

Development according to pubertal stage in Brazilian children and adolescents with short-term diabetes

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Abstract

The anthropometric status and metabolic control of 51 recently diagnosed Brazilian schoolchildren with type 1 diabetes (DM1), during the first 5 years of the disease, were compared with those of normal children (60 girls and 132 boys) belonging to the same environmental condition and pubertal stage. Metabolic control was evaluated on the basis of fasting plasma glucose (FPG) and HbA1c levels. The criteria of the National Center for Health Statistics were used for anthropometric evaluation. FPG (205 ± 51 mg/dl for girls vs 200 ± 34 mg/dl for boys) and % above upper normal limit of median HbA1c (1.8% for girls vs 2.5% for boys with diabetes) were not significantly different during follow-up. The Z-score of the last height evaluation was lower in the girls' group (-0.14 vs -0.53 , $P < 0.05$). By forward stepwise analysis, the Z-score of the initial height was statistically significant as a determinant factor for height at the end of the study in both girls and boys with DM1. The Z-score of weight at last evaluation was not different from that at diagnosis in either sex. However, analysis according to pubertal stage showed a tendency to a weight increase in the girls. The weight recovery and height loss in girls with DM1 follows the trend of the normal Brazilian population.

Key words

- Brazilian type 1 diabetes
- Growth and development
- Pubertal stage

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Introduction

Normal growth and development, in addition to the prevention of chronic diabetic complications, are the main goals in the management of children and adolescents with diabetes mellitus. Growth rate and development studies of these individuals are controversial (1-4). Some studies reported that chil-

dren at type 1 diabetes mellitus (DM1) diagnosis may present increased (2,5-7), normal (8,9) or low (1,10) height. These data suggest that clinically silent endocrine and metabolic alterations (7,10-12) can modify the growth and development of these patients before the first clinical signs of this disease are observed.

Studies performed in order to evaluate

the effect of insulin deficiency and metabolic control on the somatic and sexual development of diabetic children have considered mainly age, gender and presence or absence of pubertal signs (13,14). Besides the effect of metabolic control on the growth and development of diabetic children, environmental conditions and pubertal stage at diagnosis or in the first years of the disease could be significant factors to be considered. Thus, it is necessary to compare diabetic and normal children belonging to the same environment, growth stage and pubertal development. So the major problem in growth studies is the choice of adequate reference data. There is a lack of studies within this context in Latin American children. The aim of the present study was to examine the weight and height of Brazilian children and adolescents at DM1 diagnosis and after the first 5 years of conventional insulin therapy. We compared these patients to normal children belonging to the same environmental conditions and pubertal stage.

Subjects and Methods

Subjects

Fifty-one children and adolescents (24 girls: median age = 10.9 years and 27 boys: 10.6 years at different pubertal stages) with an early diagnosis (less than 6 months) of type 1 diabetes were recruited for this study, which was approved by the Institutional Ethics Committee of Hospital São Paulo, Escola Paulista de Medicina, UNIFESP, São Paulo, SP, Brazil. The diagnosis of type 1 diabetes was defined according to the criteria established by the National Diabetes Data Group (15). Exclusion criteria were the presence of any other abnormalities such as hormonal,

renal, respiratory, gastrointestinal or hematological diseases and pathologic short stature. The patients were evaluated at 3-month intervals from diagnosis to the end of the study.

These patients were compared with a group of 192 healthy schoolchildren regarding chronological age, gender and pubertal development using an equation for adjustment (see below).

Auxology and puberty

Anthropometric determinations were recorded on the occasion of each patient's consultation. The individuals were evaluated wearing minimal clothes and without shoes. Weight was obtained using a conventional scale with a precision of 100 g. Height was measured in the orthostatic position using a conventional anthropometer. Body mass index (BMI, kg/m²) was calculated as weight (kg) divided by square height (m²) (16).

