

Growth Changes in Children and Adolescents With Short-Term Diabetes

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OBJECTIVE — Height and weight changes during the first 3 years of diabetes were prospectively followed in 152 diabetic children and adolescents.

RESEARCH DESIGN AND METHODS — The study sample consisted of 152 Caucasian diabetic patients (84 boys; 68 girls) followed from diabetes onset in the Paediatric Diabetes Unit and 80 Caucasian normal subjects (49 boys; 31 girls) assessed in the Outpatient General Paediatric Clinic of the same hospital for routine examination and not affected by problems that might influence growth. Diabetic patients and control subjects were consecutively enrolled in the study between 1989 and 1992; diabetic patients with positive markers for celiac disease (positive antiendomysial antibodies) and thyroid disease (positive antimicrosomal antibodies) or any other chronic disease were not considered in the study. Mean age of diabetic patients (8.9 ± 4.1 years) and control subjects (8.5 ± 4.2 years) at recruitment in the study was similar.

RESULTS — At onset of diabetes, the mean height expressed as the height standard deviation score (HSDS) was significantly greater than the expected values ($P < 0.0001$) and was independent of sex and pubertal stage. During the first 3 years of diabetes, HSDS decreased significantly ($F = 6.9$; $P < 0.001$). Meanwhile, growth velocity as standard deviation score (SDS) decreased significantly between the 1st and 2nd year (-0.12 ± 2.1 ; -0.76 ± 2.6 , respectively; $P < 0.05$), but it was similar between the 2nd and 3rd year of diabetes. Weight expressed as SDS increased significantly during the first 2 years of diabetes but not thereafter. Height changes during the study period were independent from pubertal stage and sex. Metabolic control and insulin requirement, in our series, were not clearly related to height and weight changes.

CONCLUSIONS — Diabetic patients at onset of diabetes are taller than age- and sex-matched nondiabetic subjects. During the first years of the disease, linear growth decreases independently of metabolic control and weight changes.

In 1925, Joslin et al. (1) suggested that children with diabetes were taller at onset of the disease than nondiabetic peers, and thus far, contrasting data have been reported on this issue. Two studies have reported different growth patterns during prediabetes. One study reported a faster growth velocity before than after onset of diabetes (2), but the second one, based on identical nondiabetic twins, reported a decreased growth before diabetes (3).

Diabetic children and adolescents at onset of the disease have been reported to be taller (4,5), similar (6,7), or shorter (8,9)

than healthy control subjects. Reasons for these conflicting findings have not been clearly identified. After onset of IDDM, growth could be influenced by variables such as the degree of metabolic control (10), child age (11), and child pubertal stage (12). The influence of weight gain on acceleration of linear growth velocity has also been documented (13), although few studies have reported data tracking weight change after onset of IDDM (6,14).

The aim of the study was to evaluate changes in height and weight in diabetic children and adolescents during the first 3

years of diabetes. We examined these changes as a function of age, pubertal stage, and metabolic control.

RESEARCH DESIGN AND

METHODS — The study sample consisted of 152 Caucasian diabetic patients (84 boys; 68 girls) followed from diabetes onset in the Paediatric Diabetes Unit and 80 Caucasian normal subjects (49 boys; 31 girls) assessed in the Outpatient General Paediatric Clinic of the same hospital for routine examination and not affected by problems that might influence growth. Diabetic patients and control subjects were consecutively enrolled in the study between 1989 and 1992; diabetic patients with positive markers for celiac disease (positive antiendomysial antibodies) and thyroid disease (positive antimicrosomal antibodies) or any other chronic disease were not considered in the study. Mean age of diabetic patients (8.9 ± 4.1 years) and control subjects (8.5 ± 4.2 years) at recruitment in the study was similar.

