

Decreased Growth Velocity Before IDDM Onset

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Diabetes can retard growth. Growth was studied prospectively in 12 nondiabetic identical twins aged <14 yr and in their co-twins with insulin-dependent diabetes mellitus (IDDM) to determine whether changes in growth occur before the onset of IDDM. Seven of the 12 nondiabetic twins subsequently developed IDDM; the remainder are now unlikely to become diabetic. A significantly reduced growth velocity was observed more frequently in the nondiabetic twins (7 of 12) than in their diabetic co-twins (1 of 12; $P = 0.03$). Of the 7 nondiabetic twins who were prediabetic, 6 had a reduction in growth velocity to below the 3rd percentile before the onset of diabetes compared with 1 of their diabetic co-twins ($P = 0.03$). However, only 1 of the 5 nondiabetic twins who did not develop diabetes showed a reduction in growth velocity. The nadir of growth in the twins who developed diabetes occurred a mean of 1.2 yr before diagnosis (range 0.3–2.3 yr). All 7 of the prediabetic twins had islet cell antibodies when first seen, and 3 had them before they showed either decreased growth velocity or impaired glucose tolerance. In 4 prediabetic twins, the decreased growth preceded impaired glucose tolerance. The prediabetic twins tested had lower testosterone or estradiol levels at the time they showed decreased growth than their diabetic twins. We conclude that decreased growth velocity is an early sensitive marker of IDDM. *Diabetes* 40:211–16, 1991

Growth is a sensitive indicator of health in childhood. Diabetes can retard growth, and before insulin was discovered, growth ceased entirely in children who developed the disease (1). We noted that some twins with insulin-dependent diabetes mellitus (IDDM) were shorter at the time of diagnosis than their nondiabetic co-twins (2). Because identical twins normally grow at the same rate and to much the same final height, we concluded that diabetes can affect growth before the disease is diagnosed (2,3). Moreover, the estimated period of impaired growth was considerably longer than the dura-

tion of diabetic symptoms (2). We postulated that impaired growth (growth delay or arrest) might occur in patients months or even years before the clinical onset of IDDM. Growth was therefore studied prospectively in nondiabetic identical twins of IDDM patients. We now present evidence that a decrease in growth velocity can occur in these twins particularly in those who later develop diabetes.

RESEARCH DESIGN AND METHODS

We studied 12 identical twins selected because: 1) they were the nondiabetic twins of an IDDM patient, 2) they were <14 yr old during the study period, and 3) accurate growth data were available from height measurements taken at least 0.5 yr apart. Monozygosity was established as previously described (4). The diabetic twins were measured at the same time as the nondiabetic twins, and the twins were studied from 1977 to 1986. None of the twins had a major illness during the study; both members of each pair were living together throughout the study. Subjects or their parents gave informed consent, and the study was approved by the ethical committees at Westminster Hospital and King's College Hospital.

The characteristics of the 12 twin pairs at the time of referral of the diabetic index twin are shown in Table 1. The 12 twin pairs were studied on 55 occasions (median 4 occasions/twin, range 2–11). One of the diabetic twins (pair 5) had asthma and had received oral steroids at an earlier age. Height was measured with either a Harpenden stadiometer, which measures height to the nearest millimeter, or a measuring scale fixed to the wall with a mobile arm, which

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TABLE 1
Initial characteristics of 12 identical twin pairs