The pubertal development stage was recorded by the same physician (F.V.T.) according to development of breasts (B) in girls and genitals (G) in boys according to the method of Marshall and Tanner (17,18). Breast development and menarche were recorded for girls and testicular volume was measured in boys using a Prader orchidometer. The beginning of breast development and the increase in testicular volume above 3 ml were taken as definite signs of pubertal onset.

The criteria of the National Center for Health Statistics (NCHS) (19) were followed for anthropometric evaluation. The weight and height 50th percentiles were the criteria used for the calculations of the respective Z-scores (19). The Z-score formula is:

$$Z\text{-score (*)} = \frac{\text{individual value} - \text{mean of reference standard for chronological age (CA)}}{\text{SD of populational reference standard for CA}}$$

(*): height or weight

The height (m), weight (kg), BMI (kg/m²) and the Tanner stages of these patients were recorded at the beginning and the end of a mixed longitudinal and cross-sectional study.

The patients were compared with a local sample (60 girls and 132 boys between the 5th and 95th percentile for height and weight) of the same socioeconomic level and their anthropometric evaluation was related to both chronological and bone age and known hormonal levels (estrogen for girls and testosterone for boys). From this sample, adjustment equations Y_H or $Y_W = A + B X$ were obtained, in which Y_H represents the height adjusted to chronological age and pubertal stage, Y_W represents the weight adjusted to age and pubertal stage, X represents the chronological age in years for each pubertal stage from B1 to B4 + B5 in girls and G1 to G5 in boys (20,21), and A and B are adjustment constants (Table 1).

Height was considered normal for age when above -1 Z-score.

Mild stunting was defined in children with height for age below -1.4 Z-score (equivalent to <93% of the median of the NCHS reference; 19), calculated using the ANTRHO program (20) but with normal weight for height (± 1 Z-score or 90-110%).

Assessment of glycemic control

The metabolic control of these patients

was measured by means of fasting plasma glucose (FPG, mg/dl) and glycohemoglobin (% HbA1c), evaluated during the study period. Twelve FPG and four HbA1c determinations were made for each patient. Fasting venous blood glucose samples were collected 8-12 h after the last meal and glucose levels were obtained by the glucose oxidase method (normal values ranging from 70 to 110 mg/dl). The HbA1c values above the upper normal limit (% AUNL HbA1c) were used as a comparative score in order to analyze the HbA1c values determined by each method. Therefore, % AUNL HbA1c = HbA1c values - upper normal limit of that specific method. The methods used to determine HbA1c levels were: affinity chromatography I (upper normal limit = 5.3%), affinity chromatography II (upper normal limit = 8.0%) and ion-exchange chromatography (upper normal limit = 8.5%).

Treatment

A mixture of intermediate (NPH) and rapid (regular) insulin was administered at least twice daily. Insulin dose was adjusted according to clinical and metabolic control parameters.

Statistical analysis

All data are reported as means \pm SD unless otherwise stated. Differences between

Table 1. Equations of height and weight adjustments to chronological age (years) at each sexual maturation stage of girls and boys of the present study.

	Girls (N = 60)		Boys (N = 132)		
	Height	Weight	Height	Weight	
B1:	$Y_H = 75.8 + 6.6 X$	$Y_W = 4.0 + 3.1 X$	G1:	$Y_H = 101.0 + 3.6 X$	$Y_W = 7.7 + 2.3 X$
B2:	$Y_H = 85.9 + 5.1 X$	$Y_W = 1.7 + 3.1 X$	G2:	$Y_H = 122.9 + 2.2 X$	$Y_W = 38.8 + 0.2 X$
B3:	$Y_H = 86.3 + 5.0 X$	$Y_W = 10.0 + 2.2 X$	G3:	$Y_H = 93.7 + 4.7 X$	$Y_W = 17.4 + 1.9 X$
B4 + B5:	$Y_H = 111.0 + 3.2 X$	$Y_W = 28.2 + 1.3 X$	G4:	$Y_H = 108.4 + 3.8 X$	$Y_W = 11.3 + 2.9 X$
			G5:	$Y_H = 123.6 + 3.0 X$	$Y_W = -1.8 + 3.9 X$

