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Original Article

Cognitive function in Indonesian children with type 1 diabetes mellitus

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Abstract

Background Children with type 1 diabetes mellitus (T1DM) are at risk of cognitive impairment. While the pathophysiology is still unclear, cognitive impairment in children with T1DM can result in significant negative effects on quality of life.

Objective To evaluate the cognitive function of Indonesian children with T1DM and its association with glycemic control and to identify factors affecting cognitive function in children with T1DM.

Methods The cognitive function of children aged 6 years or older with T1DM was measured using the Wechsler Intelligence Scale for Children-Revised (WISC-R). We analyzed for potential associations between cognitive function and glycemic control based on mean HbA1c levels and other factors, such as the age of onset, duration of illness, and maternal educational attainment. We also identified failure to achieve age-appropriate results on any of the WISC-R subtests (cognitive impairment) and associated factors.

Results A total of 46 subjects were included in this study, with a mean age of 12.8 (SD 3.4) years. There were 27 (58.7%) girls and 19 (41.3%) boys. Subjects' mean full-scale IQ (FSIQ) was 91.35 (SD 11.43). A moderate negative correlation was found between FSIQ and mean HbA1c levels ($r=-0.43$; $P<0.01$). Children with mothers who had university degrees had significantly higher IQs (mean difference 7.39; 95%CI 3.10 to 13.66; $P=0.02$) than those with mothers without degrees. Failure of any WISC-R subtest was noted in 34 subjects, consisting of 17 verbal, 1 performance, and 34 verbal and performance subtests. A higher proportion of those with cognitive impairment had mean HbA1c >10%. However, compared to those with mean HbA1c ≤10, the difference did not reach a statistical significance (OR 5.0; 95%CI 0.95 to 26.31; $P=0.50$)

Conclusion Glycemic control and maternal educational attainment are associated with cognitive function in Indonesian children with T1DM. Poor glycemic control is also associated with a higher risk of cognitive impairment. **[Paediatr Indones. 2024;64:44-51; DOI: 10.14238/pi64.1.2024.44-51**].

Keywords: *cognitive function; children; type 1 diabetes mellitus; intelligence quotient*

Type 1 diabetes mellitus (T1DM) is a systemic disorder caused by impaired glucose metabolism and pancreatic β-cell function that may be caused by autoimmune processes resulting in the cessation or reduction of insulin production.[1] The incidence of T1DM varies among several countries, ranging from 0.1 to 52.2 per 100,000 children aged 0-14 years.[2]

Recurrent hyperglycemia in diabetes can result in serious complications such as vascular disorders. This situation may ultimately cause disturbances in various systems, including the central nervous system, and may have a negative effect on cognitive function, especially in children. Several studies have found lower cognitive performance in children with T1DM compared to non-diabetic controls across several domains such as intelligence, attention, and psychomotor speed.[3-7] Several factors may increase the risk of cognitive impairment in T1DM, including younger age at onset, longer duration of illness, poor metabolic control, exposure to glycemic extremes (severe hyper- and hypoglycemia), and diabetic

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ketoacidosis (DKA).[4,6,8-10] Most of these factors are associated with glycemic control, which in developing countries such as Indonesia, has been generally poor. Impairment of cognitive functions in children with T1DM can unfavorably influence their quality of life. Therefore, we aimed to evaluate the cognitive function of Indonesian children with T1DM and its association with glycemic control and to identify factors affecting cognitive function in children with T1DM.

Methods

We performed cognitive evaluation on children with T1DM aged 6 years to 17 years and 11 months who visited the Pediatric Endocrinology Clinic of Dr. Mohammad Hoesin General Hospital, Palembang, South Sumatera, between September 2021 and August 2022. Children with a history of central nervous system insults, intellectual disability, structural brain abnormalities such as cerebral palsy, microcephaly, or pervasive developmental disorders such as autism spectrum disorders were excluded. Written informed consent was obtained from parents before recruitment.

