Improved Metabolic Control in Children and Adolescents With Type 1 Diabetes

A trend analysis using prospective multicenter data from Germany and Austria

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OBJECTIVE—To investigate the temporal trend of metabolic control and potential predictors in German and Austrian children and adolescents with type 1 diabetes.

RESEARCH DESIGN AND METHODS—This study is based on a large, multicenter database for prospective longitudinal documentation of diabetes care in Germany and Austria. Data from 30,708 patients documented in 305 diabetes centers between 1995 and 2009 were analyzed. Generalized linear mixed regression models were used to adjust trend analysis for relevant confounders.

RESULTS—Unadjusted mean HbA_{1c} decreased from 8.7 ± 1.8% in 1995 to 8.1 ± 1.5% in 2009. In multiple regression analysis, treatment year, age, sex, diabetes duration, migration background, BMI-SDS, and daily insulin dose were significant predictors of metabolic control ($P < 0.001$). After multiple adjustment, mean HbA_{1c} decreased significantly by 0.038% per year (95% CI 0.032–0.043%), average odds ratio (OR) per year for HbA_{1c} >7.5% (>9.0%) was 0.969 (95% CI 0.961–0.977) (0.948, 95% CI 0.941–0.956). Intensified insulin regimen was associated with lower frequency of poor metabolic control (HbA_{1c} >9%; $P = 0.005$) but not with average HbA_{1c} ($P = 0.797$). Rate of severe hypoglycemia and hypoglycemic coma decreased significantly (relative risk [RR] per year 0.948, 95% CI 0.918–0.979; RR 0.917, 95% CI 0.885–0.950) over the study period. Diabetic ketoacidosis rate showed no significant variation over time.

CONCLUSIONS—This study showed a significant improvement in metabolic control in children and adolescents with type 1 diabetes during the past decade and a simultaneous decrease in hypoglycemic events. The improvement was not completely explained by changes in the mode of insulin treatment. Other factors such as improved patient education may have accounted for the observed trend.

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The Diabetes Control and Complications Trial (DCCT) showed that improved metabolic control reduces the risk of long-term complications in both adult and adolescent patients with type 1 diabetes (1,2). The observational follow-up study of the DCCT (the Epidemiology of Diabetes Interventions and Complications [EDIC] study) further proved that good glycemic control had persistent beneficial effects on long-term complications (3). Based on the results of the DCCT/EDIC study, it was recommended to optimize glycemic control as early and close to normal as possible in all patients with type 1 diabetes in order to prevent development and progression of microvascular complications.

Diabetes treatment has been intensified in pediatric and adolescent patients during the past 15 years. Insulin therapy has changed from twice-daily injection regimen to intensified therapy with multiple daily injections (MDI) and continuous subcutaneous insulin infusion (CSII). This has been reported from single-center and multicenter studies (4–10). In the 1990s, mainly an increased use of MDI was observed, whereas since 2000, pump therapy increased considerably, paralleled by a decrease in MDI therapy (11). With the intensification of insulin regimen, the frequency of daily self-monitoring of blood glucose (SMBG) increased continuously (5,10–12), as close glucose monitoring is a precondition for intensified insulin therapy with an appropriate dose adjustment. Likewise, the use of short-acting insulin analogs has continuously increased since the mid-1990s and the use of long-acting analogs since 2000 (4,5,10).

Despite these far-ranging changes in diabetes therapy, the anticipated improvement in metabolic control in children and adolescents with type 1 diabetes has not been achieved in all settings. The multicenter Hvidoere studies did not observe any improvement in glycemic control during 1995–2005 (6–8). Other studies, however, reported a significant decrease in average HbA_{1c} level over the past two decades (4,5,10,11,13). Concordantly, several studies indicated a notable increase in the proportion of children and adolescents with good metabolic control (HbA_{1c} <7.5 or <8%) over the past years (11,13).

In the DCCT study, the tradeoff with intensified insulin therapy was a marked increase in episodes of severe hypoglycemia

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*A complete list of diabetes centers can be found in the Supplementary Data.

(2). Several studies reported a higher hypoglycemia risk with lower HbA_{1c} level (4,6,7,10,14), but others did not (15,16). Results on the trend of severe hypoglycemic events over the past 15 years are also inconsistent (4,5,8,9,11).

The aim of this study was to give a current update on the temporal trend of metabolic control in German and Austrian children and adolescents over the past 15 years (1995–2009), to identify potential determinants of metabolic control, and to analyze the simultaneous trend of severe hypoglycemic and diabetic ketoacidotic events.

