GROWTH DATA IN LARGE SERIES OF 587 CHILDREN AND ADOLESCENTS WITH TYPE 1 DIABETES MELLITUS

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Objective. Discordant data were found in recent growth studies in children with type-1 diabetes mellitus. This study focuses on growth data and final height in the largest cohort of diabetic children studied so far.

Methods. 7598 growth data collected in a longitudinal / cross sectional way between 1971 and 1996 in 587 diabetic subjects (317 males, 270 females) were available for analysis of height and BMI, together with 3889 HbA_{1c} measurements. Final height data were correlated with target height in 123 subjects. The individual growth and BMI linear regression curve of each patient was compared to growth standards and correlated with HbA_{1c}.

Results. Children of both sexes were taller at the first observation (males, SDS 0.15±1.10, mean±SD, P=0.02, females, SDS 0.74±1.46, P<0.001) and tended to lose height afterwards (males, P<0.001, females, n.s.). Males reached a final height of 176.5 cm (n=62, target height 176.8, n.s.) and females 167.0 cm (n=61, target height 165.6, n.s.). Children of both sexes had a higher than normal BMI at first observation (males, SDS 0.32±1.31, P<0.001, females, SDS 0.10±0.52, P=0.02). Females but not males gained weight over-proportionally afterwards. HbA_{1c} did not predict any of the variables.

Conclusions. Diabetic children are taller close to the diabetes onset, which may be due to the synchronization of onset of diabetic symptoms with the mid-childhood growth spurt or the pubertal growth spurt accompanied by elevated growth hormone and/or androgen levels and increased insulin resistance. The subsequent growth deceleration may represent a physiological lag-down growth. This concept is supported by normal adult heights following growth deceleration.

Keywords: Type 1 diabetes mellitus – Children – Growth – Final height – BMI – HbA_{1c}

Several decades ago, insulin dependent diabetes mellitus used to be listed among causes of severe growth retardation in children, as summarized by Clarke et al. (1993). Subsequently, the understanding of more physiological insulin substitution, the new treatment modalities and self-monitoring techniques gradually improved the clinical course and outcome of childhood diabetes. With the exception of small cohorts of poorly controlled patients, retardation of growth and puberty is no more a dominant clinical problem in diabetic children at least in countries with a well developed system of diabetes care, as previously reported by several authors (Arreola et al. 1991; Gens and Michaelis 1990; Gunczler et al. 1996; Holl et al. 1994; Jos et al. 1996; Penfold et al. 1995; Soliman et al. 1996; Tuvemo et al. 1997; Vanelli et al. 1992; Donaghue et al. 2003).

Nevertheless, the actual therapeutic strategies in diabetic children are not optimal and have just a limited potential of permanent and complete normaliza-

tion of metabolism, at least if expressed as glycated hemoglobin (HbA_{1c}).

The main conclusion of the papers on this topic from the last decade was that the impact of childhood diabetes on growth is of no major relevance in developed countries, as observed by AHMED et al. (1998), ARREOLA et al. (1991), BOGNETTI et al. (1998), BROWN et al. (1994), CLARKE et al. (1993), DANNE et al. (1997), DU CAJU et al. (1995), GENS and MICHAELIS (1990), GUNCZLER et al. (1996), HOLL et al. (1994,1998a), IZUMI et al. (1995), JOS et al. (1996), MALONE (1993), PENFOLD et al. (1995), PITUKCHEEWANONT et al. (1995), SALERNO et al. (1997), SOLIMAN et al. (1996), THON et al. (1992), TUVERNO et al. (1997), VANELLI et al. (1992), WISE et al. (1992) and ZACHRISSON et al. (1997). However, on several aspects controversial results were presented. Diabetic children at onset of the disease have been reported taller by BLOM et al. (1992), BOGNETTI et al. (1998), CONNORS et al. (1997), DANNE et al. (1997), HOLL et al. (1994,1998a), MALONE (1993), PRICE and BURDEN (1992), SCHEFFER-MARINUS et al. (1999) and ZACHRISSON et al. (1997), of similar height by THON et al. (1992) and CIANFARANI et al. (2000), or shorter than healthy control subjects or non-diabetic family members (by HOSKIN et al. 1985 and SONGER et al. 1986). Contrasting data exist as well on the impact of the disease on final height (with regard to the data published by BROWN et al. 1994; DANNE et al. 1997; DU CAJU et al. 1995; HOLL et al. 1994; JOS et al. 1996; PENFOLD et al. 1995; SALERNO et al. 1997; SOLIMAN et al. 1996; WISE et al. 1992; ZACHRISSON et al. 1997) and on the relation between the overall metabolic control expressed as $HbA1_{1c}$ and height gain, as reported by several authors (AHMED et al. 1998; ARREOLA et al. 1991; BOGNETTI et al. 1998; DANNE et al. 1997; IZUMI et al. 1995; PITUKCHEEWANONT et al. 1995; SOLIMAN et al. 1996; WISE et al. 1992; ZACHRISSON et al. 1997).

