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Original Article

Glycemic Control in Adolescent Girls with Type 1 Diabetes Mellitus

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Abstract:
Background: Optimal glycemic control is essential during type 1 diabetes (T1D) management to minimize the occurrence of both short and long term complications. Many factors might influence diabetes control including puberty which is a challenging period.
Aim of the work: To assess the effect of puberty on glycemic control in adolescent females with T1D and to compare glucose levels, insulin demand and carbohydrate intake in the week of menstruation to those in the luteal phase.
Methods: This cross-sectional, pilot study took place in the Diabetes, Endocrine and Metabolism Pediatric Unit, Cairo University Children's Hospital, Egypt. It included 30 prepubertal Tanner stage 1 girls (Group-1) and 30 full pubertal girls Tanner stage 5 (Group 2) with regular menstruation were included in the study. Mean blood glucose levels, insulin doses and glycated hemoglobin (HbA1C) (average of the last 4 readings over 1 year) were compared.
Results: Ages of enrolled girls ranged from 10-15 years (group 1: mean age ± SD=11.67±1.33; group 2: 13.93±.0.94; p< 0.001) with T1D durations of 5.12-5.42 years. Mean HbA1c and insulin doses were similar in both pubertal and prepubertal girls after adjusting data for BMI SDS and participation in exercise (p=0.164 and 0.157 respectively). Mean blood glucose levels, insulin doses and carbohydrate intake were significantly higher (by 8%, 18% and 7.5% respectively) during menstruation (early follicular) than in the luteal phase (p<0.001).
Conclusion: Glycemic control in pubertal females with T1D was challenged by the higher BMI, lack of activity and growth spurt that characterize this stage of development. Contrary to some other studies, among our studied cohort glycemic control also exhibited deterioration in the early follicular phase that was associated with greater carbohydrate consumption compared to the luteal phase.

Level of Evidence of Study: IIB (1).
Keywords: Type 1 diabetes mellitus; glycemic control; menstruation; insulin resistance; luteal phase.
Abbreviations: BMI: body mass index; EGDR: Estimated Glucose Disposal Rate; HbA1c: glycated hemoglobin; HOMA-IR: homeostatic model assessment of insulin resistance; NPH: Neutral Protamine Hagedorn; SBGM: self-blood glucose monitoring; SDS: standard deviation scores; T1D: Type 1 diabetes.

Introduction

Appropriate management of type 1 diabetes (T1D) involves a combination of insulin injections, dietary restrictions, exercise, and self-blood glucose monitoring (SBGM). Adolescence is a difficult time for children with type T1D due to demands of glycemic control, concerns about complications and parental conflicts with the adolescent's wish for autonomy (*2*, *3*). In addition, puberty has a detrimental effect on diabetes control (*3*). This may be due to poor adherence to treatment and meal planning; and/or insulin resistance which appears during puberty (*4*).

Insulin resistance has been associated with elevated levels of growth hormone (a potent anti-insulin) and adrenal androgens (*5*, *6*). For girls, insulin sensitivity starts to deteriorate with the start of puberty and remains low throughout that period, whereas in boys, insulin sensitivity tends to rise again after Tanner stage 3 (*7*). Insulin resistance is greater in girls than in boys, maybe as a result of greater body fat composition (*8*). Insulin resistance associated with deterioration of glycemic control throughout the luteal phase starting from ovulation might be due to the predominant progesterone levels secreted by the corpus luteum (*9*, *10*). The aim was to assess the effect of puberty on glycemic control in adolescent girls with T1D and to compare glucose levels, insulin demand and carbohydrate intake in the week of menstruation to those in the luteal phase.

Subjects and Methods

This cross-sectional, pilot study included 60 adolescent females with T1D (prepubertal and pubertal females) aged between 10-15 years following up in the Diabetes Endocrine, Metabolism Pediatric Unit, Cairo University Children's Hospital, Egypt. The study received approval from the Institutional Review Board of Cairo University (I-080415) and was carried out in accordance with the Helsinki declaration (*11*). Informed consent was obtained from caregivers and assent from study participants.

Participants

Children were divided into 2 groups: Group1 (30 prepubertal females, Tanner stage 1) and Group 2 (30 full pubertal females, Tanner stage 5). Blood glucose measurements were taken for one week (Groups 1) and for two weeks in Group-2 (the week before menstruation and the week of menstruation).

a) Inclusion criteria: Adolescents aged 10-15 years with T1D of at least two years duration and, for Group 2, regular menstruation for at least 2 years (Regular menstruation was defined as menses occurring every 21-36 days and lasting for 3-5 days) (*12*).

b) Exclusion criteria: Patients with comorbid conditions particularly those that disturb glycemic control (e.g. thyroid disorders or celiac disease), those with other autoimmune diseases, long-term complications of T1D, polycystic ovarian disease, hypertension, use of medications that alter the menstrual cycle (e.g. oral contraceptives or blood thinners) or corticosteroids and patients in the honeymoon period (receiving an insulin dose <0.5U/kg/day and HbA1c≤ 6%) (*13*).

