Effect of Puberty on Insulinlike Growth Factor I and HbA_1 in Type I Diabetes

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Objective: To assess the effect of puberty on the relationship between glycemic control and insulinlike growth factor I (IGF-I) levels in children with insulin-dependent (type I) diabetes mellitus. Research Design and Methods: Simultaneous HbA_1 and plasma IGF-I levels were determined in 71 prepubertal (Tanner stage I) and 112 pubertal (Tanner stages II–V) subjects aged 2.7–17.8 yr. Results: Overall, IGF-I levels were positively correlated with both age ($r = 0.31$, $P < 0.001$) and Tanner stage ($r = 0.32$, $P < 0.001$) but only weakly associated with HbA_1 values ($r = -0.16$, $P = 0.025$). A strong negative association existed between IGF-I and HbA_1 levels ($r = -0.45$, $P < 0.001$) in the pubertal subjects, but no such association was apparent in the prepubertal subjects. Multiple regression analyses disclosed a significant independent negative association between IGF-I and HbA_1 levels in the pubertal group ($P < 0.001$) but not in the prepubertal group. Conclusions: Glycemic control appears to strongly influence IGF-I levels only after the onset of puberty. *Diabetes Care* **14:1031–35, 1991**

Linear growth of diabetic children in poor metabolic control is decreased compared with that of well-managed diabetic children (1). Also, diabetic members of twins do not grow as well as their nondiabetic twins (2).

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Because of a possible relationship between diabetic metabolic control and linear growth, many investigators examined insulinlike growth factor I (IGF-I) levels in diabetic subjects and studied possible relationships between IGF-I levels and glycemic control. The results were ambiguous. Various studies showed decreased (3–6) or normal (7–14) levels of plasma IGF-I in diabetic children. Previous studies also failed to consistently show a relationship between IGF-I levels and HbA_1 values in diabetic subjects. A negative relationship between IGF-I levels and HbA_1 values has been reported by some studies (4–6,10), although others show no correlation (13,14). These studies neglected the pubertal status of their subjects and the effect that puberty may have had on the relationship between glycemic control and IGF-I levels.

In rats with experimental diabetes mellitus, circulating IGF-I levels are considerably lower than normal (15–18). Insulin administration to diabetic rats restores IGF-I levels, whereas exogenous administration of growth hormone does not (17). It is surprising then that an effect of glycemic control on IGF-I levels has not been consistently found in humans, because insulin administration so strongly affects IGF-I levels in diabetic animals (17,18).

This study examined the effect of puberty on possible associations between plasma IGF-I levels, HbA_1 values, age, and body mass index (BMI) in children with insulin-dependent (type I) diabetes mellitus.

RESEARCH DESIGN AND METHODS

The study consisted of 183 subjects with type I diabetes aged 2.7–17.8 yr. The subjects' height, weight, and pubertal development were recorded at each clinic visit

TABLE 1
Sex distribution, age, duration of insulin-dependent diabetes mellitus, body mass index, insulinlike growth factor I (IGF-I), and HbA_1 in each pubertal stage group

	Pubertal stage					
	I	II	III	IV	V	Total
n	71	31	28	32	21	183
Sex (%)						
M	73	35	43	31	48	52
F	27	64	57	69	52	48
Age (yr)	8.4 ± 2.6 (2.7–14.5)	11.9 ± 1.6 (8.5–15.0)	13.2 ± 1.3 (10.0–15.5)	14.7 ± 1.2 (12.5–17.0)	16.5 ± 1.2 (12–17.8)	11.7 ± 3.6 (2.7–17.8)
Diabetes duration (yr)	2.7 ± 2.4	4.4 ± 3.5	4.5 ± 3.0	4.3 ± 3.2	5.7 ± 3.6	3.8 ± 3.2
>1 yr (%)	59	80	89	81	95	75
Body mass index (kg/m^2)	17.5 ± 2.5	17.9 ± 2.6	19.3 ± 2.3	22.6 ± 3.1	23.5 ± 2.6	19.4 ± 3.5
IGF-I (ng/ml)†	259 ± 76	316 ± 75	331 ± 98	330 ± 71	320 ± 73	299 ± 84
HbA_1 (%)‡	12.5 ± 2.1	13.6 ± 3.4	14.6 ± 2.9	13.9 ± 3.1	13.2 ± 2.8	13.3 ± 2.8

Values are means ± SD except where noted. Ranges in parentheses. Tanner's pubertal stages defined in METHODS.
†$P < 0.05$ pubertal stage I vs. II–V by Duncan's multiple-range test.
‡$P < 0.05$ pubertal stage I vs. III by Duncan's multiple-range test.

