Pubertal Growth, Sexual Maturation, and Final Height in Children With IDDM

Effects of age at onset and metabolic control

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OBJECTIVE — To evaluate growth and pubertal development in children with IDDM and the influence of the age at onset of IDDM and the degree of metabolic control on final height.

RESEARCH DESIGN AND METHODS — We conducted a retrospective evaluation of 62 subjects followed longitudinally both clinically and metabolically from the onset of IDDM until final height was reached.

RESULTS — Height at diagnosis was within the normal percentiles in boys (0.5 ± 1.0 standard deviation score [SDS]) and girls (0.4 ± 1.0 SDS), but above the genetic target height (−1.0 ± 0.9 SDS in boys and −1.1 ± 0.6 SDS in girls; $P = 0.0001$ for both comparisons). Although a lesser height gain was observed during the ensuing years, the final height reached by boys (−0.4 ± 1.1 SDS) and girls (−0.4 ± 0.9 SDS) was higher than the genetic target height. Blunted total pubertal growth was observed both in boys (24.5 ± 3.6 cm) and girls (20.1 ± 4.2 cm). The decrease in height gain was independent of the duration of IDDM, the degree of metabolic control, or the insulin requirement. The greater the height at diagnosis, with respect to the genetic target height, the lesser was the subsequent height gain to reach final adult height ($r = 0.34$, $P < 0.01$). BMI increased with age as normally occurs in healthy children, independent of the duration of disease and the degree of metabolic control. Pubertal development began and progressed normally both in boys and girls. In boys, a testicular volume of 4 ml was reached at a mean age of 12.1 ± 0.9 years. In girls, breast enlargement occurred at a mean age of 10.4 ± 1.2 years and the mean age of menarche was 12.8 ± 1.4 years. Pubertal development and progression occurred independent of the age at onset of IDDM, the glycemic control, or the insulin requirement during the pubertal period.

CONCLUSIONS — Children with IDDM have normal onset of puberty and normal sexual maturation. Even though final height falls within the normal percentiles, the diminished height gain after diagnosis requires further investigation.

Impaired longitudinal growth and pubertal delay were common complications in children with uncontrolled diabetes (1). With the improvement in therapeutic regimen, regular diet, and physical activity, normal growth should be expected in children with IDDM. However, data on growth and pubertal development still remain controversial (2–5), and above all it is unclear whether the degree of metabolic control or the duration of the disease affect sexual development and final height (3,6–8). Although the literature is replete with descriptions of height at diagnosis, there are still few data regarding longitudinal growth to final height of children with diabetes.

The aim of this study, therefore, was *1*) to review pubertal growth and sexual maturation in 62 patients with IDDM followed longitudinally to final height and 2) to evaluate the influence of the age at clinical onset of IDDM and the degree of metabolic control both on pubertal development and final height.

RESEARCH DESIGN AND METHODS

The study population consists of 62 children (32 boys and 30 girls) followed longitudinally in our department from the onset of IDDM (range, 0.8–12.7 years) to the attainment of adult height. Subjects with additional problems that could affect growth (i.e., thyroid or celiac disease, etc.) were excluded. The parents of the children gave informed consent for participation in the study.

All patients were treated with 2 or 3 doses per day of a mixture of regular and intermediate insulin. The dose and composition of the insulin injections were adjusted according to home glucose monitoring. Patients were seen every 3 months for clinical evaluation, assessment of metabolic control by the determination of HbA_{1c} levels, and to discuss further treatment. Metabolic control during puberty was expressed as the mean of HbA_{1c} values obtained every 3 months during the pubertal period. The HbA_{1c} assay was performed using Diamant high-performance liquid chromatography system; the range for nondiabetic children was 3.7–6.7%. HbA_{1c} values of the children during puberty ranged from 6.0 to 14.5%. A mean pubertal value of HbA_{1c} <8.0% was considered good metabolic control. Height, measured by Harpenden stadiometer, was expressed as a standard deviation score (SDS) for chronological age according to Tanner (9). British growth standards were chosen since they are very similar to our regional percentiles (10). Final height, evaluated at a mean age of 18.7 ± 0.8 years in male subjects and 17.6 ± 1.1 years in female subjects, was defined as a growth velocity of less than 1 cm in the preceding year. Parental height was measured at the first observation and the genetic target height (GTH) calculated according to Tanner (11). BMI was calculated and evaluated according to Hammer et al. (12).

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FH, final height; GTH, genetic target height; HDX, height at diagnosis; HPO, height at onset of puberty; SDS, standard deviation score.