Methods

Complete history was taken including age at start of study, age at onset of T1D, diabetes management, menstrual history (age at menarche and regularity), active participation in exercise (exercise for at least half an hour three times/week) and number of attacks of diabetic ketoacidosis and/or severe hypoglycemic events (defined as hypoglycemia associated with severe cognitive impairment requiring immediate attention by caregiver) (*14*) in the previous year.

General Examination: Patients were examined for signs of metabolic syndrome (acanthosis nigricans, high blood pressure), goiter, anthropometric measurements (height standard deviation scores (SDS), weight SDS and body mass index (BMI) SDS), injection sites to detect lipodystrophy, genital and breast examination for Tanner stage of puberty (onset of puberty in females relates to a breast size≥B2) (*15*).

Carbohydrate Intake Assessment: Girls were asked to keep a record of food intake in the week before and the week of menstruation. Basic carbohydrate counting using insulin carbohydrate exchange (each serving=15 gm carbohydrate) was employed (1 carb choice). The point system was adopted (*16*). Patients revised this point system and glycemic index of different foods with our certified diabetes dietician before the start of the study. Bolus meal insulin doses were calculated from the total carbohydrates consumed at each meal and insulin/carbohydrate ratio (*17*).

Laboratory Investigations: mean blood glucose levels during the weeks of the study (three fasting and two postprandial measures), glycated hemoglobin (HbA1c) (average of the last four results done every three months in the year predating the study and up until the study period – measured by immune chromatography- retrieved from patient-files) and thyroid functions (normal as a prerequisite to inclusion in the study) were measured.

Group-2 patients were asked to take five daily glucose readings the week before and the week of menstruation. The luteal phase was confirmed by a progesterone level >5ng/ml (measured by chemiluminescence immunoassay, Immulite, Siemens) and expected menstruation was based on previous dates of menses (*18*). New glucometers (One Touch Ultra-2, LifeScan/Johnson & Johnson, Milpitas, CA) and blood glucose strips were provided by the study group. Correction doses of bolus insulin were to be given as needed depending on blood glucose levels.

Statistical Analysis

Data were coded and entered using the statistical package SPSS (Statistical Package for the Social Sciences) version 25. Quantitative data were analyzed using mean, standard deviation, minimum and maximum and categorical data as frequency and relative frequency (percentage). One-way ANOVA was used for comparison of three groups and post-hoc pairwise comparison when a significant difference was found. For comparing categorical data, Chi square test was performed. Correlations between quantitative variables were done using Spearman correlation coefficient ($p<0.05$ was considered statistically significant).

Results

Characteristics of prepubertal girls (group-1), and pubertal girls (group-2) are shown in Table 1. Group-2 were significantly older at onset of T1D but diabetes duration was similar in both groups ($p= 0.003$ and $p= 0.828$ respectively). Height SDS was significantly lower in the group of pubertal females (Group 2) whereas, weight SDS and BMI SDS were significantly higher ($p <0.001$, $p <0.001$ and $p = 0.002$ respectively), with less exercise time in that group than in prepubertal females (p value 0.001).

Regarding insulin therapy, there was no statistically significant difference between both groups. Around 67% of prepubertal females (group 1) and 73.3% pubertal females were on basal insulin in the form of intermediate Neutral Protamine Hagedorn (NPH). The rest were receiving long-acting insulin analogs. All were on short-acting bolus insulin with the three main meals. Almost all the group 1 participants were managed by both the mother and the child whereas group 2 exhibited more independence (only 66.6% was managed by both) and the rest of group 2 were managed by the adolescents only. Significantly more children in group-1 than in group-2 practiced regular exercise (80% versus 66.7%, $p<0.001$).

Table 1: Demographic data of studied groups.