| Twin pair | Sex | Age at diagnosis (yr) | Initial age (yr) | Initial height (cm) | Initial weight (kg) | Growth nadir (cm/yr) |
|-----------|-----|-----------------------|------------------|---------------------|---------------------|----------------------|
| Index | M | 10.9 | 10.9 | 140 | 31 | 4.0 |
| Co-twin | M | 12.3 | 10.9 | 142 | 34 | 3.2 |
| Index | M | 12.5 | 12.7 | 146 | 37 | 5.6 |
| Co-twin | M | 14.5 | 12.7 | 145 | 35 | 0.8 |
| Index | M | 11.1 | 11.3 | 139 | 34 | 6.0 |
| Co-twin | M | 14.8 | 11.3 | 141 | 32 | 2.2 |
| Index | F | 9.1 | 10.3 | 128 | 31 | 5.0 |
| Co-twin | F | 12.4 | 10.3 | 128 | 31 | 9.6 |
| Index | F | 8.7 | 10.8 | 141 | 31 | 6.0 |
| Co-twin | F | 12.1 | 10.8 | 158 | 45 | 3.4 |
| Index | F | 7.9 | 8.2 | 131 | 20 | 2.3 |
| Co-twin | F | 9.1 | 8.2 | 132 | 20 | 3.6 |
| Index | F | 12.0 | 12.2 | 140 | 35 | 6.3 |
| Co-twin | F | 14.5 | 12.2 | 141 | 31 | 2.7 |
| Index | F | 10.0 | 11.7 | 154 | 40 | 4.8 |
| Co-twin | F | | 11.7 | 150 | 39 | 3.8 |
| Index | F | 11.7 | 11.7 | 145 | 35 | 6.6 |
| Co-twin | F | | 11.7 | 144 | 34 | 5.8 |
| Index | M | 12.5 | 12.7 | 143 | 36 | 6.4 |
| Co-twin | M | | 12.7 | 140 | 32 | 7.3 |
| Index | M | 4.4 | 6.2 | 116 | 18 | 5.5 |
| Co-twin | M | | 6.2 | 117 | 17 | 5.5 |
| Index | M | 11.0 | 11.0 | 141 | 48 | 6.1 |
| Co-twin | M | | 11.0 | 150 | 64 | 4.0 |

All twin pairs were initially discordant for diabetes, and 5 twins remained nondiabetic.

records height to the nearest centimeter. The nadir of growth was documented in 10 of 12 twin pairs with a Harpenden stadiometer, whereas in the remaining 2 pairs, the growth nadir was measured by the same observer (R.D.G.L.) with a measuring scale; any error in this latter method would be systematic and should not affect calculations of growth velocity. Two nondiabetic co-twins (pairs 1 and 5) had their initial growth velocity estimated from height measurements in a pediatric clinic before the onset of diabetes in the index twin. Relative height was determined with Tanner-Whitehouse growth charts and expressed as percentile ranking. Growth was calculated between two points at least 0.5 yr apart. Growth was considered abnormal if the velocity was above the 97th percentile or below the 3rd percentile for that age. Weight was measured with portable weight scales and compared with standardized weight charts. Body mass index (BMI) was calculated for each twin.

Fasting venous whole blood glucose was measured in all nondiabetic twins on each occasion to exclude diabetes (5). All but two of the nondiabetic twins had an oral glucose tolerance test during the study period (median of 2 tests/twin, range 0–7). The subjects were studied after an overnight fast and 15 min after a venous cannula was inserted into an antecubital vein. Blood samples were taken at –10 and 0 min, and a glucose load (1.75 g/kg) dissolved in 0.33 L water was consumed over 4 min. Further samples were taken at 30, 60, 90, and 120 min for measurement of whole blood glucose and serum insulin. Whole blood glucose was analyzed by a glucose oxidase method (YSI, Yellow Springs, OH), and serum insulin was measured with a modification of a double-antibody radioimmunoassay (6). Fasting values were taken as the mean of –10- and 0-min values. Impaired glucose tolerance was defined with conventional criteria (5).

Pubertal status was assessed with estradiol and testosterone in preference to Tanner staging. Tanner staging was performed by different observers during the study period, but the results are not reported here due to observer variation. Estradiol or testosterone levels were measured in fasting sera obtained between 0830 and 1000 in both twins (7). Results in twins were compared with healthy nondiabetic control subjects from the local community.

Sera were also tested by indirect immunofluorescence on a fresh pancreas (group 0) for the presence of conventional islet cell antibodies (8). All sera were tested on a single occasion by two independent observers on a single pancreatic substrate under standard incubation conditions. The same pancreas, reagents, and incubation conditions with the putative islet cell antibody standard being assessed for the International Immunology and Diabetes Workshop gave end-point titers of 32. The results are presented as positive or negative with positive tests being >10 U. All nondiabetic twins with islet cell antibodies were followed until they developed IDDM, those nondiabetic twins without islet cell antibodies were followed for a minimum of 5 yr from the diagnosis of the index twin when we calculated their risk of developing diabetes as being <5% (9).

Results are presented as means \pm SD. Results were compared with either a χ^2 -test with Fisher's exact or a two-tailed Student's *t* test for paired or unpaired samples and a Wilcoxon's signed-rank test. *P* < 0.05 was considered significant.