Cognitive evaluations were carried out by a clinical psychologist using the *Wechsler Intelligence Scale for Children-Revised* (WISC-R) Indonesian version.[11] Before the cognitive evaluation, a blood sugar examination was done to ensure a range of 70-250 mg/dL at the time of the testing. The test battery included verbal intelligence that consisted of six subtests (information, comprehension, arithmetic, vocabulary, similarities, and digit span) and performance intelligence that also consisted of six subtests (picture completion, picture arrangement, block design, object assembly, coding, and mazes). The test results included verbal, performance, and full-scale intelligence quotient (IQ). We also examined the performance of the children for each subtest. Any failure to meet the age-appropriate norm for each subtest was noted and grouped as failure for verbal or performance intelligence subtests. Failure on any individual subtest was considered to be a cognitive impairment. Normal cognitive function was defined as full-scale IQ (FSIQ) of >85, borderline cognitive disability as FSIQ between 70 and 85, and cognitive disability as FSIQ of <70.[11]

We analyzed for possible associations between cognitive function and several factors, including age at enrolment into the study, gender, family income, maternal education, duration of illness, history of diabetic ketoacidosis (DKA), frequency of hypoglycemic episodes, and glycemic control based on the mean HbA1c level in the six months before the study. History of DKA and HbA1c levels were obtained from medical records. We used mean HbA1c level from at least two measurements within 6 months prior to the study. Hypoglycemic episodes were recorded from patients' personal medical diaries which contained the results of every blood glucose level testing documented by parents. Family income was classified as below or above the regional minimum wage of IDR 3,043,111 based on the standard from the regional government of South Sumatera province.[12] All analyses were done using *SPSS for Windows version 22* software (*IBM*, Armonk, New York). The difference in full-scale intelligence quotient (FSIQ) between risk groups was analyzed using Student's T-test. The proportion of cognitive impairment (failure on any individual WISC-R subtest) was analyzed using the chi-square or Fisher's exact tests. A P value of <0.05 was considered to be statistically significant. This study was approved by the Ethics Committee of Dr. Mohammad Hoesin Hospital and Universitas Sriwijaya Medical School, Palembang.

Results

A total of 46 subjects were included in our study. The mean age of the subjects was 12.77 (SD 3.42) years and the mean age of onset was 8.67 (SD 4.21) years. Subjects' glycemic control was generally poor, with 80.4% having a mean HbA1c above 7%. The clinical characteristics of subjects can be seen in **Table 1**.

The results of cognitive testing are shown in **Table 2**. No subject had cognitive disability (FSIQ <70), while 17 children had borderline cognitive disability (FSIQ 70 to 85). The majority of subjects (73.9%) did not pass at least one subtest, mostly within the verbal intelligence category (71.7%).

We analyzed for correlations between age at enrollment, age at diagnosis, duration of illness, and FSIQ. FSIQ was not correlated with age of onset (Spearman's rho=-0.11; P=0.48) or duration of illness

Table 1. Baseline characteristics of study subjects

Characteristics	(N=46)
Age, n (%)	
6 to <10 years	12 (26)
>10 to ≤18 years	34 (74)
Sex, n (%)	
Male	19 (41.3)
Female	27 (58.7)
Nutritional status, weight/height, n (%)	
Severely wasted	0
Wasted	11 (23.9)
Normal	16 (34.8)
Overweight	9 (19.6)
Obese	10 (21.7)
Family income, n (%)	
Below minimum wage	10 (21.7)
Above minimum wage	36 (78.3)
Maternal educational attainment, n (%)	
Junior high	6 (13.0)
Senior high	15 (32.6)
College	25 (53.4)
Duration of illness, n (%)	
≤ 12 months	8 (17.4)
> 12 months	38 (82.4)
Frequency of DKA within the past 6 months, n (%)	
One or less	41 (89.1)
Two or more	5 (10.1)
Frequency of hypoglycemia per week within the last 6 months, n (%)	
< 1	34 (73.9)
1-3	11 (23.9)
> 3	1 (0.2)
Average Mean HbA1c in the past 6 months, n (%)	
> 10%	19 (41.3)
7-10%	18 (39.1)
< 7%	9 (19.6)

Table 2. Results of cognitive testing

Cognitive parameters	(N=46)
Mean full scale IQ (SD)	91.35 (11.43)
Median verbal IQ (range)	81.50 (62-113)
Median performance IQ (range)	100 (0-127)
Failure of WISC subtest, n (%)	
Verbal subtest only	17 (36.9)
Performance subtest only	1 (2.2)
Verbal and performance subtests	16 (34.8)
Total/any subtest	34 (73.9)