Table 1—*Major clinical features of the 62 patients with IDDM*

	Boys	Girls
n	32	30
Age at diagnosis (years)	8.5 ± 3.2	8.2 ± 2.6
Age at onset of puberty (years)	12.1 ± 0.9	10.4 ± 1.2
Duration of IDDM at the onset of puberty (years)	3.6 ± 3.5	2.3 ± 3.0
Age at menarche (years)	—	12.8 ± 1.4
HbA_{1c} (%) concentration during puberty	9.2 ± 1.7	9.1 ± 1.9
Height at diagnosis (SDS)	0.5 ± 1.0	0.4 ± 1.0
Height at the onset of puberty (SDS)	−0.1 ± 1.1	0.01 ± 1.1
Final height (SDS)	−0.4 ± 1.1	−0.4 ± 0.9
Genetic target height (SDS)	−1.0 ± 0.9	−1.1 ± 0.6
Total pubertal growth (cm)	24.5 ± 5.2	20.1 ± 4.2
Insulin requirement ($U \cdot kg^{-1} \cdot day^{-1}$)	0.85 ± 0.19	0.91 ± 0.35
Final height − height at diagnosis (SDS)	−0.9 ± 0.7	−0.8 ± 0.8
Final height − height at the onset of puberty (SDS)	−0.3 ± 0.8	−0.4 ± 1.0
Final height − genetic target height (SDS)	0.6 ± 0.9	0.7 ± 0.9
Height at diagnosis − genetic target height (SDS)	1.5 ± 0.8	1.5 ± 0.8
Height at puberty onset − genetic target (SDS)	0.9 ± 1.1	1.1 ± 1.0

Data are *n* or means ± SD.

Pubertal onset was defined by the beginning of breast development in girls and by the enlargement of testicular volume (to 4 ml) in boys. Pubertal growth was evaluated using the total pubertal height gain (13) from the onset of puberty to final height. To evaluate the influence that the onset of puberty had on growth, patients were divided into two groups on the basis of the duration of IDDM, either greater than or less than 1 year with respect to the onset of puberty.

Statistical analysis

Statistical analysis was performed by Mann-Whitney or Wilcoxon's tests as appropriate and by linear regression analysis. Data are expressed as means ± SD, unless otherwise indicated.

RESULTS — Main clinical data of growth and pubertal development for both boys and girls are reported in Table 1. Height at diagnosis (HDX) fell within the normal percentiles but above the GTH in all patients ($P = 0.0001$). After diagnosis, a progressive and significant decrease in height gain was observed both at the onset of puberty and at final height (Fig. 1). The greater the height at diagnosis with respect to the GTH (HDX − GTH) the lesser was the subsequent height gain to final height (FH − HDX) ($r = -0.34$, $P = 0.01$). The lesser height gain was not correlated with HbA_{1c} levels or insulin requirement. Mean pubertal growth was decreased in both girls (20.1 ± 4.2 cm) and boys (24.5 ± 5.2 cm), compared with mean values reported by Tanner (25 cm in girls and 28 cm in boys) (10). However, mean adult height reached was still above the mean GTH both in men and women (Fig. 1). A positive correlation was observed between the height at the onset of diabetes and *1*) height at the onset of puberty (HPO; $r = 0.82$, $P < 0.001$), 2) final height ($r = 0.73$, $P < 0.001$), and 3) GTH ($r = 0.64$, $P < 0.001$). Puberty occurred within the normal age in both boys and girls. Menarche occurred at a mean age of 12.8 ± 1.4 years, which was similar to the age observed in a regional control group of 50 healthy young women (12.5 ± 1.0 years).

Age at onset

The age at onset of IDDM correlated with HPO ($r = -0.4$, $P < 0.001$). However, Tables 2 and 3 show that patients with an onset of IDDM around puberty have the same growth and pubertal patterns of patients with an onset of IDDM before puberty. The lesser height gain from diagnosis to final height in the patients with near-pubertal onset of IDDM occurred during the pubertal period, whereas in the patients with prepubertal onset of IDDM the lesser height gain occurred mainly before pubertal development. However, all subjects reached an adult stature within the genetic target height.

