

Pubertal Growth in IDDM Is Determined by HbA_{1c} Levels, Sex, and Bone Age

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OBJECTIVE — In cross-sectional studies of subjects with IDDM, the relationship between suboptimal pubertal growth, glycemic control, and abnormal insulin-like growth factor I (IGF-I) levels has proved difficult to define. The objective of this study was to examine these relationships in a longitudinal prospective study.

RESEARCH DESIGN AND METHODS — A total of 46 children (23 boys) were measured every 3 months, and their bone age was assessed annually. Blood samples were obtained for HbA_{1c}, IGF-I, and C-peptide. Growth data were compared with national standards, and IGF-I data were compared with a parallel longitudinal study of normal schoolchildren. Data were analyzed as SD scores (mean ± SD).

RESULTS — The onset of puberty was not delayed, although in the girls, bone age was advanced (bone age, 11.48 ± 1.01 years vs. chronological age, 10.93 ± 0.86 years [mean ± SD]; $P = 0.04$). The timing of peak height velocity (PHV) was normal in both sexes, but the magnitude was reduced in girls (PHV SDS = -0.56 ± 0.90, $P < 0.02$), and reductions in height SDS between diagnosis and final height were observed ($P = 0.014$). At PHV, IGF-I levels were reduced in both sexes, and there were no sex differences in HbA_{1c} levels and insulin doses. IGF-I SDS correlated with insulin dose ($r = 0.47$, $P = 0.004$) but not with PHV SDS, whereas HbA_{1c} correlated negatively with PHV SDS in both sexes ($r = -0.35$, $P = 0.03$). In a stepwise multiple regression analysis, the major determinants of PHV SDS were HbA_{1c} ($P = 0.04$), sex ($P = 0.0007$), and bone age ($P = 0.01$).

CONCLUSIONS — We conclude that the magnitude of the pubertal growth spurt is related to HbA_{1c} levels in both sexes, but it is reduced only in girls. This sexual dimorphism cannot be explained by differences in IGF-I levels and may relate to the bone age advance at the onset of puberty in the girls.

Over the last 50 years, the prognosis for growth of young people with IDDM has improved (1–4). Controversial data concerning height at diagnosis exists: some authors report tall stature at diagnosis (5–7) and others report no differences between children with IDDM and control subjects (8–10). These differences may reflect the choice of control subjects, age at diagnosis (11), or genetic differences between populations studied (12,13). Most recent studies have reported that puberty is no longer delayed in children with IDDM (6,11), although there have been excep-

tions (14,15). However, the pubertal growth spurt is invariably suboptimal, especially in girls (6,11,14,16).

Suboptimal pubertal growth could reflect difficulties in achieving optimal glycemic control during the pubertal years (17,18). Even the highly motivated teenagers in the Diabetes Control and Complications Trial had higher glycated hemoglobin (HbA_{1c}) levels than did the adults studied (19). Yet it has proved to be difficult to identify a clear relationship between HbA_{1c} and growth in IDDM. Although two studies have identified a link (20,21), there

have been other studies where no association was observed (6,22,23).

Abnormalities of the growth hormone/insulin-like growth factor I (GH/IGF-I) axis have been documented during puberty, and these could account for the poor growth. Despite GH hypersecretion (24,25), levels of IGF-I and IGF binding protein 3 tend to be low or in the low-normal range (26–28). These abnormalities may arise because insulin has a central role in the regulation of the GH receptor (29) and levels of IGF binding protein I, a potential inhibitor of IGF-I action (30). The reduced circulating IGF-I levels and reduced IGF bioactivity might have a direct effect on pubertal growth, yet one large cross-sectional study failed to observe any direct correlations between IGF levels and growth velocity (27).

The cross-sectional or mixed cross-sectional/longitudinal design of many earlier studies of pubertal growth in IDDM may be a reason why the relationships between IGF-I, HbA_{1c}, and growth have proved difficult to define. We have carried out a prospective longitudinal study examining these relationships in a large cohort of subjects with IDDM.

RESEARCH DESIGN AND METHODS

Patients

Forty-six children (23 boys and 23 girls) attending the children's diabetes clinic at the John Radcliffe Hospital in Oxford were recruited prior to the onset of puberty. The median age (range) was 11.27 (10.53–12.83) years for boys and 10.36 (8.54–11.36) years for girls. Duration of diabetes at recruitment (median and range) was 6.17 (1.87–10.16) years in the boys and 2.69 (0.55–9.15) years in the girls. All patients were on two injections of intermediate and soluble insulin daily at recruitment, but 75% were changed, during puberty, to multiple injection therapy with three preprandial injections of soluble insulin and intermediate-acting insulin given right before bedtime.

