم لتسجيل تاريخهم المرضي بما يخص انخفاض سكر الدم والحماض الكيتوني السكري، ثم تم مقابلة المرضى شخصياً من اخصائي علم نفس سريري لتقييم الوظيفة المعرفية باستخدام نسخة عربية معتمدة من اختبار Stanford–Binet.

**النتائج**: ارتبطت مستويات داء السكري من النوع الأول المرتفعة بالخلل المعرفي في ثلاثة مجالات لفظية: الاستدلال السائل، والاستدلال الكمي، والذاكرة العاملة. أثّر نقص سكر الدم المتكرر سلباً على المعرفة اللفظية. في المقابل، أثّر نقص سكر الدم بشكل ملحوظ على كل من المجالات اللفظية وغير اللفظية للإدراك، وتحديدًا الاستدلال السائل اللفظي وغير اللفظي، والمعرفة، والذاكرة العاملة. كان أداء الأطفال الذين يعانون من الحماض الكيتوني السكري المتكرر أقل من المتوسط في مهام الاستدلال السائل غير اللفظي. بالإضافة إلى ذلك، يؤثر الحماض الكيتوني السكري المتوسط أو الشديد على حاصل الذكاء العام للأطفال.

**الخلاصة**: بغض النظر عن بداية المرض، فإن التعرض لتقلبات نسبة السكر في الدم يعرض الأطفال والمراهقين لخلل إدراكي، مما يؤثر على جودة الحياة.

**Objectives:** To investigate the effect of chronic hyperglycemia, hypoglycemia, and diabetic ketoacidosis (DKA) on the cognitive function of children and adolescents with type 1 diabetes mellitus (T1DM), and explore whether early disease onset correlated with cognitive impairment.

**Methods:** Children and adolescents with T1DM who attended the Pediatric Diabetes Clinic between January 2019 and 2020, aged between 5–14 years, with a mean of 3 glycated hemoglobin (HbA1c) readings ≥7% (53 mmol/mol) during the study period reflecting a hyperglycemic status and who agreed to participate were interviewed about their history of hypoglycemia and DKA. Participants were personally interviewed by a clinical psychologist to assess their cognitive function using a validated Arabic version of the Stanford–Binet test.

**Results:** Higher mean HbA1c levels were associated with cognitive dysfunction in three verbal domains: fluid reasoning, quantitative reasoning, and working memory. Frequent hypoglycemia negatively affected verbal knowledge. In contrast, significant hypoglycemia affected both verbal and nonverbal domains of cognition, specifically verbal and nonverbal fluid reasoning, knowledge, and working memory. Children with recurrent DKA performed below average in nonverbal fluid reasoning tasks. Additionally, moderate or severe DKA, regardless of its frequency, affected children's overall intelligence quotient.

**Conclusion:** Regardless of disease onset, exposure to glycemic variability subjects children and adolescents to subtle and measurable cognitive dysfunction resulting in significant morbidity.

**Keywords:** type 1 diabetes mellitus, hyperglycemia, hypoglycemia, diabetic ketoacidosis, cognition

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Diabetes mellitus (DM) is a well-known and common metabolic disorder worldwide. Type 1 diabetes mellitus (T1DM) has an estimated annual worldwide incidence of 98,200 new cases in children under 15 years of age.[1] According to a local record published in 2018, the Kingdom of Saudi Arabia (KSA) has the highest prevalence of T1DM in the Middle East, with 35,000 cases.[2]

Macrovascular and microvascular complications are associated with poor diabetes control.[3] Chronic hyperglycemia and hypoglycemic episodes affect brain structure and function. Normal brain development is altered by exposure to glycemic extremes during early childhood.[4] These complications are controlled by achieving the target glycemic control of glycated hemoglobin (HbA1c) <7% (53 mmol/mol).[5]

We studied the relationship between poor glycemic control (manifesting as hyperglycemia, hypoglycemia, and diabetic ketoacidosis [DKA] and cognitive dysfunction. As a secondary outcome, we explored whether pediatric population with early onset T1DM (before age 5) experienced a negative significant impact on cognitive function.

