Assessment of Cognitive Impairment among Children and Adolescents With type 1 Diabetes Mellitus

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ABSTRACT

Introduction: Children are more vulnerable to cognitive impairment compared to adults due to ongoing brain development. Children with diabetes are at risk of developing various types of cognitive impairment.

Objective: To assess the frequency of cognitive impairment among children and adolescents with type 1 diabetes. To assess the correlation between glycemic control and cognitive impairment among children and adolescents with type 1 diabetes (T1 DM).

Methods: This cross-sectional study included 150 T1DM participants recruited from Pediatrics and Adolescents Diabetes Unit (PADU), Children's Hospital, Ain Shams University during the period from January 2023 to June 2023. Participants were divided into two groups according to diabetic control based on HbA1c. Neurocognitive function was evaluated in two groups based on glycemic control: those with well-controlled blood glucose levels (HbA1c < 7.5%) and those with poor control (HbA1c ≥ 7.5%). Assessments included the Wechsler Intelligence Quotient (WIQ), Benton Visual Retention Test (BVRT), and the computerized Wisconsin Card Sorting Test (WCST).

Result: Children and adolescents with type 1diabetes who had poor glycemic control had significantly lower Total IQ (p<**0.001**), verbal IQ (p<**0.001**) and performance IQ(p<**0.001**) and disability at both visual memory and attention denoted by poor performance at BVRT also their score in WCST was poor in comparison to those with good glycemic control denoting disability in brain executive function.

Conclusions: Participants with poor glycemic control type 1 diabetes (HbA1c ≥ 7.5%) had lower cognitive function, as well as deficits in visual memory, attention, and executive function, compared to those with good control type 1 diabetes (HbA1c < 7.5%).

Key words: Type1DM, Intelligence Quotient, cognitive impairment.

INTRODUCTION:

Cognition refers to the mental process of acquiring and understanding information. Cognitive impairment (CI) is believed to result from factors such as insulin resistance, inflammation, oxidative stress, and neurovascular dysfunction[(1)].

Children with diabetes frequently experience cognitive alterations, notably affecting memory, executive function, attention, and academic performance, making these among the most significant impairments associated with the condition[(2)].

Cognitive impairment (CI) is now widely acknowledged as a significant complication of diabetes, often linked to challenges arising from diabetes management and its related complications[(3)].

Early onset of type 1 diabetes (T1D) has been consistently associated with reduced cognitive performance on multiple IQ assessments. Prolonged exposure to glycemic fluctuations further increases the likelihood of significant cognitive impairments in affected children[(4)].

PATIENTS AND METHODS:

Study procedure: This cross-sectional study included 150 T1DM participants recruited from Pediatrics and Adolescents Diabetes Unit (PADU), Children's Hospital, Ain Shams University during the period from January 2023 to June 2023. Participants were divided in two groups according to diabetic control based on HbA1c level by taking average HbA1c through last 6 months. 38 children and adolescents exhibited good glycemic control (HbA1c < 7.5%) while 112 participants demonstrated poor glycemic control (HbA1c ≥ 7.5%)

Inclusion criteria: Children ≥ 5years ≤18 years old previously diagnosed with T1DM according to ISPAD clinical guidelines (2018) ***(DiMeglio et al., 2018).***

Exclusion Criteria: participants diagnosed with chronic illness other than diabetes or diagnosed syndromes, any diagnosed neurological or psychiatric illness.

Sample Size: Using the PASS 11 program for sample size calculation, reviewing results from the previous study (Kumar et al., 2018) showed that the prevalence of mild Cognitive Impairment was 71.42% among type 1diabetes patients. The sample size of 150 participants will produce a two sided 99% confidence interval with a width equal to 0.2 when the sample proportion is 0 .710

Ethical consideration:

- This study was approved by Ain Shams University Research Ethics Committee (REC).000017585
- An informed consent was taken from all enrolled participant and/or care givers before starting.
- Data from medical records were collected and used for
- private and confidential research purposes.
- No conflict of interest regarding the study or publication.
- No fund regarding the study or publication

All participants were subjected to the following:

A thorough medical history was collected, encompassing the patient's age, duration, and onset of diabetes mellitus (DM), along with any co-existing medical conditions and relevant family history. Information regarding the insulin regimen included the method of administration, total daily dose (units/kg/day), and insulin type. Additionally, records of hypoglycemic episodes, diabetic ketoacidosis (DKA) occurrences, and previous hospital admissions were reviewed.

