

Factors Affecting Glycemic Control in Pediatric Type 1 Diabetes Mellitus: A Multivariate Regression Analysis

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Abstract- Several factors have been reported to affect glycemic control, the significance of most of which is still a topic of discussion. Therefore, we aimed to investigate such effects in more detail. We conducted our cross-sectional analysis on 163 children and adolescents 2 to 18 with T1DM. Moreover, we obtained their demographic and clinical information in addition to glycated hemoglobin (HbA1C) levels and performed a multivariate regression analysis to determine their effects. Among the investigated factors parents living together ($P<0.001$), higher parental education ($P<0.001$), level of monthly income ($P<0.001$), and residing in urban areas ($P<0.001$), positive history of hospitalization due to ketoacidosis ($P=0.001$), injection site lipodystrophy ($P=0.005$), physical activity ($P<0.001$), regular endocrinology clinic visits ($P<0.01$), physician long distance access ($P<0.001$), social media usage ($P<0.001$), nutritionist supervision ($P<0.001$), regular visits by a mental health expert ($P=0.02$), body mass index ($P=0.449$, $P<0.001$), daily insulin units ($r=0.447$, $P<0.001$), height Z score ($r=-0.177$, $P=0.024$), and duration of Diabetes ($r=-0.199$, $P=0.011$) significantly affected HbA1C levels. Furthermore, the regression model significantly predicted 56.4% of the changes in HbA1C. With environmental and family-related factors proving pivotal, educational interventions and implementing relevant policies are crucial. Financial aid to those affected by facilitating access to healthcare-related technologies and state-of-the-art care centers can also pay substantial dividends.

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Introduction

As the most prevalent pediatric endocrinological disorder, type 1 Diabetes Mellitus (T1DM) necessitates appropriate management and follow-up (1). In addition, the disorder's incidence has been on a continuous rise during the last decade, with more than a million affected children and adolescents worldwide and the middle and low-income countries impacted the most (2,3).

The disorder stems from insulin deficiency and persistently high blood sugar (BS) levels, which should be consistently kept below a certain level (also termed glycemic control). However, failure to achieve such a feat

would lead to significant short-term and long-term macro-vascular and micro-vascular adversities, including diabetic ketoacidosis, retinopathy, nephropathy, atherosclerosis, ischemic heart disease, and lower extremities' hypoxia and subsequent necrosis (2). Nevertheless, several studies have indicated that desirable glycemic control is barely achieved in an overwhelming percentage of the population suffering from DM, especially children (4-6).

Hemoglobin A1c (HbA1c) is a widely recognized indicator of how well glycemic control has been achieved, with below 7.5% levels indicating desirable control in the months before (7). However, many studies

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have shown that countless factors impact glycemic control, with age, sex, insulin regimen and adherence, duration of Diabetes, frequency of blood glucose monitoring and insulin injections, daily required insulin units, and physical and mental comorbid disorders all playing considerable parts (8-13). Nonetheless, the extent to which these factors affect our T1DM glycemic targets has been controversial. Therefore, an appropriate risk stratification strategy to highlight which factors to dedicate more time and attention to is paramount, which we aimed to investigate in our study.

Materials and Methods

This cross-sectional study was conducted in Iran's southeast pediatric endocrinology referral clinic between 2021 and 2022. In addition to following the guidelines in the Declaration of Helsinki, we obtained approval from the Institutional Review Board (IRB). Moreover, as we ensured the confidentiality of their personal information, the legal guardians of the children deemed eligible for the investigations provided their written informed consent.

Population

We targeted children and adolescents referred to our clinic with confirmed type 1 diabetes mellitus (T1DM) via a census method due to the relative scarcity of available cases. However, we included those aged 2 to 18 years who had been diagnosed with T1DM at least 12 months prior and were not suspected of type 2 or infantile DM.

Outcomes and data collection

Upon inclusion, we recorded the necessary personal and demographic characteristics, consisting of the patient's age, gender, height, weight, body mass index, physical activity, socioeconomic status (e.g., family monthly income), place of residence (i.e., urban or rural), their level of education, and their primary caretakers' (e.g., parents) level of education and employment status and whether they lived together or separately. We also asked if a psychologist or a psychiatrist regularly visited the patients or their caretakers to determine their overall mental health and coping methods. Moreover, we checked if the patients or their caretakers utilized the social media platforms to be appropriately and regularly updated on information regarding DM control. In addition, we documented factors related to the patients' DM, including its duration and family history.