The aim of the study is to add to the current literature a data from an Arab country in a tertiary center.

**Methods.** This study was approved by the Institutional Research Committee of Prince Sultan Military Medical City (PSMMC), Riyadh, KSA. Between January 2019 and 2020, we retrospectively identified children and adolescents attending the pediatric diabetes clinic at PSMMC for follow-up of T1DM using relevant diagnoses/problems suggestive of T1DM based on the International Classification of Diseases (ICD-10).

Of the 300 patients randomly selected from diabetes clinics using electronic simple randomization, 225 were excluded because they either did not meet the inclusion criteria or had moved to adult endocrine services. Twenty-five of the remaining 75 patients who met the inclusion criteria refused to participate; therefore, 50 participants were enrolled (66% acceptance rate) (Figure 1).

Participants included were between the ages of 5–14 years, had been diagnosed with T1DM for at least 24 months before enrollment, and had an HbA1c of ≥7% (53 mmol/mol) measured every 3±1 months during the study period, reflecting the hyperglycemic status of our cohort. All participants were administered multiple daily doses of subcutaneous insulin or an insulin pump.

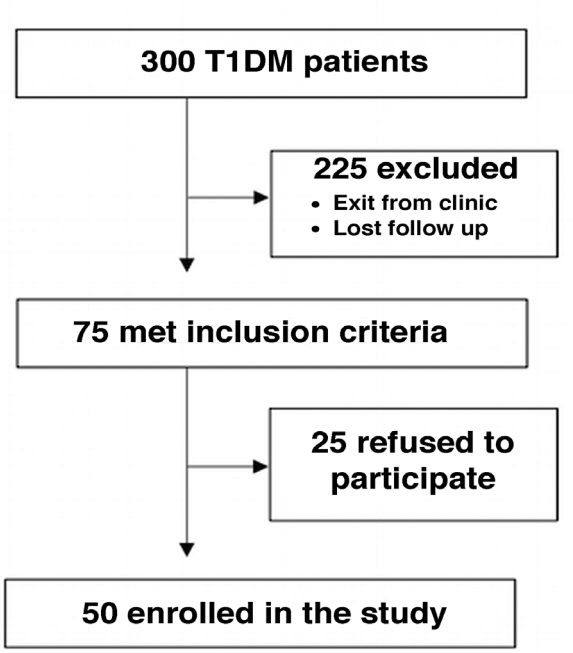


**Figure 1 -** A flowchart of the participants approach and selection. TIDM: type 1 diabetes mellitus,

The study exclusion criteria were age <5 years or >14 years at the time of the clinical interview, incomplete follow-up (<3 HbA1c readings), diagnosis <24 months before the time of enrollment, presence of other comorbidities impacting cognition (for example, untreated anemia, hypothyroidism, diseases affecting the reliability of HbA1c tests, and psychological conditions affecting attention), extreme preterm birth (<28 weeks of gestation), or history of severe head trauma.

Parents/legal guardians of those who met the inclusion criteria and agreed to participate and undergo a cognitive test were contacted and interviewed on the phone to complete a questionnaire on the participants' personal and clinical variables, such as demographics (date of birth, gender, and age at diagnosis), history of hypoglycemia, and DKA. Electronic medical files were accessed by investigators to confirm the history of DKA provided by legal guardians, as well as other study variables, including HbA1c at diagnosis and hyperglycemic status (demonstrated by an HbA1c >7% at diagnosis which continued to be above the target until the time of the study), and the type of insulin used.

**Disclosure.** Authors have no conflict of interests, and the work was not supported or funded by any drug company.

In our study, socioeconomic status was not considered initially upon designing the study and was identified as a confounding factor at the time of data analysis.