We report the auxological data related to onset and 1st, 2nd, and 3rd years of diabetes. Height was measured by Harpenden stadiometer (Holtain, Crymych, Dyfed, U.K.) and weight with a gauged scale; auxological data at the follow-up visit were measured at the anniversary of diagnosis ± 1 week. Height was calculated in two ways using the growth computer Kabi Pharmacia Growth Calculator (Pharmacia and Upjohn, Stockholm, Sweden): 1) the height standard deviation score (HSDS) and 2) the growth velocity standard deviation score (SDS). Weight was expressed as weight standard deviation score (WSDS). Puberty was assessed clinically according to Tanner's Table: prepubertal patients (Tanner stage P1), early pubertal patients (Tanner stage P2–P3), and late pubertal patients (Tanner stage P4–P5). At onset of diabetes, patients mean HbA_{1c} was $11.3 \pm 2.2\%$.

Pubertal stages and clinical data for follow-up statistical analyses were obtained at the end of the 1st, 2nd, and 3rd years of follow-up.

All patients or their parents were instructed, at onset of diabetes, to self-monitor blood and urine for glucose and to change insulin doses to maintain blood

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Abbreviations: ANOVA, analysis of variance; HSDS, height standard deviation score; SDS, standard deviation score; WSDS, weight standard deviation score.

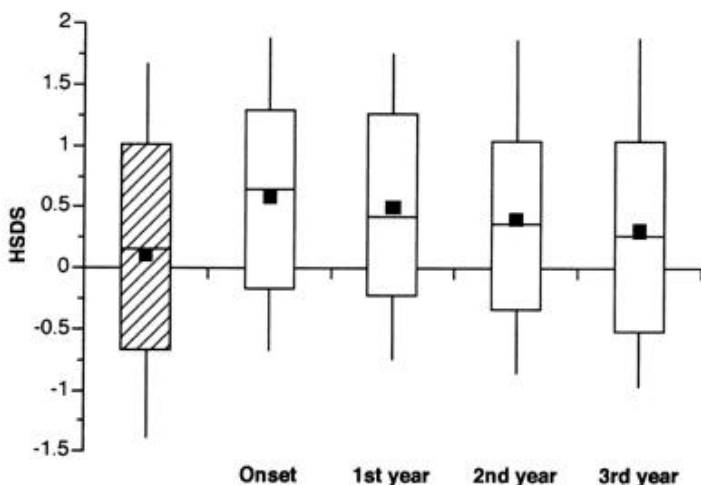


Figure 1—HSDS in normal subjects (▨) and diabetic patients (□) at onset and 1st, 2nd, and 3rd years of diabetes. The top and bottom of the box and the line through the middle correspond to the 75th, 25th, and 50th percentile, respectively; lines above the top and below the bottom of the box correspond to the 90th percentile and 10th percentile, respectively; square symbol represents the arithmetic mean. ANOVA between onset of IDDM and the three follow-up time points: $F = 6.9$; $P < 0.001$. One-sample t test: NS; onset IDDM ($P < 0.0001$); 1st-year IDDM ($P < 0.0001$); 2nd-year IDDM ($P < 0.002$); 3rd-year IDDM ($P < 0.01$).

glucose levels before meals between 80 and 120 mg/dl and blood glucose levels after meals between 100 and 160 mg/dl. The patients were released from the hospital with 3–4 insulin injections/day of long- and short-acting insulin and a balanced diet according to age. Patients were followed every 2–3 months at the Outpatient Paediatric Diabetes Clinic of our Institution. HbA_{1c} was assayed by high-performance liquid chromatography (HPLC; Diamat Biorad, Milan, Italy); reference value in normal subjects for our laboratory is $<6\%$. The mean HbA_{1c} during the 1st, 2nd, and 3rd year of diabetes was $7.9 \pm 0.3\%$; $8.1 \pm 1.9\%$; $8.1 \pm 1.5\%$, respectively.

Statistical analysis has been performed by analysis of variance (ANOVA), one-sample/two-sample Student's t test, and linear correlation for continuous data using a commercially available statistical software (Statview, Brainpower, Calabasas CA.). HSDS has been analyzed by one-sample t test entering as reference value zero, because normal HSDS is equal to zero. Data were expressed as means \pm SD.

