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The Relationship Between Glycosylated Hemoglobin (HbA1c) Levels and Depression in Children and Adolescents with Type 1 Diabetes Mellitus

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Abstract

Background: Type 1 diabetes mellitus (T1DM) imposes a significant psychological burden on children, and depression is a common comorbidity. Evidence on the quantitative relationship between depression severity and glycemic control (HbA1c) among Iranian children is limited. This study investigated the association between HbA1c levels and depression severity in children and adolescents with T1DM.

Methods: This cross-sectional study enrolled 70 children aged 7–16 years with T1DM from the Pediatric Endocrinology Clinic at 22 Bahman Hospital in Mashhad, Iran, between 2024 and 2025. Data were collected using a demographic-clinical questionnaire and the Children's Depression Inventory (CDI). HbA1c was averaged from the three most recent measurements over the preceding six months. Statistical analyses included Mann-Whitney, Kruskal-Wallis, Pearson correlation, and General Linear Model tests.

Results: The mean age was 12.39 ± 2.66 years, and 60% were female. The mean HbA1c was 9.41 ± 2.24%. Based on CDI scores, 34.3% had clinical depression, 34.3% were at threshold, and 31.4% had no depressive symptoms. A significant positive correlation was observed between HbA1c and depression scores (r=0.55, P=0.0001). The mean HbA1c was significantly higher in the depressed group (11.04 ± 2.25) than in the threshold (8.70 ± 1.71) and healthy groups (8.40 ± 1.75) (P=0.0001). Daily insulin dose also correlated positively with depression (r=0.35, P=0.02). Disease duration and sex showed no significant association with depression. In the multivariable General Linear Model, HbA1c (F=24.93, P<0.0001) and insulin dose (F=5.23, P=0.025) remained independently associated with higher depression scores.

Conclusion: Poor glycemic control and higher daily insulin requirements are significantly and independently associated with depression severity among children with T1DM, though the cross-sectional design precludes establishing causality. Routine psychological screening should be integrated into standard diabetes care, particularly for patients with elevated HbA1c or increasing insulin requirements.

Key Words: Children, Children's Depression Inventory (CDI), Depression, Glycosylated Hemoglobin, Type 1 Diabetes Mellitus.

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1- INTRODUCTION

Type 1 diabetes is an autoimmune disease that causes high blood glucose due to insufficient insulin and affects about 15 million children worldwide. Its complications reduce life expectancy by about 10 years. Glycosylated hemoglobin (HbA1c) reflects long-term blood sugar control, and measuring it three to four times annually is recommended for managing the condition (1-4).

Complications of type 1 diabetes can be short-term, such as hypoglycemia and hyperglycemia, or long-term, affecting blood vessels in organs such as the eyes, kidneys, brain, and heart, or causing neuropathy. These issues limit occupational, social, and family life and require lifestyle changes for management. Chronic disease and treatment may lead to psychological disorders such as depression. Improving quality of life and psychological health is essential for better outcomes. Living with diabetes involves constant blood glucose monitoring, insulin injections, diet management, and physical activity, which is exhausting for children and families. The challenge is to maintain metabolic control and reduce complications while preserving a flexible, high-quality lifestyle, often causing stress and psychological problems such as anxiety, depression, somatic complaints, and social withdrawal in children who internalize these stresses (5-7).

Depression is a mood disorder marked by low mood, decreased energy, guilt, concentration issues, appetite loss, thoughts of death or suicide, sleep disturbances, weight loss, and functional impairment. It is common among diabetic patients, with 15–32.5% affected, and 17–63% among children and adolescents with diabetes. People with diabetes have a 28.5% lifetime risk of depression, 2 to 3 times higher than that of non-diabetics. Depression can result from pain due to neuropathy or poor glycemic control, with hyperglycemia linked to severity. Diabetes-related cerebrovascular issues often accompany depression (8-11). In mild diabetes cases, subtle central nervous system dysfunction occurs without cerebrovascular events or recurrent hypoglycemia. It initially appears as mild cognitive impairment and, with progression, often manifests as depression (12). Visual impairment due to retinopathy, frequent hospitalizations, and sexual dysfunction are other factors contributing to depression in diabetic patients (13). The HbA1c test screens for diabetes by measuring glucose bound to hemoglobin, reflecting average blood sugar over 2-3 months. Elevated levels indicate poor control and a higher risk of complications (14).