Through clinical examination and Lab investigations: Predesigned data extraction sheet was filled using annual follow records of the clinic file including (CBC, lipid profile, thyroid profile, liver function tests, urinary albumin creatinine ratio, celiac screening, average HbA1c of the last 6 months and fundus examination.

Study tools: A psychologist at the Psychiatry Institute of Ain Shams University conducted cognitive evaluations using the Arabic-validated version of the Wechsler Intelligence Scale for Children (WISC-III), designed for individuals aged 6 to 16 years[(5)].

The Benton Visual Retention Test (BVRT), Form C [6], was used to assess visual memory and attention. It involved presenting 10 designs to the child, each shown for ten seconds, after which the child was asked to reproduce the design from memory. The obtained scores were compared to normative data, with greater score discrepancies indicating a higher likelihood of visual and attentional disorders.

The Computerized Wisconsin Card Sorting Test (WCST) [7] was utilized to evaluate functions of the frontal cortex, including planning, cognitive flexibility, shifting, and sustained attention. During the test, four stimulus cards of the screen, each varying in color, shape, and number, requiring participants to identify sorting rules based on feedback. The child was presented with a fifth card and asked to match it with one of the four stimulus cards based on the most appropriate attribute. Feedback was provided to indicate whether the choice was correct or incorrect, guiding the child to adjust their strategy throughout the remaining 128 cards. The evaluation focused on key indices such as total trials, correct answers, errors, persevering and non-persevering attempts required to complete the first category, total categories completed, and the ability to maintain a set. Completing four categories indicated normal cognitive function.

Statistical Analysis: The collected data was reviewed, coded, organized, and entered into a personal computer for analysis using SPSS version 20.

RESULTS

Our results show no statistically significant difference between the group with good glycemic control and that with poor glycemic control regarding clinical characteristics and medical history including age, weight, presentation and hypoglycemic attacks per weak. There is statically significant difference between the two groups regarding duration of diabetes as the group with poor glycemic control had a longer duration of diabetes *(P=0.00)*, compared to the group with good glycemic control. Our results also shows that the frequency of cognitive impairment was77.3% (116participant from the total participants (150 participant)

Table (1): Benton visual retention test (BVRT) according to glycemic control of the studied participants

		Poor control (HbA1C>7.5%)	**Good control (HbA1C<7.5%)**	**Test value**	**P-value**	**Sig.**
		No. = 112	**No. = 38**			
Difference between expected error score and obtained error score	Median (IQR)	8 (7 - 10)	6.5 (5 - 10)	-2.239	0.025	S
	Range	3 – 19	1 – 19			
EES(expected error score)	Median (IQR)	7 (6 - 9)	6.5 (6 - 8)	-2.512	0.012	S
	Range	5 – 11	4 – 11			
OES(obtained error score)	Median (IQR)	16 (13 - 18)	13 (7 - 18)	-2.560	0.010	S
	Range	6 – 25	3 – 25			
Difference between expected correct score and obtained correct score.	Median (IQR)	6 (5 - 7)	5 (3 - 6)	-2.662	0.008	HS
	Range	0 – 9	0 – 8			
ECS (expected correct score)	Median (IQR)	9 (8 - 10)	10 (10 - 11)	-6.277	0.000	HS
	Range	4 – 20	8 – 20			
OCS(obtained correct score)	Median (IQR)	4 (2 - 5)	5 (3 - 7)	-2.877	0.004	HS
	Range	0 – 9	0 – 9			

Table 1 showed that participants with poor control of diabetes showed statically significant higher DIF, EES, OES, DIF, (p= 0.025, p= 0.012, p=0.010, p=0.008) respectively while participants

with good control of diabetes shows statically significant higher EEC, OCS with p=0.000, p=0.004 respectively.

