Tracking of Metabolic Control from Childhood to Young Adulthood in Type 1 Diabetes

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Objective This prospective longitudinal survey was designed to follow patients with diabetes from disease onset in childhood over an extended period of time including puberty until young adulthood with respect to metabolic control.
Study design An electronic diabetes patient documentation system used in diabetes centers in Austria and Germany was utilized for standardized data collection. Complete documentation of metabolic control for prepuberty (≤13 years), puberty (14-19 years), and adulthood (≥20 years) was available in 1146 patients.
Results Median age at diabetes manifestation was 7.2 (IQR 4.7-9.4) years; 49% were male. In the prepubertal stage, median glycated hemoglobin A1c (HbA1c) was 7.5 (IQR 6.8-8.3), during puberty 8.0 (IQR 7.3-8.9), and after puberty 7.8 (IQR 7.1-9.0). A significant intra-individual correlation was found for prepuberty to puberty HbA1c levels (R = 0.55, $P < .001$), puberty to adulthood (R = 0.59, $P < .001$), as well as prepuberty to adulthood (R = 0.30, $P < .001$). When patients were divided into tertiles of prepubertal HbA1c, HbA1c increased in all 3 groups over time, however, significant group differences tracked into adulthood ($P < .001$ at all stages). A regression model identified pre-pubertal HbA1c as a significant and relevant predictor of metabolic control in young adulthood adjusted for confounders ($P < .001$).
Conclusions This survey provides evidence for long-term tracking of metabolic control from childhood until adulthood, suggesting an early focus on metabolic control. *(J Pediatr 2014;165:956-61)*.

In type 1 diabetes, the importance of metabolic control for the development of micro- and macrovascular complications is well recognized,[1,2] and glycated hemoglobin A1c (HbA1c) strongly correlates with the risk of coronary heart disease.[3] Therefore, despite other confounders, metabolic control is established as the main factor for diabetes outcome. As prevention of type 1 diabetes is currently not available and diabetes duration is not modifiable, the identification of additional contributors for diabetes outcome is important. Improvement of long-term metabolic control is of major interest in young patients with type 1 diabetes.[4-6] Hormonal changes during puberty[7-9] are known to lead to poor metabolic control. Alterations of the growth hormone/insulin-like growth factor-1 axis[10] and abnormalities of ovarian function in girls[11] may contribute to insulin resistance.

However, higher HbA1c levels during puberty are not only explainable by demographic and treatment factors, reduced compliance because of psychosocial difficulties, and by hormonal changes during puberty; factors tracking from disease onset onward seem to play an important role in metabolic diabetes outcome.

Although the phenomenon of 'tracking' has already been described in other conditions, for example blood pressure and body mass index (BMI),[12] tracking of metabolic control has rarely been investigated. A retrospective analysis carried out in the Oxford area assumed that within an overall improvement in HbA1c, persistent individual tracking does exist.[13]

In the present study, therefore, we explore the tracking of HbA1c, representing metabolic control within the first decades of diabetes. We test this hypothesis in a multicenter setting, following HbA1c levels in a set of patients with type 1 diabetes from disease onset in childhood (younger than 12 years of age) through prepuberty and puberty until young adulthood.

Methods

DPV is an electronic documentation system for patients with diabetes broadly used in Austria and Germany. Based on this continuous data acquisition system for prospective surveillance, a prospective multicenter survey was designed. The

ADA	American Diabetes Association
BMI	Body mass index
HbA1c	Glycated hemoglobin A1c

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data documentation started in 1990 and comprises complete demographic, anthropometric, and diabetes-related characteristics of patients with type 1 diabetes and is used as a quality control system.[6] Anonymous longitudinal data are transmitted for central validation and analysis twice yearly. Inconsistent data are reported back to the participating centers for confirmation or correction and are then re-entered into the joint database. Based on asymmetric encryption (hash-key), patients can be followed after the transition from pediatric to adult diabetes care if treatment continues at a diabetes center participating in the DPV initiative. Up to March 2013, 372 diabetes centers took part in this study (238 pediatric and 134 adult centers).

The observation period in each individual patient was divided into 3 diabetes stages defined by age. The period ≤13 years of age (starting after a diabetes duration of at least 1 year) was defined as prepubertal, 14-19 years as pubertal, and ≥20 years as postpubertal or young adulthood. The classification into pubertal stages could only be performed by age, as Tanner stages were not available in the data set. During each period, the median of all available HbA1c-values was calculated for each patient.