(Spearman's rho=-0.19; P=0.20). A weak negative correlation was found between FSIQ and age at enrollment (Spearman's rho=-0.38; P=0.01), while a moderate negative correlation was found between FSIQ and mean HbA1c (Pearson's r=-0.43; P<0.01). **Figure 1** depicts the correlation charts between age at enrolment, mean HbA1c, and FSIQ. **Table 3** lists the cognitive function in children aged 6 years and above in association with factors studied. There were trends of increased FSIQ levels in subjects with higher maternal educational attainment and family incomes. Multivariable linear regression analysis was done incorporating mean HbA_1c, maternal educational attainment, family income, and age at enrolment. Only maternal educational attainment and mean HbA_1c remained significant in the resulting FSIQ prediction model, which was as follows: FSIQ=102.41 + (5.81 x maternal educational attainment) + (-1.53 x mean HbA1c), where maternal educational attainment was assigned a value of 1 if the mother had a university education and zero if she had not. This model had an R2 value of 24.2%.

We also performed an analysis on the risk of failure of any WISC subtest (cognitive impairment) (**Table 4**). Similar to the parametric analysis, we found tendencies of older age at enrollment, lower maternal educational attainment, and poorer glycemic control to be predictive of cognitive impairment, however, none reached statistical significance. Of these three factors, glycemic control had the strongest association with the risk of WISC subtest failure.

Discussion

We measured the cognitive function in children aged 6 years and above with T1DM in Indonesia. To the best of our knowledge, there has been no large-scale collection of IQ data in the normal, non-diabetic pediatric population in Indonesia available for comparison. A study in Egypt found a similar mean FSIQ of 88.84 (SD 7.09), but inversely lower verbal and higher performance quotients compared to our study.[3] Using a threshold of any failure to meet an age-appropriate norm on a subtest, the majority of our subjects had some cognitive impairment, mostly in verbal intelligence, in line with the verbal quotient obtained. Moreover, almost all of those who failed a performance intelligence subtest also failed a verbal subtest. Many studies have demonstrated cognitive impairments across most of the intelligence domains in children with T1DM; these impairments may be associated with reduced cerebral white and gray