RESULTS

Height and weight did not differ significantly between the groups of nondiabetic and diabetic co-twins either initially

or during the study (Table 1). The diabetic twin with asthma (Table 1, pair 5) was 17 cm shorter than her nondiabetic twin at the start of the study and remained substantially shorter throughout; she had been asthmatic from 3 yr of age and was treated with steroids. Of the 12 diabetic twins, 7 were initially shorter than their nondiabetic twin, 4 were taller, and 1 was the same height. Of the 4 twin pairs (Table 1, pairs 1, 7, 9, and 12) examined within 2 mo of the diagnosis of the diabetic twin, 3 diabetic twins were shorter than their nondiabetic twins. The initial weight of both the nondiabetic and diabetic twins was in the normal range with one exception (Table 1, pair 12), in which both twins of a pair were above the 97th percentile for weight. None of the twins lost weight during the study.

The growth velocity throughout the whole study period in the 12 nondiabetic twins (5.0 ± 2.6 cm/yr) did not differ significantly from that in their diabetic co-twins (6.2 ± 1.5 cm/yr). A significant decrease in growth velocity at some stage of the study period below the 3rd percentile was observed in 7 of the 12 nondiabetic twins (Figs. 1 and 2) but in only 1 of their diabetic twins studied concurrently ($P = 0.03$). The height and growth velocity of 1 nondiabetic twin was above the 97th percentile (Table 1, pair 5; Fig. 2);

that twin later showed a significantly decreased growth velocity and then developed diabetes.

Estradiol levels were similar in the female nondiabetic twins (102 ± 70 pM) and their diabetic twins (102 ± 6 pM); testosterone was lower in the 5 male nondiabetic twins (0.7 ± 0.5 nM) than in their diabetic twins (4.1 ± 2.8 nM; $P = 0.04$). Islet cell antibodies were detected in 7 of the 12 nondiabetic twins and in 10 of their 12 diabetic co-twins.

Of the 12 nondiabetic twins initially studied, 5 remained nondiabetic and were unlikely to develop the disease (9). The initial height and weight of these 5 twins were similar to their diabetic co-twins (Table 1). In one twin pair (Table 1, pair 12), the diabetic twin at diagnosis was substantially shorter and lighter than his nondiabetic twin; no cause other than diabetes was apparent for this discrepancy (2).

The mean growth velocity over the whole study period in the five twins who remained nondiabetic (6.9 ± 1.2 cm/yr) was similar to the growth in their diabetic twins over the same period (5.8 ± 2.8 cm/yr). None of the twins in these five pairs had an increased growth velocity during the study period. A decreased growth velocity below the 3rd percentile was observed in one of the nondiabetic twins but in none of their diabetic co-twins.