Some of the controversies may be due to different study designs and sample sizes, to the selection of control subjects or growth standards, or to the analysis and statistical methods.

The current study focuses on growth data, weight gain and final height in a large cohort of diabetic children.

Subjects and Methods

Subjects. Long-term data from 587 unselected patients (317 males, 270 females) from the universi-

ty pediatric diabetic clinics in Vienna, Austria and in Prague, Czech Republic were available for the study. The patients were born between 1962 and 1993 and their insulin dependent diabetes mellitus was diagnosed between 1970 and 1996 at age 0.3 – 20.3 years (median males 7.9 years, median females 8.4 years).

Study design. Body height, body weight and HbA_{1c} levels were recorded every 6 months at regular outpatient controls. Patients' data were collected in a longitudinal / cross sectional manner, only patients with data from more than one visit were included.

A total number of 7598 height and weight measurements were recorded in 587 patients between 1971 and 1996. The first observation was recorded 0 – 12.6 years (median males 0.2, females 0.2) after the onset of clinical symptoms of diabetes, at age 1.1 – 24.8 years (median males 9.2, females 9.9). The last observation was recorded after 0.2 – 21.1 years (median males 5.5, females 5.0) of diabetes duration, at age 1.5 – 27.6 years (median males 15.3, females 14.7 years). The number of available height and weight data for each patient ranked between 2 and 36 (median 9).

In 359 patients, complete data on parental heights were available. From these, 123 (62 males, 61 females) already reached their adult height defined as age >16 (females) or >18 (males) and a growth rate of <0.5 centimeters during the last 6 months. In this subgroup of patients, final height was compared to target height. Target height was calculated as midparental height +6.5 cm males and –6.5 cm in females.

HbA_{1c} measurements were available from 296 patients (85 males, 211 females) at 3889 time-points. HbA_{1c} levels estimated at least 6 months apart were included into the analysis.

