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*

A list of participating DPV Centers is available in the online appendix at http://care.diabetesjournals.org

Short running title: Long-acting insulin analogs and DKA

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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 diabetes 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 = 5317) had a higher DKA incidence than individuals using NPH insulin (n = 5365, 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 to NPH insulin.
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 to 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) Initiative (9) a study was performed to evaluate the incidence of diabetic ketoacidosis (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 ≥80%.

Subjects aged ≤20 years with diabetes duration ≥2 years using ≥3 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 hemoglobin A1C was standardized to the Diabetes Control and Complication 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 \( \chi^2 \)-statistics were used for comparison among groups followed by the Holm adjustment (Bonferroni stepdown) 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 confidence interval.

**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 = 4553), change in basal insulin during the last 18 months (n = 9334), <3 injections/day or no documented basal insulin (n = 1053), missing documentation of insulin therapy (n = 792) or the use of zinc intermediate-acting insulin (n = 225) were excluded. In effect, 10,682 individuals (mean age 14.2 ± 4.1, median 15.3 years) were included in the analysis.

Clinical characteristics of patients using long-acting basal insulin analogs (n = 5317) or NPH insulin (n = 5365) 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 (standard error (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 to the NPH insulin group (p = 0.015, OR 1.357 [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 = 2652) 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 to NPH insulin (p = 0.003, OR 1.639 [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 [0.978–1.643] and OR 1.526 [1.092–2.133]). In patients with poor metabolic control, even higher DKA incidences associated with insulin glargine or detemir compared to NPH were found (p = 0.011, OR 1.470 [1.046–2.065] and OR 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 non-significant 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 derived from an observational, non-randomized 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 diabetes patients, including treatment adherence, socioeconomic status, infections, or residual beta 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 to NPH insulin. The possibility of increased DKA risk in pediatric patients injecting insulin glargine or detemir warrants further attention.

ACKNOWLEDGEMENTS

Participating DPV centers are listed in the appendix which can be found in an online appendix at http://care.diabetesjournals.org. Supported by the Competence Network for Diabetes mellitus funded by the Federal Ministry of Education and Research (FKZ 01GI0859), Berlin, Germany; EFSD; Excellence Center “Metabolism”, BW. DPV Software development supported by Novo
Nordisk Pharma GmbH. The authors declare that they have no conflicts of interest relevant to this article.
REFERENCES
**Table 1:** Clinical characteristics and incidence of diabetic ketoacidosis in 10,682 patients with type 1 diabetes from 271 centers

<table>
<thead>
<tr>
<th></th>
<th>Long-acting insulin analog* ( n = 5317 )</th>
<th>NPH insulin ( n = 5365 )</th>
<th>P-value#</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, %</td>
<td>52</td>
<td>55</td>
<td>0.007</td>
</tr>
<tr>
<td>Age, years</td>
<td>15.0 ± 3.1 (15.8)</td>
<td>13.5 ± 4.2 (14.4)</td>
<td>&lt; 0.001</td>
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<tr>
<td>Age at diabetes onset, years</td>
<td>8.2 ± 3.8 (8.3)</td>
<td>8.2 ± 4.3 (8.1)</td>
<td>0.411</td>
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<tr>
<td>Diabetes duration, years</td>
<td>6.8 ± 3.7 (6.1)</td>
<td>5.4 ± 3.3 (4.3)</td>
<td>&lt; 0.001</td>
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<tr>
<td>Migration background, %</td>
<td>13.5</td>
<td>16.5</td>
<td>&lt; 0.001</td>
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<tr>
<td>Body mass index, SDS*</td>
<td>0.52 ± 0.93 (0.55)</td>
<td>0.48 ± 0.90 (0.47)</td>
<td>&lt; 0.001</td>
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<td>Hemoglobin A1C, %°</td>
<td>8.5 ± 1.8 (8.1)</td>
<td>7.9 ± 1.7 (7.6)</td>
<td>&lt; 0.001</td>
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<tr>
<td>Total insulin dose, units per</td>
<td>0.96 ± 0.93 (0.9)</td>
<td>0.90 ± 0.87 (0.8)</td>
<td>&lt; 0.001</td>
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<td>kg and day</td>
<td>Use of short acting insulin</td>
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<tr>
<td>analogs, %</td>
<td>66.5</td>
<td>31.8</td>
<td>&lt; 0.001</td>
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<tr>
<td>Ratio total daily</td>
<td>0.55 ± 0.10 (0.56)</td>
<td>0.50 ± 0.13 (0.50)</td>
<td>&lt; 0.001</td>
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<td>prandial/basal insulin,</td>
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<td>units/units</td>
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<tr>
<td>DKA incidence, events/100</td>
<td>6.65 ± 0.35</td>
<td>3.56 ± 0.26</td>
<td>&lt; 0.001</td>
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<tr>
<td>patient-years§</td>
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</table>

Plus-minus values are means ± standard deviation (medians)

*insulin glargine or insulin detemir

#unadjusted Kruskal Wallis or \( \chi^2 \) test (all significant differences remained after Holm adjustment)

+standard deviation score

°DCCT reference range 4.05–6.05%

§± standard error