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Secular trends in growth in diabetes: are we winning?

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Aim: To determine potential effects of modern treatment on growth in diabetic children.

Methods: Retrospective analysis of growth in diabetic children stratified by their year of diagnosis between 1974 and 1995. A total of 451 children and adolescents attending the Diabetes Outpatient and Outreach Clinics of Royal Alexandra Hospital for Children in Sydney and rural NSW, Australia were studied. Standard deviation scores (SDS) for height and body mass index (BMI) were assessed at diagnosis, five years later ($n = 451$), and 10 years later ($n = 111$).

Results: After five years of diabetes duration height SDS loss correlated with higher HbA_{1c} and fewer injections. BMI SDS gain correlated with HbA_{1c} and age at diagnosis. Although there was no significant difference in their height SDS or age at diagnosis, children diagnosed 1974–90 were significantly shorter than children diagnosed 1991–95 (height SDS 0.07 v 0.37) after five years diabetes duration. Furthermore, over 5 and 10 years, the 1979–90 group had lost significant height SDS (mean change –0.20 at 5 years, –0.29 at 10 years); this did not occur in the 1991–95 group (–0.01 at 5 years, –0.13 at 10 years). The BMI SDS increased significantly after 10 years in the 1974–90 group (mean change 0.37) but not in the 1991–95 group. There was no significant difference in the 174 females' age of menarche (13.0 v 12.8 years).

Conclusions: Children with diabetes treated with modern regimens maintain their increased height from diagnosis better, and after five years diabetes duration, were taller than children diagnosed before 1991.

Longitudinal growth of children with diabetes has been a concern for paediatricians. Initial reports highlighted reduced linear growth, especially with poor glycaemic control.^{1–3} During the course of more reasonably managed diabetes, a blunted growth spurt has been observed, especially in girls, with reduction in final height.^{4–6}

During the past two decades improvements in diabetes management include home blood sugar monitoring, the use of human insulin, and the development of age adjusted educational programmes provided by multidisciplinary teams. In 1993 the results of the Diabetes Control and Complications Trial firmly established the advantage of intensive insulin therapy for reduction in diabetes microvascular disease.⁷ One of the disadvantages of intensive therapy for the participating adolescents and adults was greater weight gain. Body mass index (BMI) is a consistent, pragmatic index of obesity in children and adolescents accepted by the International Obesity Taskforce.⁸

The aim of this study was to determine potential effects of more modern treatment, by evaluating linear growth and BMI changes in diabetic children stratified by their year of diagnosis between 1974 and 1995.

METHODS

Growth and BMI were assessed at diabetes onset and five years later in 451 children diagnosed between 1974 and 1995. Height, measured by Harpenden stadiometer, was expressed as standard deviation score (SDS) for chronological age and gender according to Hamill and colleagues.⁹ BMI SDS was also calculated according to Hamill *et al* for subjects older than 6 years. Ten year data were available in 111 children.

Children and adolescents attended the Diabetes Outpatient and Outreach Clinics of the Royal Alexandra Hospital for Children in Sydney and rural New South Wales, Australia. In this service, home blood glucose monitoring was introduced in 1979, glycated haemoglobin measurement in 1981, and human insulin in 1989. Families were instructed to change

insulin dose in order to maintain preprandial blood glucose concentrations between 4 and 8 mmol/l (children younger than 6 years: 5–12 mmol/l). Children with coeliac or other chronic diseases were not considered in this evaluation. Most patients (93%) were white.

Patients were stratified into two groups according to their date of diagnosis (1974–90 and 1991–95). The database was developed in 1986 and retrospective data were input for patients seen between 1986 and 1990. Glycaemic control was assessed by measuring glycated haemoglobin (GHb) colorimetrically from 1981 until 1993¹⁰ and haemoglobin A_{1c} (HbA_{1c}) by high performance liquid chromatography (HPLC, Diamat BioRad; normal range 4–6%) subsequently. GHb values were converted to HbA_{1c}¹¹ and the median value over 5 and 10 years was calculated for each patient. Date of menarche was available in 174 females.