Design

The children were seen three or four times/year, and height was measured by the

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Abbreviations: CV, coefficient of variation; GH, growth hormone; IGF-I, insulin-like growth factor I; PHV, peak height velocity; SDS, standard deviation score; SHBG, sex hormone-binding globulin.

Table 1—Height SDS in subjects with IDDM at diagnosis, during puberty, and at final height (corrected for midparental height SDS)

IDDM	Diagnosis	Tanner B ₂ /G ₂	PHV	Final height	Midparental height SDS	Child's final height SDS corrected for midparental SDS
Boys (n)	0.235 (15)	-0.044 (23)	0.131 (20)	-0.043 (16)	0.158 (23)	-0.174 (16)
Girls (n)	0.814 (20)	0.284 (23)	0.133 (19)	-0.037* (19)	0.398 (21)	-0.359† (18)

*P = 0.014 from diagnosis to final height; †P = 0.005 for final height corrected for parents' heights.

same observer (M.L.A.) using a Harpenden stadiometer (31); weight was assessed using a beam balance and pubertal staging assessed by the method of Tanner (32). Blood samples were taken annually for C-peptide, every 6 months for IGF-I, and every 3–4 months for HbA_{1c}. Bone age was assessed annually by the Tanner Whitehouse RUS system (33).

Control data

Growth and pubertal development were compared with the British standards of Tanner et al. (34). Control data for IGF-I levels were obtained from a contemporary group of normal children (35) assessed longitudinally from 9–16 years of age, using identical auxological techniques.

Assay details

HbA_{1c} levels were measured by high-pressure liquid chromatography (Diamat; Bio-Rad Laboratories, Hemel Hempstead, Herts, U.K.). Normal range was 4.3–6.1%. The intra-assay coefficients of variation (CVs) were 1.9 and 2.2% at HbA_{1c} levels of 6.9 and 11.5%, respectively. Interassay CVs were 2.7 and 2.3% at HbA_{1c} levels of 7.0 and 11.6%, respectively.

Plasma IGF-I levels were determined by radioimmunoassay after acid-ethanol extraction (36). The intra-assay CVs were 5.2 and 4.8% at 27.5 and 220 ng/ml, respectively. The interassay CVs were 12.7 and 10.6% at levels of 77 and 242 ng/ml, respectively.

C-peptide levels were assayed by a double antibody radioimmunoassay (Diagnostic Products, Llanberis, Caernarfon, Wales, U.K.). Intra-assay CVs were 4.9, 3.0, and 5.9% at C-peptide levels of 358, 651, and 1995 pmol/l, respectively. Interassay CVs were 5.3, 3.5, and 8.7% at levels of 556, 1,307, and 2,680 pmol/l, respectively.

Data analysis

Peak height velocity (PHV) in control and diabetic cohorts was determined using a smoothed distance curve for height with

annualized velocities calculated every three months. PHV was defined as the maximal annual velocity. The standard deviation score (SDS) for PHV was calculated from the data of Tanner et al. (34) with allowance made for variation in the age at which PHV was attained. Height SDSs were also calculated for subjects with IDDM at diagnosis, at the onset of puberty (Tanner B₂/G₂), and at final height. Final height data were corrected for midparental height SDS. Each parent's height was converted to an SDS, and the mean of this was taken as the midparental SDS. The difference between the child's final height SDS and their midparental SDS is their adjusted final height SDS. All scores were calculated appropriate for each age and sex as follows: (measurement - mean)/SD; SDS = (x - \bar{x})/SD.

SD scores were also derived for IGF-I concentrations in relation to PHV in the IDDM subjects using the CHARD IGF-I means and SDs.

All data are expressed as means ± SD unless otherwise stated. Statistical analyses were by *t* tests, least squares, and stepwise multiple regression analysis. SPSS for Windows (version 3.1) and Excel (version 5) were used. Statistical significance was defined as *P* ≤ 0.05.

RESULTS — The median (range) duration of follow-up in the IDDM cohort was 6 (3–8) years. PHV was ascertained in 39 children (20 boys), and 35 subjects reached final height (growth velocity <1 cm/year); 19 girls achieved menarche.