*Cognitive assessment.* After parents or legal guardians provided written informed consent, all participants were interviewed in person at the pediatric outpatient clinic by a trained clinical psychologist who performed a validated Arabic version of the Stanford-Binet test to assess their cognitive function. The families were instructed a day before the assessment to ensure that the participants had at least 6 hours of sleep, ate sufficient breakfast, and wore glasses or hearing aids, if necessary.

The neurocognitive abilities of the children and adolescents were assessed on a full scale for both the verbal and non-verbal subclasses. Full-scale intelligence quotient (IQ) assesses the ability to reason, solve problems, and adapt to the cognitive demands of the environment, and the 5 major facets of intelligence of both verbal and non-verbal IQ, including reasoning, knowledge, memory, visualization, and the ability to solve novel problems. Verbal IQ was presented to the cohort in words and sentences (printed or spoken), whereas, non-verbal IQ was presented in pictorial, figural, and symbolic forms. Both were used to assess the participants' ability to reason, solve problems, visualize, and recall important information.

The study cohort was divided into 2 groups: those whose performance was average and above were considered to have normal cognition and those who performed borderline or less were considered to have impaired cognition (2 standard deviations from the mean).

*Statistical analysis.* Statistical Package for the Social Sciences, Windows version 20.0 (IBM Corp., Armonk, N.Y., USA) was used for all the statistical analyses. Continuous variables were expressed as mean with standard deviation (SD) or range, while categorical variables were expressed as frequencies and percentages. We used Chi-square tests for differences in categorical variables, whereas, for continuous variables, independent t-test was applied with a confidence interval of 95%. A linear regression model was applied for the univariate analysis to analyze the independent effects of demographics, clinical variables, and survey responses for the IQ. Statistical significance was set at $p<0.05$. Variables found to be significantly associated with lower IQ in the univariate analysis were subjected to multivariate linear regression analysis to analyze and determine independent predictors, while effect size was determined using the partial eta squared value.

**Results.** Fifty participants aged between 5-14 years were enrolled (25 males and 25 females). The mean age at diagnosis was 5.78 years (SD± 2.87) and at the interview was 10.94 years (SD± 2). Seventy percent of the patients were diagnosed after age 5. Most of the patients received subcutaneous insulin (94%, n=47). The demographic and clinical characteristics of the study population are presented in Table 1.

*Cognitive assessment of the cohort.* The mean IQ of the study cohort fell within the average range for the full scale and subclasses (verbal and non-verbal). Six of the 50 participants scored borderline on the full scale, and some had isolated impaired cognition in the subclasses, as indicated in Table 2.

**Table 1 -** Demographics and clinical characteristics (N=50).

| Characteristics | n (%) |
|---|---|
| *Gender* | |
| Male:female ratio | 25:25 |
| *Age at interview* | |
| Mean (years) - range | 10.94 - 6 to 14 years |
| *Age at diagnosis* | |
| Mean (years) - range | 5.78 - 9 months to 12 years |
| *Onset of disease* | |
| Late onset | 35 (70.0) |
| *HbA1c at diagnosis* | |
| Mean (SD) | 10.6 (1.9) |
| *HbA1c mean during study period* | |
| Mean (SD) | 9.5 (1.6) |
| *Type of insulin* | |
| Insulin pen | 47 (94.0) |

Values are presented as numbers and percentages (%) unless otherwise stated. HbA1c: glycated hemoglobin, SD: standard deviation

**Table 2 -** Cohort performance in IQ assessment classified into low and normal IQ (N=50).

| IQ classes | Low IQ | Normal IQ |
|---|---|---|
| Full scale | 6 (12) | 44 (88) |
| *Verbal* | | |
| Fluid reasoning | 3 (6) | 47 (94) |
| Knowledge | 6 (12) | 44 (88) |
| Quantitative reasoning | 5 (10) | 45 (90) |
| Visual spatial | 19 (38) | 31 (62) |
| Working memory | 12 (24) | 38 (76) |
| *Non-verbal* | | |
| Fluid reasoning | 6 (12) | 44 (88) |
| Knowledge | 12 (24) | 38 (76) |
| Quantitative reasoning | 3 (6) | 47 (94) |
| Visual spatial | 9 (18) | 41 (82) |
| Working memory | 8 (16) | 42 (84) |