HbA_{1c} was estimated by high-pressure liquid chromatography (Diamat, BioRad Laboratories) either at the central laboratory in Vienna or in Prague. Both laboratories were using the same laboratory procedure. Comparison of results between both laboratories was provided by parallel analysis of 31 blood samples of diabetic patients within 48 after sampling. The mean HbA_{1c} value of these estimations was 8.8 % in Prague compared to 8.9 % in Vienna. The coefficient of variation of these analyses was 5.73 % in Prague compared to 4.07 % in Vienna (n.s.). The normal range in both laboratories was 4-6 %.
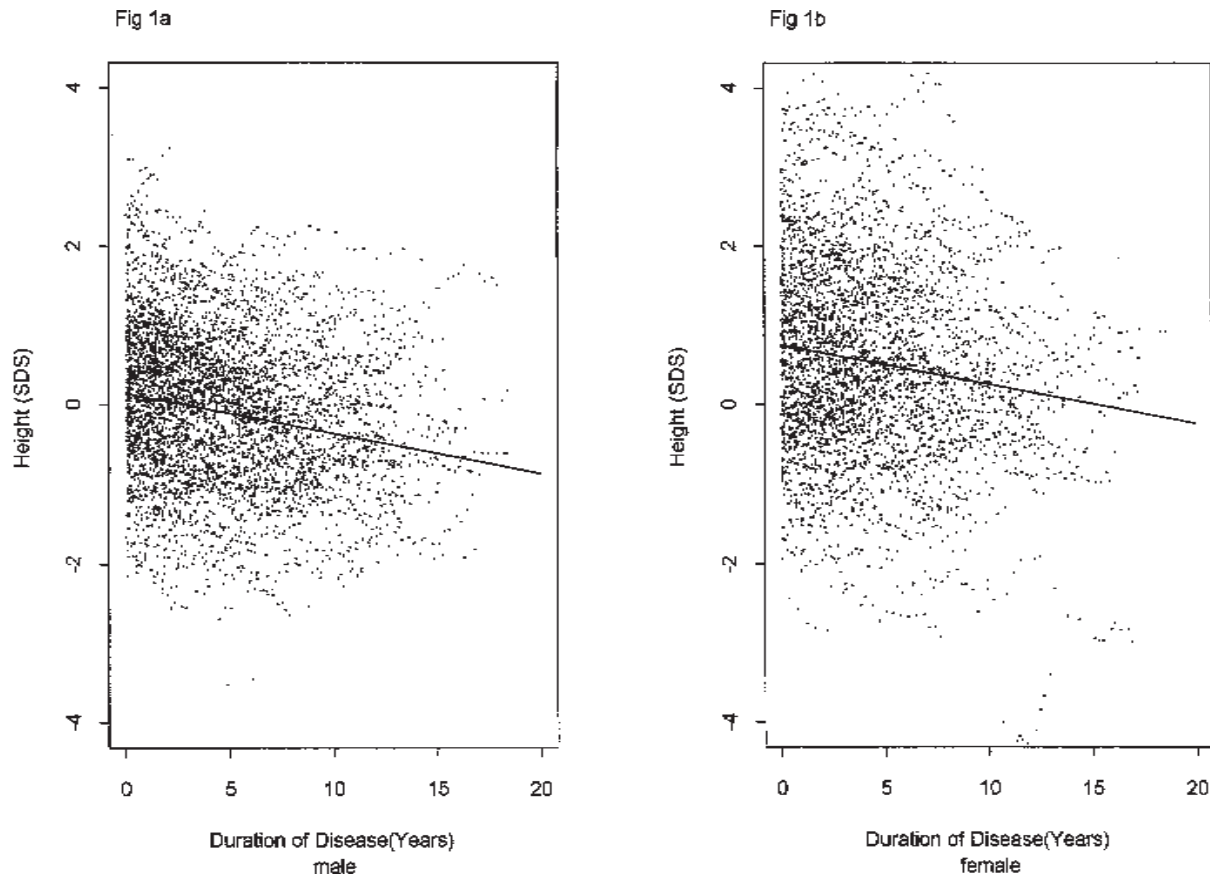
Fig 1a

Fig 1b

Fig 1a,b Height SDS in diabetic children and adolescents from the onset of the disease and onwards in males (a) and females (b)

Heigth measurements. In both departments, body height was measured using a wall-mounted stadiometer by a trained medical personal.

Population standards (height, body mass index). The Zurich longitudinal growth study as reported by PRADER et al (1989) was used as a population standard for height and for body mass index; data for BMI from the same study were kindly supplied by A. Prader. These data are based on measurements of a population geographically and ethnically comparable to the study population. Also the time-span of collection of normal data (year of publication 1989) corresponds quite fairly with the observation period in the study population (1971-1996) which makes a major influence of secular changes unlikely.