The chronological age at the onset of puberty (Tanner B₂, G₂) was not significantly different between the subjects with IDDM (12.1 ± 0.71 years in boys and 10.93 ± 0.86 years in girls) and normal control subjects. However, girls with IDDM had an advanced bone age (11.48 ± 1.01 years) relative to their chronological age (10.93 ± 0.86 years, *P* = 0.04), whereas bone ages in boys were slightly delayed (11.75 ± 1.07 years) compared with chronological age (12.10 ± 0.71 years, *P* = 0.20). Age at PHV

was not different in subjects with IDDM (boys 14.0 ± 1.29 years, girls 11.96 ± 0.71 years) compared with control subjects, but bone age remained advanced in girls at PHV (12.28 ± 0.85 vs. 11.96 ± 0.71 years). Age at menarche was not significantly different from that of control subjects (13.23 ± 0.69 vs. 13.0 ± 1.0 years).

The pattern of change in height SDS was different in boys and girls (Table 1). The girls at diagnosis and at the start of puberty were tall relative to control subjects. However, at final height they were shorter than control subjects (height SDS = -0.037). The loss of height SDS from diagnosis to final height was significant (*P* = 0.014) in the girls; at final height, they were significantly shorter with respect to midparental height SDS (*P* = 0.005).

The boys were taller than control subjects at diagnosis (height SDS = 0.235), but by the onset of puberty their mean height SDS was -0.044 ± 1.05, similar to the value at final height (-0.043 ± 0.78) and not significantly different from midparental height SDS.

The magnitude of the growth spurt in the boys (9.54 ± 1.54 cm/year) was similar to that in control subjects (9.5 ± 1.1 cm/year), whereas in the girls the growth spurt (7.71 ± 1.13 cm/year) was significantly lower than in control subjects (8.4 ± 0.9 cm/year, *P* < 0.05). PHV SDS was significantly reduced in the girls (-0.56 ± 0.90, *P* < 0.02) but not in the boys with IDDM (0.04 ± 1.09, *P* = 0.43).

The changes in insulin dose, HbA_{1c}, and IGF-I SDS in the years before and after PHV are summarized in Table 2. HbA_{1c} increased in both sexes during the period of study, although levels tended to be lower in girls in the years before PHV. Despite differences in PHV SDS, there were no differences in HbA_{1c} at PHV between boys (9.72 ± 1.96%) and girls (8.86 ± 1.47%). The increase in insulin dose during the growth spurt was similar in both sexes (maximum 1.14 U · kg⁻¹ · day⁻¹ in boys and 1.15 U · kg⁻¹ · day⁻¹ in girls) and there were differ-

Table 2—Years before and after PHV: insulin dose, HbA_{1c}, and IGF-I SDS

Years before and after PHV	Insulin dose (U · kg ⁻¹ · day ⁻¹)		HbA _{1c} (%)		IGF-I SDS	
	Boys	Girls	Boys	Girls	Boys	Girls
	–3	0.92 ± 0.20	0.78 ± 0.19	9.07 ± 1.82	8.42 ± 1.31	–0.034 ± 1.514
–2	1.01 ± 0.18	0.87 ± 0.29	9.73 ± 1.55	8.00 ± 1.93*	–0.936 ± 0.961	0.035 ± 2.620
–1	1.04 ± 0.16	0.95 ± 0.24	9.73 ± 1.67	9.11 ± 1.01	–0.797 ± 0.992	–0.284 ± 1.012
0	1.14 ± 0.17	1.10 ± 0.26	9.72 ± 1.96	8.86 ± 1.47	–1.526 ± 0.888	–0.623 ± 0.971†
+1	1.13 ± 0.15	1.13 ± 0.19	9.64 ± 1.55	9.73 ± 1.69	–1.604 ± 2.184	–0.724 ± 0.934
+2	1.08 ± 0.14	1.15 ± 0.21	9.89 ± 2.20	9.73 ± 1.66	–1.885 ± 1.402	–0.629 ± 0.640‡
+3	1.04 ± 0.14	1.03 ± 0.19	9.88 ± 2.36	10.15 ± 1.88	–3.464 ± 1.030	0.931 ± 1.348§

Data are means ± SD. A significant difference exists between boys and girls for: *HbA_{1c} at PHV –2, $P < 0.027$; †IGF-I SDS at PHV = 0, $P < 0.006$; ‡IGF-I SDS at PHV +2, $P < 0.004$; §IGF-I SDS at PHV +3, $P < 0.00001$.

ences in the time at which this dose was achieved (at PHV in boys, 2 years later in girls). Insulin dose at PHV was not significantly different in boys (1.14 ± 0.17 U · kg⁻¹ · day⁻¹) and girls (1.10 ± 0.26 U · kg⁻¹ · day⁻¹).