RESEARCH DESIGN AND METHODS

Data source

The current study is based on prospective data from the German and Austrian DPV documentation system (Diabetessoftware für Prospektive Verlaufsbeobachtung) (12,13). Within the framework of the quality assurance and scientific research project DPV, German and Austrian diabetes centers (hospitals and practices) document treatment and outcome of routine diabetes care prospectively using the DPV software. Twice a year, locally collected anonymous longitudinal data are transmitted for central plausibility checks and analyses. Inconsistent data are reported back to participating centers for validation and correction. Overall, 326 German and 9 Austrian diabetes centers participated in the DPV project up to 2010.

Study population

For the present analysis, data from patients with type 1 diabetes were selected from the available DPV database in September 2010. Patients and medical data were eligible for inclusion in the analysis when meeting the following criteria: documented data within 1995–2009, age at follow-up visit <20 years, and disease duration at follow-up visit >2 years. Applying the described criteria and then selecting individual patient data of the most recent year of follow-up resulted in a study sample of 30,708 patients from 305 diabetes centers (296 German and 9 Austrian centers) with 86,914 documented medical visits. Finally, individual patient data of the most recent year were aggregated for each patient to set up the final analysis dataset.

Variables

Demographic data included age at onset and at follow-up, sex, duration of diabetes, year of follow-up, and migration background. Patients with at least one parent born outside of Germany or Austria were considered to have a migration background.

Clinical data were weight, height, modalities of insulin treatment (number of injections or pump therapy), daily dose of insulin (units per kilogram body weight), HbA_{1c}, and the occurrence of hypoglycemic events and diabetic ketoacidosis (DKA). Acute complications were assessed at each follow-up visit for the period since the past visit (but at most for a 1-year period), giving an observation period of at most 2 years. Information on BMI (kg/m^2), insulin dose, and hypoglycemic events was not available for 687, 404, and 2,748 patients, respectively.

In total, 86,914 HbA_{1c} measurements in 30,708 patients were available for analysis. The number of measurements per year increased from 675 (in 332 patients) in 1995 to 7,207 (in 2,286 patients) in 2008 and added up to 31,921 measurements (in 13,557 patients) in 2009. During 1996–2008, the average number of HbA_{1c} measurements per patient and year ranged between 2.8 (1996) and 3.4 (2004). The overall mean (SD) of the annual averages was 3.1 (0.4). In order to adjust for different laboratory methods, local HbA_{1c} values were mathematically standardized to the DCCT reference range (4.05–6.05%) using the "multiple of the mean" transformation method (1). BMI values were transformed to standard deviation scores (BMI-SDS) based on German reference values by applying the LMS method (17,18).

For each patient, clinical data (BMI-SDS, HbA_{1c}, number of injections, and daily insulin dose) from the most recent year of follow-up were averaged, and numbers of hypoglycemic and DKA events were added up. According to current recommendations of the International Society for Pediatric and Adolescent Diabetes (ISPAD) (19), HbA_{1c} values <7.5, 7.5–9.0, and >9.0% were considered as good, moderate, and poor metabolic control, respectively.

For analysis of metabolic control and acute complications, age at visit and duration of diabetes were categorized as >2–5, >5–10, >10–15, and >15–20 years and >2–5, >5–10, and >10 years, respectively. BMI-SDS and insulin dosage were classified into terciles.

Insulin therapy was categorized as conventional therapy (CT) (one to three daily injection time points), MDI (greater than or equal to four daily injection time points), and CSII. Patients were classified into therapy groups according to the treatment that they received for the most part during the most recent year. Treatment centers were grouped into large or small centers (according to >100 or ≤100 patients treated annually during 2005–2009, respectively) and general care or rehabilitation facilities.

Hypoglycemic events were classified, according to ISPAD guidelines (20), as severe hypoglycemia when requiring assistance (ISPAD grade 2 and 3) and as hypoglycemic coma (ISPAD grade 3) when loss of consciousness or seizures occurred. An event of DKA was defined as hyperglycemia with pH value <7.3 and/or hospital admission due to DKA.

Statistical analyses

For descriptive analysis, mean, SD, or SE were calculated for continuous variables and percentages for categorical variables. Rates of ketoacidosis and hypoglycemia were estimated by the person-years (PYs) method assuming Poisson distribution of events and given as incident number of events per 100 PYs ± SE.