RESULTS

Height and weight at onset of diabetes

HSDS was significantly greater than zero (the normal population mean) in diabetic patients (0.59 ± 1.04 ; $P < 0.0001$) but not significantly greater in healthy control sub-

jects (0.11 ± 1.3 ; NS). In diabetic patients, HSDS was similar between boys and girls (0.49 ± 1.0 vs. 0.72 ± 1.1 , respectively) and between prepubertal, early pubertal, and late pubertal patients (0.63 ± 1.0 vs. 0.54 ± 1.1 vs. 0.51 ± 1.0 , respectively). WSDS was significantly lower in diabetic than healthy control subjects (-0.04 ± 0.94 vs. 0.42 ± 1.41 , respectively; $P < 0.01$). In diabetic patients, weight was similar between boys and girls (0.01 ± 0.90 vs. -0.09 ± 0.99 , respectively), and between prepubertal, early pubertal, and late pubertal patients (-0.06 ± 0.99 vs. 0.15 ± 0.77 vs. -0.14 ± 0.90 , respectively). HSDS was inversely related to HbA_{1c} ($r = -0.174$; $P < 0.05$) and independent from age. WSDS was directly related to HSDS ($r = 0.515$; $P < 0.0001$), inversely related to HbA_{1c} ($r = -0.180$; $P < 0.05$), and independent from age.

Height and weight at follow-up

HSDS decreased significantly between onset of IDDM and the first 3 years of diabetes ($F = 6.9$; $P < 0.001$). However, at each time point, HSDS significantly exceeded the population mean: 1st year ($P < 0.0001$); 2nd year ($P < 0.002$); 3rd year ($P < 0.01$; Fig. 1). HSDS was independent from pubertal stage. The mean HSDS among prepubertal, early pubertal, and late pubertal patients was 0.37 ± 0.94 , 0.32 ± 1.32 , and 0.58 ± 1.21 , respectively ($F = 1.5$; NS). HSDS was also similar for boys and girls matched for pubertal stage.

Growth velocity SDS decreased significantly between the 1st (-0.12 ± 2.1) and the 2nd year (-0.76 ± 2.6), $P < 0.05$, but it was similar between the 2nd (-0.76 ± 2.6) and the 3rd year (-0.39 ± 2.4). Glycosylated hemoglobin was independent from HSDS, but inversely related to growth velocity as SDS ($r = -0.147$; $P < 0.02$). Insulin dose was independent from HSDS but positively correlated to growth velocity SDS ($r = 0.148$; $P < 0.01$).

WSDS changed significantly between onset of IDDM and the follow-up ($F = 26.3$; $P < 0.0001$); WSDS increased significantly between diabetes onset and the 1st-year follow-up, but not subsequently (Fig. 2). WSDS was related to HSDS ($r = 0.542$; $P < 0.0001$), but independent from growth velocity SDS and pubertal stage. Mean WSDSs for prepubertal, early pubertal, and late pubertal patients were 0.56 ± 0.05 ; 0.07 ± 0.90 ; 0.36 ± 0.76 , respectively ($F = 4.02$; $P < 0.05$). Boys and girls, matched for pubertal stage, were similar regarding weight. Insulin dose as units per kilograms body weight per day and HbA_{1c} were not related to weight during the follow-up period.

During follow-up, HbA_{1c} was independent from pubertal stage. Mean HbA_{1c} values for prepubertal, early pubertal, and late pubertal patients were 7.9 ± 1.1 , 7.9 ± 1.0 , and $8.1 \pm 1.2\%$, respectively ($F = 0.4$; NS). However, insulin dose changed significantly with pubertal stage. The mean insulin values for prepubertal, early pubertal, and late pubertal patients were 0.73 ± 0.18 , 0.76 ± 0.21 , and 0.69 ± 0.22 , respectively ($F = 3.5$; $P < 0.05$). Boys and girls, matched for pubertal stage, were similar regarding HbA_{1c} and insulin dose in early and late pubertal patients, but not in prepubertal patients: 0.70 ± 0.15 vs. 0.80 ± 0.17 U \cdot kg⁻¹ \cdot day⁻¹; $P < 0.0001$.