Statistical evaluation. The standardizations of height and of body mass index were done using the standards by PRADER et al. (1989). An additional eval-uation of the percentiles was done using the spline function of the WHO Program GROSTAT according to RASBASH et al. (1989). After standardization, a linear regression for each patient's data was performed and the intercept and coefficients were tested using Wilcoxon Ranksum test with 0-hypothesis median=0. This procedure was provided to rule out a stronger impact of patients with more available data (which could lead to a bias towards patients with a longer diabetes duration and/or a longer observation period). To diminish the statistical influence of extreme values, a non parametric test was performed. All tests were done 2-sided. P values <0.05 were considered statistically significant.

For HbA$_{1c}$ results, the same analysis was performed. The group analysis of HbA$_{1c}$ values was provided using the SUPSMU function of the SPLUS package.
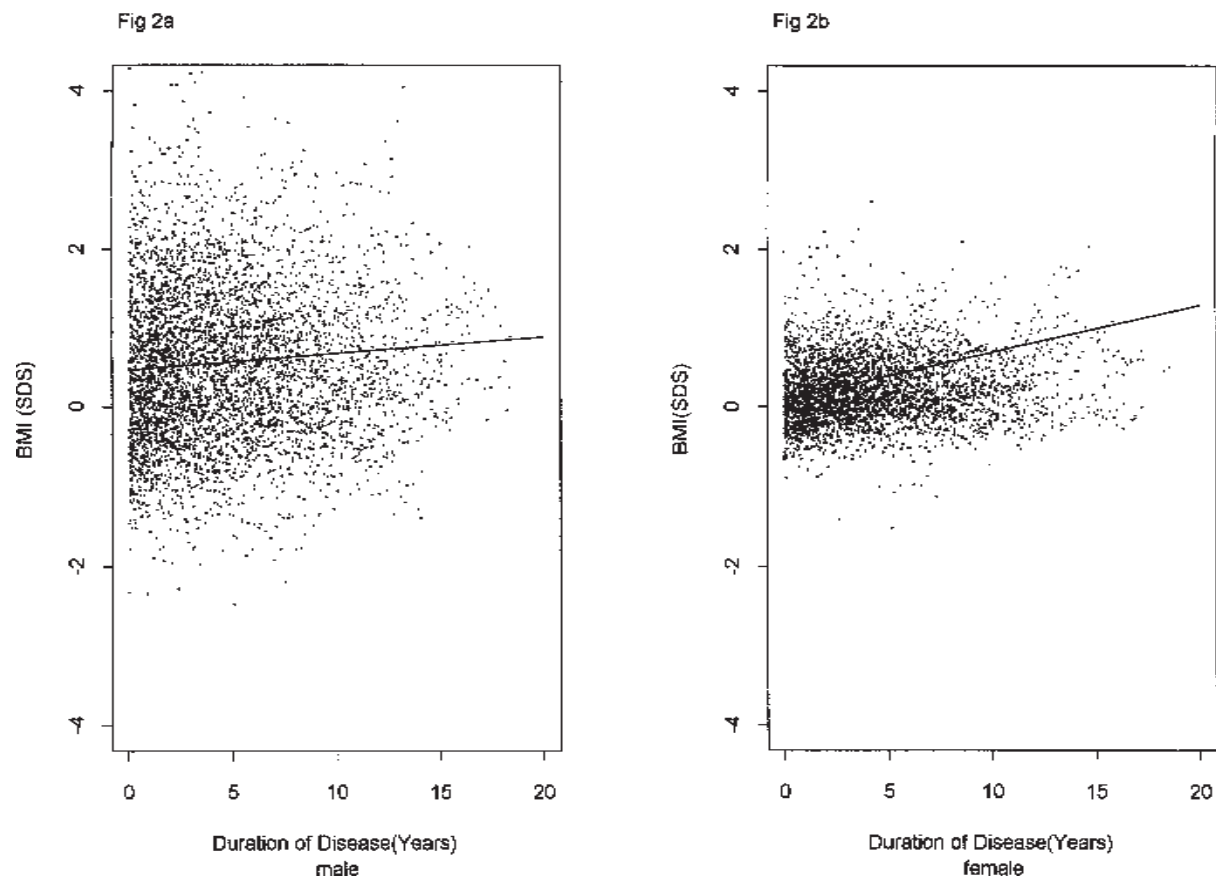
Fig 2a,b BMI SDS in diabetic children and adolescents from the onset of the disease and onwards in males (a) and females (b)