Values are presented as numbers and percentages (%). IQ: intelligence quotient

***Relationship between early disease onset and cognitive function.*** Fifteen (30%) of the 50 participants were diagnosed before age 5 and were interviewed for cognitive assessment a minimum of 4 years after exposure to poor glycemic control (mean HbA1c 9.59±0.92%) while receiving multiple daily subcutaneous insulin injections. Few scored borderline on the cognitive assessment. However, the difference was not statistically significant ($p$>0.05; Table 3).

Furthermore, among those with early onset, 6 (40%) experienced significant hypoglycemia, and 11 (73%) had recurrent DKA.

***Relationship between hyperglycemic status and cognitive function.*** For the entire cohort, the mean HbA1c level at diagnosis (10.6%, SD±1.94%) was higher than during the study period (9.5%, SD±1.6%).

**Table 3 -** Linear regression of participants with early onset of disease who scored Borderline and less in IQ assessment (n=15).

| IQ classes | n ($p$-value) | Confidence interval 95% |
|---|---|---|
| Full scale | 1 (0.458) | (-0.255,0.558) |
| *Verbal* | | |
| Fluid reasoning | 1 (0.251) | (-0.233,0.871) |
| Knowledge | 3 (0.264) | (-0.631,0.177) |
| Quantitative reasoning | 2 (0.616) | (-0.553,0.331) |
| Visual spatial | 5 (0.664) | (-0.214,0.333) |
| Working memory | 2 (0.257) | (-0.132,0.483) |
| *Non-verbal* | | |
| Fluid reasoning | 0 (0.091) | (-0.056,0.738) |
| Knowledge | 3 (0.672) | (-0.245,0.377) |
| Quantitative reasoning | 1 (0.899) | (-0.595,0.524) |
| Visual spatial | 1 (0.179) | (-0.109,0.570) |
| Working memory | 2 (0.743) | (-0.303,0.422) |

Value is presented as numbers. IQ: intelligence quotient

Exposure to poor glycemic control is associated with impaired cognition in some verbal domains. It was observed that individuals with diabetes with low IQ in the fluid reasoning domain had a higher glycemic status (mean HbA1c 12.5%, SD±2.13%) than those with normal IQ (9.35%, SD±1.41%; $p$=0.002, CI 1.149–4.638%). Similarly, the quantitative reasoning and working memory domains were affected in the group who had higher levels of HbA1c (11.38%, SD±2.09% and 10.45%, SD±2.38%) compared to the levels of the group that scored at or above average (9.32%, SD±1.42%; $p$=0.005, CI 0.652–3.474% and 9.23%, SD±23%; $p$=0.020, CI 0.199–2.233%); Table 4.

***Relationship between hypoglycemia and cognitive function.*** Almost all participants experienced hypoglycemia (98%, n=49). Approximately 90% of these patients had experienced it more than once since diagnosis. Hypoglycemic symptoms were classified according to their severity as significant or non-significant. Significant hypoglycemia was assigned to participants who experienced seizures or syncope and accounted for 20% of all patients with symptomatic hypoglycemia.

However, the exact frequency was not obtained while interviewing the parents. Experiencing hypoglycemia did per se result in the impairment of verbal knowledge ($p$=0.006). A worse impact on cognition was observed in participants with significant hypoglycemia, where verbal fluid reasoning ($p$=0.038, CI 0.029, 0.964) and knowledge ($p$=0.002, CI 0.208, 0.853) were significantly affected compared to those who did not experience significant hypoglycemia. Moreover, non-verbal fluid reasoning ($p$=0.002, CI 0.208, 0.853)