IGF-I levels fell in relation to control data in both sexes. IGF-I SDSs were lower in boys than in girls in the years before and after PHV (Table 2). At PHV, the IGF-I SDS was significantly reduced in boys (-1.53 ± 0.89 , $P < 0.001$) and girls with IDDM (-0.62 ± 0.97 , $P < 0.01$).

When data from both sexes were analyzed separately or combined, HbA_{1c} correlated negatively with PHV SDS ($r = -0.35$, $P = 0.03$; Fig. 1). There was no relationship between insulin dose or IGF-I SDS and PHV SDS, but insulin dose and IGF-I SDS were closely related ($r = 0.47$, $P = 0.004$; Fig. 2).

To explore the determinants of PHV SDS in IDDM, we entered the following variables into a stepwise multiple regression analysis: IGF-I SDS, HbA_{1c}, sex, bone age, C-peptide, and duration of diabetes (all variables determined at PHV). The major determinants of PHV SDS were HbA_{1c} ($P = 0.04$), sex ($P = 0.0007$), and bone age ($P = 0.07$). Overall analysis of variance gave an $F = 6.9$ with $P = 0.0009$.

CONCLUSIONS — The timing of the onset of puberty and PHV were not significantly different from normal in our longitudinal study of children with IDDM. This is in contrast to many earlier studies that reported delays in the onset of puberty and the growth spurt (10,23,37). The prognosis for growth in IDDM has improved, and most recent studies are in agreement with ours (6,11), although two recent studies have reported conflicting results. Du Caju

et al. (14) reported a marked delay in the age at onset of puberty in boys, whereas Tillmann et al. (15) reported a delay in girls. These differences may reflect variations in glycemic control or difficulties in choosing appropriate control data. The Tanner data that we used are now nearly 40 years old and may not reflect the secular trend towards earlier maturation. We considered using data from recent cohorts (38), but the populations studied are small and not valid for use as standards. There remains a possibility that the age at onset of puberty may be delayed in IDDM compared with contemporary control subjects, but the difference is likely to be small.

The differences in the magnitude of PHV between the sexes in IDDM cannot be explained by choice of control data. Similar findings have been observed in many recent studies (6,11,14,16). The impact of this poor pubertal growth is reflected in the loss of height SDS between diagnosis and final

height in the girls, but not the boys, with IDDM that we studied. The clinical impact of this loss of pubertal growth on final height is not great (11,39), as height at diagnosis may be increased, particularly in subjects diagnosed at 5–10 years of age (11). Nevertheless, in the girls we studied, final height SDS was significantly reduced when corrected for midparental height SDS, and there may be a significant impact on final height in girls diagnosed under 5 years who may be smaller than control subjects (11).

The differences in PHV and the subsequent loss of height during puberty between the sexes cannot be explained by differences in glycemic control, because mean HbA_{1c} values at PHV were identical. Furthermore, in the years leading up to PHV, HbA_{1c} levels were lower in girls. Nevertheless, when the sexes were combined, there was a significant negative correlation between PHV SDS and HbA_{1c} values in both simple and multiple regression analy-

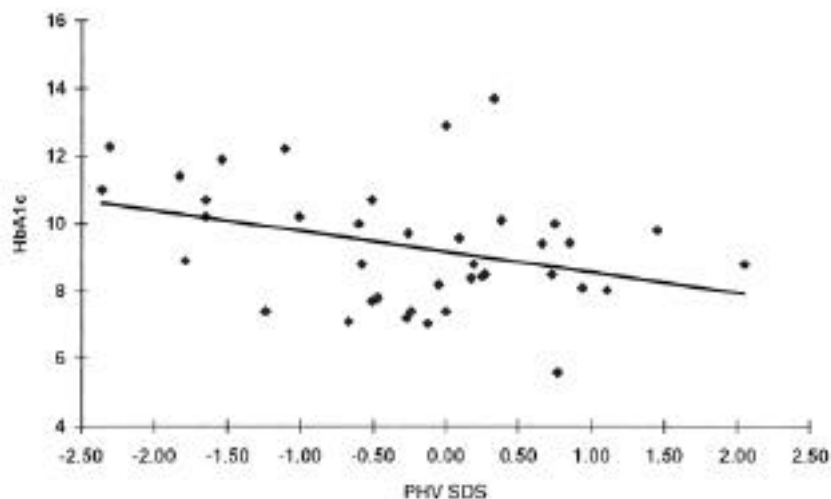


Figure 1—Relationship between PHV SDS and HbA_{1c} in children with IDDM ($r = 0.35$, $P = 0.03$).