Table (2): Wechsler intelligence scale (WISC) according to glycemic control among studied participants

Variables		Poor control (n=112)	Good control (n=38)	P Value
Total IQ	*Mean ± SD*	87.7 ± 7.45	95.9 ± 6.93	
	Range	(75 – 102)	(75 – 105)	**<0.001**
Performance IQ	*Mean ± SD*	86 ± 7.14	93.5 ± 8.05	
	Range	(72 – 102)	(72 – 103)	**<0.001**
Verbal IQ	*Mean ± SD*	87.3 ± 6.27	95.4 ± 7.54	
	Range	(76 – 98)	(76 – 106)	**<0.001**

Table 2 revealed that participants with good glycemic control had significantly higher Total IQ, performance IQ and verbal IQ with (P<0.001) than participants with poor glycemic control.

Table (3): Wisconsin card sorting test (WCST) according to glycemic control among studied participants

		Poor control (HbA1C>7.5%) No. = 112	Good control (HbA1C<7.5%) No. = 38	Test value	P-value	Sig.
Wisconsin total errors	Median (IQR)	80 (20 - 85)	22 (15 - 80)	-3.043	0.002	HS
	Range	10 – 89	10 – 86			
Wisconsin preservative responses	Median (IQR)	78 (20 - 84)	20 (12 - 78)	-2.995	0.003	HS
	Range	10 – 88	10 – 90			
Preservative errors	Median (IQR)	78 (20 - 84)	34.5 (13 - 80)	-2.038	0.042	S
	Range	10 – 89	10 – 89			
Non - preservative errors	Median (IQR)	78 (22.5 - 85)	30 (10 - 78)	-2.993	0.003	HS
	Range	10 – 89	10 – 88			
Trails to complete the 1st category	Median (IQR)	16 (7 - 18)	7.5 (6 - 15)	-3.427	0.001	HS
	Range	4 – 25	4 – 22			
Conceptional level response	Median (IQR)	65 (45.5 - 89)	79 (60 - 93)	-2.300	0.021	S
	Range	20 – 96	20 – 98			
Failure to maintain set	Median (IQR)	3 (1 - 4)	1 (0 - 3)	-2.690	0.007	HS
	Range	0 – 4	0 – 4			
Category Completed	Median (IQR)	2 (1 - 3)	3 (2 - 4)	-2.127	0.033	S
	Range	0 – 4	0 – 4			
Correct responses	Mean ±SD	38.22 ± 33.51	60.61 ± 35.6	-3.502	0.001	HS
	Range	7 – 94	10 – 95			

Table (3) revealed a significant difference between the two groups across all subtests of the Wisconsin Card Sorting Test. Participants with better glycemic control outperformed those with poor control, indicating

impairments in executive functions and visuospatial working memory among the latter group. These impairments were reflected in a higher number of administered trials, increased errors, more failed attempts to finish the four-categories, and greater difficulty in maintaining a consistent response set.

Table (4): Correlation of BVRT and WISC and WCST with clinical and characteristics of the studied participants