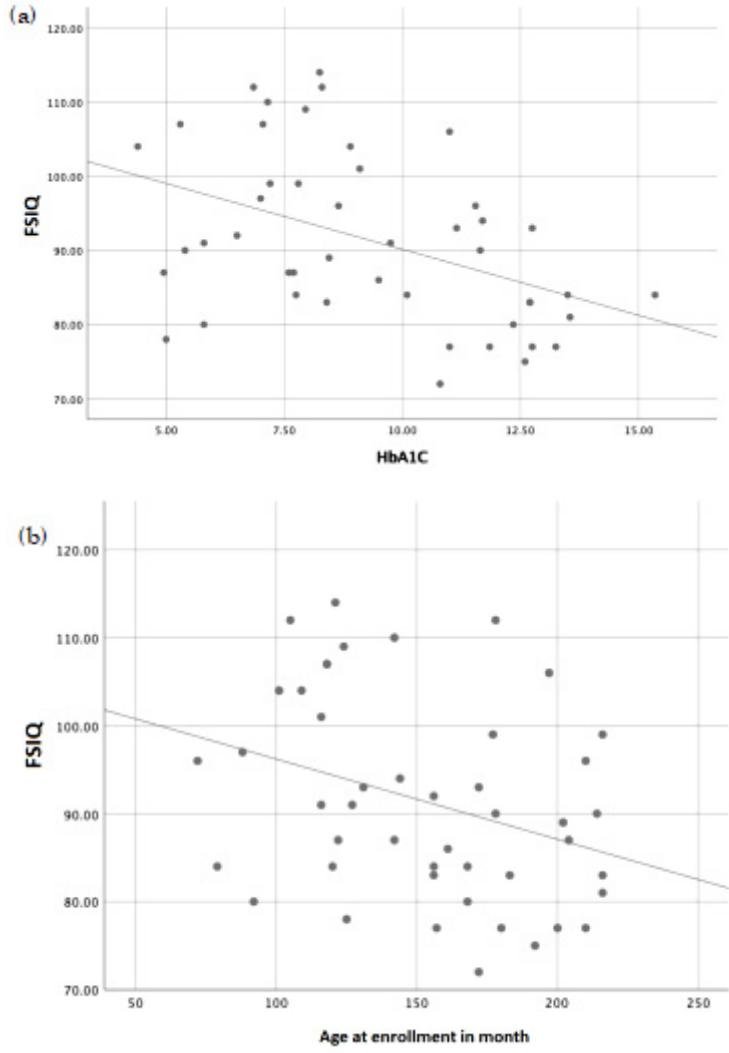

Figure 2. Scatter graphs depicting correlations between full scale IQ with (a) mean HbA1c and (b) age at enrollment

Table 3. Differences in full scale IQ based on risk groups

Factors	n	Mean (SD) FSIQ	Mean difference (95% CI)	P value
Sex				
Female	27	92.70 (10.49)	3.28 (-3.62 to 10.19)	0.34
Male	19	89.42 (12.68)		
Family income				
Above minimum wage	36	92.61 (11.65)	5.81 (-2.33 to 13.95)	0.16
Below minimum wage	10	86.80 (9.81)		
Maternal educational attainment				
Up to senior high school	21	87.33 (7.86)	7.39 (3.10 to 13.66)	0.02
College	25	94.72 (12.94)		
DKA frequency in the last 6 months				
One or less	41	91.00 (10.98)	- 3.20 (-14.19 to 5.45)	0.56
Two or more	5	94.20 (15.83)		
Frequency of hypoglycemia per week within past 6 months				
Less than one	34	90.03 (11.66)	- 5.05 (-12.72 to 2.61)	0.19
One or more	12	95.08 (10.30)		

Table 4. Analysis risk factors for cognitive impairment (failure in any of the WISC subtests)

Risk factors	Any WISC subtest failure		OR (95%CI)	P value
	Yes (n=34)	No (n=12)		
Age group, n				
6-<10 years	7	5	0.36 (0.09 to 1.49)	0.15*
>10-≤18 years	27	7		
Sex, n				
Male	15	4	1.58 (0.4 to 6.26)	0.38*
Female	19	8		
Family income, n				
Below minimum wage	8	2	1.54 (0.28 to 8.52)	0.48*
Above minimum wage	26	10		
Maternal educational attainment, n				
Junior high or below	5	1	-	0.25
Senior high school	13	2		
College	16	9		
Duration of illness, n				
>12 months	28	10	0.93 (0.16 to 5.4)	0.66*
≤12 months	6	2		
DKA frequency in the past 6 months, n				
One or less	3	2	0.48 (0.07 to 3.32)	0.39*
More than one	31	10		
Frequency of hypoglycemia per week within last 6 months, n				
>3	1	0	-	0.59
1-3	7	4		
<1	26	8		
Mean HbA1c in the last 6 months, n			5.0 (0.95 to 26.31)	0.50
>10%	17	2		
≤10%	17	10		

Chi-square test, * Fisher's exact test

matter.[4,7,9] Similar to our findings, a meta-analysis found that the standardized mean difference in verbal intelligence quotient was higher than that of performance quotient [standardized mean difference -0.95 (95% CI -2.08 to 0.18) *vs.* -0.15 (95%CI -1.15 to 0.15), respectively] in children with T1DM who were exposed to glycemic extremes.[4] An earlier meta-analysis found reduced cognition across intelligence, psychomotor activity, information processing, attention/executive function, and academic achievement domains, but not in learning or memory.[7]

No correlation was found between FSIQ and duration of illness, but there was a weak negative correlation between FSIQ and age at enrollment. A previous study identified a stronger cognitive decline in children with earlier onset of T1DM (<7 years).[7] This association may be explained by the fact that younger children have higher metabolic demands of brain development that are more sensitive to the negative effects of hypo- or hyperglycemia in T1DM.[13] Some inaccuracies may occurred in determining the duration of illness in our study, and more likely to be underestimations (a longer period of illness had actually occurred compared to the reported duration), so that hypoglycemia or hyperglycemia may play a bigger role in our study. The association between these factors and cognitive function may appear later and even after adulthood.[8]

