

Longitudinal Data on Growth and Final Height in Diabetic Children

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ABSTRACT

The available data on growth in children with insulin-dependent diabetes mellitus are conflicting and are mainly derived from cross-sectional studies. In this longitudinal study, height, weight, skeletal age, and pubertal development were recorded until final height was attained in 46 children (22 girls and 24 boys) with onset of diabetes before the age of 10 y. At the onset of diabetes, height SD score (SDS) averaged 0.41 in girls and 0.56 in boys, which was normal when corrected for the secular trend. Prepubertal growth was unaffected in both sexes. Diabetic boys had a marked delay in onset of puberty (mean age at genitalia stage 2: 13.7 y) but attained a normal final height (final height SDS: 0.48 ± 0.89). In girls final height was slightly reduced (height SDS 0.27 ± 0.97) due to a suboptimal pubertal growth spurt. Mean pubertal height gain in girls was 16.6 cm and

mean age at breast stage 2 was 11.6 y. Diabetic girls also tended to become obese during puberty. Skeletal maturation was normal at all ages. These data suggest that conventional therapy does not guarantee optimal growth, especially in girls. (*Pediatr Res* 38: 607-611, 1995)

Abbreviations

SDS, SD score
BMI, body mass index
TPHG, total pubertal height gain
HbA_{1c}, hemoglobin A_{1c}
B₂, breast stage 2
G₂, genitalia stage 2

Impaired growth, obesity, and delayed puberty have been described in children with very poorly controlled diabetes such as the Mauriac syndrome. The introduction of improved insulin preparations and home blood glucose monitoring has resulted in a much better metabolic control. The question whether diabetes, well treated with conventional means, still compromises the growth of diabetic children, remains controversial. Many studies claim that longitudinal growth is impaired in diabetic children (1-7). Some investigators have observed catch-up growth in poorly controlled diabetic children after a better degree of control had been achieved (8-10). Other authors claim that growth remains impaired, irrespective of the degree of metabolic control (1, 2, 11). Their pessimistic view is supported by data from identical twins in whom one twin developed diabetes before puberty. Compared with the normal twin, growth impairment persisted even with adequate therapy (3). In contrast, several other studies have shown that children in good metabolic control have a growth pattern which is identical to that in control children (8, 9, 12, 13).

There also remains controversy about which growth phase is impaired in diabetic children. In some children with early onset of diabetes prepubertal growth was claimed to be blunted (11,

14). In other studies, the reduction in height has largely been attributed to a delayed and/or blunted pubertal growth spurt (2, 3, 7, 11).

We therefore analyzed in a longitudinal study growth and pubertal development in a group of 46 diabetic children who were followed up until final height was attained. Childhood growth was evaluated in an additional cohort of 27 diabetic children followed longitudinally until the age of 10 y.

METHODS

Growth and development were analyzed longitudinally in two cohorts of patients with insulin-dependent diabetes mellitus. The first cohort consisted of 46 children (22 girls and 24 boys) who were followed from an age below 10 y until final height. Early prepubertal growth was recorded for at least 3 y in a second cohort of 27 children (11 girls, 16 boys) in whom diabetes started before the age of 7. Exclusion criteria were non-Caucasian origin, other endocrine disorders, chromosomal aberrations, and enteropathies. Standard guidelines for treatment were provided to all patients. All children were treated with conventional insulin therapy consisting of two daily injections of a combination of long-acting and short-acting insulin. The insulin dosage was adjusted to prevent glucosuria and hyperglycemia. Metabolic control of diabetes was assessed by the level of HbA_{1c}, which was determined by ion-exchange

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column chromatography with reference range of 4.2–5.7% in nondiabetic children.

Standing height was measured at least every 6 mo by the same investigator using a fixed Harpenden stadiometer. Growth data were analyzed after transformation into SDS according to Tanner *et al.* (15). Target height was calculated using the equation devised by Tanner and corrected for the secular trend: for boys: (father's height + mother's height + 13 cm)/2 + 2.5 cm; for girls: (father's height + mother's height - 13 cm)/2 + 2.5 cm. Pubertal development was rated according to Marshall and Tanner (16, 17). The onset of puberty was defined as the appearance of a testicular volume of 4 mL or more (G_2) in boys and budding stage (B_2) in girls. TPHG was calculated by subtracting the height at onset of puberty from the final height. Final height was defined as a height increment of less than 1 cm over the last year. BMI was calculated by dividing weight in kilograms by the square of the height in meters. BMI-SDS was calculated using the reference values published by Rolland-Cachera *et al.* (18). Skeletal age was assessed by the method of Greulich and Pyle (19) and predicted adult height was estimated by the method of Bayley and Pinneau (see Ref. 19).

