Age-Related Differences in the Frequency of Ketoacidosis at Diagnosis of Type 1 Diabetes in Children and Adolescents

Short running title: Ketoacidosis at diagnosis in children

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Submitted 23 December 2009 and accepted 1 April 2010.

This is an uncopyedited electronic version of an article accepted for publication in Diabetes Care. The American Diabetes Association, publisher of Diabetes Care, is not responsible for any errors or omissions in this version of the manuscript or any version derived from it by third parties. The definitive publisher-authenticated version will be available in a future issue of Diabetes Care in print and online at http://care.diabetesjournals.org.
Objective — We studied the prevalence of DKA at diagnosis of type 1 diabetes in children in Finland.

Research design and methods — During 2002-2005 data on virtually all children <15 years diagnosed with type 1 diabetes in Finland was collected (n=1656).

Results — DKA was present in 19.4% of the cases and 4.3% had severe DKA. In children aged 0–4, 5–9 and 10–14 years DKA was present in 16.5%, 14.8% and 26.4%, respectively (P<0.001). Severe DKA occurred in 3.7%, 3.1% and 5.9% (P=0.048). DKA was present in 30.1% and severe DKA in 7.8% of children <2 years.

Conclusion — The overall frequency of DKA in children is low in Finland at diagnosis of type 1 diabetes. However, both children <2 years and adolescents aged 10-14 years are at increased risk of DKA.
The incidence of diabetic ketoacidosis (DKA) in children with newly diagnosed type 1 diabetes may be decreasing in developed countries (1,2).

RESEARCH DESIGN AND METHODS
In Finland, all children presenting with type 1 diabetes are treated in pediatric units, and their parents/guardians are asked whether the child may be recorded in the nationwide Finnish Pediatric Diabetes Register established in 2002 (3). We used data from this register and in addition, asked the pediatric centers to recheck their hospital records and report the gender, age and blood pH at diagnosis for all cases who were diagnosed with type 1 diabetes between June 1, 2002 and May 31, 2005. The final data encompassed all children <15 years of age diagnosed with type 1 diabetes in Finland during the 3-year study period. Diabetes was diagnosed according to WHO criteria (4). The study was approved by the local ethics committees and the register steering committee.

The study cohort comprised 1656 children (936 boys; 56.5%) a majority of whom were recorded in the Finnish Pediatric Diabetes Register (1518/1656, 91.7%). The mean age at diagnosis was 8.0 years (range 0.28-14.99 years), and DKA data was available from 1616 children (97.6%). The children were treated in 27 centers, five of which were university hospitals. In three university hospitals the prospective Type 1 Diabetes Prediction and Prevention (DIPP) project has been running since the mid 1990s to establish strategies for predicting and preventing type 1 diabetes (5). One child, an 8-year-old girl, died soon after diagnosis with a clinical picture of cerebral edema.

The duration of symptoms before diagnosis was recorded. The degree of consciousness at diagnosis, based on evaluation by the attending doctor, was reported to be normal in 94.5% of the cases, impaired in 5.2%, while 0.3% were considered to be unconscious. Body weight and height were measured on admission and body mass index (BMI) was calculated (kg/m\(^2\)).

Standard laboratory methods were used to measure plasma glucose and blood pH. Diabetic ketoacidosis was defined as blood pH <7.30 and considered severe if pH was <7.10.

Data was analyzed using SPSS for Windows (version 15.0; SPSS, Chicago, IL). Student’s two-tailed t-test, Mann-Whitney U-test, cross-tabulation and Chi-square statistics, one-way analysis of variance, Kruskal–Wallis test and Pearson’s correlation analysis were applied when appropriate.

RESULTS
At diagnosis of type 1 diabetes, 313 children out of 1616 (19.4%) had DKA and DKA was severe in 69 cases (4.3%). The mean age at diagnosis was higher in boys than in girls (8.2 vs. 7.7 years; \(P=0.012\)) and the proportion of boys increased by age (Table 1). There was no difference in the frequency of DKA between girls and boys (20.6% vs. 18.4%; \(P=0.274\)), but girls more often had severe DKA (5.7% vs. 3.2%; \(P=0.012\)). The duration of symptoms was also more often longer than 2 weeks among girls (39.4% vs. 33.2%; \(P=0.021\)).

When comparing three age groups (0-4.99, 5.0-9.99 and 10.0-14.99 years at diagnosis) we observed that the frequency of DKA and severe DKA was highest in the oldest children (Table 1). Furthermore, a significant inverse correlation was observed between pH and age at diagnosis (r= −0.13; \(P<0.001\)). No differences were observed in the degree of consciousness between the three age groups. Cases with DKA had in most age groups a lower BMI at diagnosis than those without DKA (Table 1).
Children <2 years more often had DKA and severe DKA at diagnosis when compared with older children (Table 1), and the degree of consciousness was more often impaired in these very young children (14.9% vs. 4.8%; \( P < 0.001 \)). We compared children diagnosed in the university hospitals with those diagnosed in other pediatric centers and observed that the frequency of DKA was higher in subjects admitted to the university hospitals (23.1% vs. 17.1%, \( P = 0.003 \)). Furthermore, severe DKA occurred more frequently in children treated in the university hospitals (6.3% vs. 3.0%; \( P = 0.001 \)). The proportion of children <2 years of age at diagnosis was higher in the university hospitals (7.9% vs. 5.2%; \( P = 0.026 \)).