In our study, mean HbA_1c and FSIQ had a significant negative correlation. The group with the poorest glycemic control (mean HbA_1c >10%) tended to have cognitive impairments based on failure to meet age-appropriate norms on any of the WISC-R subtests. A study found an association between chronic hyperglycemia (measured by mean HbA_1c over 2 years) and executive function and memory. High mean HbA_1c levels have been associated with lower memory, psychomotor retardation, and decreased verbal reasoning in adolescents. Negative correlations were found between HbA_1c and several cognitive parameters, including visual-perceptual, fine

motor, attention, auditory processing, and academic achievement scores.[14] Another study found that hyperglycemia was associated with impaired executive functions, IQ, learning, and memory. The significant association in their study was identified at mean $HbA_1c > 6\%$, a lower threshold than that used in our study.[15] The mechanism of cognitive decline caused by hyperglycemia in diabetes is not fully understood. Advanced glycation end-products present in chronic glycemia may cause oxidative stress and neurodegeneration.[9] Chronic hyperglycemia may also be associated with cerebral microvascular dysfunction through increased expression of inflammatory cytokines such as IL-6 and TNF-α and subsequent chronic inflammation.[13] We would like to note that because more of our subjects had higher mean HbA_1c levels, the degree of correlation may differ from populations that generally have better glycemic control and lower HbA_1c levels.

While previous studies have suggested that recurrent hypoglycemia has negative effects on cognitive function,[6] we did not find such an association. A meta-analysis found only slightly lower cognitive performance in children with frequent severe hypoglycemia compared to those without it, with the strongest in memory and learning.[6] Another meta-analysis suggested that glycemic extremes (combinations of severe hypo- and hyperglycemia) were more significantly associated with cognitive dysfunction.[4] Similar to our study, Cato *et al*.[5] found that hyperglycemia, rather than hypoglycemia, was significantly associated with cognitive dysfunction. The association between cognitive and glycemic variables, including hypoglycemia, may be more easily detected after a longer duration of illness or later age.[5,8] However, a study found a significant association between cognitive function and chronic hyperglycemia and recurrent severe hypoglycemia, in children within 2 years after they were diagnosed with T1DM.[16] The relatively stronger association between poorer cognitive function and hyperglycemia was in children who mostly had poorer glycemic control. Also, our small sample size probably contributed to the lack of a significant association between hypoglycemia and cognitive function in our study.

Higher maternal educational attainment had a positive association with FSIQ, similar to findings observed in several other studies.[17-19] Mothers with higher educational attainment are likely to invest more in their children's education and/or books. They are also more likely to engage their children in activities that stimulate cognitive development. Maternal educational attainment is also strongly correlated with family income, and, thus, access to a better educational environment.[19] Furthermore, higher parental educational attainment had has been associated with their children's better glycemic control.[20,21] Such parents may have better knowledge about diabetes, its treatment, and complications, which may result in better supervision and enforcement of monitoring and treatment for their children. The R2 value of our multivariable model indicated that 24.2% of the variance in FSIQ could be attributed to maternal educational attainment and glycemic control (mean HbA_1c).

A limitation of this study was its cross-sectional design, with only one measure of cognitive function used (WISC-R). Glycemic status, including hypo- and hyperglycemia, were obtained from patient diaries documented by parents, which may have missed some episodes due to incomplete documentation by parents. In addition, blood glucose examinations were performed by self-monitoring rather than continuous monitoring in all patients, thus, all instances of glycemic extremes may not have been detected. Also, subjects' IQ data before diagnosis was not available. A prospective cohort study with cognitive evaluations at the time of diagnosis and then repeated after a period of time, may give a better overall picture of glycemic status and other factors associated with cognitive function in children with T1DM.

In conclusion, a significant moderate negative correlation was found between FSIQ and mean HbA_1c in a group of Indonesian children with T1DM. Maternal educational attainment had a positive association with FSIQ. Our findings suggest that better glycemic control may help prevent cognitive dysfunction in children with T1DM. Parental education about diabetes care and cognitive stimulation for children may be a sound, short-term strategy to improve glycemic control and cognitive function in children with T1DM.

Conflict of interest

None declared.

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