Statistical analysis was performed using the Wilcoxon matched pairs signed rank test. Differences were determined by two-tailed tests and were considered to be significant at the $p < 0.05$ level. The results were expressed as mean \pm SD.

RESULTS

Table 1 summarizes the auxologic data from cohort 1. Mean height SDS at the onset of diabetes was 0.41 ± 0.99 in girls and 0.56 ± 0.68 in boys. Mean final height SDS was lower than the height SDS at onset (0.27 ± 0.97 in girls and 0.48 ± 0.89 in boys). Comparison of the height SDS at onset with the height SDS at final height for each individual did not show a significant difference ($p = 0.33$ for girls; $p = 0.36$ for boys). Final height was significantly lower than the target height in girls (163.7 ± 5.9 cm and 167.1 ± 5.0 cm, respectively; $p < 0.05$). In contrast, the boys attained a final height comparable to their target height (177.1 ± 6.1 cm and 178.1 ± 6.0 cm, respectively). The individual differences between final height SDS and height SDS at diagnosis were not correlated with the duration of diabetes.

Prepubertal growth until the age of 10 y was little affected, because the height SDS at 10 y was not different from the height SDS at onset. This finding was corroborated by the analysis of the growth parameters in a separate cohort (cohort

2) of young children in whom height SDS at the age of 7 y was not significantly different from the height SDS at the age of 10 y (data not shown).

The evolution of height SDS from the age of 10 onward was different in boys compared with girls (Fig. 1). During the last 2 y of prepubertal growth, height SDS decreased significantly in boys. Mean height SDS in boys at G_2 was -0.17 ± 1.13 ($p < 0.001$ when compared with height SDS at onset and height SDS at final height) and in girls at B_2 0.15 ± 1.25 (NS when compared with height SDS at onset or final height). Once puberty had started, height SDS returned to values attained at final height within 2 y.

The decline in height SDS is explained by the delay in onset of puberty which is more pronounced in boys than in girls. Figure 2 compares the cumulative distribution curve for the age of attaining B_2/G_2 in our patients with the reference data collected by Largo and Prader (20, 21). In diabetic boys, the mean age for attaining G_2 was 13.7 ± 1.1 y as opposed to 11.2 ± 1.5 y in control boys. This finding was not explainable by a constitutional delay in puberty. In only 4 out of the 24 boys, one of the parents had a history of delayed puberty. After exclusion of these 4 boys, the mean age for attaining G_2 was still 13.5 ± 1.1 y. On the other hand, the mean age for attaining B_2 was 11.6 ± 1.0 y in this study compared with 10.9 y in the

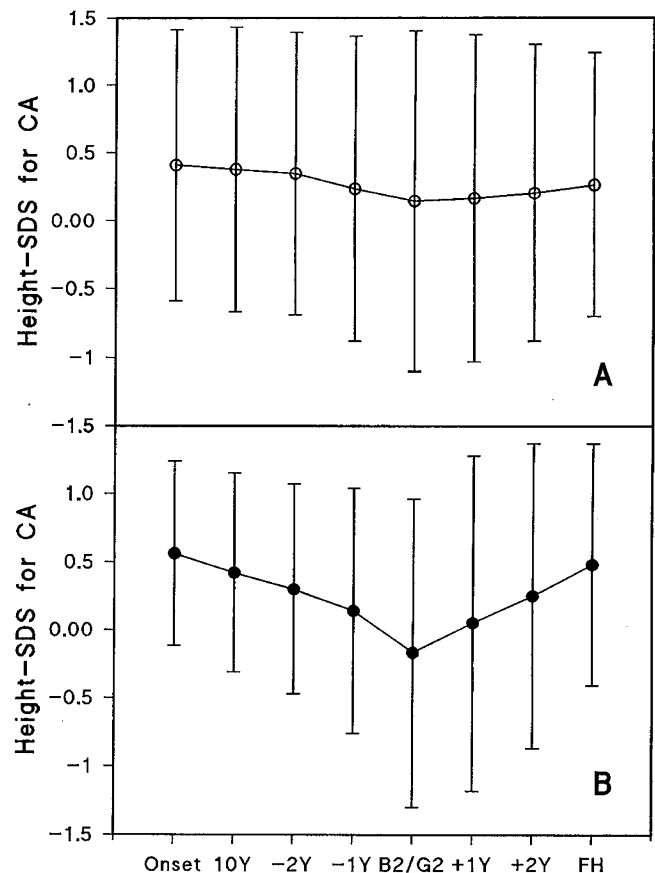


Figure 1. Evolution of the height SDS for chronologic age (mean \pm SD) in 22 girls (A) and 24 boys (B) followed longitudinally from onset of diabetes to final height. Height SDS was calculated at onset of diabetes, at the age of 10 y, at the age of onset of puberty (B_2/G_2), 1 and 2 y before and after B_2/G_2 and at final height