Multiple generalized linear mixed regression models were used to assess the effect of potentially influencing factors on metabolic control (linear regression for HbA_{1c} and logistic regression for HbA_{1c} >7.5% and for HbA_{1c} >9.0%) and rates of hypoglycemia and DKA (Poisson regression) in order to account for confounding effects. Age and diabetes duration at follow-up, sex, BMI-SDS (terciles), year of treatment, migration background, type of insulin treatment, insulin dose (terciles), and size and type of center were modeled as independent fixed effects. In order to account for variation between diabetes centers, treatment center was modeled as random effect. In Poisson regression models, overdispersion of rates was taken into account. Results of regression analyses are presented as multiple adjusted means, multiple adjusted rates, odds ratios (ORs), or relative risks (RRs) including 95% CIs. Within the regression approach, *F* tests were used to test for differences between groups.

$P < 0.05$ was considered statistically significant. All analyses were performed with SAS for Windows version 9.2 (SAS Institute, Cary, NC).

RESULTS

Description of the study cohort

Mean age of the cohort (n = 30,708) was 14.6 ± 3.7 years. Mean age at onset and

mean diabetes duration were 7.9 ± 4.0 and 6.7 ± 3.6 years, respectively; 52.1% (n = 16,014) of patients were male. Migration background was present in 12.0% (n = 3,683) of patients.

Among the 305 diabetes centers, 211 (96.2%) were pediatric centers, 155 (50.8%) were classified as large, and 293 (96.1%) were general care facilities; 73.1% (n = 22,462) of patients were treated in large centers, 95.8% (n = 29,433) in pediatric centers, and 94.5% (n = 29,020) in general care facilities.

Treatment mode, metabolic control, and acute diabetes complications

Overall, 10.1% (n = 3,100) of the patients were treated with CT, 65.0% (n = 19,962) with MDI, and 24.9% (n = 7,646) with CSII. The overall average number of daily injections of patients on injection therapy, i.e., on CT or MDI, was 4.5 ± 1.1. Mean daily insulin dose (n = 30,304) was 0.90 ± 0.29 units/kg body weight.

Average HbA_{1c} was 8.4 ± 1.7%. 33.7% (n = 10,341) of patients achieved HbA_{1c} values below the recommended target of 7.5%. 38.1% (n = 11,695) of patients had values between 7.5 and 9.0%, and 28.2% (n = 8,672) of patients were in poor metabolic control with HbA_{1c} >9.0%.

Eight point nine percent (n = 2,477) of patients had at least one severe hypoglycemic event and 2.4% (n = 683) at least one hypoglycemic coma. During a total of 22,633.12 PYs, 4,315 events of severe hypoglycemia and 903 of hypoglycemic coma were observed in the cohort, corresponding to crude event rates of 19.1 ± 0.29 and 4.0 ± 0.13 per 100 PYs. Among patients with episodes of severe hypoglycemia, average HbA_{1c} was lower (8.1 ± 1.5 vs. 8.4 ± 1.7%, $P < 0.001$) and consistently the proportion of patients with HbA_{1c} <7.5% was higher (38.0 vs. 33.7%, $P < 0.001$) compared with those without severe hypoglycemia. Multiple adjustment for confounders affected estimates only slightly.

At least one DKA event occurred in 4.1% (n = 1,259) of patients. A total of 1,476 DKA episodes (total PYs, 24,917.50) were observed, giving a crude DKA incidence rate of 5.9 ± 0.15 per 100 PYs.

Time trends in treatment mode and metabolic control

Mode of insulin therapy changed importantly during the study period (Supplementary Fig. 1). In 1995, 37.7% of patients were treated with CT. This proportion decreased to 7.1% in 2009. The rate of MDI therapy increased from 61.4% in 1995 to 78.1% in 2003 and decreased thereafter to 56.3% in 2009. Contemporaneously, the portion of patients with CSII rose continuously from 0.9% in 1995 to 36.6% in 2009.

Unadjusted mean HbA_{1c} decreased from 8.7 ± 1.8% in 1995 to 8.1 ± 1.5% in 2009, with an average absolute annual decrease in HbA_{1c} of 0.054% (95% CI 0.048–0.059%, $P < 0.001$). The annual decrease in HbA_{1c} differed significantly between treatment groups (P = 0.005). The unadjusted decrease was greater in the CSII group (0.075%; 0.059–0.091%) than in the MDI (0.049%; 0.043–0.055%) and CT groups (0.045%; 0.032–0.057%).