	Prepubertal girls Tanner stage 1 Group 1 (n:30)	**Pubertal girls Tanner stage 5 Group 2 (n:30)**	**P value**
Age (in years)	11.67±1.33	13.93±.0.94	< 0.001
Age at onset of T1D (years)	6.25±3.14	8.68±2.15	0.003
T1D duration (years)	5.42±3.01	5.25±2.24	0.828
Height SDS	-1.02±1.48	-1.28±1.12	< 0.001
Weight SDS	-0.35±1.51	-0.12±0.81	< 0.001
BMI SDS	0.34±0.98	0.58±0.77	0.002
Regular Exercise	24(80%)	20 (66.7%)	0.001

T1D: Type 1 diabetes mellitus; BMI: Body mass index

There were no difference between the two groups regarding short term complications. Diabetic ketoacidosis occurred in 36.7% of group 1 and 43.3% of group 2 patients. Both groups experienced an average between 1 and 6 attacks. Severe hypoglycemic events occurred in 30% of group 1 patients and 53.3% of group 2 patients. Of these, 16.6% of group 1 and 33.3% of group 2 experienced monthly attacks. Lipohypertrophy was present in 33.3% of group 1 and 50% of group 2 patients. Mean blood glucose was significantly higher in group 2 after adjustment of values for BMI SDS and exercise time ($p= 0.012$) as shown in table 2; however, when comparing the HbA1c

and insulin doses in both groups, values did not reach statistical significance after adjustment for BMI SDS and exercise, (p=0.164 and 0.157 respectively) (Table 2). A positive correlation was detected between HbA1c and number of hypoglycemic events during the previous year in group-1 patients (r=0.39, p=0.034), and between HbA1c and insulin dose (U/kg/day) in group-2 patients (r=0.5, p=0.005) as shown in Figure 1 and this correlation remained statistically significant after adjustment for BMI (r=0.47, p=0.009).

In group-2 girls, onset of menarche occurred at 12.38+1.01years. Blood glucose levels increased by 8%, carbohydrate intake by 7.5% and insulin doses by 18% during the week of menstruation (early follicular phase) compared to the week before (late luteal phase) (p<0.001) (Table 3). However, after adjusting for carbohydrate intake and BMI SDS, the difference between blood glucose levels before and during menses was not significant (P=0.089). In 23/30 of the patients, food cravings were noticed 1 day before the onset of menstruation (late luteal) and continued for a few days into menstruation (early follicular).

Table 2: Comparison of glycemic control after adjustment for BMI SDS and regular exercise time.

	Prepubertal girls Tanner stage 1 Group 1	**Pubertal girls Tanner stage 5 Group 2**	***P* value**
Daily insulin dose (units/kg/day)	1.22±0.38	1.32±0.46	0.157
Blood glucose in one week (g/dL)	230.43±62.77	274.27±50.94	0.012
HbA1c (%)	7.86±0.82	8.35±0.88	0.164

HbA1c: Glycated hemoglobin.

Table 3: Mean blood glucose, carbohydrate intake and insulin dose in pubertal females before adjustment for BMI or carbohydrate intake (n=30)

	Week before menstruation	**Week of menstruation**	**Percent increase**	***P* value**
Blood glucose (mg/d)	274.27±50.94	296.30±54.79	8	<0.001
Carbohydrate intake (servings/d)	15.85±1.78	17.05±1.84	7.5	<0.001
Insulin dose (U/kg/d)	1.22±0.38	1.44±.45	18	<0.001

Carbohydrate serving=approximately 15gm carbohydrate

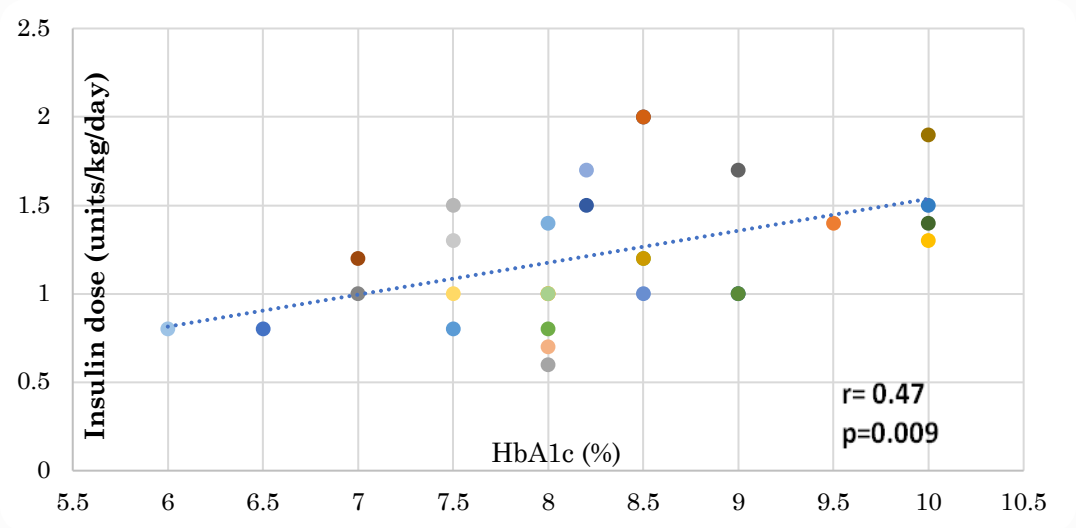

Figure 1: Correlation between HbA1C and insulin dose in pubertal girls.