Table 1. Growth data in children with diabetes (mean \pm SD)

	Girls (n = 22)	Boys (n = 24)
Age at onset diabetes, y	7.5 \pm 2.6	7.4 \pm 3.0
Age at onset puberty, y	11.6 \pm 1.0	13.7 \pm 1.1
Age at menarche, y	13.6 \pm 1.0	
Height SDS at onset diabetes	0.41 \pm 0.99	0.56 \pm 0.68
Height SDS at the age of 10 y	0.38 \pm 1.05	0.42 \pm 0.73
Height SDS at onset puberty	0.15 \pm 1.25	-0.17 \pm 1.13
Height SDS at final height	0.27 \pm 0.97	0.48 \pm 0.89
TPHG, cm	16.5 \pm 3.6	19.9 \pm 4.2

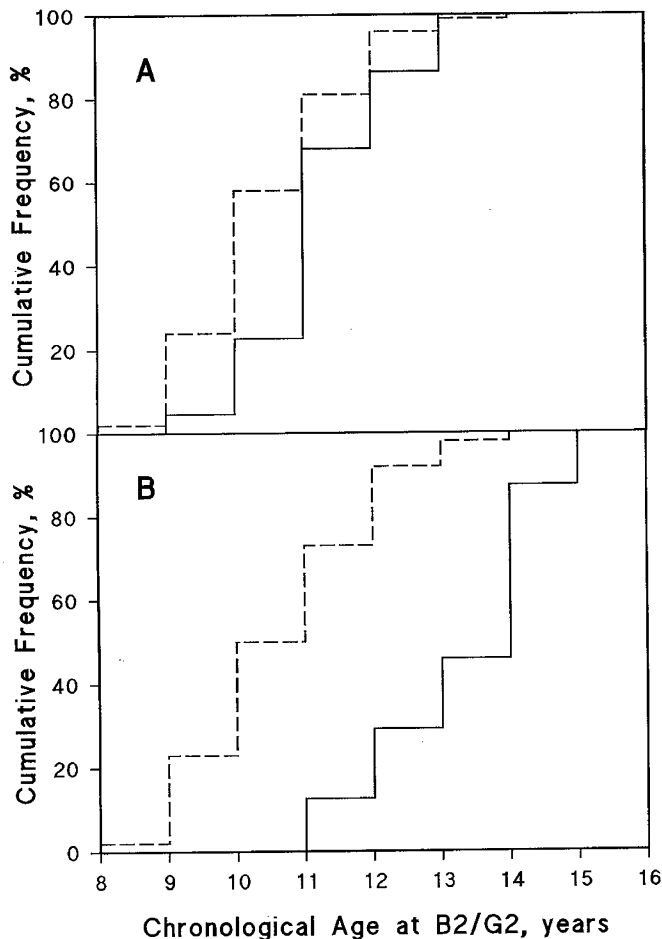


Figure 2. Cumulative frequency data of chronologic age at the onset of puberty (B_2/G_2) in girls (A) and boys (B). The solid lines represent the data in diabetic children, the broken lines represent the data in normal children published by Largo and Prader (20, 21).

controls. Only 2 girls had a family history of pubertal delay. The mean age at menarche (13.6 ± 1.0 y) was comparable with the reference data.

No relation was found between the age at onset of diabetes and the chronologic or skeletal age at G_2/B_2 in both sexes. In boys, a positive correlation between the age at onset of puberty and the mean insulin dosage during the preceding 2 y was observed ($r = 0.56$; $p < 0.005$).

The metabolic control of diabetes assessed by HbA_{1c} levels and the daily insulin dosage before and after the onset of puberty are shown in Table 2. HbA_{1c} levels were usually higher in boys than in girls but did not vary widely during

puberty. The dosage of insulin/kg body weight increased with the onset of puberty in both sexes.