B1-B5 = breast; G1-G5 = genital development according to the Tanner scale. Y_H or Y_W = height or weight adjusted for age and pubertal age. X = chronological age in years.

groups were analyzed by the Mann-Whitney, Kruskal-Wallis or Wilcoxon rank-sum tests. Multiple stepwise regression analysis was used to identify factors exerting independent effects on final height, and Z-score using chronological age, pubertal stage, fasting plasma glucose, HbA1c and daily insulin dose as linear variables. Statistical significance was set at $P \leq 0.05$.

Results

Diabetic ketoacidosis was present at diagnosis in 12/24 (50.0%) girls and 11/27 (40.7%) boys. On that occasion, blood glucose was 502 ± 270 mg/dl (mean \pm SD) in the girls' group and 562 ± 189 mg/dl in the boys' group (not significant).

At the beginning of the study no significant differences were found between girls and boys regarding any of the parameters analyzed (chronological age, prepubertal stage percentage, period after diagnosis, height and weight Z-scores, Y-control for both height and weight, or BMI), as shown in

Table 2.

At diagnosis, girls were between the 5th and 95th percentile regarding weight and between the 2.5th and 95th percentile regarding height, according to NCHS standards. Among the boys, three (11%) were in the prepubertal stage. These three patients were below the 5th percentile regarding weight and one of them also presented mild stunting characteristics.

When the diabetic children were compared with pubertal controls, both girls and boys were distributed equally around the Y-parameter regarding height (Figure 1A (initial) and B (final) for girls and Figure 2A and B initial and final, respectively, for boys) and weight. The Z-scores of these measurements were not significantly different among the groups studied at the beginning of the survey (Figure 3).

At the final evaluation, the duration of diabetes was similar for girls (3.5 ± 1.4 years) and boys (3.9 ± 1.2 years). BMI (girls: 20 ± 3.0 kg/m² vs boys: 18.6 ± 2.3 kg/m²), FPG (girls: 205 ± 34 mg/dl, N = 11 samples,

Table 2. Clinical characteristics of children with type 1 diabetes mellitus at diagnosis and at the end of follow-up.

	Girls (N = 24)		Boys (N = 27)	
	Initial	Final	Initial	Final
Age (median [range], years)	11 [5.4-15.6]	14.4 [7.8-16.8]	10.6 [5.7-13.9]	13.8 [8.4-17.8]
Prepubertal, N (%)	10 (41.7)	4 (16.7)	19 (70.3)	7 (25)
Time from diagnosis [#]	27 \pm 47 days	3.5 \pm 1.4 years	67 \pm 71 days	4.0 \pm 1.1 years
Height (cm) [#]	137.5 \pm 15.9	150.4 \pm 12.7	137 \pm 15.4	155.3 \pm 16.0
Z-score	-0.14	-0.53*	-0.29	-0.48
Y-control for height				
Above, N (%)	10 (42.0)	7 (29.2)	7 (25.9)	8 (29.6)
Equal, N (%)	6 (25.0)	3 (12.5)	4 (14.8)	5 (18.5)
Below, N (%)	8 (33.3)	14 (58.3)	16 (59.3)	14 (51.8)
Weight (kg) [#]	32 \pm 12	45.8 \pm 13.5	32 \pm 9.6	46.1 \pm 14.1
Z-score	-0.03	-0.02	-0.21	-0.34
Y-control for weight				
Above, N (%)	9 (37.5)	14 (58.2)	8 (29.6)	7 (25.9)
Equal, N (%)	2 (8.3)	3 (12.3)	1 (3.7)	0
Below, N (%)	13 (54.2)	7 (29.2)	18 (66.7)	20 (74.1)
BMI (kg/m ²) [#]	17 \pm 3	20 \pm 3	16 \pm 2	18 \pm 2

[#]Data are reported as means \pm SD. N (%) = number (percentage).

