Testing the Accelerator Hypothesis

The relationship between body mass and age at diagnosis of type 1 diabetes

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OBJECTIVE — Previous reports have predicted greater risk of type 1 diabetes among people who were heavier as young children. The Accelerator Hypothesis predicts earlier onset in heavier people, without necessarily a change in risk, and views type 1 and type 2 diabetes as the same disorder of insulin resistance, set against different genetic backgrounds. Insulin resistance is a function of fat mass, and increasing body weight in the industrialized world has been accompanied by earlier presentation (i.e., acceleration) of type 2 diabetes. We wanted to establish whether increasing body weight was also asociated with the earlier presentation of type 1 diabetes, as the Accelerator Hypothesis would predict.

RESEARCH DESIGN AND METHODS — The relationships between fatness and age at diagnosis were examined in context of birth weight, weight change since birth, weight at diagnosis, BMI at diagnosis, and BMI 12 months later in 94 children aged 1–16 years (49 boys and 45 girls) presenting for management of acute-onset type 1 diabetes.

RESULTS — BMI standard deviation score (SDS) at diagnosis, weight SDS change since birth, and BMI SDS 12 months later were all inversely related to age at presentation ($r = -0.39$ to -0.40, $P < 0.001$). The boys were significantly fatter than the girls (BMI SDS 0.56 vs. -0.08, respectively; $P = 0.006$) and presented with diabetes at a significantly younger age (6.74 vs. 8.32 years, respectively; $P < 0.05$). The sex difference in age at diagnosis, however, disappeared when corrected for BMI ($P = 0.31$), suggesting that fatness or something related to it was the responsible factor.

CONCLUSIONS — The data are consistent with the hypothesis that the age at presentation of type 1 diabetes is associated with fatness. The implications for prevention of type 1 diabetes may be important.

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The prevalence of diabetes is increasing rapidly in industrialized countries. Although most attention has focused on the increase in type 2 diabetes, there has been a parallel increase in type 1 diabetes, which requires explanation (1). Type 2 diabetes is believed to result from the loss of β-cell function in association with insulin resistance (2). The Accelerator Hypothesis regards type 1 diabetes in the same way (3).

Awareness of overlap between type 1 and type 2 diabetes is not new. There has long been interest in insulin resistance in type 1 diabetes, although related more to its implications for management and outcome than to its pathogenesis (4–8). The term "type one-and-a-half" diabetes, referring to the progression in some from type 2 to type 1 diabetes, was coined years ago and remains an area of lively debate (9). In a modern context, the increasing difficulty in distinguishing type 1 from type 2 diabetes in obese young people has given rise to the designation "double diabetes," in which recognition is given to the coexistence of autoimmunity and insulin resistance (10).

The insulin resistance that underlies type 2 diabetes seems to result mainly from lifestyle factors: weight increase and physical inactivity (11,12). Insulin resistance upregulates the β-cells metabolically and accelerates their loss through glucotoxicity (13). The tempo is normally slow. The Accelerator Hypothesis argues that people in whom type 1 diabetes develops are subject to the same weight increase, the same insulin resistance, the same metabolic upregulation, and the same acceleration in β-cell loss as those with type 2 diabetes. They are, in addition, genetically susceptible to mounting an aggressive immune response to metabolically upregulated β-cells (14,15). Depending on the genotype, this further accelerator can greatly increase the tempo of β-cell loss. Those with type 1 diabetes nevertheless remain a subset of type 2 diabetes, sharing the same basic accelerator: insulin resistance. Indeed, the Accelerator Hypothesis predicts that if people in whom type 1 diabetes would develop lacked the immunogenetic accelerator, they would still be at risk for type 2 diabetes at a later time.

One of the issues currently surrounding type 2 diabetes is the relative contribution of birth weight, weight change, and current weight to the insulin resistance that underlies it (16). The "fetal origins" (17) and subsequent "thrifty phenotype" (18) and weight "catch-up" (19,20) hypotheses examine populations of low birth weight, arguing that poor nutrition during gestation leads both to low birth weight and insulin resistance. However, it is no longer possible to demonstrate a relationship between birth weight and insulin resistance in contemporary

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Abbreviations: SDS, standard deviation score.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

See accompanying editorial, p. 2954.