Data were analysed using the statistical software SAS. Summary statistics are presented as mean with standard deviation (SD) for normally distributed variables or otherwise as median (interquartile range). Estimates are expressed as mean with standard error (SE). Height and BMI SDS of patients were compared to the reference population using a *t* test by testing the mean SDS against zero. Multiple regression was used to investigate the influence of biological parameters (gender, insulin dose/weight, number of insulin injections, HbA_{1c}, and age, height/BMI SDS at diagnosis) on growth and BMI changes.

RESULTS

In the total cohort mean height SDS was 0.36 (SE 0.05) and mean BMI SDS was 0.08 (SE 0.06) at diabetes onset. After five

Abbreviations: BMI, body mass index; GHb, glycated haemoglobin; HbA_{1c}, haemoglobin A_{1c}; HPLC, high performance liquid chromatography; SD, standard deviation; SDS, standard deviation score; SE, standard error

Table 1 Growth and demographic variables for children stratified according to the date of diabetes diagnosis

	Diagnosed 1974–90	Diagnosed 1991–95	p value*
<i>At diagnosis</i>	(n=115)	(n=336)	
Age (years)	8.6 (5.2 to 10.6)	8.1 (5.0 to 10.9)	0.41
<5	23%	26%	
5 to <10	45%	43%	0.82
10–15	31%	31%	
Height SDS	0.28 (SD 1.01)¶	0.38 (SD 0.99)§	0.32
BMI SDS	−0.07 (SD 1.03)	0.13 (SD 1.01)	0.15
<i>At 5 years follow up</i>			
Age (years)	13.4 (10.0 to 15.6)	12.8 (9.7 to 15.5)	0.30
Height SDS	0.07 (SD 0.99)	0.37 (SD 0.94)§	0.0035
BMI SDS	0.35 (SD 0.78)§	0.40 (SD 0.72)§	0.50
Median HbA _{1c} (%)	8.3 (7.6 to 9.0)	8.3 (7.8 to 8.9)	0.43
At risk of overweight†	13/111 (12%)	43/330 (13%)	0.72
Overweight‡	7/111 (6%)	15/330 (5%)	0.46
No. of insulin injections			
1–2/day	72 (84%)	166 (60%)	0.001
3–4/day	14 (16%)	110 (40%)	
<i>At 10 years follow up</i>	(n=64)	(n=47)	
Age	16.3 (13.7 to 18.5)	16.0 (12.9 to 17.6)	0.25
Height SDS	0.04 (SD 0.87)	0.36 (SD 0.89)**	0.06
BMI SDS	0.50 (SD 0.88)§	0.52 (SD 0.77)§	0.89
Median HbA _{1c} (%)	8.3 (8.0 to 9.0)	8.3 (7.8 to 8.8)	0.26

*p values refer to differences stratified by year of diagnosis.

†BMI centile ≥85% to <95%.

‡BMI centile ≥95%.

SDS different from reference population: §p<0.0001; ¶p=0.004; **p=0.008.

years of diabetes, there was no significant change in height SDS for the whole group: the mean change was −0.06 (SE 0.03, $p = 0.10$). However, BMI SDS after five years diabetes duration had significantly increased: mean change 0.30 (SE 0.05, $p < 0.0001$).

Interestingly, after five years the subgroup of children diagnosed 1974–90 had lost significant height SDS (mean change

−0.20, $p = 0.003$; fig 1) and was significantly shorter than the subgroup diagnosed 1991–95, without a difference in their BMI SDS (table 1). The former group was also receiving significantly fewer insulin injections per day. The age of menarche, available in 53 of 61 females diagnosed 1974–90, was 13.0 (interquartile range 12.0 to 13.8) years, which was not significantly different than the age of menarche of 12.8

Figure 1 Height SDS of children with diabetes mellitus over a study period of 10 years after diabetes onset, stratified by year of diagnosis. The mean and 95% confidence limits are shown.

