Pubertal Development in Children Diagnosed with Diabetes Mellitus Type 1 before Puberty

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A B S T R A C T

Study Objective: To investigate an association between pubertal development and timing of menarche with glycemic control, disease duration, and body mass index (BMI) in patients diagnosed with diabetes mellitus type 1 (DM1) before puberty.
Design: Retrospective study.
Setting: The study was performed at the diabetes outpatient clinic of Instituto de Puericultura e Pediatria Martagão Gesteira–IPPMG of the Federal University of Rio de Janeiro–UFRJ.
Participants: A total of 131 children, 61 girls and 70 boys, diagnosed with DM1 before puberty participated in the study.
Main Outcome Measures: The study investigated how age at puberty onset relates to mean glycated hemoglobin (HbA1c) before puberty, BMI percentile, and disease duration; how puberty duration relates to mean HbA1c before and during puberty and to disease duration; and how timing of menarche relates to mean HbA1c before puberty, BMI percentile, and disease duration.
Results: Age at puberty onset was positively correlated with mean HbA1c before puberty ($r = 0.204$, $R^2 = 0.042$; $P = .019$) and disease duration ($r = 0.451$, $R^2 = 0.203$; $P < .0001$), and negatively correlated with BMI percentile ($r = -0.289$, $R^2 = 0.084$; $P = .001$). Timing of menarche was negatively correlated with BMI percentile ($r = -0.556$, $R^2 = 0.310$; $P < .001$).
Conclusions: Children with longer disease duration began puberty later than those diagnosed more recently. Girls in higher BMI percentiles reached menarche sooner.
Key Words: Diabetes mellitus type 1, Puberty, Glycemic control, Menarche

Introduction

The fact that diabetic patients have late sexual maturation and higher timing of menarche, especially when the disease begins before puberty, has been known since 1950. Diabetics may have normal or low gonadotropin levels and low response to gonadotropin-releasing hormone (GnRH), indicating that they probably have a limited ability to maintain an adequate pituitary reserve. In girls that manifest the first symptoms of the disease after age 11 years (expected timing of menarche), menarche occurred much later than in nondiabetics, indicating a disorder in the hypothalamic-pituitary-gonadal (HPG) axis.[1]

Late pubertal development due to disease duration and degree of metabolic control has been described in diabetics. Studies done twenty years ago mention a puberty delay of roughly 12 to 16 months,[2,3] but studies published in the last 5 years reduce the delay to less than 6 months,[4,5] most likely because of the recent treatment advances, contributing to better disease control.[6]

A German study compared age at puberty onset and pubertal development between nondiabetics and diabetes mellitus type 1 (DM1) children and adolescents; and analyzed the effects of glycemic control, body mass index (BMI), disease duration, and insulin dosage and frequency on age of puberty onset and pubertal development, including menarche. The study concluded that high glycated hemoglobin and low BMI are associated with late puberty onset but not with late sexual maturity. On the other hand, high BMI reduced age at puberty onset, even more so on girls than on boys or both. Disease duration, insulin dosage, and treatment intensity did not affect pubertal development. The study also found that glycated hemoglobin (HbA1c) and diabetes duration were positively correlated with timing of menarche, that is, as HbA1c and disease duration increase, timing of menarche also increases. High serum levels of advanced glycation end (AGE) products may explain why high HbA1c delays menarche and puberty since AGE products may suppress the activation of gonadotropin-releasing hormone (GnRH). BMI and insulin dosage are negatively associated with timing of menarche: as BMI and insulin dosage increase, timing of menarche decreases, given that menarche requires a minimum amount of body fat.[7]

In the last century, timing of menarche tended to decrease. This trend was also seen in DM1 girls in the last 4 decades, but girls diagnosed before menarche still experience late menarche.[8]

Given the hypotheses of delayed sexual maturation and menarche in DM1 patients, the present study aimed to assess whether puberty onset, puberty duration, and timing of menarche are related to glycemic control, disease duration, and BMI in these patients.

The authors indicate no conflicts of interest.