Effect of metabolic control

In evaluating the effect of metabolic control during puberty, a different pattern of growth was observed between girls and boys (Tables 4 and 5). Girls with good metabolic control showed a lesser height gain from the onset of puberty to final height (−1.3 ± 0.6

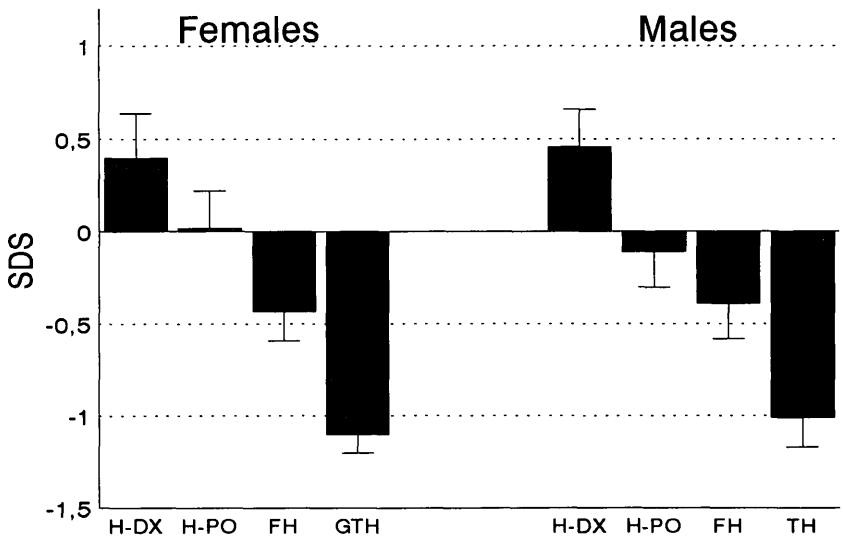

Figure 1—*Comparison between height at diagnosis (HDX), height at onset of puberty (HPO), final height (FH), and genetic target height (GTH) in 30 girls and 32 boys with IDDM. Data are means ± SE. For girls: height at diagnosis versus height at onset of puberty, P < 0.0001; height at diagnosis versus final height, P < 0.0001; height at diagnosis versus genetic target height, P < 0.0001; final height versus genetic target height, P < 0.002. For boys: height at diagnosis versus height at onset of puberty, P < 0.0001; height at diagnosis versus final height, P < 0.0001; height at diagnosis versus genetic target height, P < 0.0001; final height versus genetic target height, P < 0.001.*

Table 2—*Major clinical features of girls who were in the early phase of puberty or prepubertal when diagnosis of IDDM was made*

	Developmental status at the time of diagnosis of IDDM	
	Early phase of puberty	Prepubertal
n	15	15
Age at diagnosis (years)	9.9 ± 1.3	6.4 ± 2.4*
Age at onset of puberty (years)	10.1 ± 1.1	10.7 ± 1.3
Duration of IDDM at the onset of puberty (years)	0.3 ± 0.3	4.4 ± 3.1†
Age at menarche (years)	12.6 ± 1.6	13.1 ± 1.2
HbA_{1c} (%) concentration during puberty	9.1 ± 1.7	9.1 ± 1.0
Height at diagnosis (SDS)	0.3 ± 1.2	0.5 ± 0.8
Height at the onset of puberty (SDS)	0.3 ± 1.2	−0.2 ± 1.0
Final height (SDS)	−0.5 ± 0.8	−0.3 ± 0.9
Genetic target height (SDS)	−1.1 ± 0.6	−1.1 ± 0.5
Total pubertal growth (cm)	19.8 ± 4.0	20.4 ± 4.6
Insulin requirement ($U \cdot kg^{-1} \cdot day^{-1}$)	0.8 ± 0.4	1.0 ± 0.3‡
Final height − height at diagnosis (SDS)	−0.8 ± 0.7	−0.8 ± 0.8
Final height − height at the onset of puberty (SDS)	−0.8 ± 0.7	−0.1 ± 1.0

*P = 0.001; †P = 0.0001; ‡P = 0.01.

SDS) compared with girls with higher HbA_{1c} levels (−0.1 ± 0.9 SDS, P = 0.003). However, pubertal growth was similar in both groups, and all reached a final height within their genetic target. On the contrary, metabolic control did not affect growth in boys. Height gain from the onset of puberty to final height did not differ among boys with good (0.1 ± 0.9 SDS) and those with poor metabolic control (−0.3 ± 0.8 SDS).

Mean insulin requirement

Although the mean insulin requirement significantly increased from the time of pubertal onset (0.75 ± 0.3 $U \cdot kg^{-1} \cdot day^{-1}$) to adult age (0.97 ± 0.3 $U \cdot kg^{-1} \cdot day^{-1}$, $P < 0.0001$), it did not affect sexual maturation, pubertal growth, or final height.