* $P < 0.05$ compared to the initial value (Mann-Whitney test).

vs boys: 200 ± 51 mg/dl, $N = 12$ samples), HbA1c (% AUNL) (girls: $1.8 \pm 1.3\%$, $N = 4$ samples, vs boys: $2.5 \pm 1.6\%$, $N = 3$ samples), and insulin dose ($\text{U kg}^{-1} \text{ day}^{-1}$) (girls: 0.88 ± 0.27 vs boys: 0.80 ± 0.24) were also similar. These parameters were not statistically different between girls and boys.

Concerning girls' weight at final evaluation, two (8.3%) of them were below the 5th percentile and none was obese according to NCHS standards. However, 14 girls (58.2%) were overweight when compared with the pubertal control group. In relation to NCHS, height was impaired in 16 (66.7%) girls and 14 (58.2%) were below the respective pubertal Z-score control at the final evaluation (Figure 3).

Twenty boys (74.1%) presented weight below the respective pubertal control at final evaluation. Regarding boys' height, seven (26%) who were G1 or G2 at diagnosis, evolved to below or equal to the 5th percentile. A comparison of diabetic boys with their pubertal control group showed that 14 (51.8%) were below the respective Y-height parameter at final evaluation.

The daily insulin dose did not show a correlation with BMI in either gender during treatment. Among prepubertal girls and boys at diagnosis, 6/10 (60%) and 8/19 (42%) evolved to Tanner's stage II at the chronological age of 10.6 ± 1.2 years and 12.3 ± 1.3 years, respectively. Menarche occurred at age of 13 ± 0.7 years in eight girls.

Multiple stepwise regression analysis was used to identify factors exerting independent effects on height at final evaluation: chronological age, pubertal stage, initial (height, weight and BMI) and final (weight) anthropometric measurements, and metabolic parameter.

HbA1c measured during follow-up and daily dose of insulin were considered independent variables, whereas final height and Z-score of the final height were considered dependent variables. These analyses were performed in the total group (51 diabetic

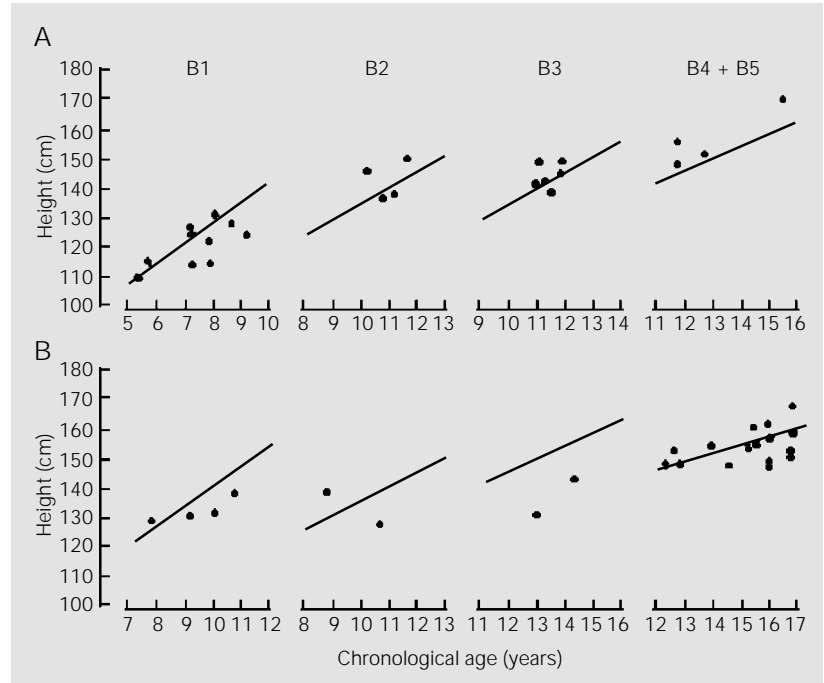


Figure 1. Height in relation to age and pubertal stage (Tanner's classification; B1 to B4 + B5) at diagnosis (A) and at final evaluation (B) in type 1 diabetic girls. B1-B5: breast development.