Discussion

We included children with similar T1D duration to exclude differences related to treatment reluctance and fatigue, which can occur due to the pressure posed by the chronic disease (*19*). Pubertal girls were heavier, shorter and had higher BMIs than prepubertal girls (age range: 10-14 years). In T1D a higher BMI is associated with an earlier onset of puberty and menarche, similar to that detected in healthy girls (*20*). Lower heights may be related to long-standing suboptimal glycemic control (*21*, *22*), or mere earlier onset of T1D before 5 years of age (*23*).

A multidisciplinary team including an endocrinologist, a dietitian, psychologist and a gynecologist should be involved in the management of adolescent females with T1D to identify the aspects that might affect glycemic control. Menstruation constitutes a tremendous part of the life of any pubertal female. This study demonstrated an 8% increase in mean blood glucose and a 7.5% increase in carbohydrate intake in pubertal females in the first week of menstruation (early follicular phase) compared to the previous week (late luteal phase) despite an 18% increase in insulin doses during this time. This difference disappeared when we adjusted for carbohydrate intake and BMI SDS. Others reported that females with T1D had higher blood glucose levels in the late luteal phase when compared to follicular phase related to insulin resistance, and that some had hyperglycemia in the first part of the cycle (early follicular phase) (*24*). They noticed that across most menstrual cycles, patterns of decreased insulin sensitivity and hyperglycemia tended to be consistent in the same patient.

In our study group, increased carbohydrate intake in pubertal girls was linked to cravings and increased appetite beginning on the day before menstruation and continuing for another two days. It is not clear why the cravings were noted in these days, as mostly the noted cravings occur -if any (*25*)- in the luteal phase associated with an increase in calories in the form of carbohydrates, fats and proteins (*26*, *27*).

Levels of blood glucose and HbA1c in the pubertal girls were similar to prepubertal girls when data was adjusted for BMI and lower participation in exercise. Prior to adjustment for these 2 variables, it was noticed that the higher the BMI and the lower the physical activity, the worse the glycemic control (*7*) so maintenance of a healthy BMI is critical for adolescent girls with T1D however, the effect of obesity has not been studied in the current study. Healthy BMI could be achieved through close monitoring of glycemic control through scheduling regular clinic visits in addition to encouraging regular exercise, psychological and nutritional counselling delivered through specialized Diabetes Educators. A systematic review of 172 studies that were investigating the degree of involvement of girls in sports in the Middle East and Arab countries revealed significantly lower levels of female engagement. Barriers mentioned included hot weather, inadequate transportation and religious restrictions (*28*).

Management of T1D should be individualized through a multidisciplinary team and should aim at achieving near euglycemia while avoiding hypoglycemia. This could be achieved using insulin analogues, insulin pumps and continuous glucose monitoring (*29*, *30*). Recurrent hypoglycemia may be an obstacle for proper control as patients/parents cut back on insulin doses in response to such events. We observed this in prepubertal females where HbA1c correlated positively with the number of hypoglycemic events. Ideally, the response to hypoglycemia should begin with redistributing insulin doses between basal and bolus types (18,28).

Limitations of the study include the short study as 1-2 weeks do not adequately reflect blood glucose along the whole year. We did not study the effect of obesity on glycemic control in our study group as number of the patients included who had a BMI SDS or weight SDS above +2 SDS was limited. The effect of hormonal fluctuations during the menstrual cycle was not studied. Homeostatic Model Assessment of Insulin Resistance (HOMA- IR) was not measured in our study group to determine the degree of insulin resistance. The psychological aspect of nutritional compliance in females with T1D was not assessed.

Conclusion

Higher BMI, lower physical activity, growth spurt and increased carbohydrate intake are factors that affect diabetes control. Young women must be encouraged to maintain a healthy BMI and engage in physical exercise. Close blood glucose monitoring during menstruation taking

into consideration changing carbohydrate intake, with the help of dietitians, is needed when planning insulin doses.

Author Contributions:
All authors shared in conceptualization, supervising, data curation, data analysis, writing original draft, data interpretation, writing original draft, supervising and revising. All authors reviewed the final manuscript. All authors have read and agreed to the published version of the manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest in connection with the study.

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