Figure 2 BMI SDS of children with diabetes mellitus over a study period of 10 years after diabetes onset, stratified by year of diagnosis. The mean and 95% confidence limits are shown.

(12.1 to 13.6) years in the 121 of 195 females diagnosed 1991-95 ($p = 0.59$).

After excluding 121 subjects who reached final height within five years from onset, higher HbA_{1c}, fewer injections, and lower height SDS at onset were associated with a decrease in height SDS during the first five years of diabetes. The regression equation was: [height SDS change = $1.47 - 0.30$ (height SDS at onset) $- 0.17$ (HbA_{1c}) $+ 0.22$ (3-4 injections)]. This model accounted for 22.2% ($p < 0.0001$) of variance for height SDS change after five years of diabetes. Gender, age at diagnosis, and insulin dose/weight had no predictive value for linear growth.

Lower BMI SDS at diagnosis, lower HbA_{1c}, and older age at diagnosis were associated with BMI SDS gain. The regression equation was: [BMI SDS change = $0.32 - 0.49$ (BMI SDS at onset) $+ 0.11$ (age at diagnosis) $- 0.13$ (HbA_{1c})]. This model accounted for 50.9% ($p < 0.0001$) of variance for BMI SDS change after five years of diabetes. Gender, insulin dose/weight, and number of injections were not significant predictors of BMI SDS change.

After 10 years of diabetes duration, auxological data were available in 64 children with diabetes onset between 1979 and 1990 and in 47 children diagnosed 1991-95 (table 1). There was a significant loss in height SDS (mean change -0.29 , $p = 0.015$; fig 1) in the earlier diagnosed group but not in the later diagnosed group (mean change -0.13 , $p = 0.29$). There was a significant increase in BMI SDS after 10 years in the group diagnosed 1979-90 (mean change 0.37 , $p = 0.01$) but not in those diagnosed 1991-95 (mean change 0.20 , $p = 0.31$; fig 2).

DISCUSSION

The weakness in this study is the lack of a non-diabetic control group with which to compare possible diabetes independent trends in growth. In an attempt to overcome this problem, SDS were compared between the two groups stratified by year of diabetes onset (1974-90 and 1991-95), and change in SDS from diagnosis was compared for individuals over time.

At diabetes onset the total cohort was taller than the reference population (Hamill *et al*) without significant difference in the height SDS between the two groups. However, in contrast to the children with diabetes onset between 1991 and 1995, those diagnosed 1974-90 did not remain significantly taller than the reference group after 5 or 10 years of diabetes. Similarly, an incident Italian cohort of 152 diagnosed 1989-92 lost height SDS within three years of diabetes onset.¹² The new data in this study suggest that diabetes diagnosed and treated from 1991 did not affect height to the same degree, if at all.

The increased height at diabetes onset, especially in prepubertal children, has been well documented.^{5 12 13} A possible mechanism is a compensatory increase, during the prediabetic period, in growth factors because of progressive insulin deficiency, while the subsequent observed height SDS decrease may reflect the reduction of this growth factor excess.¹⁴ The growth factor, however, may actually be insulin itself as a result of the greater weight gain. Two groups have documented increase in linear height and relative weight above non-diabetic populations many years prior to onset of diabetes, indeed from infancy. This was independent of parental height, suggesting that those with earlier growth spurts are at greater risk of diabetes.^{15 16}

After allowing for the positive effect of height SDS at diagnosis, intensification of insulin management may positively influence the further growth in children with diabetes. Indeed in this study the five year height SDS change was negatively influenced by increased HbA_{1c} levels and positively by more injections. In the past, others have not always been able to document an effect of metabolic control on linear growth.^{6 12 17} However, frequent longitudinal measurements in the Oxford cohort did show an association of higher HbA_{1c} with reduced peak growth velocity.¹⁸