This study aimed to investigate the utility of HbA1c as an indicator of disease management in pediatric patients diagnosed with type 1 diabetes, with a specific focus on the role of depression as a significant contributor to psychological disorders. Although existing literature explores the relationship between HbA1c and depression in adult populations, there is a paucity of research addressing this issue in children and adolescents. Given the critical nature of this topic and the demand for more substantial evidence, we undertook this examination. The results of this study have the potential to guide interventions that target pivotal factors for preventing complications such as depression and for enhancing diabetes management.

2- MATERIALS AND METHODS

2-1. Study Design and Ethical Considerations

This cross-sectional study was approved by the Ethics Committee of Islamic Azad University, Mashhad Medical Sciences Branch (Ethics Code: IR.IAU.MSHD.REC.1402.199) and conducted in 2024–2025 after obtaining

informed consent from parents and children. All patient information was kept confidential and coded.

2-2. Study Population and Sample

The target population included all children aged 7 to 16 years with a confirmed diagnosis of type 1 diabetes mellitus based on ADA criteria (fasting blood glucose ≥126 mg/dL, random blood glucose ≥200 mg/dL with clinical symptoms, or HbA1c >6.5%) who were referred to the Pediatric Endocrinology Clinic at 22 Bahman Hospital, Islamic Azad University of Mashhad. Inclusion criteria were age 7–16 years and at least 6 months since the initial diabetes diagnosis (to ensure relative stability of the therapeutic regimen and reduce the effect of initial diagnosis-related stress). Exclusion criteria were congenital central nervous system disorders, chronic renal or hepatic failure, hemoglobinopathies (due to their confounding effect on HbA1c), previously diagnosed psychiatric disorders, and acute psychological trauma (bereavement, parental divorce) in the past 6 months.

2-3. Sample Size and Sampling Method

The sample size was calculated using the formula $n = t^2pq/d^2$, based on the study by Razi Roudi et al. (15), in which 55% of children were at the threshold for depression, with a 95% confidence level and a 10% margin of error, yielding 96 individuals. However, because recruitment was conducted at a single specialized pediatric endocrinology clinic and applied stringent eligibility criteria (specifically excluding patients with newly diagnosed diabetes < 6 months, prior psychiatric diagnoses, recent acute family trauma, or systemic comorbidities), a total of 70 eligible patients who consented to participate were ultimately enrolled through convenience sampling during the study period. With n = 70, the actual margin of error for descriptive prevalence estimation was 11.6%. For the primary analytical objective—evaluating the linear association between HbA1c and CDI depression scores—a post-hoc power sensitivity analysis (using G*Power 3.1 at α = 0.05, two-tailed) confirmed that a sample size of 70 provides 80% statistical power to detect a minimum correlation of r = 0.33, and achieved >99.9% statistical power for the observed correlation of r = 0.55.

2-4. Data Collection Tools

Demographic and routinely recorded clinical information, including age, sex, duration of diabetes (years), total daily prescribed insulin dose (Total Daily Dose), and laboratory HbA1c measurements, were extracted from patients' medical records. Other potential psychosocial and clinical covariates, such as lifetime hospitalization frequency or familial psychiatric history, were not consistently documented in outpatient charts and were therefore unavailable for quantitative extraction. To improve accuracy, the mean of the last three HbA1c measurements obtained over the past 6 months (at approximately 2- to 3-month intervals) was calculated and used as the final metabolic control index in the analyses.

Children's Depression Inventory (CDI): This 21-item self-report scale, developed by Maria Kovacs, uses three response options (0, 1, 2) for each question, reflecting symptom severity over the past two weeks. The score ranges from 0 to 42. Depression severity classification in the present study: 0–8 = no depression, 9–19 = at threshold for depression, 20–42 = clinical depression (16,17). The validity and reliability of the Persian version of this instrument were confirmed by Dehshiri et al., with an internal consistency (Cronbach's alpha) of 0.83 and test-retest reliability of 0.82. It also shows a high

correlation with the Beck Depression Inventory (r=0.87) (18).