(19,20). At the time of evaluation, 71 subjects were prepubertal (breast and pubic hair, Tanner stage I). One hundred twelve subjects were classified as pubertal. Girls with Tanner stage II breast and Tanner stage I pubic hair were assigned to pubertal stage II. Once pubic hair was present in either sex, only pubic hair Tanner staging was used to assign pubertal status. In 137 children, the duration of diabetes was >1 yr. In 46 children, diabetes was of recent onset, ranging from 1 to 12 mo. None of the children had been hospitalized for diabetic ketoacidosis within 1 mo before the study. Population characteristics are presented in Table 1. BMI were within the normal range for age and gender (Table 1). They were consistent with good nutritional status and increased as expected through puberty (21). Samples were obtained after meals during routine visits to the diabetes clinic.

Blood was collected in EDTA-containing tubes and kept at 4°C until separated for HbA_1 determination by thiobarbituric acid assay (22). Packed erythrocytes maintained at 4°C were assayed within 4 days of collection. Our normal mean ± SD HbA_1 values were 7.5 ± 0.7%. The plasma obtained from these specimens was stored frozen (−20°C) for up to 1 mo until assayed for IGF-I.

Plasma IGF-I was measured by radioimmunoassay with antisera obtained from the National Hormone and Pituitary Program (23; provided by L.E. Underwood and J.J. Van Wyk, Univ. of North Carolina). Recombinant ^{125}I-labeled IGF-I (Amersham, Arlington Heights, IL) was used as tracer, and recombinant IGF-I (Amgen, Thousand Oaks, CA) was used for standards. All samples were first extracted with acidified ethanol to remove binding proteins before assay (24). The inter- and intra-assay coefficients of variation were 7.0 and 5.4%, respectively. The IGF-I immunoreactivity of a plasma pool from normal adults was equivalent to 264 ± 19 ng/ml pure IGF-I.

Statistical calculations were performed with the CLINFO data management and analysis package. All population characteristics are presented as means ± SD. Differences between pubertal groups were determined by one-way analysis of variance and Duncan's multiple-range test. Relationships between variables were assessed by simple correlation and independence of variables by multiple regression.

RESULTS

When the five pubertal stage groups were compared, IGF-I levels were significantly lower ($P < 0.05$) in the prepubertal subjects than the pubertal groups (Table 1).

TABLE 2
Correlations of insulinlike growth factor I with age, body mass index (BMI), pubertal stage, and HbA_1

	Age	BMI	Pubertal stage	HbA_1
All subjects (*n* = 183)	0.310 (<0.001)	0.278 (<0.001)	0.318 (<0.001)	−0.164 (0.025)
Prepubertal (*n* = 71)	0.170 (0.156)	0.206 (0.08)		0.114 (0.343)
Pubertal (*n* = 112)	−0.048 (0.613)	0.108 (0.252)	0.024 (0.804)	−0.452 (<0.001)

P values are given in parentheses.

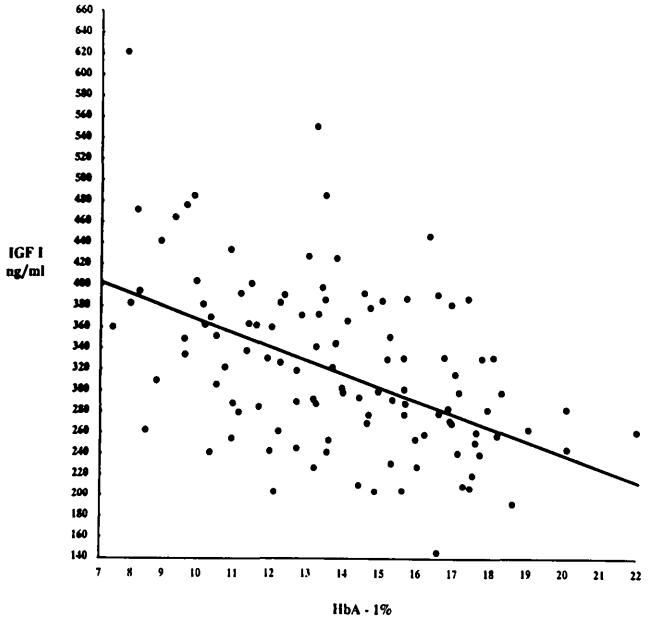

FIG. 1. Relationship between insulinlike growth factor I (IGF-I) levels and HbA_1 values in pubertal (Tanner stages II–V) diabetic children ($y = 485 - 11.6x$, $r = -0.45$, $P < 0.001$).