There are no Australian references for growth or onset of puberty. The age of menarche for children with diabetes in this study did not change significantly between those diagnosed 1979-90 and those diagnosed 1991-95, which does not support a change in the timing of puberty. Though they were not significantly shorter at diagnosis, children with onset

before 1991 were significantly shorter after five years duration than those diagnosed and treated after 1990: height SDS of 0.07 compared with 0.37 at mean ages of 13.4 and 12.8 years. Over this time, between 1985 and 1997, there has been a small increase in height documented in Australian schoolchildren.¹⁹ Converting the published raw values to the same height SDS values, 12 year old girls had a mean SDS of -0.34 in 1985, which increased to a mean of -0.19 in 1997. Similarly, 12 year old boys increased their mean height SDS from -0.25 to 0.01. Such a secular increase in height in children may explain some of the increase in height seen for those diagnosed after 1991, but this increase would not explain the magnitude of increased height SDS at diagnosis or documented after five and 10 years of diabetes. Rather than due solely to a diabetes independent increase in height in the population, the difference in height in the later onset group is likely to indicate a positive effect of treatment regimens. Intensification of insulin therapy has occurred at our institution as shown by the higher frequency of children on more than two injections; surprisingly this did not translate into an improvement in glycaemic control as measured by a median value of HbA_{1c} for each patient. A relative improvement in metabolic control may have occurred with less postprandial glycaemic excursions, or the metabolic control may have been unevenly recorded in the earlier years of our database. Another possible source of bias is a change in referral pattern to our service. However, with a 67% attainment rate, we have previously shown uniformity of glycaemic control across rural and urban New South Wales with minimal impact of socioeconomic factors.²⁰

Recent publications suggest that young patients with diabetes tend to be overweight,²¹ especially when tight metabolic control is achieved.⁷ In this study, an increasing weight to height relation was documented during the course of diabetes, which was related to age at diabetes onset and HbA_{1c}, but not gender. Some of the weight gain is obviously the initial regain of the weight lost which occurred as a result of the initial glycosuria prior to diagnosis. Alternately children with diabetes may have been more obese before the onset of glycosuria which caused weight loss down to the normal range (SDS close to zero). Treatment of glycosuria may only restore their weight to their premorbid SDS trajectory.

It is reassuring that despite changes in therapy, the trend to obesity does not appear to have increased over the period of observation.¹⁹ After five and 10 years children diagnosed 1991–95 did not have a higher BMI SDS compared to those diagnosed 1974–90. In fact a significant increase in BMI SDS was only documented in the group diagnosed 1974–90. Similarly the percentage who have BMI SDS above the 95th centile (6%) compares favourably with a recent review of studies of Australian schoolchildren in which 7% of 12–15 year olds had BMI above this level and were classified as “overweight”.²² Between 1985 and 1997, there has been a small increase in body mass index documented in Australian schoolchildren.¹⁹ Again converting the published raw values to BMI SDS values, 12 year old girls had a mean SDS of -0.04 in 1985 and a mean of 0.09 in 1997. Similarly, 12 year old boys increased their mean BMI SDS from 0.05 to 0.13. This is less than the magnitude of increased SDS found in the total diabetic cohort after five years (from 0.08 to 0.38). Possibly this lack of an increase between years of diagnosis is the result of education programmes focusing on physical exercise as an important part of diabetes management. However, one should not be complacent over a higher BMI SDS as those in the higher quadrant have considerably higher cardiovascular risk factors, increasing their chance of morbidity and mortality.²³

Based on these data, we conclude that children diagnosed with diabetes after 1990 showed enhanced linear growth compared to children diagnosed before 1991. Furthermore they were better able to maintain their increased linear height

present at diagnosis after five and 10 years. Conversely, no greater rate of obesity was observed in this cohort of patients compared to those children with diabetes onset before 1991. We can be guardedly optimistic for the growth of children treated with current therapeutic techniques.

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