Likewise, the unadjusted proportion of patients with HbA_{1c} >7.5% decreased steadily from 75.6 ± 2.4% (±SE) in 1995 to 61.9 ± 0.4% in 2009. The respective average OR per year was 0.961 (95% CI 0.954–0.968, $P < 0.001$). The unadjusted proportion of patients with poor metabolic control (HbA_{1c} >9.0%) decreased even more steeply from 39.8 ± 2.7% in 1995 to 20.6 ± 0.3% in 2009, with a corresponding OR of 0.931 (0.925–0.938, $P < 0.001$). The decreasing trend in proportion of patients with HbA_{1c} >7.5 or >9.0% differed significantly between treatment regimens ($P < 0.001$). The unadjusted ORs for HbA_{1c} >7.5% were 0.934 (0.913–0.955), 0.958 (0.950–0.966), and 0.986 (0.969–1.002) for the CSII, MDI, and CT regimen, respectively. Corresponding ORs for HbA_{1c} >9.0% were 0.897 (0.878–0.917), 0.941 (0.933–0.948), and 0.940 (0.924–0.957).

After multiple adjustment for confounders, the decline in mean HbA_{1c} over the study period remained significant in the whole cohort, with an estimated average absolute annual decrease of 0.038% (95% CI 0.032–0.043%, $P < 0.001$) (Fig. 1*A* and Supplementary Table 1). However, differences in the annual decrease between treatment regimens disappeared (P = 0.703); the adjusted annual decreases were 0.032% (0.016–0.048%), 0.039% (0.032–0.045%), and 0.036% (0.024–0.048%) for the CSII, MDI, and the CT regimen, respectively.

The decreasing trends in proportions of patients with HbA_{1c} >7.5 or >9.0% were also slightly attenuated after multiple adjustment but remained significant (Fig. 1*B* and *C* and Supplementary Table 1). The overall adjusted average ORs per year for HbA_{1c} >7.5 or >9.0% were 0.969 (95% CI 0.961–0.977, $P < 0.001$) and 0.948 (0.941–0.956, $P < 0.001$), respectively. This corresponds to an annual decrease in the odds for HbA_{1c} >7.5 or >9.0% by 3.1% (95% CI 2.3–3.9%) and 5.2% (4.4–5.9%). Trend differences in the proportion of patients with HbA_{1c} >7.5% between insulin regimens were diminished after multiple adjustments but remained significant (P = 0.036), in contrast trend differences in the proportion of patients with HbA_{1c} >9.0% dissolved (P = 0.697). The adjusted OR for HbA_{1c} >7.5% was still lower for CSII (0.970; 95% CI 0.947–0.993) and MDI (0.964; 0.955–0.973) compared with CT (0.989; 0.972–1.007). Respective ORs for HbA_{1c} >9.0% were 0.940 (0.919–0.962), 0.950 (0.941–0.958), and 0.946 (0.929–0.964).

Predictors of metabolic control

In multiple regression analysis age, sex, diabetes duration, migration background, BMI-SDS, and daily insulin dose were significant predictors of metabolic control (assessed as HbA_{1c}, proportion HbA_{1c} >7.5 or >9.0%) (Table 1). Older and female patients, patients with longer diabetes duration, higher insulin dose, or a migration background, and patients in the upper BMI-SDS tercile had poorer metabolic control. Mode of insulin therapy was significantly associated only with the proportion of patients having HbA_{1c} >9.0%; patients with more intensive insulin therapy were less frequent in poor metabolic control.

In multiple regression, size of diabetes center was significantly associated with mean HbA_{1c} but not with moderate or poor metabolic control. Adjusted mean HbA_{1c} was higher among patients treated in large centers. Metabolic outcomes did not significantly differ between patients treated in general care or rehabilitation facilities, but rehabilitation patients tended to have poorer metabolic control.