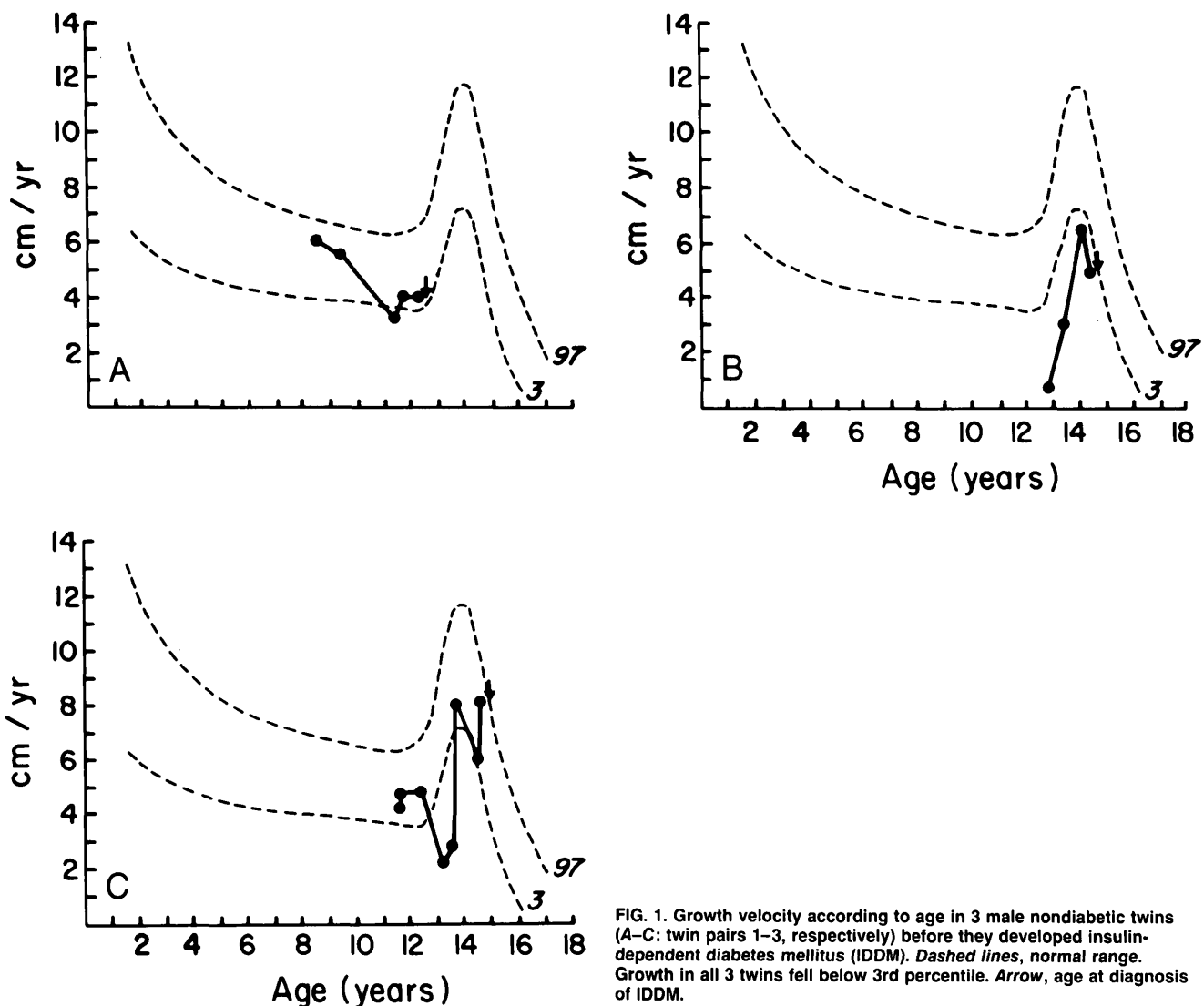


FIG. 1. Growth velocity according to age in 3 male nondiabetic twins (A–C: twin pairs 1–3, respectively) before they developed insulin-dependent diabetes mellitus (IDDM). Dashed lines, normal range. Growth in all 3 twins fell below 3rd percentile. Arrow, age at diagnosis of IDDM.