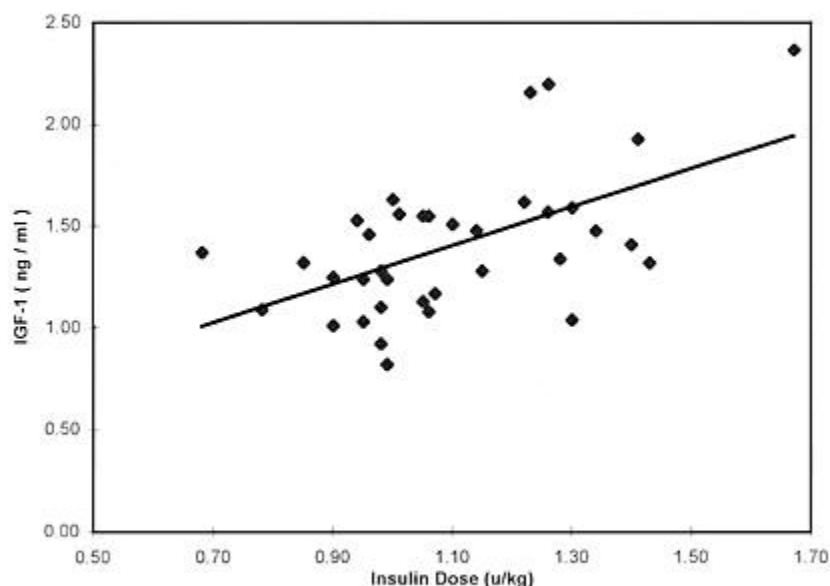


Figure 2—Relationship between insulin dose and IGF-I SDS at the time of PHV ($r = 0.465$, $P = 0.004$).

sis. Thus, the effect of HbA_{1c} on growth during puberty is similar in both sexes, but there are other factors that lead to preserved growth in the boys, but not in the girls, with IDDM.

IGF-I levels were reduced in both the girls and the boys with IDDM, and, in fact, the IGF-I SDS of -1.53 ± 0.89 in the boys was significantly lower ($P = 0.006$) than the IGF-I SDS of -0.62 ± 0.97 in girls at PHV. In both sexes, IGF-I levels were closely related to insulin dose, as has been previously reported (26,30,40). The doses of insulin in our subjects during puberty were not as high as those recommended by some investigators (2,17). Correlations between insulin dose and IGF-I levels have been reported (26), but only one study has reported improved growth with intensified insulin therapy (41). We were not able to observe any correlation between IGF-I SDS and PHV SDS, in keeping with observations made recently in a large cross-sectional study by Strasser-Vogel et al. (27). Thus, the sexual dimorphism in pubertal growth in IDDM cannot be explained by differences in IGF-I levels.

Apart from HbA_{1c} and sex, the other important determinant of PHV in our subjects was bone age. The girls in our study had a relatively advanced bone age at the onset of puberty and at PHV. The advanced bone age could reflect differential effects of sex steroids in the regulation of growth. Sex hormone-binding globulin (SHBG) levels

decline steeply during puberty (42), and low levels have been reported in girls with IDDM (43,44). Thus, one could argue that “free” androgen levels during adrenarche in girls could advance bone age. An alternative explanation for the poor pubertal growth in girls might be a greater dependence on an intact GH/IGF-I axis. Merimee et al. (45) reported that pubertal growth in girls is dependent on the GH/IGF-I axis, whereas in boys it is more related to testosterone levels. In male baboons, androgen levels may be a more important regulator of circulating IGF-I levels than growth hormone (46). One might infer that higher “free androgen” levels in boys consequent upon low SHBG may act to preserve growth velocity.

We conclude that the timing of pubertal growth is normal in IDDM, but the magnitude of PHV is greatly reduced in the girls. Although PHV is closely related to HbA_{1c} levels in both sexes, growth is normal in the boys. These sex differences cannot be attributed to IGF-I levels, which were equally low in both sexes. PHV SDS was also related to bone age at PHV, and the advanced bone age in girls at the onset of puberty may explain their subsequent blunted pubertal growth spurt.

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