Time trends in acute diabetes complications

Unadjusted rate of severe hypoglycemia decreased steadily from 54.1 ± 5.8 per 100 PYs in 1995 to 15.1 ± 0.4 per 100 PYs in 2009. According to the estimated RR for a 1-year period (0.950; 95% CI 0.920–0.980, P = 0.001), the rate of severe hypoglycemia dropped on average by 5.0% (95% CI 2.0–8.0%) per year. The unadjusted rate of hypoglycemic coma decreased even more during the study period from 15.4 ± 3.1 per 100 PYs in 1995 to 2.3 ± 0.2 per 100 PYs in 2009. The respective average RR estimate

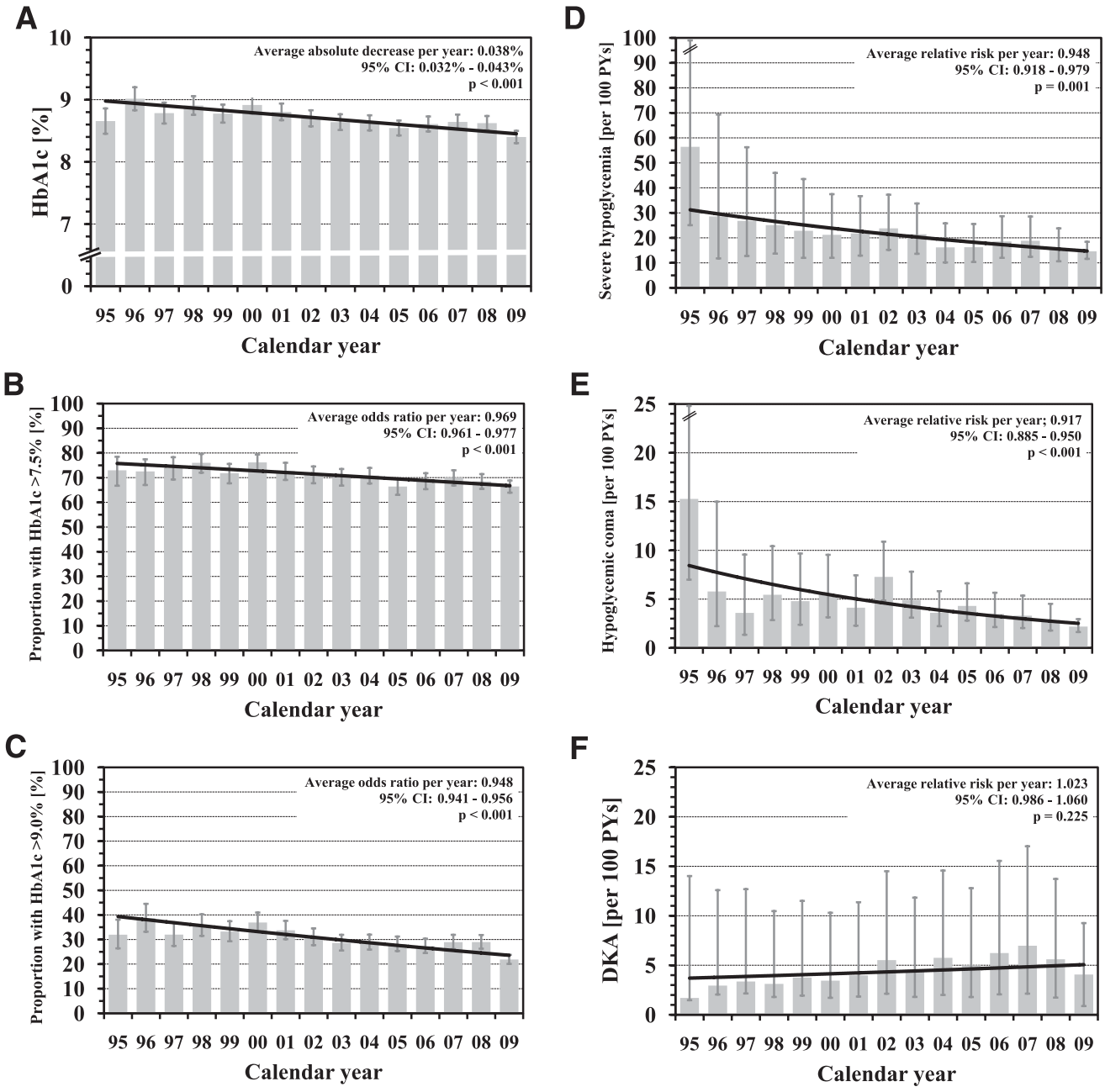

Figure 1—*Time trends of metabolic control and acute diabetes complications. Multiple adjusted estimates of mean HbA_{1c}* (A)*, proportion of patients with HbA_{1c} >7.5%* (B) *or HbA_{1c} >9.0%* (C)*, and rates of severe hypoglycemia* (D)*, hypoglycemic coma* (E)*, and DKA* (F) *by year of treatment. Estimates are derived from multiple (generalized) linear mixed models including year of treatment, age at follow-up, sex, diabetes duration, migration background, BMI-SDS, mode of therapy (CT, MDI, or CSII), insulin dose per kg body weight and day, and size and type of diabetes center as fixed independent variables and diabetes center as random independent variable. Analyses for metabolic control and DKA are based on 30,021 patients because of missing values for BMI-SDS and/or daily insulin dose* (n = *687), and analyses for hypoglycemic events are based on 27,586 patients because of missing values for hypoglycemic events* (n = *2,748) and BMI-SDS and/or insulin dose* (n = *374). Time trends in dependent variables (represented by solid lines) and estimates of average changes per year (absolute decrease, OR, and RR) were derived from multiple (generalized) linear mixed models by including a linear trend term for calendar year. Vertical whiskers represent 95% CIs.*

per 1-year period was 0.926 (0.910–0.943, $P < 0.001$).

The unadjusted rate of DKA varied significantly over the study period between 2.0 ± 0.9 per 100 PYs in 1995 and 8.8 ± 0.7 per 100 PYs in 2007 ($P < 0.001$). However, the DKA rate showed no significant log-linear time trend according to the estimated annual RR of 1.017 (95% CI 0.989–1.045, $P = 0.241$).

Adjustment for confounders affected the decreasing trends for hypoglycemic events only slightly and the trends remained significant ($P < 0.001$) (Fig. 1*D* and *E* and Supplementary Table 2). On average, the rate of severe hypoglycemia decreased by 5.2% (95% CI 2.1–8.2%) per year and the rate of hypoglycemic coma by 8.3% (5.0–11.5%) per year. The overall variation of the DKA rate