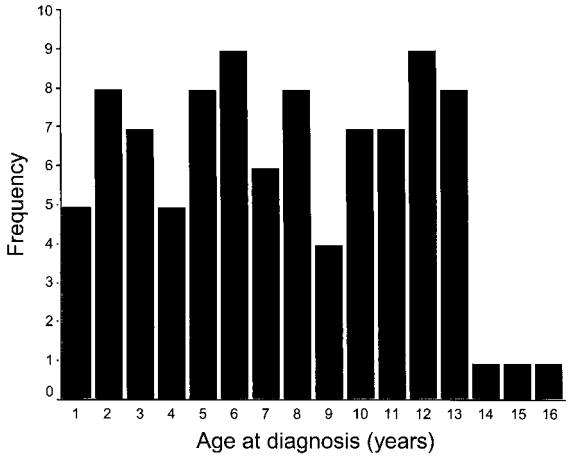

Figure 1—*Histogram illustrating the frequency distribution of type 1 diabetes presentation according to age.*

children, in whom low birth weight is unusual (21). Current weight, on the other hand, correlates with insulin resistance whatever the birth weight, whereas weight change seems to be merely a cocorrelate of current weight (21).

It is already known that people in whom type 1 diabetes develops are heavier in early childhood than nondiabetic people (22–26) and tend to be taller (27). Moreover, the prevalence and titer of GAD antibodies are also related to BMI both in first-degree relatives of type 1 diabetic subjects (28) and in the normal population (29). The Accelerator Hypothesis goes further and predicts that, among those who develop type 1 diabetes, the heavier children will do so at a younger age, in the same way that greater body mass accelerates the onset of type 2 diabetes (30). It goes on to suggest a mechanism whereby insulin resistance could interact with the type 1 diabetes susceptibility genotype to further accelerate β-cell loss. Because only a defined subgroup of the population is genetically susceptible, the Accelerator Hypothesis predicts that increasing obesity in children would cause the age at presentation to decrease without necessarily changing lifetime risk. Recent epidemiological data suggest that this may be the case (31,32). In this study, we test the Accelerator Hypothesis in a group of type 1 diabetic children of widely varying age and body mass. We asked the question "Do fatter children become type 1 diabetics at a younger age?"

RESEARCH DESIGN AND METHODS

— The study was conducted retrospectively on 94 children (49 boys and 45 girls) aged 1–16 years presenting for management of acute-onset type 1 diabetes to the James Cook University Hospital, Middlesbrough, U.K., during the period 1980–2000. All but two patients were white, and twin births (n = 4) were excluded. The criteria for inclusion were those diagnostic of type 1 diabetes: high blood glucose, presence of ketoacidosis, and/or requirement of insulin. Islet-related antibodies were not tested. The relationships between fatness and age at diagnosis of diabetes were examined in the context of birth weight, weight change since birth, weight at diagnosis, and BMI at diagnosis, all expressed as the standard deviation score (SDS) adduced from the 1990 U.K. growth standards (33,34). Measurements were made by a single clinic team on cantilever scales and a Harpenden stadiometer. The children were reviewed weekly after presentation for 6 weeks, and "at diagnosis" relates to height and weight recorded at week 6, when rehydration is likely to have been complete. We also compared the data "at diagnosis" with BMI SDS recorded 12 months later, when stable growth trajectories are likely to have been reestablished. We also recorded the duration of symptoms and identified those presenting with ketoacidosis.

Statistical analysis

The study had sufficient power to show a correlation of $r = 0.29$ with 80% power and 95% certainty. Proportions were compared using the χ^2 test. Simple correlations were calculated between age at diagnosis and birth weight SDS, weight change SDS, weight SDS, height SDS, and BMI SDS at diagnosis and 12 months later. Stepwise regression was performed to determine which combination of independent variables best predicted age at diagnosis (the dependent variable). Partial correlations (correlations controlled for the effect of the model variables) were also calculated for variables not selected in the regression model. The children were grouped into age-at-diagnosis quartiles. Mean birth weight SDS, weight SDS change since birth, weight SDS, and BMI SDS at diagnosis were calculated for each age-at-diagnosis quartile and were compared using ANOVA. Correlations and comparisons were also conducted on BMI recorded 12 months after diagnosis.