We also considered possible or known factors impacting or related to the extent of blood sugar (BS)

control brought below:

- Daily, weekly, and monthly frequency of BS measurements,
- Number of insulin injections per day,
- Using the carbohydrate counting method for insulin injections,
- Injecting additional insulin for added snacks,
- Insulin injections during school hours,
- Parental supervision during injections,
- Long-distance availability of the primary caretaking physician,
- Being under the supervision of a specialized nutritionist,
- Frequency of outpatient visits (during and after the pandemic),
- Hospitalization due to diabetic ketoacidosis (DKA) or hypoglycemia,
- Insulin daily dosage (i.e., basal and bolus doses) and regimen (i.e., insulin pens or the conventional regular and NPH insulin vials),
- Presence of lipodystrophy or lipoatrophy at the insulin injection sites.

Furthermore, we measured the patients' Glycated hemoglobin (HbA1C), either through their latest available laboratory data (if done in the past three months) or by sending blood samples for laboratory investigation (via the colorimetric method), to determine whether they had appropriate DM metabolic control. Ultimately, we investigated the effects of the mentioned factors on the HbA1C levels.

Statistical analysis

The 22nd version of the SPSS statistical package (SPSS Inc., IBM, USA) was used to analyze the data, with categorical variables described by frequency and percentage and continuous variables described by mean and standard deviation (SD). In addition, the Chi-square, Student's t, and Pearson's r tests were used to analyze the mentioned data. We then carried out a multivariate regression analysis to assess the extent of the effects of investigated factors. $P < 0.05$ were also considered statistically significant.

Results

Most of the 163 children and adolescents were girls (54%). However, although only a minority were under 12 years old (26.5%), most did not experience signs of puberty (50.9%). Regarding socioeconomic status, we found that most families resided in urban areas (69.9%), had primary or academic education, and the majority of

fathers were employed (92%), yet most mothers were housewives or unemployed (63.2%).

The serum HbA1C levels were 8.21 ± 1.58 , with only 37.3% having desirable BS controls as indicated by HbA1C levels $< 7.5\%$. In addition, 14.6% had HbA1C levels above 10%. However, most did not experience DKA (62%) or hypoglycemia (87.7%) episodes after DM diagnosis.

We found that most children did not have a family history of DM (57.1%), used insulin pens (96.9%), used carbohydrate counting for insulin dose measurements (54.6%), and did not inject after an additional snack (68.7%) or during school hours (73.9%). Moreover, most of the injections were performed under the direct supervision of their caretakers (50.3%) and did not have lipodystrophic or lipoatrophic changes at injection sites on examination (50.3%). In addition, most children had adequate physical activity (57.4%).

The endocrinology clinic visits occurred every three months in most (71.8%) before the pandemic but reduced to every six months during and after it (57.7%). Nevertheless, most had long-distance access to their caretaking physician (76.1%). Most patients also reported that they used social media only to communicate with their caretaking physician (62.3%), and, therefore, only a few online educational outlets followed on Diabetes (18.5%). In addition, most patients (62.6%) were not supervised by a specialized nutritionist and were not regularly visited by a psychologist or a psychiatrist (84%) (Table 1).

Our analysis demonstrated that mean Serum HbA1c levels were not significantly different based on the patient's gender ($P=0.7$), puberty ($P=0.13$), family history of DM ($P=0.06$), latest education received ($P=0.28$), medical conditions ($P=0.42$), using the carbohydrate counting method ($P=0.87$), insulin regimen ($P=0.65$), additional insulin injections for snacks ($P=0.08$) or during school hours ($P=0.22$), parental supervision of injections ($P=0.27$), history of experiencing hypoglycemia episodes ($P=0.32$)

However, parents living together ($P<0.001$), higher parental education ($P<0.001$), level of monthly income ($P<0.001$), and residing in urban areas ($P<0.001$) were associated with lower HbA1C levels. Even though children of employed fathers had lower HbA1c levels ($P<0.001$), the levels were significantly higher in children of employed mothers ($P<0.001$).

In addition, higher mean levels of HbA1C were noted in those with histories of hospitalization due to DKA episodes ($P=0.001$), lipodystrophic or lipoatrophic changes at injection sites ($P=0.005$), inadequate physical activity ($P<0.001$), less frequent visits to the endocrinology clinic ($P=0.001$ for before the pandemic, $P<0.001$ for during and after), no long distance access to the caretaking physician ($P<0.001$), not using social media ($P<0.001$), not under the supervision of a specialized nutritionist ($P<0.001$), and not regularly visited by a psychologist or a psychiatrist ($P=0.02$) (Table 2).