Table 1—*Predictors of metabolic control. Multiple adjusted estimates of mean HbA_{1c} and proportion of patients with HbA_{1c} >7.5 or >9.0% by patients' characteristics and aspects of diabetes management*

Variable	*N* (%)	Mean HbA_{1c} (%) (95% CI)	*P*	Proportion of patients with HbA_{1c} >7.5% (%) (95% CI)	*P*	Proportion of patients with HbA_{1c} >9.0% (%) (95% CI)	*P*
Age at follow-up (years)							
≤5	385 (1.3)	8.02 (7.84–8.21)	<0.001	57.1 (51.1–62.9)	<0.001	8.2 (5.5–12.2)	<0.001
>5–10	3,678 (12.3)	8.01 (7.90–8.12)		56.1 (52.9–59.2)		9.5 (8.2–11.0)	
>10–15	9,140 (30.4)	8.44 (8.34–8.54)		68.1 (65.6–70.5)		24.9 (22.9–27.0)	
>15–20	16,818 (56.0)	8.76 (8.66–8.86)		72.0 (69.8–74.1)		33.6 (31.3–35.9)	
Sex							
Male	15,643 (52.1)	8.51 (8.41–8.60)	<0.001	67.9 (65.5–70.3)	<0.001	25.0 (23.1–27.0)	<0.001
Female	14,378 (47.9)	8.62 (8.52–8.72)		69.8 (67.5–72.1)		28.0 (25.9–30.2)	
Diabetes duration (years)							
>2–5	11,633 (38.7)	8.45 (8.35–8.55)	<0.001	64.8 (62.2–67.3)	<0.001	24.1 (22.2–26.2)	<0.001
>5–10	12,631 (42.1)	8.59 (8.50–8.69)		69.9 (67.6–72.2)		27.4 (25.3–29.5)	
>10	5,757 (19.2)	8.71 (8.61–8.82)		74.1 (71.8–76.4)		29.2 (26.9–31.6)	
Migration background							
No	26,395 (87.9)	8.53 (8.44–8.63)	<0.001	68.1 (65.8–70.4)	<0.001	25.7 (23.8–27.7)	<0.001
Yes	3,626 (12.1)	8.75 (8.64–8.86)		73.8 (71.2–76.2)		32.1 (29.4–35.0)	
BMI-SDS							
1. tercile	9,999 (33.3)	8.57 (8.47–8.67)	<0.001	65.4 (62.9–67.9)	<0.001	26.4 (24.4–28.6)	<0.001
2. tercile	10,010 (33.3)	8.50 (8.41–8.60)		67.7 (65.2–70.7)		25.1 (23.1–27.2)	
3. tercile	10,012 (33.4)	8.61 (8.51–8.71)		73.2 (70.9–75.3)		27.8 (25.6–30.0)	
Insulin therapy							
CT (1–3 injections)	2,966 (9.9)	8.56 (8.45–8.67)	0.797	67.5 (64.5–70.3)	0.086	28.2 (25.6–31.0)	0.005
MDI (≥4 injections)	19,538 (65.1)	8.56 (8.47–8.66)		68.7 (66.3–70.9)		26.8 (24.8–28.9)	
CSII	7,517 (25.0)	8.55 (8.45–8.65)		69.9 (67.4–72.3)		24.8 (22.7–27.0)	
Daily insulin dose							
1. tercile	10,007 (33.3)	8.20 (8.11–8.30)	<0.001	59.8 (57.1–62.5)	<0.001	19.0 (17.3–20.7)	<0.001
2. tercile	10,007 (33.3)	8.51 (8.41–8.61)		68.5 (66.1–70.9)		25.3 (23.3–27.5)	
3. tercile	10,007 (33.3)	8.96 (8.86–9.06)		76.9 (74.8–78.8)		36.7 (34.3–39.3)	
Size of diabetes center							
≤100 patients	8,115 (27.0)	8.40 (8.28–8.53)	0.016	66.8 (63.8–69.8)	0.193	25.2 (22.8–27.8)	0.357
>100 patients	21,906 (73.0)	8.62 (8.49–8.74)		69.6 (66.6–72.4)		26.9 (24.4–29.5)	
Type of diabetes center							
General	28,342 (94.4)	8.55 (8.45–8.64)	0.260	68.4 (66.0–70.6)	0.110	26.0 (24.0–28.0)	0.077
Rehabilitation	1,679 (5.6)	8.80 (8.36–9.25)		76.4 (66.5–84.0)		34.8 (25.2–45.8)	