BMI

BMI showed a progressive increase from the time of diagnosis throughout the course of follow-up. However, both boys and girls remained in the same percentile throughout the follow-up. In boys, BMI increased from 17.1 ± 2.7 kg/m^2 at the time of diagnosis (50th to 75th percentile) to 18.2 ± 2.7 kg/m^2 at the time of pubertal onset (50th to 75th percentile) to 22.4 ± 2.0 kg/m^2 at the attainment of adult height (50th to 75th percentile); in girls, BMI increased from 16.5 ± 2.7 kg/m^2 at the time of diagnosis (50th to 75th percentile) to 17.5 ± 2.7 kg/m^2 at the time of pubertal onset (50th to 75th percentile) to 23.2 ± 2.6 kg/m^2 at the attainment of adult height (50th to 75th percentile). The increase in BMI was independent of the age at onset of IDDM and glycemic control.

Table 3—*Major clinical features of boys who were in the early phase of puberty or prepubertal when diagnosis of IDDM was made*

	Developmental status at the time of diagnosis of IDDM	
	Early phase of puberty	Prepubertal
n	9	23
Age at diagnosis (years)	11.7 ± 0.8	7.3 ± 2.9*
Age at onset of puberty (years)	11.9 ± 0.9	12.2 ± 0.9
Duration of IDDM at the onset of puberty (years)	0.6 ± 0.1	4.9 ± 3.2*
HbA_{1c} (%) concentration during puberty	9.5 ± 2.7	9.1 ± 1.3
Height at diagnosis (SDS)	0.4 ± 1.5	0.5 ± 0.7
Height at the onset of puberty (SDS)	0.4 ± 1.5	−0.3 ± 0.9
Final height (SDS)	−0.4 ± 1.5	−0.4 ± 0.9
Genetic target height (SDS)	−1.0 ± 1.0	−1.0 ± 0.8
Total pubertal growth (cm)	22.4 ± 4.0	25.4 ± 5.4
Insulin requirement ($U \cdot kg^{-1} \cdot day^{-1}$)	0.7 ± 0.2	0.9 ± 0.2†
Final height − height at diagnosis (SDS)	−0.7 ± 0.5	−0.9 ± 0.8
Final height − height at the onset of puberty (SDS)	−0.7 ± 0.6	−0.09 ± 0.8‡

*P = 0.00001, †$P < 0.02$, ‡P = 0.04.

CONCLUSIONS — The question of whether linear growth and pubertal development are impaired in diabetic children is still debated. Even though at diagnosis children with IDDM are often reported to be taller than average (3,7,14,15), our data suggest, in accordance with others (5,6,16), that height at diagnosis is normal when compared with Tanner standards. During the ensuing years, a progressive decrease in height gain is observed until the attainment of final height that nevertheless is higher than GTH. This diminished height gain seems to be independent of both the duration of the disease and the degree of metabolic control. BMI shows a progressive increase with age, as normally occurs in healthy children, independent of the age at onset of IDDM and of glycemic control.

Conflicting results are reported in the literature concerning the influence that the degree of metabolic control or age at onset of IDDM exert on growth and pubertal development. Some authors report an impaired growth in children with poor glucose control (2,14) or an improvement in growth after a better period of metabolic control (17). Others provide evidence of a strong relationship between the duration of diabetes and pubertal growth or final height (6–8). A reduced and delayed pubertal growth spurt has been reported in relation to the duration of the disease before puberty (6), whereas others report a decrease pubertal growth in girls diagnosed around the time of puberty (7). Our results indicate that puberty begins within the normal age and normally progresses independent of the duration of the disease and the degree of metabolic control.

In summary, conventional management of children with IDDM leads to normal sexual development, whereas even though the final height falls within the normal range, the diminished height gain after diagnosis of diabetes requires further investigation.

Table 4—*Influence of metabolic control during puberty on final height: 7 girls with good metabolic control (HbA_{1c} <8%) compared with 23 girls with poor metabolic control (HbA_{1c} ≥8%)*

	HbA_{1c} <8%	HbA_{1c} ≥8%
n	7	23
HbA_{1c} (%) concentration during puberty	6.9 ± 0.8	9.8 ± 1.6*
Height at the onset of puberty (SDS)	0.9 ± 0.8	−0.3 ± 1.1†
Final height (SDS)	−0.5 ± 0.6	−0.4 ± 1.0
Genetic target height (SDS)	−0.8 ± 0.4	−1.2 ± 0.6
Total pubertal growth (cm)	20.3 ± 5.7	20.1 ± 3.9
Insulin requirement ($U \cdot kg^{-1} \cdot day^{-1}$)	0.8 ± 0.4	0.9 ± 0.3
Final height − height at the onset of puberty (SDS)	−1.3 ± 0.6	−0.1 ± 0.9‡
Final height − genetic target height (SDS)	0.3 ± 0.9	0.8 ± 0.9
Height at puberty onset − genetic target (SDS)	1.7 ± 1.1	0.9 ± 1.0

*P = 0.0001, †P = 0.006, ‡P = 0.003.