2-5. Statistical Analysis

The collected data were coded and entered into SPSS version 28. Normality of the variable distributions was assessed using the Shapiro-Wilk test. The Mann-Whitney U test was used to compare quantitative variables between two groups, and the Kruskal-Wallis test with Bonferroni correction was used for more than two groups. Correlations between variables were evaluated using Pearson's correlation coefficient (r). To evaluate variables independently associated with depression scores and to control for the simultaneous effects of confounding variables, the General Linear Model (Univariate ANOVA) was used. Statistical significance was set at $P<0.05$ and is indicated by an asterisk (*) in the tables.

3-RESULT

A total of 70 children and adolescents aged 7 to 16 years with type 1 diabetes were enrolled in the study. The gender distribution was 42 girls (60.0%) and 28 boys (40.0%). The mean age was 12.39 ± 2.66 years (median: 13 years, range: 7–16 years). The mean diabetes duration was 4.00 ± 2.70 years (median: 4 years, range: 0.5–13 years). The mean prescribed daily insulin dose was 40.37 ± 17.94 units, and the mean HbA1c (based on the average of three measurements over the past six months) was 9.41 ± 2.24% (median: 9%, range: 6–14%). The mean total CDI score in the entire population was 14.64 ± 9.35 (range: 1–38). Based on the predetermined classification, 22 individuals (31.4%) were in the "healthy" group (CDI ≤ 8), 24 (34.3%) were in the "at threshold for depression" group (CDI 9–19), and 24 (34.3%) were in the "clinical depression" group (CDI ≥ 20).

The average depression score was 15.67 ± 9.86 for girls and 13.11 ± 8.48 for boys. Notably, 40.5% of females and 25.0% of males fell within the clinical depression category, suggesting higher levels of depression among females. However, inferential analysis using the Mann-Whitney test revealed no statistically significant difference between the sexes regarding depression scores ($P = 0.394$).

The Pearson correlation analysis between age and depression scores indicated a positive, significant, yet weak relationship ($r = 0.28$, $P = 0.02$). Furthermore, the results showed that children aged 10 years and older had significantly higher depression scores than those under 10 years ($P = 0.010$). No significant correlation was found between diabetes duration and depression scores ($r = 0.18$, $P > 0.05$). Additionally, a comparison of patients with disease duration less than 5 years versus 5 years or more showed no significant difference ($P = 0.627$).

The primary finding of this study revealed a direct, positive, and significant correlation between HbA1c levels (measured as a 6-month average) and total depression scores ($r = 0.55$, $P < 0.001$) (Figure 1). This correlation had the highest coefficient among all variables assessed. Furthermore, a positive and significant correlation was also observed between total daily insulin dose (TDD) and depression scores ($r = 0.35$, $P = 0.002$).

For further analysis, participants were categorized into three groups based on depression severity (Table 1).

The Kruskal-Wallis test indicated a highly statistically significant difference in mean HbA1c levels among the three groups ($P = 0.0001$). Subsequent Bonferroni pairwise comparisons showed that this difference was primarily evident between the "depressed" group and the "at threshold" group ($P < 0.05$) and between the "depressed" group and the "healthy" group ($P < 0.05$). Specifically, HbA1c levels in the clinical depression group (11.04 ± 2.25%) were markedly higher than those in

the other two groups. Regarding insulin levels, a discernible upward trend was observed; however, this difference did not reach statistical significance (P = 0.056).