In a cross-sectional analysis of 183 subjects, IGF-I level was positively associated with the subject's age ($r = 0.31$, $P < 0.001$), pubertal stage ($r = 0.32$, $P < 0.001$), and BMI ($r = 0.28$, $P < 0.001$) but only weakly associated with HbA_1 values ($r = -0.16$, $P = 0.025$; Table 2). When pubertal subjects ($n = 112$) were analyzed separately, there was a strong negative association between IGF-I and HbA_1 ($r = -0.45$, $P < 0.001$; Fig. 1) but no significant association with either pubertal stage, BMI, or age (Table 2). In the prepubertal subjects, IGF-I levels did not correlate with either age, BMI, or HbA_1 values (Table 2, Fig. 2). One 7.5-yr-old boy with diabetes for 9 mo and otherwise in good health had an IGF-I level of 639 ng/ml (Z score = 5). When this outlier was excluded from analyses, the expected positive linear associations between IGF-I levels and age ($n = 70$, $r = 0.24$, $P = 0.041$) and between IGF-I levels and BMI ($r = 0.30$, $P = 0.013$) were evident in the prepubertal subjects.

Multiple regression analysis was performed to determine which variables (age, pubertal stage, BMI, or HbA_1 values) were independently associated with IGF-I levels (Table 3). For these analyses, the outlier mentioned above was excluded. Overall, there was a significant independent negative association between IGF-I and HbA_1 ($P < 0.001$) and a significant independent positive association between IGF-I and age ($P = 0.020$) but no association between IGF-I and BMI or pubertal stage. In pubertal subjects, there was a significant independent negative association between IGF-I and HbA_1 values ($P < 0.001$) but no association with pubertal stage, age, or BMI. In prepubertal subjects, there were no significant independent associations between IGF-I and either age or HbA_1. However, multiple regression analysis revealed a positive independent association between IGF-I and BMI ($P = 0.037$) in prepubertal subjects.

Because there was an increased percentage of boys in prepubertal subjects (Table 1), pubertal boys and girls were analyzed separately to be certain there was no effect of gender on the negative association between IGF-I and HbA_1 observed in pubertal subjects. IGF-I was negatively associated with HbA_1 in both pubertal boys ($n = 43$, $r = -0.46$, $P = 0.001$) and girls ($n = 69$, $r = -0.33$, $P = 0.003$).

CONCLUSIONS

Our study revealed that plasma IGF-I levels are negatively associated with HbA_1 values in pubertal subjects but not in prepubertal subjects with type I diabetes. The impression that this effect exists in all diabetic subjects may be secondary to a selection bias toward adolescent subjects in most studies that have shown a negative association between IGF-I levels and HbA_1 values (4,5,10).

Blethen et al. (10) reported that IGF-I levels increased during puberty in diabetic subjects in a manner similar to that in nondiabetic subjects (25–27). After controlling for the expected rise of IGF-I during puberty, Blethen et al. demonstrated a statistically significant negative association between plasma IGF-I and HbA_1 in 155 subjects 1–20 yr of age (10). However, this study did not separate prepubertal and pubertal subjects into groups