	Age (Yrs)		**Duration of Diabetes (years ago)**		**HgA1c**		**Attacks of Hypoglycemia per week**		**Attacks of Hyperglycemia per week**	
	R	**p-value**	**R**	**p-value**	**r**	**p-value**	**R**	**p-value**	**r**	**p-value**
Benton visual retention test										
DIF	0.028	0.737	**0.230****	**0.005**	**0.185***	**0.024**	0.069	0.404	0.070	0.392
EES(expected error score)	0.013	0.871	**0.221****	**0.007**	**0.216****	**0.008**	0.022	0.786	0.130	0.114
OES (obtained error score	-0.088	0.282	0.105	0.199	0.049	0.548	0.049	0.553	0.103	0.210
DIF.(difference)	-0.047	0.565	**0.232****	**0.004**	0.071	0.389	0.054	0.512	0.085	0.298
ECS (expected correct score)	-0.009	0.913	**-0.207***	**0.011**	**-0.327****	**0.000**	0.022	0.785	-0.105	0.201
OCS (obtained corrected score)	0.134	0.101	**-0.233****	**0.004**	-0.041	0.619	-0.105	0.199	-0.097	0.240
Wechsler intelligence scale children										
T.IQ	0.043	0.605	-0.036	0.660	-0.025	0.765	-0.096	0.245	0.067	0.418
Picture completion	0.053	0.518	-0.072	0.384	-0.045	0.588	-0.104	0.207	-0.024	0.768
Block design	0.078	0.340	-0.042	0.611	-0.064	0.437	-0.072	0.379	-0.008	0.927
Coding	0.051	0.533	-0.099	0.230	-0.155	0.058	-0.050	0.547	-0.021	0.795
Co-Comprehensive	0.086	0.294	-0.067	0.417	-0.045	0.587	-0.101	0.218	-0.014	0.867
Arithmetic Abbility	0.032	0.695	0.007	0.931	-0.101	0.220	-0.077	0.350	0.016	0.847
Similarity	0.102	0.215	-0.035	0.667	-0.082	0.321	-0.074	0.371	-0.027	0.747
Digit Span	0.125	0.127	-0.056	0.495	-0.105	0.202	-0.060	0.464	0.024	0.767
Wisconsin card sorting test (WCST)										
Correct responses	0.113	0.170	-0.118	0.152	-0.083	0.314	-0.070	0.391	0.004	0.961
Wisconsin total errors	-0.008	0.924	0.079	0.337	0.105	0.199	0.053	0.520	-0.031	0.709
Wisconsin preservaive responses	**-0.209***	**0.010**	0.023	0.776	0.104	0.206	0.055	0.506	-0.071	0.389
Preservaive errors	-0.159	0.051	0.045	0.584	0.024	0.770	0.053	0.516	0.051	0.534
Non - preservative errors	-0.100	0.224	0.068	0.410	0.070	0.392	0.070	0.394	0.029	0.723
Trails to complete the 1st category	-0.071	0.385	0.094	0.253	0.104	0.207	0.044	0.596	0.017	0.834
Conceptional level response	0.129	0.116	-0.042	0.610	-0.014	0.865	-0.053	0.523	-0.012	0.882
Failure to maintain set	**-0.191***	**0.019**	-0.013	0.875	0.056	0.493	0.078	0.343	-0.032	0.700
Category Completed	0.148	0.072	0.014	0.863	-0.027	0.746	-0.136	0.098	0.024	0.770

Table 4: Shows that the duration of diabetes was positively correlated with DIF (Difference, EES expected error score) and also negatively correlated with ECS (expected corrected score and OCS (obtained corrected score) scores. The table also shows that there was statistically significant positive correlation between HbA1c level and DIF and also EES scores while there was statistically significant negative correlation between HbA1c level and ECS score. It also shows that there was statistically significant negative correlation between age of the studied participants and Wisconsin preservative responses and also failure to maintain the set.

DISCUSSION:

This study highlighted the value of glycemic control in the lives of children and adolescents living with diabetes particularly in the domain of cognitive functions. Using IQ tests for two different groups with good and bad glycemic control, all functions were better with the more controlled group. As regard BVRT this study revealed a statistically significant difference between the two groups across all subsets of visual memory measured by the Benton Visual Test (BVRT), with results favoring the good glycemic control group. The subtests of the BVRT yielded the following p-values: Expected Error Score (EES) (p=0.012), Obtained Error Score (OES) (p=0.010), Difference (DIF) (p=0.025), Expected Correct Score (ECS) (p=0.003), Obtained Correct Score (OCS) (p=0.000), and DIF (p=0.008).

