Glycated hemoglobin A1c as a risk factor for severe hypoglycemia in pediatric type 1 diabetes


Objective: To assess the risk of severe hypoglycemia related to glycated hemoglobin A1c (HbA1c) levels in a population-based cohort of pediatric type 1 diabetes patients during two time periods since 1995.

Methods: The association between HbA1c levels and severe hypoglycemia (defined as requiring assistance from another person) or hypoglycemic coma (loss of consciousness or seizures) was analyzed by multivariable regression analysis in children and adolescents with type 1 diabetes from the DPV Diabetes Prospective Follow-up in Germany and Austria in 1995–2003 (n = 15 221 patients) and 2004–2012 (n = 22 318 patients).

Results: Mean adjusted rates of severe hypoglycemia and hypoglycemic coma decreased from 19.18 [95% confidence interval (CI), 17.95–20.48] and 4.36 (3.93–4.83) per 100 patient-years in 1995–2003 to 15.01 (14.18–15.88) and 2.15 (1.94–2.39) in 2004–2012, respectively (p < 0.001). From the first to the second period, the relative risk (RR) for severe hypoglycemia and hypoglycemic coma per 1% lower HbA1c decreased from 1.22 (1.15–1.30) to 1.06 (1.01–1.12) and from 1.27 (1.15–1.40) to 1.04 (0.94–1.16), respectively. Risk of severe hypoglycemia and coma declined most in patients with HbA1c levels of 6–6.9% (RR 0.70 and 0.43, respectively) and with HbA1c of 7–7.9% (RR 0.63 and 0.38, respectively). Mean HbA1c levels fell from 8.4% in 1995–2003 to 8.2% in 2004–2012, while the use of insulin pumps, short- and long-acting insulin analogs, and glucose monitoring increased (p < 0.001).

Conclusions: In contrast to 1995–2003, low HbA1c has become a minor risk factor for severe hypoglycemia and coma in pediatric patients with type 1 diabetes in the 2004–2012 period.
Lower glycated hemoglobin A1c (HbA1c) levels are associated with fewer and delayed micro- and macrovascular complications in patients with type 1 diabetes undergoing intensive insulin therapy (1–3). Severe hypoglycemia is the most frequent acute complication of insulin treatment in children and adolescents (4) accounting for an estimated 4–10% of disease-related mortality (5–8). Therefore, the risk of severe hypoglycemia is considered a major barrier to attain optimal glycemic control (4).

Historically, lower HbA1c levels were associated with an increased incidence of severe hypoglycemia (2, 3, 9, 10), and higher HbA1c targets, especially for younger children, have been advocated due to concerns of adverse effects of hypoglycemia on the developing brain (11). More recent observations, however, suggested that lower HbA1c may no longer constitute a significant risk factor for severe hypoglycemia as in previous decades (12–14). HbA1c levels and hypoglycemia event rates were mostly studied in center-based small cohorts of children with type 1 diabetes within a definite time period (15–19), but due to various study design and populations the results obtained in different time periods are not fully comparable.

To assess changes in the risk of severe hypoglycemia and hypoglycemic coma related to HbA1c levels over the last two decades, we compared two large cohorts of children and adolescents with type 1 diabetes treated in the 1995–2003 and 2004–2012 periods, both derived from a population-based prospective diabetes documentation system.

Methods

The DPV Prospective Diabetes Follow-up has documented treatment of individuals with diabetes mellitus since 1995 in Germany and Austria (14, 20). Up to 2012, 372 diabetes centers participated in the DPV initiative, representing a nationwide coverage of more than 80% of pediatric diabetes patients in these countries. Analysis of anonymized data was approved by the Ethics Committee of Ulm University, Ulm, Germany. Patients were included into this study if they had type 1 diabetes mellitus; were aged 1–20 yr; had consistent data on insulin regimen, severe hypoglycemia, and glycated hemoglobin values; and treatment was performed during 1995–2012. Patients were excluded if they had a diabetes duration <2 yr; glycated hemoglobin levels of less than 6% (<42 mmol/mol); associated celiac disease; and if parents were born outside of Germany or Austria. To investigate the association of severe hypoglycemia and HbA1c levels in previous vs. recent treatment periods, the study population was grouped into two separate cohorts (i.e., 1995–2003 and 2004–2012) according to each patient’s first year of documentation in the DPV database. Patient data of the most recent documented year within the assigned period were used for cross-sectional analysis.