Results

No significant differences were found between patients from both cities (Prague, Vienna) with regard to the age at diabetes onset or to the diabetes dura-

Table 1
Body height in children with insulin dependent diabetes mellitus at the initial measurement

body height (SDS)	males		females	
	intercept	slope	intercept	slope
No	316	316	270	270
Mean	0.145	-0.049	0.743	-0.048
Median	0.166	-0.039	0.787	-0.035
SD	1.100	0.219	1.462	0.439
P value	0.02	<0.01	<0.01	0.18

tion at the first and last observations. Both subgroups were therefore pooled into the global analysis.

Diabetic children of both sexes were slightly but significantly taller at the first observation (Table 1). The statistical analysis of their individual growth regression lines suggests that both girls and boys tended to decrease their standardized height compared to population standards thereafter. Because of the greater diversity of this tendency in females, a significant decline was found in boys only (Table 1, Fig. 1a,b). In 123 diabetic patients who had finished their growth the final heights do not differ from the target heights neither in boys nor in girls (Table 2).

The BMI was slightly increased at the first observation in children of both sexes (Table 3). As the first observation was not identical to the onset of symptoms of diabetes in most subjects (median 0.2 years after first insulin injection), this finding reflects rather
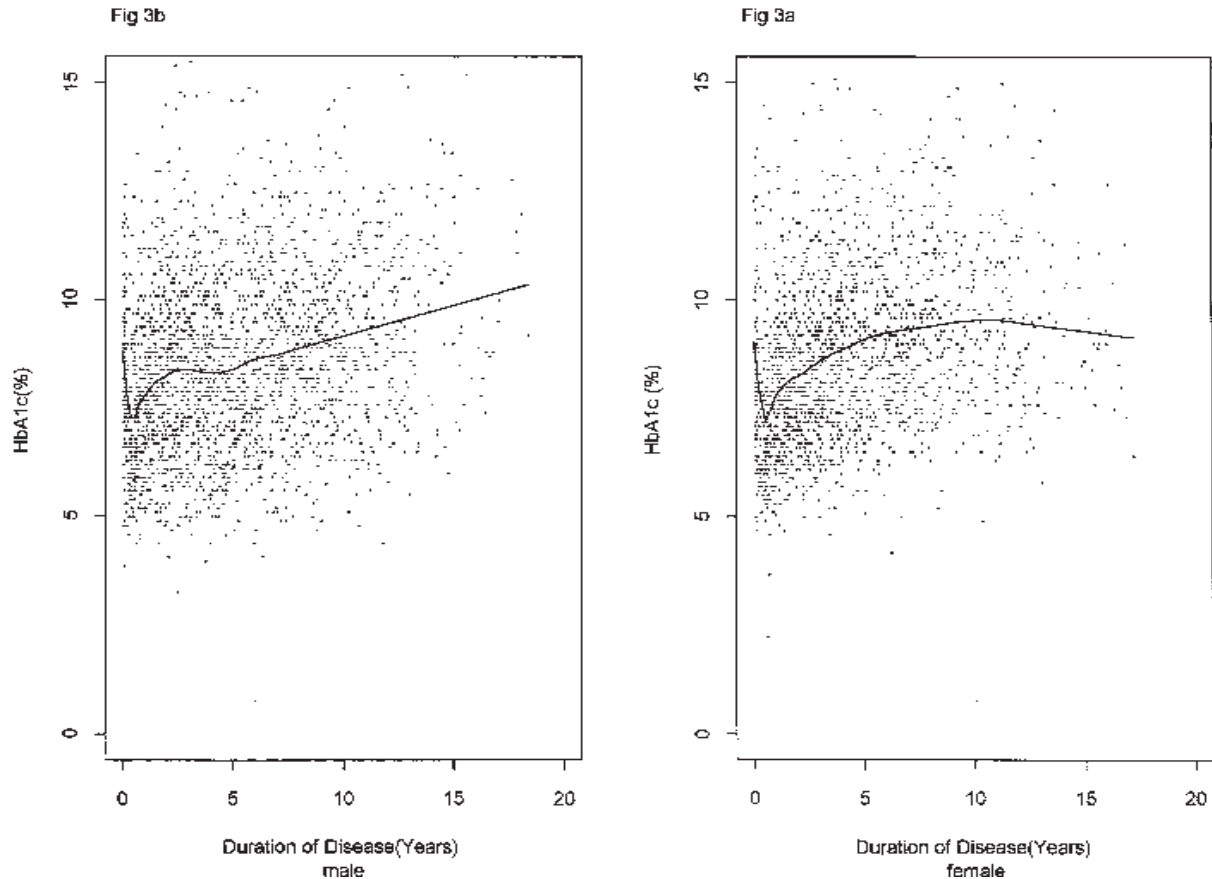
Fig 3a,b HbA$_{1c}$ in diabetic children and adolescents from the onset of the disease and onwards