Table 5—*Influence of metabolic control during puberty on final height: 7 boys with good metabolic control (HbA_{1c} <8%) compared with 25 boys with poor metabolic control (HbA_{1c} ≥8%)*

	HbA_{1c} <8%	HbA_{1c} ≥8%
n	7	25
HbA_{1c} (%) concentration during puberty	6.9 ± 0.4	9.7 ± 1.5*
Height at the onset of puberty (SDS)	0.5 ± 0.4	−0.2 ± 1.2†
Final height (SDS)	0.7 ± 0.7	−0.5 ± 1.1†
Genetic target height (SDS)	−0.6 ± 0.7	−1.1 ± 0.9
Total pubertal growth (cm)	27.9 ± 3.7	24.6 ± 4.9
Insulin requirement ($U \cdot kg^{-1} \cdot day^{-1}$)	0.7 ± 0.3	0.9 ± 0.2
Final height − height at the onset of puberty (SDS)	0.1 ± 0.9	−0.3 ± 0.8
Final height − genetic target height (SDS)	1.3 ± 0.2	0.5 ± 0.9‡
Height at puberty onset − genetic target (SDS)	1.1 ± 1.0	0.8 ± 1.1

*P = 0.0005; †P < 0.04; ‡P < 0.01.

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References

1. Guest M: The Mauriac syndrome: dwarfism, hepatomegaly, and obesity with juvenile diabetes mellitus. *Diabetes* 2:415–417, 1953
2. Jackson RL: Growth and maturation of children with IDDM. *Pediatr Clin North Am* 31:545–567, 1984
3. Brown M, Ahmed ML, Clayton KL, Dunger DB: Growth during childhood and final height in type 1 diabetes. *Diabet Med* 11:182–187, 1994
4. d'Annunzio G, Cortona L, Vitali L, Pessino P, Lorini L: Final height attainment in girls and boys with insulin-dependent diabetes mellitus. *Diabetes Res Clin Pract* 24:187–193, 1994
5. Du Caju MV, Rooman RP, De Beeck LO: Longitudinal data on growth and final height in diabetic children. *Pediatr Res* 38:607–611, 1995
6. Jivani SKM, Rayner PHW: Does control influence the growth of diabetic children? *Arch Dis Child* 48:109–115, 1973
7. Salardi S, Tognoli S, Tassoni P, Tellarini M, Mazzanti L, Cacciari E: Growth and growth factors in diabetes mellitus. *Arch Dis Child* 62:57–62, 1987
8. Herber SM, Dunsmore IR: Does control affect growth in diabetes mellitus? *Acta Paediatr Scand* 77:303–305, 1988
9. Tanner JM, Whitehouse RH, Takaishi M: Standards from birth to maturity for height, weight, height velocity and weight velocity: British children 1965. *Arch Dis Child* 41:613–635, 1966
10. Capozzi G, Vitiello N, Granato L, Gargiulo ML, Langella S, Greco L: Factors related to growth in height: are regional standards still required? *Ital J Pediatr* 14:384–389, 1988
11. Tanner JM: *Growth at Adolescence*. 2nd ed. Oxford, U.K., Blackwell Scientific, 1962
12. Hammer LD, Kraemer HC, Wilson DM, Ritter PL, Dornbusch SM: Standardized percentile curves of body-mass index for children and adolescents. *Am J Dis Child* 145:259–263, 1991
13. Bourguignon JP: Linear growth as a function of age at onset of puberty and sex steroid dosage: therapeutic implications. *Endocr Rev* 9:467–488, 1988
14. Wise JE, Kolb EL, Sauder SE: Effect of glycemic control on growth velocity in children with IDDM. *Diabetes Care* 15:826–830, 1992
15. Holl RW, Heinze E, Seifert M, Grabert M, Teller WM: Longitudinal analysis of somatic development in paediatric patients with IDDM: genetic influences on height and weight. *Diabetologia* 37:925–929, 1994
16. Thon A, Heinze E, Feilen KD, Holl RW, Schmidt H, Koletzko S, Wendel U, Nothjunge J: Development of height and weight in children with diabetes mellitus: report on two prospective multicentre studies, one cross-sectional, one longitudinal. *Eur J Pediatr* 151:258–262, 1992
17. Rudolf MCJ, Sherwin RS, Markowitz R, Bates SE, Genel M, Hochstadt J, Tamboylane MV: Effect of intensive insulin treatment on linear growth in the young diabetic patient. *J Pediatr* 101:333–339, 1982