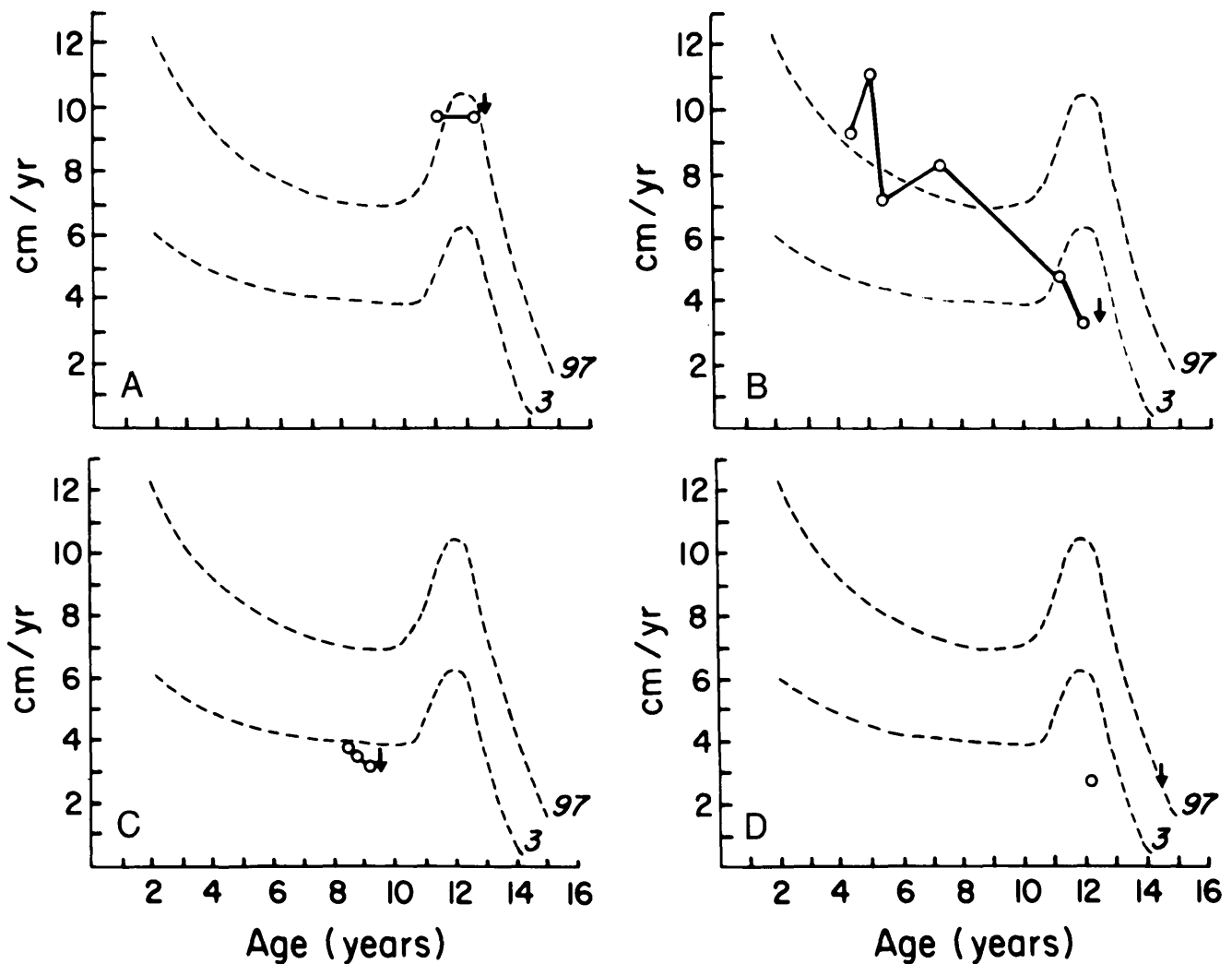


FIG. 2. Growth velocity according to age in 4 female nondiabetic twins (A–D: twin pairs 4–7, respectively) before they developed insulin-dependent diabetes mellitus (IDDM). Dashed lines, normal range. Growth in 3 of 4 twins fell below 3rd percentile. Arrow, age at diagnosis of IDDM.

The five twins who remained nondiabetic were given glucose tolerance tests and were compared with seven nondiabetic control subjects matched for mean age (13.1 ± 2.7 vs. 13.1 ± 3.5 yr), sex (3 vs. 4 males), and BMI (19.2 ± 5.8 vs. 20.2 ± 3.5 kg/m²). The nondiabetic twins and their control subjects had similar mean blood glucose when fasting (4.5 ± 0.7 vs. 4.3 ± 0.5 mM) and after a glucose load at 60 min (7.0 ± 3.0 vs. 5.4 ± 1.1 mM) and 120 min (5.9 ± 1.8 vs. 4.8 ± 0.9 mM). Insulin levels of the nondiabetic twins were also similar compared with their control subjects when fasting (99 ± 77 vs. 64 ± 44 pM) and after a glucose load at 60 min (425 ± 384 vs. 274 ± 106 pM) and 120 min (343 ± 302 vs. 182 ± 58 pM).

The levels of estradiol were similar in the two nondiabetic twins (155 and 188 pM; Table 2) and their diabetic twins (97 and 110 pM); the levels of testosterone were also similar in the two nondiabetic twins (0.6 and 0.7 nM; Table 2) and their diabetic twins (0.5 and 7.1 nM).

Islet cell antibodies were detected in none of the five nondiabetic twins and in three of their five diabetic co-twins (Table 2). One of these nondiabetic twins had significantly decreased growth velocity at a time when she also had im-

paired glucose tolerance, and both changes subsequently reverted to normal. Five years later and 8 yr after her index twin developed IDDM, she remained nondiabetic with normal glucose tolerance and no islet cell antibodies. Her estimated risk of developing diabetes was <2% (9).