the weight gain after the introduction of insulin therapy. In girls, BMI was increasing even after the first measurement (Table 3, Fig. 2a,b).

No correlation was found between the individual HbA$_{1c}$ levels and any of the growth parameters studied. In both sexes, the HbA$_{1c}$ curves throughout diabetes duration exhibit an expected uniform pattern with higher levels at the first observation, followed by a decline during the honeymoon period and by further increase thereafter (Fig. 3a,b). The mean HbA$_{1c}$

Table 2
Final height and predicted target height in diabetic patients

	males		females	
	final height	predicted target height	final height	predicted target height
No	62	62	61	61
Mean	176.5	176.8	167.0	165.6
Variance	43.0	30.6	34.9	21.0
Pearson correlation	0.55		0.35	
P value (two-tailed)	0.75		0.09	

Table 3
Body mass index in children with insulin dependent diabetes mellitus

body mass index (SDS)	males		females	
	intercept	slope	Intercept	slope
No	317	317	270	270
Mean	0.467	0.021	0.091	0.060
Median	0.320	0.020	0.042	0.041
SD	1.310	0.496	0.522	0.233
P value	<0.01	0.45	0.02	<0.01

levels were 8.2±1.8 % in males and 8.7±2.1 % in females at the first observation and 9.1±2.0 % and 9.5±2.4 % at the last observation.

Discussion

The pooled cohort of diabetic children, adolescents and young adults from university hospitals of the two neighboring central-European countries with a similar genetic background represents the largest sample of diabetic patients ever analyzed for growth.

In our cohort the children of both sexes were taller than the population standard close to the onset of symptoms of diabetes. This finding is in accordance with several other studies (BLOM et al. 1992; BOGNETTI et al. 1998; CONNORS et al. 1997; DANNE et al. 1997; HOLL et al. 1994 and 1998a; MALONE 1993; PRICE and BURDEN 1992; SCHEFFER-MARINUS et al. 1999; HYPPONEN et al. 2000) although there is some controversy. BLOM et al. (1992) suggested that a tendency to hyperinsulinemia in the pre-diabetic phase of beta-cell destruction, leading to an accelerated growth might explain this phenomenon. However, this would be based only on an anecdotic observation of SCANDELLARI et al. (1977) who suggested that episodes of hypoglycemia might precede the clinical onset of diabetic symptoms. A more plausible explanation for the significant increments in standardized height at diabetes onset would be a synchronization of one of the minor childhood or of the major pubertal growth spurt with an increased insulin resistance.