Inclusion criteria for the analysis were birth prior to 1993, onset of type 1 diabetes before the age of 11 years, diabetes manifestation between 1990 and 2000, documentation of median HbA1c in the prepubertal, pubertal, and young adult stage, together with documented insulin therapy.

The main outcome measure was HbA1c, standardized to the Diabetes Control and Complications Trial normal range using the Multiple of the Mean method.[14] HbA1c is given in percentage. Based on the prepubertal and accordingly adult HbA1c, patients were divided into tertiles: group I, representing one-third of patients (n = 382) with lowest HbA1c levels; group II, 382 patients with middle/moderate HbA1c; and group III, 382 patients with the worst metabolic control (highest HbA1c levels before puberty). Migration background was defined by patient's father and/or mother not born in Austria or Germany.

BMI as derived from weight in kilograms divided by square of height in meters, is an accepted measure of overweight and obesity in children, adolescents, and adults. Using recent German reference values,[15,16] BMI-SD scores were calculated using the least mean squares method described by Cole.[17]

Statistical Analyses

For patient description, median and IQRs were provided for continuous variables and percentage for binary variables. For group comparison (patients included in the study vs patients lost to follow-up) Wilcoxon rank test (continuous variables), and χ^2 test (binary variables) were applied. *P* values were adjusted for multiple comparisons according to Holm (Bonferroni step-down). For intra-individual comparisons of metabolic control during the prepubertal, pubertal, and postpubertal/young adult period, respective differences were analyzed by Wilcoxon signed-rank test.

Spearman correlation with Fisher z-transformation to calculate 95% CI was used to reflect tracking of metabolic control, relating median HbA1c-values in each patient during the prepubertal period with the respective values during puberty, as well as in adulthood. The χ^2test was used to analyze the relationship between tertiles of metabolic control during prepuberty and adulthood, as well as the achievement of adequate control as recommended in current guidelines.

To analyze the contribution of prepubertal metabolic control on adult HbA1c, a mixed hierarchic regression model was used (dependent variable: HbA1c in adulthood, independent variable: HbA1c during prepuberty). Center was entered as a random effect in the model (covariance structure: Cholesky), the intraclass correlation (between center variation) was 21%. Estimation was based on residual pseudo-likelihood, denominator degrees of freedom were calculated according to Kenward-Roger, and iterations were optimized according to Newton-Raphson. In addition to this simple model, a fully adjusted model including sex, migration background, and year of manifestation, diabetes duration, insulin therapy, and adult BMI together with type of treatment center was implemented.

Logistic regression models, with identical covariates as in the fully adjusted model, were used to calculate odds for good metabolic control in adulthood based on recommended HbA1c levels adopting either American Diabetes Association (ADA) or International Society for Pediatric and Adolescent Diabetes guidelines respectively.

For all analyses, a 2-sided *P* value of <.05 was considered statistically significant. The statistical software package SAS 9.3 was used for analysis (SAS Institute Inc, Cary, North Carolina).

Results

By March 2013, the DPV database included 15 162 patients with type 1 diabetes manifestation younger than 11 years of age, born prior to 1993, with complete baseline documentation. Among these, 1146 patients were followed continuously from prepuberty through puberty to adulthood. The large number of patients lost to follow-up is due to change of providers of diabetes care, especially during transition from pediatric centers to adult internal medicine. We consequently compared the study group (n = 1146) with 14 016 patients

Table I. Patient demographics

	Study cohort, complete follow-up until the age of 20 y (n = 1146)	Patient group, loss-of follow-up (n = 14 016)	*P*
Male (%) (SD)	49.4 (±0.5)	49.0 (±0.5)	n.s.
Mean age at onset (y) (SD)	6.9 (±2.8)	6.9 (±2.8)	n.s.
Mean age (y) (SD)	21.6 (±2.8)	17.8 (±2.8)	<.0001
Migration background (%)	8.0 (±0.3)	6.5 (±0.3)	n.s.
Pediatric center (%)	77.3 (±0.4)	83.4 (±0.4)	<.0001
BMI (kg/m^2) (SD)	24.5 (±3.7)	23.1 (±4.1)	<.0001
Mean HbA1c (%) (SD)	8.3 (±1.8)	8.7 (±2.0)	<.0001

n.s., not significant.
Comparison of patient demographics of the study cohort with complete documentation until the age of ≥20 years and the cohort with incomplete documentation and loss of follow-up.