Estimates are derived from multiple (generalized) linear mixed models including year of treatment, age at follow-up, sex, diabetes duration, migration background, BMI-SDS (terciles), mode of insulin therapy (CT, MDI, or CSII), insulin dose per kg body weight and day (terciles), and size and type of diabetes center as fixed independent variables and diabetes center as random independent variable. Analyses are based on 30,021 patients because of missing values for BMI-SDS and/or daily insulin dose (n = 687).

was not significant after multiple adjustment (P = 0.409). The adjusted RR per year for DKA was 1.023 (95% CI 0.986–1.060, P = 0.225), thus indicating no significant log-linear trend (Fig. 1*F* and Supplementary Table 2).

CONCLUSIONS—This large multicenter study showed a significant improvement in metabolic control in German and Austrian children and adolescents with type 1 diabetes during 1995–2009. Both average HbA_{1c} and proportion of patients with poor metabolic control decreased over time independent of confounders. After multiple adjustment, improvement in average HbA_{1c} over time was not different between treatment regimens. Besides treatment year, the main influencing factors of metabolic control were age, sex, diabetes duration, migration background, BMI-SDS, and daily insulin dose. A simultaneous decrease of hypoglycemia rate was observed, whereas the incidence rate of hospitalized DKA remained almost stable.

Although being not so distinct, the observed improvement in metabolic control over the past 15 years is in agreement with reports from several recent studies from other countries. A decline of average HbA_{1c} has been observed in cohorts from Western Australia, Denmark, and Norway (4,10,11). Concordantly, the proportion of children with an HbA_{1c} level <8% increased in Norway and the U.S. (11,5). However, the Hvidoere studies did not find an improvement in glycemic control over the period 1995–2005 (7,8).

The observed improvement in glycemic control in the current study was not explained by the considerable intensification of insulin treatment during the past decade or other confounders. Further, in the current study, improvement in average

HbA_{1c} over time was comparable for different treatment regimens. This supports the view that other factors, such as the development of multidisciplinary diabetes care teams and improvements in structural quality of diabetes care and patient education, may have accounted for the observed trend (8,21,22).

Several studies have demonstrated that intensive treatment and lower HbA_{1c} levels are associated with an increased risk of severe hypoglycemia (2,4,6,7,14), but other studies did not support such a relationship (15,16). Although patients with severe hypoglycemia had lower average HbA_{1c} than those without severe hypoglycemia, the current study provides evidence, in concordance with other reports (5,9,10), that metabolic control can be improved on average in the diabetic population in routine care without an increased risk of hypoglycemia. The DKA rate showed a slight, but nonsignificant, increase over time in the current study, in concordance with previous reports (9,11).

The overall mean HbA_{1c} level (8.4%) and the proportion of patients with good (HbA_{1c} <7.5%, 33.7%) or poor metabolic control (HbA_{1c} >9.0%, 28.2%) in the study cohort were within the ranges found in several previous studies (5–8, 13–15,21,23–25).