RESULTS

— All ages at onset from 1 to 16 years were represented in this study (Fig. 1). A total of 22 of the 94 children were ketoacidotic at presentation. The proportion of diabetic ketoacidosis in the youngest quartile (10 of 23) was significantly higher than the second (3 of 25), third (4 of 23), and oldest (5 of 23) quartiles ($P < 0.05$). Importantly, there were no differences between the quartiles in the duration of symptoms recorded and year of diagnosis ($P = 0.95$).

The mean weight SDS at birth, weight SDS and BMI SDS at diagnosis, and weight SDS change since birth according to age-at-diagnosis quartile are shown in Table 1. Change in weight SDS since birth and BMI SDS at diagnosis were each greater in those who developed diabetes at a younger age. Putting the two observations together, it might be concluded that those who gained the most weight developed diabetes at the youngest ages. However, weight SDS change was highly correlated with weight SDS at diagnosis ($r = 0.73$, $P < 0.001$); those who gained the most weight also ended up among the heaviest.

Table 2 shows the correlations between age at diagnosis, birth weight SDS, weight SDS change since birth, weight SDS at diagnosis, height SDS at diagnosis, and BMI SDS at diagnosis and 1 year later. There were inverse and statistically significant relationships for weight SDS change since birth, weight SDS at diagnosis, and BMI SDS at diagnosis but not birth weight. The inverse relationship between age at diagnosis and BMI SDS remained when the boys and girls were analyzed separately (boys $r = -0.44$, $P = 0.002$; girls $r = -0.33$, $P = 0.025$). Stepwise regression selected BMI SDS at diagnosis

Table 1—*Relationship of body weight to age-at-diagnosis quartile*

Age quartile	*n*	Age at diagnosis	Weight SDS at birth	Weight SDS at diagnosis	BMI SDS at diagnosis	Weight SDS change
Q1	23	2.5 ± 0.9	−0.15 ± 0.81	0.71 ± 1.12	0.79 ± 1.23	0.86 ± 1.31
Q2	25	5.8 ± 1.0	0.04 ± 0.96	0.44 ± 0.87	0.42 ± 0.93	0.40 ± 1.14
Q3	23	9.2 ± 1.1	0.23 ± 0.96	0.11 ± 1.16	0.03 ± 1.02	−0.12 ± 1.58
Q4	23	12.6 ± 1.2	0.25 ± 1.09	0.04 ± 1.13	−0.26 ± 1.16	−0.21 ± 1.36
All	94	7.5 ± 3.9	0.09 ± 0.96	0.33 ± 1.09	0.25 ± 1.14	0.23 ± 1.40
P value	94	<0.001	0.46	0.13	<0.01	0.03

Data are means ± SD. *P* values are based on the *F* statistic derived from ANOVA.

only for the group as a whole ($r = -0.43$, $P < 0.001$). The multiple regression analysis shown in Table 3 indicates that the other variables were all either co-correlates of BMI SDS or less predictive of age at diagnosis. None of these variables, singly or in combination, better predicted age at diagnosis, although the partial correlation of birth weight SDS with age at diagnosis, controlling for BMI SDS, became closer to significance ($r = 0.20$, $P = 0.06$).

The boys presented at a significantly younger age than the girls (6.74 years in boys, 8.32 years in girls; $P = 0.049$). However, the boys were significantly fatter than the girls at diagnosis (BMI SDS 0.56 in boys, −0.08 in girls; $P = 0.006$), and the difference in age at presentation was lost when corrected for BMI SDS (boys 7.12, girls 7.90, $P = 0.31$).

We compared the data at diagnosis with recordings of BMI made 12 months later. The correlation between the BMI SDS of individuals on the two occasions was strong ($r = 0.76$, $P < 0.001$), despite a substantial increase in mean BMI SDS from +0.18 at diagnosis to +0.94 12 months later ($P < 0.001$). Importantly, we also looked at the weight gain according to age to infer whether the younger children may simply have lost less weight before diagnosis. The change in BMI SDS between diagnosis and 12 months later was not related to the age of the subject, whether analyzed by age-at-diagnosis quartile ($P = 0.16$) or by regression ($r = 0.16$, $P = 0.14$). The gradient from regression was small: an increase of 0.03 SDS in the difference between the BMI at diagnosis and the BMI 12 months later for every 1-year increase in age at diagnosis. Finally, the relationship between age at diagnosis and BMI SDS at 12 months remained unchanged from what it had been at 6 weeks ($r = -0.40$, $P < 0.001$).