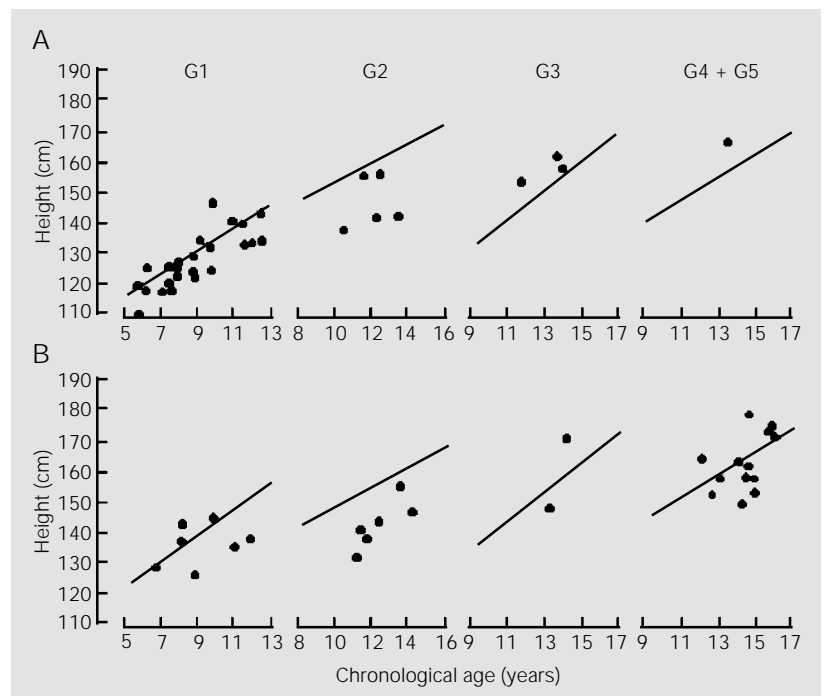


Figure 2. Height in relation to age and pubertal stage (Tanner's classification; G1 to G4 + G5) at diagnosis (A) and at final evaluation (B) in type 1 diabetic boys. G1-G5: genital development.

children) and in the gender subgroups (24 girls and 27 boys) separately. In the whole group the final height could be predicted by the combination of chronological age (initial and final) and initial height. In the girls' group the final height could be predicted by initial height and final pubertal stage. Height of diabetic boys at final evaluation could be predicted by initial chronological age and height and by pubertal stage (initial and final). These analyses showed that the Z-score of initial height is a factor that may affect final height in the whole diabetic group and also the girls' and boys' subgroups.

Discussion

In this study, the development and growth of diabetic children during approximately the first 5 years of disease were evaluated and compared with normal individuals matched to each pubertal stage. Weight and height were studied by a Y-parameter defined across the slope of the straight line (Table 1). This parameter varies according to age for each breast development stage for girls (17) and genital stage for boys (18). By comparing the diabetic group with pubertal control groups it was possible to evaluate the anthropometric development characteristics and to correct age and stage of sexual devel-

opment at each time investigated.

The height standard deviation score was lower than zero (the normal population median) in our diabetic patients at diagnosis. This finding agrees with those reported by Emerson and Savage (9) and partially confirms the data of Hauane (22) and Hoskins et al. (1). When the present data were corrected for pubertal stage and age a uniform distribution around the Y-parameter was found for female (Figure 1A) and male (Figure 2A) diabetic patients, indicating that puberty evolved as expected.