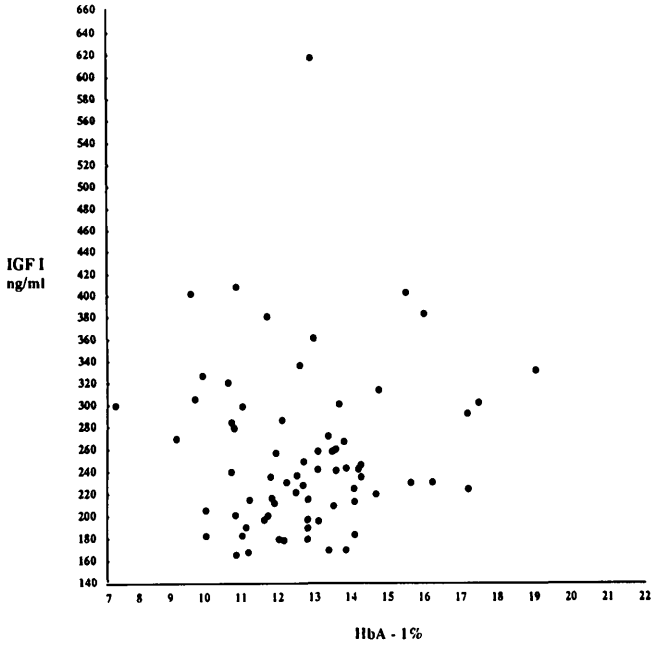

FIG. 2. Relationship between insulinlike growth factor I (IGF-I) and HbA_1 levels in prepubertal (Tanner stage I) diabetic children ($y = 207 + 4.1x$, $r = 0.11$, NS).

TABLE 3
Results of multiple regression analyses with insulinlike growth factor I as dependent variable for all analyses

Variable*	*t* for independent contribution	*P*	r^2†
All subjects (*n* = 182)			
Age	2.35	0.020	
Pubertal stage	0.89	0.373	0.21
HbA_1	−3.79	<0.001	
Body mass index	0.85	0.397	
Prepubertal (*n* = 70)			
Age	1.16	0.248	
HbA_1	0.89	0.379	0.13
Body mass index	2.12	0.037	
Pubertal (*n* = 112)			
Age	−0.39	0.698	
Pubertal stage	0.08	0.941	0.21
HbA_1	−4.97	<0.001	
Body mass index	0.77	0.445	

*One prepubertal outlier was excluded from these analyses; see METHODS for deatils.
†r^2 is for each entire multiple regression model.

to determine whether this negative association existed throughout childhood.

Cacciari et al. (14) did not observe any association between plasma IGF-I and HbA_1 levels in 20 prepubertal and 39 pubertal subjects even after controlling for higher HbA_1 levels observed in pubertal subjects (14). If the negative association between IGF-I and HbA_1 exists only in pubertal subjects, including a large proportion of prepubertal subjects in this type of analysis may cause the association between IGF-I and HbA_1 to be missed.

Studies that show an increase in IGF-I levels when diabetic subjects have dramatically improved their glycemic control also have mostly utilized adolescent subjects (5,11,12). This is noteworthy because Merimee et al. (13) showed that IGF-I levels increased with improved glycemic control only in 3 adolescent diabetic subjects who had progression of puberty during the course of their study. Five prepubertal subjects and 15 adult subjects showed no increase in IGF-I levels with improvement of glycemic control. Our study supports the contention that in children, age and stage of puberty appear to be major factors in determining whether improvement of glycemic control results in an increase of IGF-I (13).

Levels of IGF-I in our prepubertal subjects were similar to those observed in another study of nondiabetic children (26). The expected rise of IGF-I levels in our pubertal subjects appears to be blunted compared with those observed in nondiabetic pubertal children (26,27). This suggests that basal levels of IGF-I were not affected by diabetes, whereas sex hormone–dependent enhanced levels of IGF-I were affected by diabetes. This supports a recent observation that diabetic children in early puberty appear to be the most vulnerable to growth suppression secondary to poor glycemic control compared with prepubertal or late pubertal diabetic children (28).

Studies have elucidated the important role that nutrition plays in the pubertal growth spurt (29). Increasing levels of insulin observed during puberty inhibit the production of hepatic IGF-I binding protein, thus allowing more bioavailable IGF-I to act on target tissues in addition to the overall increase in IGF-I levels observed during puberty. In our prepubertal subjects, BMI, an index of nutritional status, was positively associated with IGF-I levels. In pubertal subjects, BMI was not associated with IGF-I levels, but IGF-I binding protein levels were not measured.

Glycemic control affects IGF-I levels in diabetic subjects during puberty but not before puberty. Thus, glycemic control does not appear to directly affect the growth hormone–IGF-I axis but may in part exert this effect indirectly through other factors such as sex hormones. Subjects treated with physiological dosages of testosterone or estradiol for various reasons develop increased IGF-I levels (30–32). Sex hormone levels in diabetic animals are markedly suppressed and return to normal with insulin therapy (18,33). One study documented an association between increasing sex hormone levels and IGF-I levels in insulin-treated diabetic animals (18). However, the effect of glycemic control on sex hormone levels in diabetic adolescent subjects has not been systematically investigated.

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