When comparing children diagnosed in the DIPP centers (n=353) with those treated in other university hospitals (n=263), similar DKA frequencies were observed (21.2% vs. 25.3%, respectively; \( P = 0.240 \)). Neither was the frequency of severe DKA significantly different in children diagnosed in the DIPP centers (4.7% vs. 8.2%, \( P = 0.076 \)).

**CONCLUSIONS**

In the current study the frequency of DKA in children <5 years at diagnosis of type 1 diabetes was 16.5%, this being the lowest reported so far in this age group (6–10). Earlier studies from Finland have shown that the frequency of DKA has markedly decreased over time in children diagnosed <5 years, being 32.1% in 1982-1991 and 17.7% in 1992-2001 (6, 7). In Germany and Austria, the frequency of DKA at diagnosis was 26.5% in children <5 years during 1995–2007 (10). In the United States DKA was present in 43.7% of children <6 years diagnosed with type 1 diabetes during the 1990’s in the Boston area (11), and recently a DKA frequency of 37.3% was reported in children <5 years (8).

DKA is still common among children <2 years of age, although the present results show that the frequency of DKA in these children was lower (30.1%) than in earlier surveys (6, 7). In the Finnish nationwide study in 1986–1989 the frequency of DKA in children <2 years was as high as 53.3% (7). In northern Finland the overall frequency of DKA in children younger than 2 years at diagnosis was 50.0% in 1982–1991 and 39.1% in 1992–2001 (6). These very encouraging results indicate that information and awareness have nowadays led to earlier diagnosis with milder metabolic decompensation in these very young children.

It is worrisome that children ≥10 years of age seem to have an increased risk of DKA. It is possible that the emerging independence of teenagers makes them unwilling to admit to their early symptoms of diabetes and therefore they run a higher risk of developing DKA. In addition, shared time in families has decreased in recent decades and single-parent families are more frequent. Such factors may play a role in the delayed reporting of symptoms of diabetes in adolescents.

**Author contributions:** Anne Hekkala researched data, wrote manuscript, contributed to discussion and edited manuscript. Antti Reunanen researched data. Matti Koski is the Data Manager for the Finnish Pediatric Diabetes Register, and he has generated the data base used for the analysis of the data derived from the register. Mikael Knip is the Principal Investigator for the Finnish Pediatric Diabetes Register and carries responsibility for the register data. Mikael Knip contributed to discussion and reviewed manuscript. Riitta Veijola researched data, contributed to discussion and reviewed manuscript.

**ACKNOWLEDGEMENTS**

This work was supported by the National Graduate School of Clinical Investigation, Helsinki, Finland, and the Competitive Research Funding of the Helsinki University...
We are grateful to the personnel in the pediatric centers around Finland and the personnel of the Finnish Pediatric Diabetes Register, Helsinki, Finland, for their collaboration.

REFERENCE
Table 1 – Comparison of children in different age groups at the time of diagnosis of type 1 diabetes. Values reported as means (95% confidence intervals, CI), medians (interquartile range, IQR) or proportions (%).

<table>
<thead>
<tr>
<th></th>
<th>Children 0–4 yrs</th>
<th>Children 5–9 yrs</th>
<th>Children 10–14 yrs</th>
<th>P value</th>
<th>Children &lt;2 yrs</th>
<th>Children ≥2 yrs</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=1656 (100%)</td>
<td>n=436 (26.3%)</td>
<td>n=629 (38.0%)</td>
<td>n=591 (35.7%)</td>
<td></td>
<td>n=103 (6.2%)</td>
<td>n=1553 (93.8%)</td>
<td></td>
</tr>
<tr>
<td>Proportion of boys (%)</td>
<td>53.7</td>
<td>54.2</td>
<td>61.1</td>
<td>0.020</td>
<td>60.2</td>
<td>56.3</td>
<td>0.438</td>
</tr>
<tr>
<td>Symptoms of diabetes &gt;2 weeks (%)</td>
<td>29.8</td>
<td>35.8</td>
<td>40.9</td>
<td>0.006</td>
<td>28.2</td>
<td>36.5</td>
<td>0.140</td>
</tr>
<tr>
<td>Blood pH (IQR)</td>
<td>7.39 (7.34–7.40)</td>
<td>7.38 (7.34–7.41)</td>
<td>7.36 (7.27–7.40)</td>
<td>&lt;0.001</td>
<td>7.36 (7.27–7.39)</td>
<td>7.38 (7.33–7.40)</td>
<td>0.001</td>
</tr>
<tr>
<td>Plasma glucose [mmol/l (95% CI)]</td>
<td>25.8 (24.8–26.9)</td>
<td>24.6 (23.8–25.4)</td>
<td>26.2 (25.3–27.2)</td>
<td>0.173</td>
<td>29.4 (26.8–32.1)</td>
<td>25.3 (24.8–25.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DKA, pH &lt;7.30 [ % (95% CI)]</td>
<td>16.5 (14.7–18.3)</td>
<td>14.6 (11.8–17.4)</td>
<td>26.4 (22.8–30.0)</td>
<td>&lt;0.001</td>
<td>30.1 (21.2–38.9)</td>
<td>18.6 (16.6–20.6)</td>
<td>0.004</td>
</tr>
<tr>
<td>Severe DKA, pH &lt;7.10 [ % (95% CI)]</td>
<td>3.7 (1.9–5.5)</td>
<td>3.1 (1.7–4.5)</td>
<td>5.9 (4.0–7.8)</td>
<td>0.048</td>
<td>7.8 (2.6–12.9)</td>
<td>4.0 (3.0–5.0)</td>
<td>0.070</td>
</tr>
</tbody>
</table>

*P=0.026  
**P=0.065  
***P<0.001  
#P=0.295  
##P=0.019