Seven of the 12 nondiabetic twins initially studied developed IDDM. The initial height and weight of these 7 twins were similar to their diabetic co-twins with the exception of one pair (Table 1, pair 5), in which the diabetic twin had asthma and was shorter and lighter than her nondiabetic twin. None of the twins showed a fall in weight or BMI during the study and up to the time of diagnosis.

A decrease in growth to below the 3rd percentile was observed in six of seven nondiabetic twins but in only one of their diabetic co-twins ($P = 0.03$) and in only one of the five nondiabetic twins who remained nondiabetic ($P = 0.09$). The growth nadir in these twins who became diabetic during the study occurred a mean of 1.2 yr before diagnosis (range 0.3–2.3 yr).

The five twins who had oral glucose tolerance tests during the growth nadir were compared to seven nondiabetic control subjects matched for mean age (12.4 ± 0.8 vs.

TABLE 2
Characteristics at growth nadir of 5 nondiabetic twins who did not develop diabetes

| Twin pair | Growth rate (cm/yr) | Age (yr) | Glucose tolerance | Estradiol (pM) | Testosterone (nM) |
|-----------|---------------------|----------|-------------------|----------------|-------------------|
| 8 | 3.8 | 11.7 | Impaired | 155 | |
| 9 | 5.8 | 12.4 | Normal | 188 | |
| 10 | 7.3 | 13.0 | Normal | | |
| 11 | 5.5 | 7.6 | Normal | | 0.6 |
| 12 | 4.0 | 12.4 | Normal | | 0.7 |

All twin pairs tested negative for islet cell antibodies.

13.1 ± 3.5 yr), sex (3 vs. 4 males), and BMI (17.3 ± 1.2 vs. 20.2 ± 3.5 kg/m²). The twins and their control subjects had similar fasting mean blood glucose levels (4.4 ± 0.6 vs. 4.3 ± 0.5 mM). However, mean blood glucose levels were significantly higher in the twins at 30 min (9.1 ± 1.8 vs. 6.5 ± 0.9 mM; *P* = 0.01), 60 min (8.6 ± 1.7 vs. 5.4 ± 1.1 mM; *P* = 0.003), and 90 min (7.6 ± 2.3 vs. 4.9 ± 1.0 mM; *P* = 0.02) but not 120 min (6.7 ± 2.2 vs. 4.8 ± 0.9 mM). Impaired glucose tolerance was detected in three twins before they developed diabetes and in two of them before they showed significant growth delay. Four twins had decreased growth before any changes in glucose tolerance. Insulin levels were similar compared with control subjects when fasting (110 ± 50 vs. 64 ± 44 pM) and after a glucose load at 60 (260 ± 54 vs. 274 ± 113 pM) and 120 min (254 ± 54 vs. 182 ± 58 pM).

Estradiol levels in the three female nondiabetic twins (mean 56, range 28–100 pM; Table 3) were lower than the levels in their diabetic twins (mean 105, range 101–110 pM). Testosterone levels were also lower in the three nondiabetic twins (mean 0.7, range 0.2–1.5 nM; Table 3) than in their diabetic co-twins (mean 4.3, range 1.8–6.3 nM).

In two twins (from pairs 2 and 3), diabetes was diagnosed during a growth spurt because growth increased from 0.8 to 5.0 and 2.2 to 8.2 cm/yr, respectively, and at the same time, the serum testosterone increased from 1.3 to 4.2 and 0.6 to 3.6 nM, respectively (Fig. 1). In the case of the nondiabetic twin from pair 2, this growth spurt was clearly subnormal (Fig. 1).

All seven nondiabetic twins who developed diabetes had islet cell antibodies when first tested, which persisted in all subsequent samples until diagnosis of diabetes (Table 3). Islet cell antibodies preceded both decreased growth velocity and impaired glucose tolerance in three twins before they developed diabetes.

DISCUSSION

In this study, the nondiabetic twins had a significant tendency for growth to fall below the 3rd percentile compared with their diabetic twins. These changes could be ascribed to those seven nondiabetic twins who subsequently developed diabetes. In contrast, the group of five twins who did not develop diabetes did not show these changes in growth. Growth in the twins who developed diabetes during the study fell below the 3rd percentile many months, even years, before the diagnosis of IDDM. Decreased growth was an early and common feature of impending diabetes, in some twins, occurring before glucose tolerance was impaired and long before the onset of diabetic symptoms.