Minor childhood growth spurts have been described consistently in several auxological analyses of children's individual growth and were reported by BUTLER et al. (1990), KARLBERG (1990), LEDFORD and COLE (1998), MUHL et al. (1992) and THALANGE et al. (1996). Individual height velocity curves appear to consist of a regular series of accelerations (catch-up) and decelerations (lag-down) in a cyclical fashion. The midchildhood spurt may be identified at about 7 years in boys and 6.7 years in girls, the pre-school spurt at about 4.5-5 years in both sexes, a late-childhood spurt between 8.6 and 9.2 years and in those still not in puberty, an additional prepubertal spurt at 10-10.8 years occurs, as summarized by BUTLER et al. (1990). KARLBERG (1990) identified an additional infancy-childhood growth spurt that occurs during the second half-year of life. Even within shorter periods of time, periodic seasonal growth cycles have been identified as reported by THALANGE et al. (1996). HAUSPIE et al. (1994) observed that the timing of all these growth spurts varies individually and seems to be genetically determined. Therefore they cannot be represented in regular population-based growth charts that are used as the base for evaluation of height.

The regulation of the childhood growth spurts has not been analyzed in detail. Functional maturation of adrenal cortex and onset of its androgen production (adrenarche) was attributed to the mid-childhood growth spurt by MUHL et al. (1992) but may also contribute to some the other childhood growth spurts. MUHL et al. (1992) suggested that interactions with the growth hormone-IGF-I may represent an additional mechanism of regulation of these spurts, analogically to the regulation of the pubertal growth spurt by gonadal steroids and the growth hormone-IGF-I axis.

Growth spurts mediated either by growth hormone or by adrenal or gonadal steroids represent periods of increased insulin resistance as suggested by BROOK and HINDMARSH (1992), IBANEZ et al. (1997) and SPEISER et al. (1992). In an individual with insulitis and with a stepwise decreasing capacity of insulin production, an increment of insulin resistance may lead to clinically manifest insulinopenia and the onset of clinical symptoms of diabetes. HOLL et al. (1994) suggest that this might be the explanation why children tend to be taller compared to the reference population and their siblings at the onset of diabetic symptoms.

In the subsequent years of diabetes duration, the standardized height of diabetic children is slightly decreasing, which is in agreement with findings of BOGNETTI et al (1998), HOLL et al. (1994,1998a) and SALERNO et al. (1997). In fact, this tendency may reflect just a physiological normalization of standardized height (lag-down growth) following the initial growth spurt before the onset of diabetes. This concept is supported by our findings as well as by results of DANNE et al. (1997), HOLL et al. (1994), SCHEFFER-MARINUS et al. (1999), ZACHRISSON et al. (1997) and CHOUDHURY et al. (2000). Our comparison of final heights to target heights in 123 patients clearly demonstrated that in the 1970-1990's diabetic children reached completely their genetic growth potential.

Subjects of both sexes tended to be overweight at the first observation at median diabetes duration of 0.2 years. This reflects that children overcome their

initial weight loss quite quickly and is in agreement with observations of HOLL et al. (1998b) and THON et al. (1992). Girls but not boys tend to become even more overweight during diabetes treatment. This may reflect rather behavioral than disease-related factors as suggested by HOLL et al. (1998b) and TUVERNO et al. (1997). An increase of the overall food intake due to the flexibility allowed by multiple injection therapy and a decrease of sportive activity may contribute to this effect. At least in our countries, boys tend to be fond of sports what helps to keep their weight. We found in accordance with BOGNETTI et al. (1998), SCHEFFER-MARINUS et al. (1999) and ZACHRISSON et al. (1997) no correlation between growth variables and the mean HbA_{1c} indicating that in fairly controlled type 1 diabetes neither longitudinal growth nor final height is significantly affected.

In conclusion, diabetes children were taller close to the onset of the disease. This may be due to the synchronization of onset of diabetes symptoms with the mid-childhood growth spurt. There was a subsequent growth deceleration and final height was identical with target height.

Acknowledgements

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