Our findings are consistent with those of ***Abo-El-Asrar et al.*** [12]**,** who reported notable differences in BVRT subtest performance between participants with good and poor glycemic control, with the former group performing significantly better ($p<0.05$). Similarly, Ahmed et al. (13) found that individuals with diabetes scored significantly lower on the BVRT compared to healthy controls (p=0.005), indicating deficits in visual perception, memory, and constructive abilities within the diabetic group.

Regarding WISC test this study revealed a statistically significant difference between the two groups in several areas of the Wechsler Intelligence Scale for Children (WISC). Specifically, performance IQ, which includes picture completion, block design, and coding, showed significant differences ($p < 0.001$). Similarly, verbal IQ, encompassing comprehension, arithmetic ability, similarity, and digit span, also demonstrated a significant disparity ($p < 0.001$). Additionally, total IQ scores were significantly higher in subjects with good glycemic control compared to those with poor glycemic control ($p < 0.001$).

Similarly, a systematic review by ***Hue et al.*** [14]**,** which included six studies encompassing 351 participants with Type 1 Diabetes Mellitus (T1DM), found that comparisons among the two groups revealed a significant difference in total IQ scores ($p = 0.01$). However, no significant differences were observed in verbal IQ scores between the two groups ($p = 0.08$). ***Al-Shehaili et al.*** [11] found that poor glycemic control is associated with impaired cognitive functioning in specific verbal domains. The study indicated that individuals with diabetes who exhibited low IQ in the verbal fluid reasoning domain had significantly higher glycemic levels than those with normal IQ scores ($p = 0.002$). Similarly, the quantitative reasoning and working memory domains, which are part of performance IQ, were affected in individuals with higher HbA1c levels compared to those who scored at or above the average ($p = 0.005$; $p = 0.02$). Also, ***El Kantar et al.*** [15] conducted across-sectional

observational study on a group of 30 cases with T1DM and on a control group of 30 individuals. The Wechsler Intelligence Scale for Children – Fourth Edition (WISC-IV) was utilized to assess cognitive abilities and intelligence quotient (IQ). Children with type 1 diabetes mellitus (T1DM) demonstrated significantly lower scores across various WISC-IV domains ($p < 0.01$), with their IQ notably lower compared to the control group ($p = 0.0001$). ***Chen et al.*** [16] observed that children with diabetes exhibited significantly lower scores in Full-Scale IQ, verbal comprehension, perceptual reasoning, and working memory compared to controls (all $p < 0.05$). Within the type 1 diabetes group, poor glycemic control was associated with reduced overall cognitive function ($p < 0.02$), diminished verbal comprehension ($p < 0.05$), and lower perceptual reasoning scores ($p = 0.02$).

In the present study, significant differences were observed between participants with good and poor glycemic control across all subtests of the Wisconsin Card Sorting Test (WCST) ($p < 0.05$). Those with better glycemic regulation outperformed their counterparts with poor control.

Amin et al. [17] demonstrated that diabetic participants exhibited lower cognitive performance. The diabetic group recorded a higher number of total errors on the Wisconsin Card Sorting Test (WCST) and fewer conceptual level responses than the control group ($p < 0.01$). However, there were no significant differences between the diabetic patients and controls regarding perseverance errors, the number of WCST categories completed, or the inability to sustain the set ($p > 0.05$). ***JI et al.*** [18] demonstrated Patients with insulin resistance (IR) features who have Type 1 Diabetes (T1D) performed worse on executive function tests compared to T1D patients without IR-related features. This was indicated by significantly poorer overall performance ($p = 0.025$), a higher number of perseverative errors ($p = 0.036$), and fewer completed categories ($p = 0.027$). ***He et al.*** [19] found that the DKA group exhibited a significantly higher rate of perseverative errors in the Wisconsin Card Sorting Test (WCST) compared to healthy controls, with a p-value of ($p= .006$). As for ***LY et al.*** [20] who conducted a study on 34 control subjects and 33 type 1 diabetics. The type 1 diabetes group exhibited lower scores on the Wisconsin Card Sorting Test (WCST), characterized by a higher number of perseverative errors ($P = 0.002$) and fewer completed categories ($P = 0.022$).