There are no previous studies of growth before the onset of diabetes. Studies of height at diagnosis in diabetic children have produced conflicting results reporting that the children were shorter (2,10), the same height (11), or even taller than expected (10). These discrepancies may have been due, in part, to the difficulty in obtaining exactly matched control groups. A study of many families showed that diabetic children ≥14 yr of age at diagnosis tended to be shorter than expected and also shorter than their siblings, whereas children 5–9 yr of age at diagnosis were taller than expected as were their nondiabetic siblings (10). In a study of diabetic identical twins at the time of diagnosis, we found that some diabetic twins were shorter than their nondiabetic twins consistent with growth arrest or delay before the diagnosis of the disease (2). This height difference at diagnosis was confined to twins 8–19 yr of age. The age-related height effect noted in both twin and family studies is important to this study because we observed growth delay in twins 8–14 yr of age at diagnosis; it is possible that younger diabetic children would not show these changes in growth before the onset of diabetes.

Decreased growth might be due to either metabolic ab-

TABLE 3
Characteristics at growth nadir of 7 nondiabetic twins who later developed diabetes

| Twin pair | Growth rate (cm/yr) | Age (yr) | Glucose tolerance | Estradiol (pM) | Testosterone (nM) |
|-----------|---------------------|----------|-------------------|----------------|-------------------|
| 1 | 3.2 | 13.0 | Normal | | 1.5 |
| 2 | 0.8 | 10.8 | Impaired | | 0.2 |
| 3 | 2.2 | 13.3 | Impaired | | 0.3 |
| 4 | 9.6 | 12.3 | | 28 | |
| 5 | 3.4 | 12.0 | Normal | 39 | |
| 6 | 3.6 | 8.6 | | | |
| 7 | 2.7 | 12.3 | Normal | 100 | |

All twin pairs tested positive for islet cell antibodies and developed insulin-dependent diabetes mellitus.

normalities or delayed puberty. Fasting insulin levels are positively correlated with growth velocity, and changes in insulin and glucose can be detected in the prediabetic period (12,13). In the prediabetic twins we studied at the time of growth nadir, glucose levels after a glucose load were higher than control levels, but insulin levels (fasting and after a glucose load) were similar to those of the control subjects. However, we have previously noted changes in islet β -cell function with increased levels of proinsulin in nondiabetic twins before detectable changes in insulin levels (14). Therefore, it is possible that subtle metabolic changes are responsible for the growth changes that we observed. Alternatively the changes in growth could be due to delayed puberty. In all six nondiabetic twins we tested who later developed diabetes, testosterone or estradiol levels were lower at their growth nadir than in their diabetic co-twins. These changes would be consistent with a delay in puberty before the onset of diabetes. Those twins who did not develop diabetes showed no evidence of a decrease in sex hormones compared with their diabetic co-twins. Although the cause of the decreased growth remains unclear, this study raises the possibility that subtle changes in both metabolism and pubertal development may account for the prediabetic growth delay.

The incidence of IDDM increases during the peripubertal years. In this study, two twins diagnosed during their pubertal growth spurt had both islet cell antibodies and impaired glucose tolerance several months before the growth spurt. Thus, the process that leads to diabetes preceded the growth spurt. Therefore, it seems likely that the pubertal growth spurt does not play a primary role in the pathogenesis of diabetes. However, metabolic decompensation leading to diabetes might be precipitated by the pubertal growth spurt and its associated increase in insulin requirement (15,16).

We have previously shown that immune and metabolic changes in twins can remit without leading to diabetes (14,17,18). One twin in this study had a period of both decreased growth velocity and impaired glucose tolerance from which she recovered without developing diabetes; therefore, it is possible that twins who are genetically at risk of IDDM can show decreased growth and immune and metabolic changes and yet not develop the disease.

We have demonstrated a significant decrease in growth velocity in some twins before they develop IDDM. The decrease in growth velocity can precede the onset of clinical diabetes by many months, even years. At their growth nadir, these twins had changes in both glucose tolerance and sex hormones. Thus, growth delay in the prediabetic period may be the result of subtle changes in metabolism and pubertal development.

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