We also found that BMI ($P=0.449$, $P<0.001$) and daily injected insulin units ($r=0.447$, $P<0.001$) had moderately positive correlations with mean HbA1C levels, while height Z score ($r= -0.177$, $P=0.024$) and duration of Diabetes ($r= -0.199$, $P=0.011$) had weak negative correlations. However, the patient's age ($r=0.149$, $P=0.058$) and number of daily insulin injections ($r= -0.088$, $P=0.263$) did not significantly correlate with mean HbA1C levels.

Ultimately, the multivariate regression model comprising the previously mentioned statistically significant characteristics significantly ($F(30, 137)=11.16$, $P<0.001$) predicted 56.4% of the changes in HbA1C (Adjusted $R^2=0.564$).

In addition, daily units of insulin injection ($P=0.004$), father's education level ($P=0.015$), mother's employment status ($P=0.045$), monthly income ($P=0.001$), endocrinology visits before the pandemic ($P=0.018$), and social media use ($P=0.047$) demonstrated significant effects in the model (Table 3).

Table 1. Demographic and clinical characteristics of children with type 1 diabetes

Characteristic	Total patients included (No. = 163)
	No. (%) / Mean $\pm$ SD
Age (Years)	10.22 $\pm$ 3.72
Duration of Diabetes (Years)	5.16 $\pm$ 3.06
Gender	
Boy	75 (46)
Girl	88 (54)
Puberty	
Yes	80 (49.1)
No	83 (50.9)
Height (Z score)	-0.18 $\pm$ -0.84

Cont. table 1

BMI (Percentile)	36.56 ± 30.53
Family history of DM	
Yes	70 (42.9)
No	93 (57.1)
Latest Education	
Illiterate	36 (22.2)
Primary school	83 (51.2)
Secondary school	43 (26.5)
Medical conditions	
Negative	94 (57.7)
Hypothyroidism	25 (15.3)
Celiac disease	23 (14.1)
Other	21 (12.9)
Father's education	
Illiterate	8 (4.9)
Diploma	57 (35)
Advanced Diploma	48 (29.4)
Bachelor's or higher	50 (30.7)
Mother's education	
Illiterate	7 (4.3)
Diploma	78 (47.9)
Advanced Diploma	46 (28.2)
Bachelor's or higher	32 (19.6)
Father's employment status	
Employed	150 (92)
Unemployed	13 (8)
Mother's employment status	
Employed	60 (36.8)
Unemployed	103 (63.2)
Parents living together	
Yes	150 (92)
No	13 (8)
Monthly income	
Below 50 dollars	26 (16)
Between 50 and 100 dollars	50 (30.7)
Above 100 dollars	87 (53.4)
Residence	
Urban	114 (69.9)
Rural	49 (30.1)
Number of daily blood sugar measurements	1 ± 0.7
Using the carbohydrate counting method	
Yes	89 (54.6)
No	74 (45.4)
Insulin regimen	
Pen	158 (96.9)
Conventional	5 (3.1)
Frequency of insulin injections	
Daily (U/Kg)	0.83 ± 0.41
Daily (Total)	2.99 ± 1.08
Weekly	6.31 ± 4.07
Monthly	25.03 ± 15.1
Additional Insulin injections for snacks	
Yes	51 (31.3)
No	112 (68.7)
Additional Insulin injections during school hours	
Yes	41 (26.1)
No	116 (73.9)
Supervision during insulin injections	
Injection done by caretakers	49 (30.1)
Under supervision	82 (50.3)
Without supervision	32 (19.6)

Cont. table 1

Diabetes first manifested with ketoacidosis	
Yes	66 (40.7)
No	96 (59.3)
Hospitalization due to diabetic ketoacidosis during follow-up	
Yes	62 (38)
No	101 (62)
Hospitalization due to hypoglycemia	
Yes	20 (12.3)
No	143 (87.7)
Lipodystrophic or lipoatrophic changes at the injection site	
Yes	81 (49.7)
No	82 (50.3)
Physical activity	
Yes	93 (57.4)
No	69 (42.6)
Visits at the clinic	
Before the pandemic	
Every three months	117 (71.8)
Every six months	39 (23.9)
Every year	7 (4.3)
During and after the pandemic	
Every three months	37 (22.7)
Every six months	94 (57.7)
Every year	32 (19.6)
Long-distance access to the caretaking physician	
Yes	124 (76.1)
No	39 (23.9)
Social media use	
Follows educational outlets regarding Diabetes	30 (18.5)
Only to communicate with the caretaking physician	101 (62.3)
No	31 (19.1)
Under the supervision of a nutritionist	
Yes	61 (37.4)
No	102 (62.6)
Regular psychologist or a psychiatrist visits	
Yes	26 (16)
No	136 (84)

Table 2. Hemoglobin A1C levels in children with type 1 diabetes based on the factors investigated