As regards correlation between clinical characteristics and tests results HbA1C showed statistically significant negative correlation with all subsets of Wechsler intelligence scale children (WISC) (total IQ ($p=0.004$), verbal IQ ($p=0.002$) and performance IQ<0.001) and significant positive correlation with ECS ($p=0.02$). ***Ahmed et al.*** [13] found was found that HbA1c was correlated inversely to general intelligence TIQ ($P = 0.04$) and to performance IQ ($P =0.05$), and also correlated inversely to BVRT scores Diff. E ($P = 0.005$) Diff. C ($P = 0.002$)

Our study revealed no significant association between the frequency of hypoglycemic episodes and cognitive performance on the BVRT, WISC, and WCST ($p > 0.05$).

This study revealed no significant differences between the two groups (good glycemic control and poor glycemic control) concerning age and weight. However, the group with poor glycemic control exhibited a statistically significant longer duration of diabetes ($p = 0.000$) and a greater number of Diabetic Ketoacidosis (DKA) episodes ($p = 0.000$).

These results are consistent with those of ***Stanisławska-Kubiak et al.*** [9], who conducted a study on cognitive function in children and adolescents with type 1 diabetes (T1DM). They divided participants into three groups based on HbA1c levels: Group 1 (HbA1c ≤ 6.0-7.5%), Group 2 (HbA1c7.6-8.5%), and Group 3 (HbA1c > 8.6%). Their findings revealed a statistically significant difference in the duration of diabetes among the groups ($p = 0.01$). ***Ghetti et al.*** [21] reported that children with a history of diabetic ketoacidosis (DKA), irrespective of severity, had significantly lower IQ scores compared to those without DKA ($p = .003$).

These findings are consistent with those of ***Abo-el-Asrar et al.*** [12], who conducted a study involving 50 subjects with type 1 diabetes (T1DM) and 30 healthy controls, aged between 7 and 16 years. They utilized the **Benson Visual Retention Test (BVRT), Wechsler Intelligence Scale for Children (WISC), and Wisconsin Card Sorting Test (WCST)** to assess Cognitive function. Participants with T1DM were divided into two groups based on their HbA1c levels: HbA1c ≥ 7.5% mg/mL indicated poor glycemic control, while HbA1c < 7.5% mg/mL indicated good glycemic control. This study found a statistically significant difference between the two groups regarding the duration of T1DM ($p = 0.017$).

The current study revealed a statistically significant negative correlation between the duration of diabetes and Total IQ (T.IQ) ($p = 0.002$). Conversely, there was a significant positive correlation between the duration of diabetes and one subset of the Benson Visual Retention Test (BVRT), specifically the obtained corrected score (OCS) ($p = 0.03$).

The study by ***Abo-el-Asrar et al.*** [12] found a significant correlation between the duration of Type 1 Diabetes Mellitus (T1DM) and total IQ ($p < 0.05$). This correlation was specifically observed on two subtests of the Wisconsin Card Sorting Test (WCST) and three subtests of the Benson Visual Retention Test (BVRT). Denoting the high influence of glycemic control on cognitive function

Limitations:

This study's cross-sectional design and relatively small sample size limit the ability to evaluate changes in cognitive functions over the progression of diabetes mellitus.

CONCLUSION:

Participants with poor glycemic control demonstrated notably lower scores in total, verbal, and performance IQ, along with impaired visual memory and attention, as reflected by their poorer Benton Visual Retention Test (BVRT) performance compared to those with good glycemic control. Similarly, their Wisconsin Card Sorting Test (WCST) scores indicated diminished executive brain function. Significant correlations emerged between various cognitive test subtests and clinical factors such as age and type 1 diabetes mellitus (T1DM) duration. These findings underscore the importance of maintaining optimal glycemic control to support cognitive function, growth, and healthy development, ensuring a brighter future for affected individuals.

Recommendations:

- Good control&f.up of type1 D.M.patients
- Continues assessment of cognitive functions type1 D.M. patients

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