

Long-Acting Insulin Analogs and the Risk of Diabetic Ketoacidosis in Children and Adolescents With Type 1 Diabetes

A prospective study of 10,682 patients from 271 institutions

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OBJECTIVE — To investigate if long-acting insulin analogs decrease the risk of diabetic ketoacidosis (DKA) in young individuals with type 1 diabetes.

RESEARCH DESIGN AND METHODS — Of 48,110 type 1 diabetic patients prospectively studied between 2001 and 2008, the incidence of DKA requiring hospitalization was analyzed in 10,682 individuals aged ≤ 20 years with a diabetes duration of ≥ 2 years.

RESULTS — The overall rate of DKA was 5.1 (SE ± 0.2)/100 patient-years. Patients using insulin glargine or detemir ($n = 5,317$) had a higher DKA incidence than individuals using NPH insulin ($n = 5,365$, 6.6 ± 0.4 vs. 3.6 ± 0.3 , $P < 0.001$). The risk for DKA remained significantly different after adjustment for age at diabetes onset, diabetes duration, A1C, insulin dose, sex, and migration background ($P = 0.015$, odds ratio 1.357 [1.062–1.734]).

CONCLUSIONS — Despite their long-acting pharmacokinetics, the use of insulin glargine or detemir is not associated with a lower incidence of DKA compared with NPH insulin.

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Lipolysis and ketogenesis leading to diabetic ketoacidosis (DKA) may be suppressed by the continuous provision of small doses of insulin (1,2). DKA is frequently caused by omission of insulin injections, observed in 28–65% of young patients with type 1 diabetes (3,4). In young children, the use of insulin glargine and detemir was associated with a trend to less DKA episodes compared with

NPH/zinc insulin (5), potentially related to the prolonged action of these insulin analogs (6–8). We hypothesized that long-acting insulin analogs may confer greater protection from DKA in young patients with type 1 diabetes.

RESEARCH DESIGN AND METHODS — Based on the Diabetes Prospective Documentation (DPV) Initia-

tive (9), a study was performed to evaluate the incidence of DKA in patients with type 1 diabetes using either NPH insulin or long-acting basal insulin analogs. A total of 48,110 patients with type 1 diabetes were consecutively registered between 2001 and 2008 at 271 diabetes centers in Germany and Austria, with an estimated nationwide capture rate of $\geq 80\%$.

Subjects aged ≤ 20 years with diabetes duration ≥ 2 years using three or more insulin injections daily without change of type of long-acting insulin during the last 18 months were included into the study. Insulin therapy was not modified for study purposes. DKA was defined as venous blood pH < 7.3 and the requirement of hospital treatment. DKA incidence during the recent 12 treatment months was assessed. Locally measured A1C was standardized to the Diabetes Control and Complications Trial (DCCT) reference range of 4.05–6.05% using the multiple of the mean method.

Statistical analyses were performed using SAS software (SAS version 9.1; SAS Institute, Cary, NC). Nonparametric (Kruskal-Wallis) or χ^2 statistics were used for comparison among groups followed by the Holm adjustment (Bonferroni step-down) for multiple comparisons. P values < 0.05 were considered statistically significant. Odds ratios (OR) derived from multiple logistic regression analysis were listed as point estimates and 95% Wald CI.

RESULTS — Of 48,110 eligible patients with type 1 diabetes, 26,639 individuals were aged ≤ 20 years with a diabetes duration of ≥ 2 years. Subjects with continuous subcutaneous insulin injections ($n = 4,553$), change in basal insulin during the last 18 months ($n = 9,334$), less than three injections per day or no documented basal insulin ($n = 1,053$), missing documentation of insulin therapy ($n = 792$), or the use of zinc intermediate-acting insulin ($n = 225$) were excluded. In effect, 10,682 individuals

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Table 1—Clinical characteristics and incidence of DKA in 10,682 patients with type 1 diabetes from 271 centers

	Long-acting insulin analog*	NPH insulin	P†
n	5,317	5,365	—
Male (%)	52	55	0.007
Age (years)	15.0 ± 3.1 (15.8)	13.5 ± 4.2 (14.4)	<0.001
Age at diabetes onset (years)	8.2 ± 3.8 (8.3)	8.2 ± 4.3 (8.1)	0.411
Diabetes duration (years)	6.8 ± 3.7 (6.1)	5.4 ± 3.3 (4.3)	<0.001
Migration background (%)	13.5	16.5	<0.001
BMI (standard deviation score)	0.52 ± 0.93 (0.55)	0.48 ± 0.90 (0.47)	<0.001
A1C (%)‡	8.5 ± 1.8 (8.1)	7.9 ± 1.7 (7.6)	<0.001
Total insulin dose (units/kg/day)	0.96 ± 0.93 (0.9)	0.90 ± 0.87 (0.8)	<0.001
Use of short-acting insulin analogs (%)	66.5	31.8	<0.001
Ratio total daily prandial/basal insulin (units/units)	0.55 ± 0.10 (0.56)	0.50 ± 0.13 (0.50)	<0.001
DKA incidence (events/100 patient-years)§	6.65 ± 0.35	3.56 ± 0.26	<0.001