Characteristic	Serum HbA1c level
	(Mean $\pm$ SD)
Gender	
Boy	8.16 $\pm$ 1.52
Girl	8.26 $\pm$ 1.63
Puberty	
Yes	8.41 $\pm$ 1.72
No	8.03 $\pm$ 1.58
Family history of Diabetes Mellitus	
Yes	70 (42.9)
No	93 (57.1)
Latest Education	
illiterate	8 $\pm$ 1.1
Primary school	8.1 $\pm$ 1.56
Secondary school	8.5 $\pm$ 1.73
Medical conditions	
Negative	8.38 $\pm$ 1.58
Hypothyroidism	7.81 $\pm$ 1.33
Celiac disease	8.14 $\pm$ 1.72
Other	8.07 $\pm$ 1.68
Father education***	
illiterate	10.2 $\pm$ 1.58
Diploma	9.27 $\pm$ 1.78

Cont. table 2

Advanced Diploma	7.72 ± 0.79
Bachelor's or higher	7.17 ± 0.6
Mother's education***	
illiterate	9.9 ± 2.41
Diploma	8.63 ± 1.48
Advanced Diploma	8.02 ± 1.57
Bachelor's or higher	7.12 ± 0.71
Father's employment status***	
Employed	8.08 ± 1.72
Unemployed	9.8 ± 1.59
Mother's employment status***	
Employed	8.85 ± 1.72
Unemployed	7.84 ± 1.37
Parents living together***	
Yes	8.09 ± 1.48
No	9.63 ± 1.58
Monthly income***	
Below 50 dollars	9.8 ± 1.72
Between 50 and 100 dollars	8.71 ± 1.68
Above 100 dollars	7.46 ± 0.87
Residence***	
Urban	7.93 ± 1.43
Rural	8.88 ± 1.72
Using the carbohydrate counting method	
Yes	8.23 ± 1.81
No	8.2 ± 1.27
Insulin regimen	
Pen	8.23 ± 1.6
Conventional	7.9 ± 0.27
Additional Insulin injections for snacks	
Yes	7.9 ± 1.54
No	8.36 ± 1.58
Additional Insulin injections during school hours	
Yes	7.93 ± 1.6
No	8.28 ± 1.57
Supervision during insulin injections	
Injection done by caretakers	8.12 ± 1.3
Under supervision	8.11 ± 1.52
Without supervision	8.62 ± 2.06
Diabetes first manifested with ketoacidosis	
Yes	9.06 ± 1.82
No	7.65 ± 1.08
Hospitalization due to diabetic ketoacidosis during follow-up**	
Yes	8.74 ± 1.73
No	7.89 ± 1.39
Hospitalization due to hypoglycemia	
Yes	7.89 ± 1.5
No	8.26 ± 1.59
Lipodystrophic or lipoatrophic changes at the injection site**	
Yes	8.56 ± 1.79
No	7.87 ± 1.26
Physical activity***	
Yes	7.67 ± 1.28
No	8.92 ± 1.7
Visits at the clinic	
Before the pandemic**	
Every three months	8 ± 1.43
Every six months	8.53 ± 1.81
Every year	10 ± 1.33
During and after the pandemic***	
Every three months	7.69 ± 1.39
Every six months	8.13 ± 1.38

Cont. table 2

Every year	9.08 ± 1.99
Access to the caretaking physician***	
Yes	7.96 ± 1.44
No	9.04 ± 1.74
Social media use	
Follows educational outlets regarding Diabetes	7.51 ± 1.07
Only to communicate with the caretaking physician	8.01 ± 1.53
No	9.54 ± 1.44
Regular psychologist or a psychiatrist visit*	
Yes	7.54 ± 1.56
No	8.35 ± 1.56
Under the supervision of a nutritionist***	
Yes	7.47 ± 1.26
No	8.66 ± 1.59

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$

Table 3. Linear regression model based on factors potentially impacting serum HbA1C levels