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Population and Methodology

This retrospective study collected data from the medical records of patients seen at the diabetes outpatient clinic of Instituto de Puericultura e Pediatria Martagão Gesteira–IPPMG of the Federal University of Rio de Janeiro–UFRJ. The inclusion criteria were: diagnosed according to the American Diabetes Association (ADA)[9] criteria between age 1 year and puberty onset. The collected data were sex, birth date, date at symptom onset, which corresponds to age at diagnosis, date of each visit, and data collected at each visit, namely weight (noted in grams), height (noted in centimeters), Tanner stage,[10,11] HbA1c, and menarche date.

The following were calculated by Microsoft Excel XP: body mass index (BMI) by dividing the weight in kilograms by the square of the height in meters, diabetes duration, age at puberty onset, age at each puberty stage, puberty duration, timing of menarche, and mean prepubertal and pubertal HbA1c.

The patients visited the diabetes outpatient clinic at every 2 or 3 months. Data were collected over a period of 6 months between appointments or when the pubertal stage changed.

Age at Puberty Onset and at Each Puberty Stage

Age at puberty onset was defined by Tanner stage 2, characterized by testicular enlargement in boys and development of breasts in girls or development of pubic hair in both sexes. Age at each Tanner stage was calculated by subtracting the date of the visit where the pubertal development signs were seen from the birth date.

Timing of Menarche

Timing of menarche was given by the self-reported date of the first menstruation minus the birth date.

Puberty Duration

Puberty duration was given by subtracting the age at puberty onset from the age at Tanner stage 5.

Glycemic Control

The study followed the recommendations for target HbA1c based on the percentage beyond the upper normal limit for nondiabetics established in specific tests.[12] The reference range of 4.05%-6.05% proposed by the Diabetes Control and Complications Trial was used as a standard.[13] In prepubertal children, good glycemic control was given by an HbA1c level of up to 8%, and in pubertal children, by an HbA1c level below 8.5%.[14] Mean prepubertal HbA1c was given by calculating the mean of all HbA1c percentages collected between disease onset and puberty onset (Tanner stage 2), and mean pubertal HbA1c was given by calculating the mean of all HbA1c percentages collected between puberty onset and end of puberty (Tanner stage 5). The mathematical formula[12] is:

$$\frac{\text{Patient's AIC} \times 100}{\text{Maximum reference value of the method used}}$$

Chart 1 shows the indicators of glycemic control.

Nutritional Status

The software AnthroPlus version 10.4 calculated BMI percentile and z-score based on World Health Organization (WHO) data. Nutritional status was classified as recommended by WHO (2007)[15] as follows: obese when BMI ≥ 97th percentile; overweight when BMI ≥ 85th percentile; normal weight when 3rd percentile ≤ BMI < 85th percentile; and underweight when BMI < 3rd percentile.

Diabetes Duration

Diabetes was given by subtracting the age at diagnosis from the age at puberty onset.

Statistical Analysis

A database was created in Microsoft Excel XP and the data were analyzed by the statistical software XLSTAT-PLUS version 2012. The tests were chosen according to the distribution of the values found. The software Epi Info version 3.5.2 (2010) expressed the results as means, standard deviations, and minimum and maximum values. The significance level was set at 5% ($P < .05$). Pearson's correlation coefficient (r) and the coefficient of determination (R^2) were also calculated. Pearson's coefficient is analyzed in module and classified as follows: rxy = 0 (no association); 0 < rxy ≤ 0.3 (weak association); 0.3 < rxy ≤ 0.6 (moderate association); 0.6 < rxy ≤ 0.9 (strong association); and 0.9 < rxy ≤ 1 (maximum association). The results can be used for analytical treatment in the future.

Results

A total of 131 medical records of children, 61 (47%) girls and 70 (53%) boys, diagnosed with DM1 before puberty were analyzed. All these children presented pubertal development.

Another 55 children, 30 (55%) girls and 25 (45%) boys did not have pubertal development data registered in their medical records. Of these, 7 (23%) girls and ten (40%) boys were already in puberty, older than 8 and 9 years, respectively.

Age at DM1 Diagnosis

Girls' mean age at diagnosis was 6.57 ± 2.17 years; the minimum age was 1.29 years and the maximum, 10.74 years.

Chart 1
Indicators of Glycemic Control[12,13]

Control Levels	Ideal (Non-Diabetics)	Proper Prepubertal Control	Proper Pubertal Control
DCCT standard (%)	<6.05	Up to 8	<8.5
Percentage of the reference maximum	<100%	Up to 132%	<140%