Signs of mild stunting and low stature were already present at the first evaluation in 11% of the boys' group, when most of them were prepubertal (G1) or early pubertal (G2). Bognetti et al. (7), studying a group of diabetics younger than ours, found that, at onset of diabetes, they were taller for their age and sex compared to nondiabetic subjects.

It is known that the male adult Brazilian population is approximately 7 cm shorter than the NCHS standard (23). According to the analysis of these data of the National Food and Nutritional Institute, Brasília, DF, Brazil, this final height loss is due to a gradual process starting during the second year of life and becoming more evident from 10 to 15 years of age, which in this stage coincides with the age of the male patients in stages G1 and G2 of pubertal development at DM1 diagnosis. Since most (70.3%) of the DM1 boys were prepubertal at diagnosis with a median age of 10.6 years (range: 5.7 to 13.9 years), it is possible that these conditions increased the effect of negative determinants for height at first evaluation. One of these determinants in DM1 patients may be the preclinic metabolic alteration potentiating the effects of irregular nutrition on growth rate.

The Z-score of NCHS weight at diabetes diagnosis was negative, but close to zero, for both genders, corresponding to what was found in another study (7). This weight corrected for age and pubertal stage was below

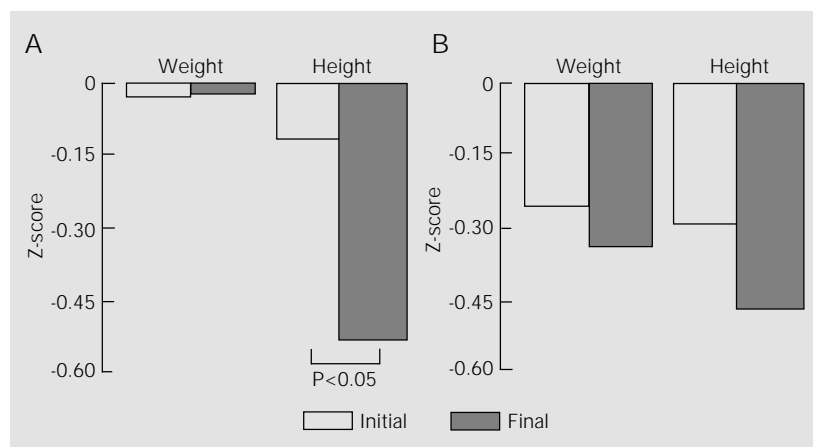


Figure 3. Weight and height Z-score at diagnosis and at final evaluation in type 1 diabetic girls (A) and boys (B).

normal in most children. This is probably a result of relative insulinopenic periods which precede the diagnosis of diabetes (24).

When FPG and HbA1c levels above normal and exogenous insulin ($\text{U kg}^{-1} \text{ day}^{-1}$) were compared during follow-up, no statistically significant differences regarding sex or pubertal stage were found. It is known that there is a 40-50% increase in insulin requirements during puberty. In general, the total daily insulin dose for these patients is approximately 1 to 1.5 U/kg body weight. We can observe that both in the boys' ($0.80 \pm 0.24 \text{ U kg}^{-1} \text{ day}^{-1}$) and girls' ($0.88 \pm 0.27 \text{ U kg}^{-1} \text{ day}^{-1}$) groups, the insulin dose was almost a half that amount. Boggetti et al. (7) used a lower insulin dose ($0.69 \pm 0.22 \text{ U kg}^{-1} \text{ day}^{-1}$) for their late pubertal patients than that used in our study. They also found a linear growth decrease during the first years of the disease. Therefore, this can be one of the factors which contribute to reducing height recovery in both diabetic girls and boys. Zachrisson et al. (25) have shown the importance of sufficient exogenous insulin supplement during the period of rapid linear growth in diabetic children (26).