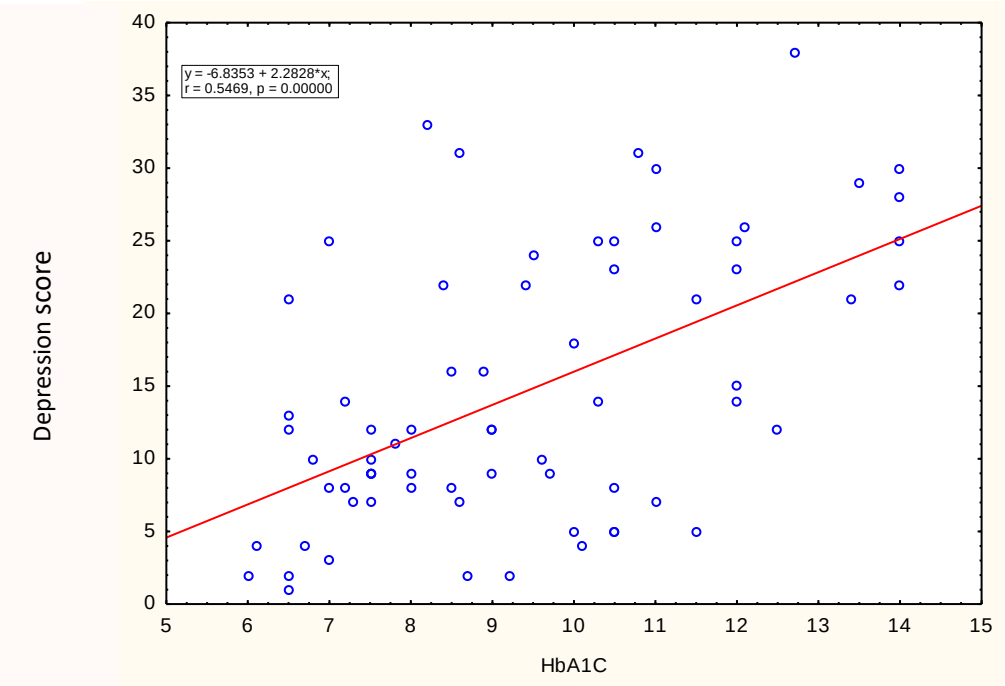


Figure-1: Correlation graph between HbA1c levels and depression scores in children with type 1 diabetes.

Table-1. Comparison of mean clinical and laboratory indices based on depression severity classification (CDI).

Variable	Healthy group (n=22)	At-threshold for depression (n=24)	Clinical depression (n=24)	P-value
Insulin dose (IU/day)	33.00 ± 12.65	39.83 ± 15.62	47.67± 21.63	0.056
HbA1c (%)	8.40 ± 1.75	8.70 ± 1.71	11.04 ± 2.25	0.0001

Note: Values are reported as mean ± standard deviation.
*P < 0.05 is considered significant.

To evaluate the independent associations of the measured clinical and demographic variables with depression scores, a General Linear Model was employed, incorporating five variables: HbA1c, insulin dose, age, sex, and diabetes duration (Table 2). The findings indicate that, after adjusting for the influence of the other variables, HbA1c (F = 24.93, P < 0.0001) and insulin dosage (F = 5.23, P = 0.025) remained independently and statistically significantly associated with higher depression scores. Conversely, age, sex, and diabetes duration did not demonstrate a significant independent association with depression once HbA1c and insulin dosage were accounted for within the model.

4- DISCUSSION

This study shows that poor metabolic control in type 1 diabetes links to depression, with significant associations between depression scores, HbA1c levels, and insulin dose in correlations and a linear model. HbA1c levels varied among healthy, at-threshold, and depressed groups. Surprisingly, diabetes duration didn't significantly relate to depression severity, challenging the idea that long-term disease inherently worsens mental health. Our findings indicate time alone isn't a risk factor for depression in children with diabetes.

The prevalence of depression among children and adolescents with type 1

diabetes in our study was 34.3%, and 34.3% of our study population were at the threshold for depression. This relatively high prevalence is consistent with other studies in developing countries. Similar studies have reported depression rates of 46.3% in Jordan, 36.9% in India, and 52.3% in Egypt (19). These rates are considerably higher than those reported by Razi- Roudi et al. (15) (5% of children in the depression group and 55% at the threshold for depression). Given that 84.3% of the children studied in our research were over 10 years of age, this difference may be attributable to age differences between the study populations. In line with the present study, research by Madanifar et al. (7) in 2021 in Isfahan showed that 55.2% of children aged 8 to 12 years with type 1 diabetes in Isfahan province had psychological problems at a clinical level. Patients with type 1 diabetes in developing countries may be affected by the additional stress of limited resources, inadequate care centers, and insurance restrictions, which could be among the reasons for this increased prevalence of depression in this population (19).

Table-2. General linear model analysis of factors independently associated with depression scores (CDI) in children with type 1 diabetes.