**Table 4 -** Univariate linear regression of participants with chronic hyperglycemia and their IQ performance (N=50).

| IQ classes | HbA1c in Low IQ group % (SD) | HbA1c in Normal IQ group % (SD) | $P$-value (CI 95%) |
|---|---|---|---|
| Full scale | 10.43% (2.60%) | 9.40% (1.41%) | 0.140 (-0.349%, 2.415%) |
| *Verbal* | | | |
| Fluid reasoning | 12.50% (2.13%) | 9.35% (1.41%) | 0.002 (1.149%, 4.638%) |
| Knowledge | 9.99% (1.16%) | 9.46% (1.65%) | 0.456 (-0.881%, 1.932%) |
| Quantitative reasoning | 11.38% (2.09%) | 9.32% (1.42%) | 0.005 (0.652%, 3.474%) |
| Visual spatial | 9.91% (2.04%) | 9.29% (1.23%) | 0.191 (-0.316%, 1.544%) |
| Working memory | 10.45% (2.38%) | 9.23% (1.15%) | 0.020 (0.199%, 2.233%) |
| *Non-verbal* | | | |
| Fluid reasoning | 9.95% (2.86%) | 9.47 (1.39%) | 0.493 (-0.924%, 1.891%) |
| Knowledge | 10.15% (2.39%) | 9.33% (1.23%) | 0.124 (-0.232%, 1.868%) |
| Quantitative reasoning | 9.31% (1.98%) | 9.54% (1.59%) | 0.809 (-2.168%, 1.701%) |
| Visual spatial | 9.96% (2.24%) | 9.43% (1.44%) | 0.373 (-0.656%, 1.717%) |
| Working memory | 9.40% (1.34%) | 9.55% (1.65%) | 0.811 (-1.402%, 1.103%) |

CI: confidence interval, IQ: intelligence quotient, SD: standard deviation, Mean HbA1c presented in percentage and SD.

and working memory ($p$=0.020, CI -0.058, 0.656) also significantly differed between participants who did and did not experience significant hypoglycemia.

***Relationship between DKA and cognitive function.*** Of all participants, 78% (n=39) were diagnosed with DKA at least once. Moreover, 64% (n=25) experienced it after age 5. A similar number of participants had mild (n=19, 49%) or moderate-to-severe DKA (n=20, 51%). Patients with more than one episode of DKA were considered to have recurrent DKA, regardless of severity (54%; n=21). Those with recurrent DKA exhibited impairments only in non-verbal fluid reasoning ($p$=0.026, CI -0.896,-0.059).

***Prognostic factors for the development of poor cognitive function.*** Multivariate regression analyses were conducted for all significant results of univariate linear regression analyses.

***Hypoglycemia.*** Participants with significant hypoglycemia were found to have significant impairments in verbal knowledge ($p$=0.011, $\eta_p^2$ 0.143), non-verbal fluid reasoning ($p$=0.024, $\eta_p^2$ 0.110), and non-verbal working memory ($p$=0.025, $\eta_p^2$ 0.102).

***Moderate and severe DKA.*** Those who were admitted to the pediatric intensive care unit (PICU) for the management of moderate or severe DKA performed markedly worse on full-scale tests ($p$=0.029, $\eta_p^2$ 0.097) and non-verbal fluid reasoning ($p$=0.016, $\eta_p^2$ 0.124) than those who were admitted to a general pediatric ward, regardless of PICU admission frequency.