Data are means ± SD (medians) unless otherwise indicated. *Insulin glargine or insulin detemir. †Unadjusted Kruskal Wallis or χ^2 test (all significant differences remained after Holm adjustment). ‡DCCT reference range 4.05–6.05%. §± SE.

(mean age 14.2 ± 4.1 years, median 15.3) were included in the analysis.

Clinical characteristics of patients using long-acting basal insulin analogs (n = 5,317) or NPH insulin (n = 5,365) are summarized in Table 1. The overall number of DKA events in the entire cohort was 549 during the recent treatment year, corresponding to a DKA incidence of 5.14 ± 0.22 (SE/100 patient-years).

Patients using long-acting insulin analogs had higher DKA risk than patients with NPH insulin (Table 1). Multiple logistic regression analysis with adjustment for A1C, diabetes duration, age at diabetes onset, sex, migration background, insulin therapy (dose of short-acting insulin analogs, daily insulin dose, prandial/basal ratio), and treatment year confirmed higher DKA risk in the long-acting insulin analog group compared with the NPH insulin group (P = 0.015, OR 1.357 [95% CI 1.062–1.734]).

Independent variables associated with higher DKA risk were higher insulin dose (P < 0.001) and higher A1C level (P < 0.001). However, dose of short-acting insulin analogs, insulin ratio (prandial/basal), age at diabetes onset, diabetes duration, sex, migration background, and treatment year were not significantly associated with DKA risk.

In patients with poor metabolic control (A1C ≥9.0%, n = 2,652), DKA incidence was 13.7 ± 0.72/100 patient-years. In these patients, 63% used basal insulin analogs. Treatment with long-acting insulin analogs was associated with higher

DKA risk compared with NPH insulin (P = 0.003, OR 1.639 [95% CI 1.180–2.277]) in this subgroup of patients.

When DKA risk was separately analyzed for insulin glargine or detemir versus NPH, the association with higher DKA risk was confirmed for both long-acting insulin analogs (P = 0.035, OR 1.268 [95% CI 0.978–1.643] and 1.526 [1.092–2.133]). In patients with poor metabolic control, even higher DKA incidences associated with insulin glargine or detemir compared with NPH were found (P = 0.011, OR 1.470 [1.046–2.065] and 1.906 [1.226–2.963]).

CONCLUSIONS— The use of long-acting insulin analogs was not associated with a lower DKA incidence in our study population, representing ≥80% of pediatric patients with type 1 diabetes of ≥2 years' duration in Germany and Austria. In this cohort of 10,682 individuals, we found 5.14 DKA events/100 patient-years, similar to previous observations (10). Patients using long-acting insulin analogs had higher DKA incidence than individuals using NPH insulin. In a previous smaller study, a nonsignificant trend of less DKA episodes was described in children injecting long-acting insulin analogs (5), but mean patient age (6.5 years) and overall DKA risk were lower in that series, which may account for the differences to our findings.

Our results were derived from an observational nonrandomized prospective study. In the study population, patients

injecting long-acting insulin analogs were older, had poorer metabolic control, and more frequently used short-acting insulins than those injecting NPH—all factors potentially increasing DKA risk. However, after adjusting for these factors, higher DKA risk in patients with long-acting insulin analogs persisted, suggesting that observed differences are indeed related to insulin therapy. A variety of additional factors may influence the risk of DKA in type 1 diabetic patients, including treatment adherence, socioeconomic status, infections, or residual β -cell function (3,10,11). In our population-based study, these variables could not be separately assessed. DKA is frequently caused by omission of particularly the long-acting component of a basal-bolus insulin regimen (10,11). Missing a once-daily injection of a long-acting insulin analog may potentially contribute to a greater DKA risk than missing one of two or three NPH injections.

In conclusion, despite their long-acting pharmacokinetic profile, the use of long-acting insulin analogs was not associated with a lower incidence of DKA compared with NPH insulin. The possibility of increased DKA risk in pediatric patients injecting insulin glargine or detemir warrants further attention.

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