Older age, female sex, and longer diabetes duration were significantly associated with worse metabolic control, affirming previously reported findings (4,6–8,10,13–16,21,23–25). The varying quality of metabolic control may in part be attributable to differences in insulin sensitivity, treatment compliance, or insulin needs related to these factors.

In the current study, migration background was also a significant predictor of poor metabolic control, as reported previously (13,15,24). This association may partly be related to language difficulties (8) and lower socioeconomic status (24).

Previous findings on the association between metabolic control and BMI are quite inconsistent. Several studies found no significant association (8,15,16,24,25), but positive (14,23) and inverse association has also been reported (21). The present results indicate that patients with a high BMI-SDS (upper tercile) may be prone to poorer metabolic control. On the other hand, longstanding poor glycemic control could lead to higher insulin dose and hence to weight gain. Because of its cross-sectional design, the current study cannot clear up the causality of the association.

The type of insulin regimen is supposed to have an impact on metabolic control. Although several studies did not indicate an association between insulin regimen/number of daily insulin injections and HbA_{1c} levels (6,14,16), in other studies, patients with an increased number of daily insulin doses exhibited poorer metabolic control (12,15,21,23,25). The insulin regimen found to be associated with best HbA_{1c} level varied between studies, ranging from conventional therapy and twice-daily regimen (8,12) to thrice-daily injections and pump therapy (10,21,25). In the current study, insulin regimen did not significantly affect the average HbA_{1c} level, but the proportion of patients with HbA_{1c} >9% among those using CT was significantly higher than among those with intensified therapy (MDI or CSII). With respect to the inconclusive data, it has to be noted that these results are from observational studies and not randomized trials. Therefore, HbA_{1c} levels are influenced by many factors beyond insulin regimen. Most importantly, in routine care, the choice of insulin regimen depends in particular on metabolic control. Patients with poor metabolic control are often transferred to intensified regimens. Thus, intensified treatment is likely to be a consequence of poor control rather than a cause.

In accordance with the results of the majority of studies (7,8,10,14,16,21,23), we found a positive association between daily insulin dose and HbA_{1c} level. The cross-sectional design of most studies, however, limits conclusions that can be drawn on the direction of the observed association. Further, it has to be considered that insulin data usually represent the recommended insulin dose, which possibly differs from the actual dose applied.

Patients treated in larger centers showed on average a higher HbA_{1c} level than patients of smaller centers. This may be attributed to the fact that large centers possibly care for a greater portion of patients with situations difficult to manage. Otherwise, large centers may not be able to attend to single patients as it might be possible in smaller centers. However, the size of the center did not affect the proportion of patients with HbA_{1c} >7.5 or 9% in the current study. In the Hvidoere studies (8), center resources were thought to account for significant differences in metabolic control between centers, but it was concluded that a motivated and well-organized diabetes care team is an important determinant of metabolic outcomes rather than the mere size of staff (8,22).

In our study, the proportion of patients with poor metabolic control (HbA_{1c} >9.0%) tended to be higher in rehabilitation compared with general care centers. This is most likely due to the fact that poor glycemic control is a major indication for the transfer to rehabilitation.

Some strength and limitations of the current study have to be noted. This large study shares the shortcomings of all observational studies compared with randomized trials. Because of the observational design, the study could not control for all influencing factors on metabolic control and acute complications, and thus observed associations could not be proven to be unbiased or to reflect causal effects. Another shortcoming is that HbA_{1c} levels were not measured centrally. However, HbA_{1c} values were mathematically standardized to the DCCT normal range in order to reduce between-laboratory variation. Therefore, the observed trend in glycemic control can be assumed to be valid. Hypoglycemic events could have been underestimated because of self-reporting. However, as differential reporting over the study period is unlikely, the trend estimates can be assumed to reflect a real trend.

The main strength of the study is that it comprises a large cohort of children and adolescents and data from small and large secondary level and university diabetes care centers. The study mirrors real-life data of daily pediatric diabetes care almost on a population basis.

In summary, this large multicenter study showed a significant improvement in metabolic control among diabetic children and adolescents during the past decade and a simultaneous decrease in the rate of severe hypoglycemic events. The improvement in glycemic control was not fully explained by demographic factors and changes in the mode of insulin treatment. Thus, other factors, such as improvement in resources, organization and attitudes of diabetes care teams, and patient education, also may have accounted for the observed trend.

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