Source	Type III Sum of Squares	df	Mean Square	F	Sig
Corrected Model	2309.332a	5	461.866	7.932	0.000
Intercept	227.524	1	227.524	3.907	0.052
sex	8.531	1	8.531	0.147	0.703
age	0.727	1	0.727	0.012	0.911
Disease duration	6.142	1	6.142	0.105	0.746
Insulin U/Day	304.788	1	304.788	5.234	0.025
HbA1C	1451.667	1	1451.667	24.930	0.0001
Error	3726.739	64			
Total	21045.000	70			
Corrected Total	6036.071	69			

The increased rate of depression among individuals with diabetes has long been recognized (20). This relationship is considered bidirectional. On the one hand, increased stress and mental illnesses have been proposed as mechanisms that may contribute to the development of type 1 diabetes (21). On the other hand, diabetes, through its physiological changes, can predispose individuals to conditions such as depression. Studies have shown that in diabetes, in addition to reduced insulin and elevated blood glucose, dysfunction of the hypothalamic-pituitary axis is also observed. This axis plays a significant role in the development of chronic stress and anxiety, and consequently, this stress contributes to elevated cortisol levels. Furthermore, neuroanatomical deficits observed in the prefrontal cortex of patients with type 1 diabetes can lead to impaired mood regulation and, consequently, a greater predisposition to conditions such as depression (22,23). Additionally, the burden of living with a chronic illness can be among the reasons for the greater association of type 1 diabetes with depression. Dietary restrictions, various treatments including multiple daily insulin injections, frequent blood glucose monitoring, more frequent hospitalizations compared to healthy individuals, and fear of hypoglycemic episodes can be exacerbating factors of psychological stress in children and adolescents (24). In a study by Afshar et al. (25) in Kashan, 98.7% of children with diabetes had an unsatisfactory quality of

life. An increased prevalence of depression is also observed among individuals with other chronic diseases such as cardiovascular diseases, cancers, and pulmonary diseases (26).

This lack of association between disease duration and depression carries an encouraging clinical message (27). The pathophysiology of chronic diseases and the psychological burden of daily management could theoretically predispose individuals to depression (28). However, our findings suggest that it is not merely the "time spent with the disease" that correlates with depressive symptom severity, but rather the "quality of metabolic control" during this period that serves as the primary clinical correlate. In other words, children who have lived with diabetes for longer durations while maintaining optimal metabolic control (lower HbA1c) did not exhibit significantly elevated depression scores in our cohort. This observation aligns with the hypothesis that consistent glycemic control may be linked to lower vulnerability to the pathophysiological and psychological stressors associated with depression in chronic diseases (29). Therefore, the primary clinical focus of parents and healthcare providers should center on supporting optimal glycemic management rather than viewing disease chronicity alone as an inevitable driver of depression (27,30).

Given that fewer than half of adolescents with mood disorders seek help from healthcare providers, the increased frequency of medical visits among children with diabetes due to their illness, along with greater understanding from those around them and the normalization of emotional difficulties in these patients, may lead to earlier referral, diagnosis, and greater detection of depression in this population (31). Therefore, the co-occurrence of diabetes and depression reported in previous studies may be attributable to increased psychiatric care and screening in the diabetic population rather than a true association between the two conditions. For this reason, further studies investigating the relationship between diabetes severity, HbA1c levels, and depression are needed to more conclusively establish a direct link between these two conditions.

Our study is among the few in Iran to examine the relationship between glycemic control and the severity of depression. In a similar 2019 study in Mazandaran by Razi-Roudi et al. (15), the rate of depression among individuals with poor glycemic control, based on HbA1c levels, was 1.36 times higher than in those with good control, but the difference was not statistically significant. Although that study, like the present study, used the Children’s Depression Inventory to assess depression levels, its statistical analysis compared the healthy group with the combined at-threshold and depression groups. The results of our study demonstrate that there is a significant difference in HbA1c levels between children at the threshold for depression and those in the depression group, which may explain the discrepancy between the two studies.

The association between higher rates of depression and poor glycemic control in diabetes remains unclear, but a bidirectional relationship between the two is likely. On one hand, poor glycemic control in diabetes can increase the risk of hospitalization, which has been linked to depression (19). Excessive focus by family members and the child on the disease can reduce attention to other aspects of the child’s life and limit enjoyment, which in itself can predispose children to psychiatric conditions such as depression (32). The pain of repeated injections and blood glucose testing, the stress of periodic care and visits to healthcare settings, adherence to a strict treatment regimen,

and a restrictive dietary plan can all increase psychological pressures on the child and heighten the predisposition to psychiatric disorders. On the other hand, depression can reduce motivation for self-care and meticulous disease management, leading to poor glycemic control and elevated HbA1c levels. Studies have shown that less frequent blood glucose monitoring is significantly associated with higher rates of depression (19,27). It remains unclear whether this association reflects increased anxiety from depression and reduced willingness to monitor blood glucose, leading to inadequate glycemic control in diabetes, or whether poor blood glucose control, through worsening of the disease, leads to increased depression.