CONCLUSIONS — The data suggest that the age at diagnosis of type 1 diabetes is a function of body mass. Three lines of evidence presented here lead to that conclusion. First, weight SDS and BMI SDS, whether analyzed for differences in distribution according to age-at-onset quartile, or in a simple regression, are significantly related to age at presentation. Second, the relationship between age at diagnosis and weight SDS change since birth was almost as strong. All children gain weight, but weight SDS change is a measure of the excess weight gained or centiles crossed (21). Third, the boys were significantly fatter than the girls and presented with diabetes at a significantly younger age. The difference in age at diagnosis disappeared, however, when adjusted for body weight, suggesting that weight or something related to it was the factor responsible.

However, the study has a number of weaknesses. First, there was a lack of genetic and serological data with which to type the children immunogenetically. Nevertheless, we believe the children were likely to have been type 1 diabetic (autoimmune) for three reasons. All required insulin to normalize blood sugar levels, none of the children were particularly obese at presentation (maximum BMI SDS 2.73), and type 2 diabetes presenting before 16 years of age has been rare in the U.K. Second, it is possible that greater weight loss because of a longer prodrome in the older child could be mis-

Table 2—*Simple correlation matrix*

n = 94	Birth weight SDS	Weight SDS at diagnosis	Weight SDS change	Height SDS at diagnosis	BMI SDS at diagnosis	BMI SDS 1 year after diagnosis
Age at diagnosis	0.15 (0.16)	−0.29 (<0.01)	−0.33 (<0.01)	0.06 (0.58)	−0.39 (<0.001)	−0.40 (<0.001)
Birth weight SDS	—	0.07 (0.49)	−0.63 (<0.001)	0.00 (0.99)	0.09 (0.39)	0.07 (0.50)
Weight SDS at diagnosis	—	—	0.73 (<0.001)	0.64 (<0.001)	0.69 (<0.001)	0.52 (<0.001)
Weight change SDS	—	—	—	0.50 (<0.001)	0.48 (<0.001)	0.35 (<0.001)
Height SDS at diagnosis	—	—	—	—	−0.09 (0.39)	−0.04 (0.71)
BMI SDS at diagnosis	—	—	—	—	—	0.76 (<0.001)
BMI SDS 1 year after diagnosis	—	—	—	—	—	—

Data are *r* (*P* value). The far right column relates to the 87 of 94 children in whom BMI SDS was recorded 12 months after diagnosis.

Table 3—*Multiple regression model*

Model	*r*	*P*
BMI SDS at diagnosis	−0.39	<0.001
Excluded variables	Partial *r*	*P*
Birth weight SDS	0.20	0.06
Weight change SDS	−0.18	0.09
Weight SDS at diagnosis	−0.04	0.74

Partial *r* is the correlation that remains between the nonselected variables and age at diagnosis after the effect of BMI SDS at diagnosis has been removed.

construed as weight-driven acceleration of the disease in those of younger onset. Type 1 diabetes is certainly associated with weight loss, and the prodrome is often more aggressive and of shorter duration in the younger child. Predisease growth charts would have provided the best evidence of true growth trajectory but were not available. Instead, we compared the data at diagnosis with recordings made 12 months later, when it is likely that metabolic health would have been restored and growth trajectories reestablished. There was a strong correlation in BMI SDS between diagnosis and 12 months later, despite a substantial mean weight adjustment. More importantly, age had no significant impact on the adjustment in BMI SDS, suggesting that, had a longer prodrome been associated with diabetes in older children, it was not responsible for the younger onset of diabetes in heavier children. Indeed, age at diagnosis was correlated as well with BMI SDS at 12 months as it was at diagnosis, suggesting that, although there are substantial weight changes around diabetes onset, children tend to retain their growth trajectories relative to each other, much as they do after chronic illness. It seems likely that BMI SDS after diagnosis is a sufficiently reliable index of premorbid body mass for group analysis. We also lacked direct measures of insulin resistance at and before development of diabetes. Insulin resistance is a well-known feature of type 1 diabetes at presentation (4–8), but the premorbid measures related to body mass, i.e., 1 year before onset, would provide the strongest evidence of cause and effect. Finally, the numbers in this study were small by epidemiological standards but nevertheless had sufficient power to reveal with clear statistical significance the relationships on which its conclusions were based.