TPHG averaged 16.5 ± 3.6 cm in girls and 19.9 ± 4.2 cm in boys and was negatively correlated with the chronologic age at the onset of puberty (Fig. 3). Multiple regression analysis indicated that TPHG in girls was mainly dependent on the age at onset of puberty, which accounted for 22% of the variability ($p < 0.05$). TPHG was not influenced by the mean HbA_{1c} value, the mean insulin dosage, and the increment in BMI during puberty, nor by duration of diabetes before the onset of puberty. In boys, TPHG was dependent on the age at onset of puberty and to a lesser extent on the insulin dosage. Together they accounted for 43% of the variability ($p < 0.005$). The other factors did not influence TPHG.

Girls tended to gain excessively in weight during their pubertal height spurt. Their BMI-SDS increased from an average of 0.26 ± 0.98 at B_2 to 0.69 ± 0.97 at attaining final height. Finally, skeletal age was comparable to chronologic age at 10 y and at B_2/G_2 (Table 3). The mean difference between final height and predicted adult height at the age of 10 y was 1.2 ± 3.4 cm in girls and -0.3 ± 4.4 cm in boys. At the time of onset of puberty, the difference averaged 0.9 ± 2.7 cm in girls and -1.2 ± 5.0 cm in boys. At the age of menarche, final height minus predicted adult height had a mean of -1.7 ± 1.8 cm.

DISCUSSION

Because of the lack of appropriate longitudinal growth charts in Belgium we used the reference data for height published by Tanner *et al.* (15) in 1966. Since the publication of this report, a significant secular trend in height has been observed. In the Dutch surveys of 1965 and 1990, the height of children younger than 10 y differed by an average of 1.4 cm (22). Within our own population the mean height for normal 18-y-old boys in 1990 was 177.5 cm, which was 2.8 cm higher than the average of the Tanner growth standards. Consequently, the apparent increased stature at the onset of diabetes and at adult age can be attributed to the secular trend. Our data therefore do not support the notion from the literature that diabetic children are taller (5, 7, 14, 23–25) or smaller (26, 27) than average at the onset of their disease, but corroborate earlier reports (2–4) of normal height in newly diagnosed diabetic children.

In both female and male subjects, final height SDS was slightly reduced but not statistically different from the height SDS at onset of diabetes. However, large differences ranging from +2.4 to -2.0 SDS were observed among patients. This

Table 2. HbA_{1c} levels and daily insulin dosage during the prepubertal and pubertal period (mean \pm SD)

Interval with stage B_2/G_2	-2 y	-1 y	0 y	+1 y	+2 y	Final height
HbA_{1c} (%)						
Girls	9.1 ± 2.4	8.9 ± 1.9	8.8 ± 2.6	8.6 ± 1.6	8.9 ± 1.4	9.1 ± 1.8
Boys	9.0 ± 1.6	9.7 ± 1.2	10.1 ± 2.1	9.8 ± 1.8	10.1 ± 1.8	9.8 ± 1.9
Insulin U/kg/d						
Girls	0.85 ± 0.24	0.79 ± 0.27	0.90 ± 0.22	1.03 ± 0.29	1.07 ± 0.23	0.99 ± 0.31
Boys	0.76 ± 0.21	0.81 ± 0.19	0.94 ± 0.23	0.95 ± 0.18	0.99 ± 0.18	0.98 ± 0.19

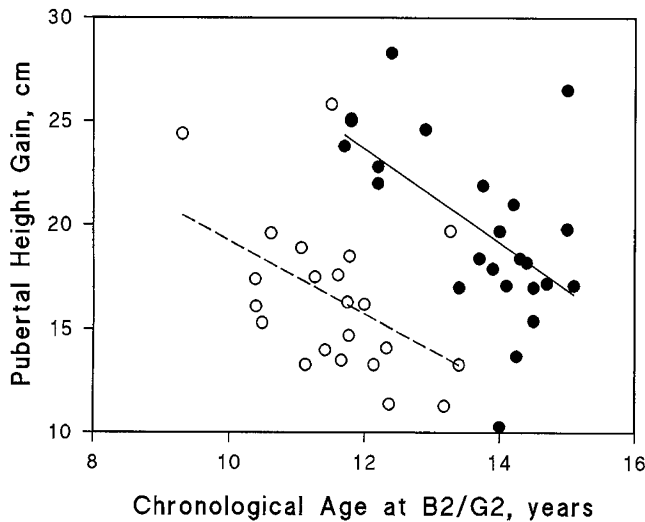


Figure 3. Relationship between TPHG and chronologic age at onset of puberty (B_2/G_2) in diabetic girls (open circles; $r = -0.47$; $p < 0.05$) and boys (closed circles; $r = -0.57$; $p < 0.05$)