CONCLUSIONS— Our data, in accordance with previous studies, suggest that diabetic children and adolescents at onset of diabetes are taller than nondiabetic subjects (2,4,5). Glycosylated hemoglobin at onset of diabetes was inversely related to HSDS excess. This could be explained by the negative effect of hyperglycemia on growth factors or by a greater loss of the metabolic fuels (glucose, proteins, fats) associated with the severe insulin deficiency, as suggested by the inverse relationship between weight and HbA_{1c} and the positive relationship between weight and HSDS. We have no data to support one of the two hypotheses; however, it

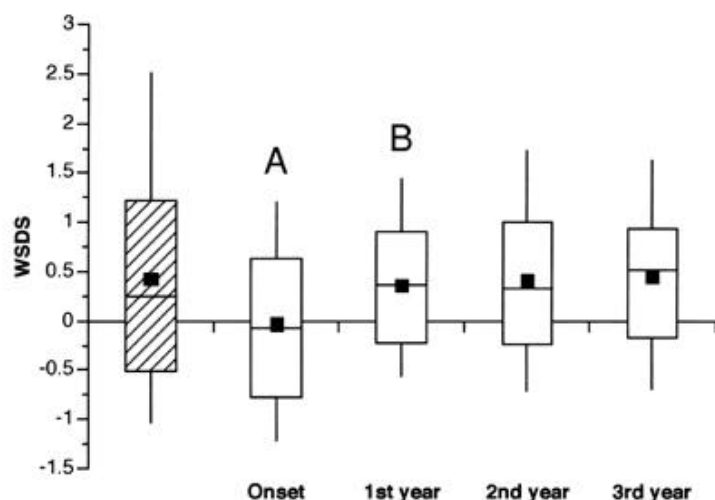


Figure 2—WSDS in normal subjects (▨) and diabetic patients (□) at onset and 1st, 2nd, and 3rd years of diabetes. The top and bottom of the box and the line through the middle correspond to the 75th, 25th, and 50th percentile, respectively; lines above the top and below the bottom of the box correspond to the 90th percentile and 10th percentile; square symbol represents the arithmetic mean. ANOVA between onset of IDDM and the three follow-up time points: $F_{2,3} = 26.3; P < 0.0001$. A: Control subjects versus onset IDDM ($P < 0.001$). B: Onset versus 1st-year IDDM ($P < 0.001$).

could be possible that during the prediabetic period, growth factors increase because of the progressive insulin deficiency, but that at the onset of diabetes, the severe metabolic derangement negatively modifies the effect of growth factors. High levels of insulin-like growth factor binding protein (IGFBP-I), which reduce the effects of IGF-I, have been reported in diabetic children during poor metabolic control (15). Moreover, during follow-up, HSDS decreased significantly; poor metabolic control significantly decreases growth in diabetic patients (10,16), but in our series, metabolic control was good and HbA_{1c} levels during follow-up were not related to HSDS. Therefore, the HSDS decrease during follow-up could reflect the reduction of growth factor excess at onset of diabetes as suggested by others (16), even if we have no biological data to confirm this hypothesis.

In patients 5–10 years old, greater HSDS than that before or after this age-group (11) has been reported by some authors but not by others (16,17); in our study, sex and age were independent from HSDS. During follow-up, insulin dose was independent from HSDS but positively related to growth velocity. Insulin reduces IGF-I binding protein (17) and conversely accelerates linear growth. During puberty, insulin resistance is associated with the increase of serum insulin concentration (15–19), and in our diabetic patients, insulin dose was slightly but significantly higher in patients with in stage P2–P3

(early puberty) than in patients in Tanner stages P1 and P4–P5 (late puberty). However, HSDS at follow-up was independent from pubertal stage.

Growth velocity in nondiabetic patients declines during weight reduction (20) and increases during weight gain (21). In our series we have observed, during the 1st and 2nd years, a progressive weight gain, but growth velocity SDS was independent of weight as previously reported by others in diabetic children and adolescents with diabetes (6).

In short-term diabetic patients, higher HSDS has been reported in late pubertal patients than in prepubertal and early pubertal patients (12), and a significant loss of HSDS, according to the final height, has been noted only in patients with onset of diabetes between 5 and 10 years of age (11). In our study, HSDS excess was independent of pubertal stage both at onset and at follow-up and was similar between boys and girls matched for pubertal stage.