Characteristic	Unstandardized coefficients (B)	[95.0% CI]	P
(Constant)***	9.66	[7.04 - 12.27]	< 0.001
Height (Z Score)	-0.2	[-0.41 - 0.01]	0.059
BMI (Percentile)	0.01	[0 - 0.01]	0.073
Daily units of insulin injection (Units)**	0.7	[0.23 - 1.17]	0.004
Duration of Diabetes (Years)	-0.01	[-0.07 - 0.05]	0.693
Higher father education level*	-0.35	[-0.64 - -0.07]	0.015
Higher mother education level	-0.03	[-0.29 - 0.22]	0.786
Father unemployed	-0.27	[-0.98 - 0.43]	0.443
Mother unemployed *	-0.4	[-0.79 - -0.01]	0.045
Higher monthly income**	-0.5	[-0.8 - -0.2]	0.001
Parents not living together	0.07	[-0.62 - 0.75]	0.846
Residing in urban areas	-0.22	[-0.66 - 0.23]	0.335
Negative history of hospitalization due to diabetic ketoacidosis	-0.31	[-0.67 - 0.05]	0.091
Lower number of endocrinology visits before the pandemic*	0.41	[0.07 - 0.75]	0.018
Lower endocrinology visits during and after the pandemic	-0.05	[-0.35 - 0.25]	0.739
Having long-distance access to the caretaking physician	-0.13	[-0.6 - 0.35]	0.597
Having regular psychologist or a psychiatrist visits	0.06	[-0.47 - 0.6]	0.822
Not being under the supervision of a nutritionist	0.33	[-0.09 - 0.74]	0.125
Not using social media for diabetes control *	0.32	[0 - 0.64]	0.047
Not having lipodystrophic or lipoatrophic changes at the injection site	-0.16	[-0.51 - 0.19]	0.357
Not having physical activity	0.27	[-0.13 - 0.67]	0.184

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$

Discussion

With many children across the world suffering from irreparable complications, appropriate and accurate control of blood glucose and metabolism in DM is quintessential. This led to the conduction of this study, aiming to investigate potentially influential factors in order to optimize BS control and follow-up, with results

of the regression analysis demonstrating that daily units of insulin injection, father's education level, mother's employment status, monthly income, and the frequency and regularity of endocrinology visits proving more pivotal than other factors for achieving a desirable HbA1C level.

Our study demonstrated that parents, if not the most, are one of the most vital components in their child's

metabolism control, with their level of education, employment status, place of residence, and monthly income status all having considerable effects on the HbA1C levels. Nevertheless, we have to note that even though the father's higher level of education and socioeconomic status inevitably led to lower HbA1C levels, the presence of the child's mother was more important as children of stay-at-home mothers had significantly lower HbA1C levels, which is in line with findings from another study (14). These findings align with previous studies that reported an inverse linear relationship between the families' socioeconomic status and HbA1C levels (14-20).

The financial burden on families to maintain appropriate metabolic control is considerable, and subsequently, low household income and rural residence are associated with even poorer disease conditions aggravated by lack of access to healthcare services (17). Therefore, strategies are required to ensure that T1DM children with low socioeconomic status receive adequate diabetes care and are routinely followed to improve their glycemic control and reduce the risk for complications.

In addition, as long-distance access to the caretaking physician was associated with lower HbA1C levels, providing or facilitating such access to the children's parents through social media is paramount. Better yet, the physician should encourage the families to follow up-to-date social media outlets on DM and improve their overall knowledge.

Similar to previous studies, we also found that lower adherence to guidelines led to less glycemic control, with histories of hospitalizations due to DKA, incorrect injection techniques and finding lipodystrophic or lipoatrophic changes at injection sites, inadequate physical activity, and less frequent endocrinology visits for follow-ups were associated with less controlled blood glucose levels (19,21-24). This finding highlights the importance of educating the children and their parents on glycemic control by encouraging using varying injection sites, promoting higher physical activity, and requesting more regular follow-up visits. In addition, as we found those under the supervision of a specialized nutritionist and those whom a psychologist or a psychiatrist regularly visited to have lower HbA1C levels, we recommend children and adolescents with T1DM also be referred to nutritionists for diet modifications and a mental health expert for relevant evaluations.

However, unlike some studies, we found no relationship between the patients' age or gender and HbA1c levels. One study, for instance, reported that girls and younger age were associated with poorer glycemic

control, while two other studies stated that older patients had better glycemic control (24-26). Considering that the parameters investigated in our study were measured differently (e.g., the instruments used for outcome measures) in the mentioned studies or not measured at all, the differences in sample sizes, and the differences in the age of included children and adolescents, we believe extending the evaluations to other age groups and adding other outcome measures to investigations would aid the accuracy and reliability of the results immensely.

Finally, we conclude that for optimal glycemic control, policymakers in healthcare should provide suitable conditions for implementing educational interventions, take meaningful steps in the direction of empowering the children and their families' knowledge and awareness of glycemic control, and provide financial incentives to enhance access to the state-of-the-art devices for both BS measurement and Insulin injections, including, for example, CGM (continuous glucose monitoring).

This study was approved by the Kerman University of Medical Sciences Ethics Committee (IR.KMU.AH.REC.1400.028). Furthermore, the patient's legal guardians provided written informed consent for participation.

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