Furthermore, our study demonstrated that a higher total daily insulin dose was significantly and directly associated with depression levels in children. Poor glycemic control and repeated injections can, through their psychological burden, increase psychological distress and mental health problems in children (28), while higher levels of depression can, through various pathways, worsen diabetes and lead to poorer disease control (33). Inadequate cooperation with proper insulin injection (9), injection into cystic areas that are less painful but have reduced absorption (34), and a lack of adherence and precision in adjusting the timing and dosage of insulin administration (35) are among the factors that contribute to increased insulin requirements as a result of depression (32). Additionally, other complications of depression, such as binge eating (36), can lead to obesity and increased insulin resistance, thereby increasing the required insulin dose and further intensifying this vicious cycle (37).

Sendela et al. (32) studied 477 children with type 1 diabetes in Poland in 2015 using the Children's Depression Inventory. The study population was divided into two groups: those with scores above 13 and those with scores below 13. Although there was no significant difference in HbA1c levels between the two groups, linear regression analysis showed that, overall, higher scores on the depression inventory were significantly correlated with HbA1c levels. Furthermore, the study demonstrated that children with diabetes who scored above 13 consumed significantly more insulin daily. Other countries in the region have also reported results similar to those of our study. A study of 295 adolescents in Turkey found that HbA1c levels showed a significant linear correlation with both the Children's Depression Inventory score ($r=0.19$, $p=0.001$) and the State-Trait Anxiety Inventory score ($r=0.18$, $p=0.002$) (38). Strong evidence also supports an association between glycemic control and depression in adults. A 2000 meta-analysis of 24 articles by Lustman et al. found that high HbA1c levels were significantly associated with depression across both type 1 and type 2 diabetes populations (33).

The results of our study underscore the need to expand mental health screening and care for children with type 1 diabetes as an integral part of their chronic disease management, particularly when there is an increasing trend in HbA1c or a disproportionate rise in insulin requirements relative to age and dietary intake. These measures can improve the overall quality of life for patients with this disease and contribute to better glycemic control in type 1 diabetes.

Several limitations should be considered when interpreting the findings of this study. First, the cross-sectional design captures clinical and psychological data at a single time point, which demonstrates statistical association rather than causation. Consequently, the temporal directionality between poor glycemic control (or higher insulin dosage) and depressive symptoms cannot be definitively established, and a

bidirectional relationship remains probable. Second, although our initial sample size calculation targeted 96 patients for prevalence estimation, strict eligibility criteria and single-center recruitment limited our final cohort to 70 participants. While post-hoc analysis confirmed high statistical power (>99%) for detecting our primary correlation between HbA1c and CDI scores, the sample size of 70 may have limited our statistical power to detect smaller subgroup differences, such as sex-based disparities. Third, although the General Linear Model adjusted for age, sex, disease duration, and insulin dose, several important potential confounding variables were not captured in our dataset—most notably the frequency of diabetic ketoacidosis (DKA) and diabetes-related hospitalizations, familial history of depression or other psychiatric disorders, family socioeconomic status, frequency of self-monitoring of blood glucose (SMBG), body mass index (BMI), and pubertal Tanner stage. Future prospective, longitudinal, multi-center cohort studies incorporating these clinical and psychosocial covariates are warranted to clarify causal pathways and control for residual confounding.

5- CONCLUSION

This cross-sectional study shows that elevated HbA1c levels and higher daily insulin doses are independently associated with more severe depressive symptoms in children and adolescents with type 1 diabetes, with approximately one-third of the cohort exhibiting clinically significant depressive symptoms. Notably, diabetes duration was not significantly associated with depression scores; rather, the quality of metabolic control was the strongest clinical correlate of psychological status. While longitudinal studies are needed to confirm causal directionality and account for broader familial and hospitalization-related confounders, our findings underscore the close interplay between metabolic control and mental health. Incorporating routine psychological screening into standard pediatric diabetes care—particularly for patients with suboptimal HbA1c or rising insulin requirements—may facilitate early identification and multidisciplinary support to improve both emotional well-being and metabolic outcomes.

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7- CONFLICT OF INTEREST

The authors have declared that they have no competing interests.

8- FUNDING

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