In conclusion, diabetic patients at onset of diabetes are taller than age- and sex-matched nondiabetic subjects. During the first years of the disease, linear growth decreases without any clear relationship with metabolic control and weight changes.

References

1. Joslin EP, Root HF, White P: Growth development and prognosis of diabetic children. *JAMA* 85:420–422, 1925

2. Price DE, Burden AC: Growth of children before onset of diabetes. *Diabetes Care* 15:1393–1495, 1992

3. Leslie RDG, Simon LO, Millward A, Honour J, Pyke DA: Decreased growth velocity before IDDM onset. *Diabetes* 40:211–216, 1991

4. Salardi S, Tonioli S, Tassoni P, Tellarini M, Mazzanti L, Cacciari E: Growth and growth factors in diabetes mellitus. *Arch Dis Child* 62:57–62, 1987

5. Drayer NM: Height of diabetic children at onset of symptoms. *Arch Dis Child* 49:616–619, 1974

6. Thon A, Heinze E, Feilen K, 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

7. Beal CK: Body size and growth rate of children with diabetes mellitus. *J Pediatr* 32:170–174, 1948

8. Songer TJ, LaPorte RE, Tajima N, Orchard TJ, Rabin BS, Eberhardt MS, Dorman JS, Cruickshanks KJ, Cavender DE, Becker DJ, Drash AL: Height at diagnosis of insulin dependent diabetes in patients and their non-diabetic family members. *Br Med J* 292: 1419–1422, 1986

9. Edelsten AS, Hughes IA, Oakes S, Gordon IRS, Savage DCL: Height and skeletal maturity in children with newly diagnosed juvenile-onset diabetes. *Arch Dis Child* 56:40–44, 1981

10. Jackson RL, Holland E, Chatman ID, Guthrie D, Hewett JE: Growth and maturation of children with insulin-dependent diabetes mellitus. *Diabetes Care* 1:96–107, 1978

11. Brown M, Ahmed ML, Clayton KL, Dunger DD: Growth during childhood and final height in type 1 diabetes. *Diabet Med* 11:182–187, 1994

12. Wise JE, Kolb EL, Sauder SE: Effect of glycemic control on growth velocity in children with IDDM. *Diabetes Care* 15:826–830, 1992

13. Vignolo M, Naselli A, Di battista E, Mostest M, Aicardi G: Growth and development in simple obesity. *Eur J Pediatr* 147:242–244, 1988

14. Bognetti E, Macellaro P, Novelli D, Meschi F, Ciralli F, Chiumello G: Prevalence and correlates of obesity in insulin-dependent diabetic patients. *Arch Dis Child* 73:239–242, 1995

15. Holly JMP, Dunger DB, Edge JA, Smith CP, Chard T, Wass JAH: Insulin-like growth factor binding protein I levels in diabetic adolescents and their relationship to metabolic control. *Diabet Med* 7:618–623, 1990

16. Malone J: Growth and sexual maturation in children with insulin dependent diabetes mellitus. *Cur Opin Pediatr* 5:494–498, 1993

17. Suikkara A, Koivisto VA, Koistinen R, Sepala M, Hannele Y: Dose-response characteristics for suppression of low molecular weight plasma insulin-like growth factor-binding protein by insulin. *J Clin Endocrinol Metab*68:135-140, 1989
18. Zadik Z, Chalew SA, McCarter RJ, Meistas M, Kowarski AA: The influence of age on the twenty-four-hour integrated concentration of growth hormone in normal individuals. *J Clin Endocrinol Metab*60:513-516, 1985
19. Block CA, Clemons P, Sperling MA: Puberty decreases insulin sensitivity. *J Pediatr* 110:481-487, 1987
20. Dietz WH, Hartung R: Changes in height velocity of obese preadolescents during weight reduction. *Am J Dis Child*139:705-707, 1985
21. Forbes GB: Nutrition and growth. *J Pediatr* 91:40-42, 1977