Earlier studies reporting a higher risk of type 1 diabetes in children who were heavier as toddlers needed a control group with which to compare the diabetic children (22–26). Although such reports predicted greater risk among heavier infants, the Accelerator Hypothesis goes further and predicts earlier onset, without necessarily a change in lifetime risk (35). Here, the analysis is one of intragroup correlation, rather than intergroup comparison, and a control group was not needed.

Contrary to the present series, many studies have recorded an earlier diagnosis of type 1 diabetes in girls. However, there is no inconsistency here, as girls are generally fatter (and more insulin-resistant) than boys (21). Puberty is associated with a sharp increase in insulin resistance, occurs earlier in girls than in boys, and has to be considered in the relationship between body mass and age at onset of diabetes. Tanner staging for pubertal development is not routine in the diabetes clinic, but sexual maturity is unlikely to have had a material impact on the question we addressed in this study. We used sex-specific SDS charts for height and weight with which to adjust for the differences between boys and girls, and the youngest (prepubertal) children contributed as much to the relationship between body mass and age at onset as the older (pubertal) ones. Importantly, the relationship remained true for both boys and girls when analyzed separately, and BMI, which can overestimate fatness in younger (shorter) children (36), did not seem to be an artifact because the relationship applied as much to simple weight SDS as to BMI SDS.

We did not find this cohort of diabetic children to be systematically heavier at birth, as might have been expected from the reports referred to above where type 1 diabetic people were heavier than their peers as young children. Only the birth weights of those in age-at-diagnosis quartiles 3 and 4, in whom onset of diabetes was least accelerated, lay above the mean for the whole group. Indeed, the younger the age at diagnosis, the lower the birth weight. Those in quartiles 1 and 2, in whom diabetes was most accelerated, lay at or below mean birth weight, not above. The combined influence on insulin resistance of lower birth weight and rapid weight gain in early childhood has been attributed to so-called "catch-up" growth (16,19,20,37). However, as we have shown previously in the EarlyBird study (21), weight "catch-up" is closely correlated with current weight and probably not, as such, a mechanism for insulin resistance. Indeed, the children from quartiles 1 and 2 in the present study were close to mean birth weight, and it is arguable that the group in whom the onset of diabetes was most accelerated were not so much children of low birth weight as those who had gained most during their early years to reach the highest BMI.

Diabetes is the outcome of a process; it is not the process itself. The process is one of progressive β-cell loss that may take years. Although insulin resistance is widely regarded to be the factor responsible in pre–type 2 diabetes, epidemiologists have until now viewed pre–type 1 diabetes as a separate process and have searched in vain for separate immunologic triggers. Among those suggested are viruses, dietary nitrosamines, and cow's milk protein (38). During the ~35 years since diabetes was first perceived histologically to be of two types, the one metabolic and the other autoimmune (39), the prevalence of obesity in the industrialized world has more than doubled (40). So has that of type 2 and type 1 diabetes (41). Indeed, wherever in the world there has been an increase in type 2 diabetes, there has been a parallel increase in childhood type 1 diabetes (42).

The data reported here are not proof that the increasing prevalence of obesity in childhood is the cause of the increasing incidence of type 1 diabetes. It is indeed possible that the increase in weight is a maladaptation to pre-diabetes accelerated by another cause. The data are only consistent with a hypothesis that will ultimately best be tested by intervention with either weight reduction or insulin-sensitizing medication. It is now possible to predict type 1 diabetes with some precision (43), and given the encouraging data from lifestyle prevention studies in pre–type 2 diabetes (44,45), it may arguably be worth considering lifestyle intervention trials to reduce insulin resistance in people with pre–type 1 diabetes before embarking on further immunomodulatory drug trials. Insulin resistance is the predictable and inevitable result of weight increase to which whole populations are now subject, and the data reported here lend support to the hypothesis that type 1 and type 2 diabetes are one and the same

disorder of insulin resistance set against different genetic backgrounds.

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