Table 3. Skeletal age and height prediction at different ages in children with diabetes (mean \pm SD)

	Girls ($n = 22$)	Boys ($n = 24$)
Skeletal age at age 10, y	10.0 \pm 0.8	10.1 \pm 0.9
Skeletal age at onset puberty, y	11.2 \pm 0.7	13.2 \pm 0.7
Skeletal age at menarche, y	13.3 \pm 0.5	
FH minus PAH at age 10 y, cm	1.2 \pm 3.4	-0.3 \pm 4.4
FH minus PAH at onset puberty, cm	0.9 \pm 2.6	-1.2 \pm 5.0*
FH minus PAH at menarche, cm	-1.7 \pm 1.8	

FH = final height; PAH: predicted adult height; * $n = 19$.

variability was not related to the duration of the disease. Only a few data on final height in diabetic patients were published in the literature. Tattersall and Pyke (3) showed that final height in patients with diabetes diagnosed before puberty, was 5 cm smaller than the height of their unaffected twin. In longitudinal studies Salardi *et al.* (7) and Dunger and Brown (11) reported a small significant reduction in final height in children with early onset diabetes. In contrast, Jackson (8) found a normal adult height in patients with metabolically well controlled diabetes. Some authors have suggested that this height loss occurs in the prepubertal growth phase (3, 11, 14). In our patients there was no loss of growth before the age of 10 y in both cohorts. Height SDS was markedly reduced at the onset of puberty, especially in boys. In girls stage B_2 was attained on average 1 y later than in the control group reported by Largo and Prader (20, 21). Boys had a delayed onset of puberty reaching stage G_2 almost 3 y later than controls. This marked delay caused a steep decline in height SDS during the last prepubertal years and may explain the prepubertal height loss reported in previous studies. Delayed puberty in boys was also reported by Jivani and Rayner (2). In contrast, Salardi *et al.* (7) found a mean age at stage G_2 of 11.3 y and Clarkson *et al.* (13) reported a mean age of 11.9 y. The mean age at stage B_2 of 11.6 y in our study was consistent with the data reported by Clarkson *et al.* (13). The mean age at menarche (13.7 y) was intermediate between the values reported by Clarkson and those reported by Kjaer *et al.* (28).

Growth during puberty was calculated as TPHG as recommended by Bourguignon (29). TPHG averaged 16.5 cm in diabetic girls and 19.9 cm in diabetic boys and progressively decreased with the age at onset of puberty. There are, however, no reference data for TPHG as a function of chronologic age at onset of puberty. Tanner *et al.* (15) calculated an average TPHG of 25 cm in girls and 28 cm in boys. Based on these data we assume that TPHG in diabetic girls was clearly insufficient. In boys, TPHG had to be corrected for their pubertal delay. If we extrapolated the regression line between TPHG and age at onset of puberty (Fig. 3) to the age of 11.2 y (which is the mean age at onset of puberty in normal subjects) TPHG practically equaled the normal range. In both diabetic girls and boys, no relationship was observed between TPHG and their relatively, impaired metabolic control. These results are in agreement with the findings of Salardi *et al.* (7) who reported a mean TPHG of 14.9 cm in diabetic girls and a mean of 28.7 cm in boys in the presence of a wide range of HbA_{1c} levels. A blunted pubertal growth spurt in girls was also reported by Vanelli *et al.* (30). The reduction in TPHG in girls probably explains why the diabetic girls in our study did not reach their target height.

The factor which influenced TPHG, as demonstrated by multiple regression analysis, was the age at onset of puberty in both sexes. In boys the insulin dosage was the second influencing factor.

Most girls gained more weight than height during puberty. Even when corrected for the normal increase in BMI during puberty, most of our diabetic girls displayed a tendency toward obesity. This association of overweight and height reduction was also described by other investigators (4, 6). Our data on skeletal maturation confirm previous reports that demonstrated a normal skeletal age for age in diabetic children (4, 7, 12).

In conclusion, the results of this longitudinal analysis showed that linear growth in diabetic girls was slightly reduced due to a blunted pubertal growth spurt. Diabetic girls also had a tendency to become obese during puberty. Boys with diabetes had a marked delay in the onset of puberty but attained a normal final height. Our data on metabolic control did not demonstrate any correlation with TPHG. However, the range of HbA_{1c} levels within this population might be too narrow to definitively exclude the possibility that a better metabolic control obtained by intensive insulin therapy can improve final height.

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