**Discussion.** In the literature, the lifelong cognitive ability of children with glycemic dysregulation has been found to be significantly disturbed, especially when dysregulation occurs during the early years of brain development. Our study demonstrates the negative effect of poor glycemic control on cognition. Hyperglycemia, hypoglycemia, and DKA significantly affected cognitive function shortly after exposure to glycemic variability. However, early disease onset was not found to be a risk factor in this study. This result could be attributed to the modest sample size, as most of the patients had a late-onset diagnosis. Indeed, previous studies have found that brain development in children aged less than 5 years at the time of diagnosis is considerably affected by severe symptomatic hypoglycemia and poor glycemic management and control.[7,8] The negative effects of early-onset diabetes on cognitive function usually occur in the presence of other factors that theoretically affect cognition.[9-11] Selective impacts have been found mainly in visuospatial processing, immediate and delayed memory, and verbal and non-verbal fluid reasonings.[12,13] Nevertheless, a subtle effect on the overall IQ has been observed, although it is not significantly pronounced in day-to-day activities.[8,14] However, this effect could impact the educational performance of children when compounded with increased disease duration.[9] The exact mechanism of cognitive impairment is not fully understood and is an area for future research.

Hyperglycemia is an issue for almost all children and adolescents with T1DM, secondary to frequent snacking, non-compliance with sufficient insulin therapy, a high-carbohydrate diet, and exposure to illness with poor knowledge about sick day management, especially in families with poor educational backgrounds and low levels of awareness.

Exposure to hyperglycemia has a negative effect on the microvasculature of organs. Notably, retinopathy, the primary and most commonly encountered complication of hyperglycemia, manifests in children with reduced visuospatial ability, memory and overall congnition.[8,12,15-19] Similarly, our findings of deficits in verbal fluid, qualitative reasoning, and memory in patients with HbA1c levels above the advisable level could suggest early retinopathy and disruption of the visual regions of the occipital lobe. However, our cohort full IQ scale was preserved.

With the current intensive insulin therapy for T1DM, hypoglycemia has become a health challenge in such children. Moreover, these children are at a risk of recurrent unwitnessed nocturnal hypoglycemia, which may have long-term effects on cognition. Regardless of severity, hypoglycemia negatively impacts specific cognitive domains, particularly when associated with poor glycemic control.[8] This risk is higher in children with early disease onset, which can be explained by brain vulnerability during the crucial periods of brain development.[12]

Our findings support most of those in the published literature. Previous studies have found that children with significant hypoglycemia and suboptimal glycemic control perform poorly in tasks requiring verbal and nonverbal memory and executive function.[12,19,20] Surprisingly, the study of Patino-Fernandez and Strudwick did not support our findings; they found that severe hypoglycemia was not associated with cognitive impairment in preschool-aged children.[18,21] This discrepancy in their results may be due to the short disease duration during the cognitive assessment.

Diabetic ketoacidosis is a metabolic dysfunction associated with cerebral edema and decreased cerebral blood flow. Studies have emphasized the effect of DKA on children's IQ, with memory dysfunction observed in children with moderate or severe DKA, hyperglycemia, and early onset diabetes.[11,12,17] In a recently published

work, Ghetti found that regardless of frequency or severity, DKA has a negative impact on cognition, affecting all domains of cognition when compared to young children with early onset of T1DM who did not experience DKA.[22] Our findings support and extend the findings of such previous studies. We agree that IQ is broadly impaired by recurrent and moderate/severe DKA; however, our findings related to other domains of impairment differ from those of previous studies.

***Study limitations.*** Although this study is one of the few to evaluate cognitive dysfunction in children and adolescents with diabetes in the Middle East, some limitations must be recognized. First, the modest sample size and cross-sectional design limit the applicability of the results. In addition, the lack of a parallel control group prevented us from comparing the cognitive function between participants with and without diabetes.

Second, the history of hypoglycemia was subjected to recall bias, as this measure was obtained via a questionnaire and relied on the memory of the participants' parents or legal guardians. Most of our study population had late-onset disease, which may have led to insignificant findings compared to those found in the literature.

Finally, most previously published studies used different tools for cognitive assessment which do not have a validated Arabic version present in our institute, complicating their comparison with our results.

In conclusion, diabetes in itself is not the cause of cognitive dysfunction. Therefore, poor glycemic control is believed to be the underlying cause of cognitive impairment. Nevertheless, the relationship between poor glycemic control in early disease onset and cognitive dysfunction remains an area of research. Further studies are required to address these limitations.

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