Danne et al. (27) have shown that even modest alterations in metabolic control can lead to a lower final height in patients with diabetes. In the present study with HbA1c around 1.8 to 2.5% above normal levels, no height recovery was observed in boys or girls during follow-up.

It is known that final height also reflects nutritional status and consequently the socioeconomic conditions of our country (23). The effects of these factors are different regarding sex as reported by large population (23) and local (28,29) studies. These studies also show the importance of a special treatment of anthropometric data according to sex. Although children of both genders were equally distributed around the respective Y-parameter for weight and height in the follow-up, these parameters presented some peculiarities in diabetic girls. In the final

evaluation, the weight of these girls was equally distributed around the 50th NCHS percentile, but when adjusted to pubertal stage, 58.2% of the girls were overweight (Table 2).

The weight gain in diabetic girls, particularly at the end of puberty, may impair somewhat compliance with treatment because there is the tendency to relegate it in an attempt to slim (4). Concerning the absence of a correlation between daily insulin dose and weight, alterations in the eating habits and individual changes in physical activities are not sufficient to explain overweight in girls (30,31). Veiga and Sigulen (28), in Brazil, observed an increase in the prevalence of obesity in female adolescents of low socioeconomic level and emphasized the importance of correcting weight for height in the nutritional evaluation. This observation, taking into account weight adjustment for age corrected by the Y-parameter for pubertal stage, was also sensitive in detecting overweight in DM1 girls.

The diabetic girls evolved with significant stature impairment as indicated by the behavior of the respective Z-scores (Figure 3). The impaired final stature of diabetic children has been reported since the classical study by Tatterssal and Pyke (32) on identical twins. Clarke et al. (33), evaluating children according to pubertal development, demonstrated a higher vulnerability to metabolic disorders resulting from hyperglycemia in the prepubertal stage. However, this was not observed in our patients during the study period, with the same level of metabolic control in the prepubertal (girls: HbA1c (% AUNL): 2.05 ± 1.29 , boys: 2.67 ± 1.76) and pubertal (girls: 1.79 ± 1.37 , boys: 2.50 ± 1.61) stage as demonstrated by the HbA1c values.

Since all girls evolved to pubertal stages (Figure 1A and B) and had their menarche at the expected ages (23), precocious puberty can be excluded as being responsible for stature impairment. Eighteen girls reached

advanced stages (B3, B4 + B5) of sexual development during the observation period, and 11 (61%) of them were below the pubertal control regarding height, suggesting reduction of the growth spurt. Although weight calls less attention than stature, regarding the effect of DM1 on child development, there are reports of a tendency to obesity among diabetic girls during puberty (10,34). Alerted by the frequency of overweight in girls, we may assume that inadequate metabolic control, associated or not with former malnutrition, led to growth deficit and weight recoveries above those corresponding to their pubertal stage, similar to the nutritional recovery already studied in girls attending public schools (29).

Finally, multiple stepwise regression analysis showed that Z-score of the initial height is a more important factor for height after 4 to 5 years of follow-up both in the diabetic group as a whole and in the subgroups of girls and boys with diabetes.

In view of the impossibility to study the genetic potential for growth in the present patients, and considering the nutritional status and socioeconomic conditions of the Brazilian low-income population in general (23),

we may assume that onset of DM1 during early pubertal stages in the boys was an additional factor of growth failure.

In conclusion, at diagnosis of the disease, Brazilian children and adolescents with DM1 have a lower but not significantly different weight and height when compared to non-diabetic subjects matched for age and pubertal stage and environmental conditions. In the first 4-5 years of disease girls tended to recover weight and showed a linear growth decrease. Boys evolved with low weight and did not reach a positive Z-score regarding height. Girls and boys with DM1 presented normal pubertal development. The age, height and pubertal stage when diabetes is diagnosed may have a positive effect on height development. The tendency to weight recovery and low height in diabetic girls follows the tendency of the normal Brazilian population.

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