Severe hypoglycemia was defined as an event requiring assistance of another person to manage carbohydrates, glucagon, or intravenous glucose (21), in children with altered mental status who cannot assist in their care, according to the ISPAD Clinical Practice Consensus Guidelines (22). We distinguished between any event of severe hypoglycemia requiring assistance from another person (all events of severe hypoglycemia) and hypoglycemic coma (loss of consciousness or seizures) (22). Hypoglycemic episodes were documented using the standardized DPV questionnaire, and identical definitions for severe hypoglycemia and hypoglycemic coma were applied during the entire study period. Glycated hemoglobin values were standardized to the DCCT reference range 4.05–6.05% using the multiple-of-the-mean transformation method (2). Glycated hemoglobin was categorized as 6–6.9% (42–52 mmol/mol), 7–7.9% (53–63 mmol/mol), 8–8.9% (64–74 mmol/mol), or ≥9% (≥75 mmol/mol). Body mass index (BMI) values were transformed to standard deviation scores (BMI-SDS) based on reference values as described (20).

Mean rates of severe hypoglycemia and coma were estimated per 100 patient-years with 95% confidence interval (CI) and compared between periods assuming Poisson distribution of events. For descriptive investigation, mean and standard deviation (SD), and median were determined for continuous parameters and percentages for categorical parameters. Clinical characteristics were compared between both cohorts (1995–2003 vs. 2004–2012) by chi-squared or Kruskal–Wallis test and p values.
Table 1. Clinical characteristics of type 1 diabetes patients of two different treatment periods

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Gender, male/female</td>
<td>52.0/48.0</td>
<td>53.0/47.0</td>
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<tr>
<td>Age, years</td>
<td>14.5 ± 3.7 (15.2)</td>
<td>14.3 ± 3.9 (15.0)</td>
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<tr>
<td>Diabetes duration, years</td>
<td>6.7 ± 3.5 (6.0)</td>
<td>5.9 ± 2.9 (6.3)</td>
</tr>
<tr>
<td>Glycated hemoglobin ± SD, %*</td>
<td>8.4 ± 1.7 (8.0)</td>
<td>8.2 ± 1.6 (7.9)</td>
</tr>
<tr>
<td>Body mass index-SDS</td>
<td>0.5 ± 0.9 (0.5)</td>
<td>0.6 ± 0.9 (0.6)</td>
</tr>
<tr>
<td>1–3 insulin injections†, n, (%)</td>
<td>1873 (12.3)</td>
<td>1041 (4.7)</td>
</tr>
<tr>
<td>≥4 insulin injections‡, n, (%)</td>
<td>11 717 (77.0)</td>
<td>12 310 (55.2)</td>
</tr>
<tr>
<td>Continuous subcutaneous insulin infusion, n</td>
<td>1631 (10.7)</td>
<td>8967 (40.2)</td>
</tr>
<tr>
<td>Total daily insulin dose per kg</td>
<td>0.88 ± 0.26 (0.86)</td>
<td>0.89 ± 0.31 (0.85)</td>
</tr>
<tr>
<td>Prandial/total insulin ratio</td>
<td>0.5 ± 0.2 (0.5)</td>
<td>0.6 ± 0.1 (0.6)</td>
</tr>
<tr>
<td>Use of short-acting analogs, n, (%)</td>
<td>4581 (30.1)</td>
<td>15 667 (70.2)</td>
</tr>
<tr>
<td>Use of long-acting analogs, n, (%)</td>
<td>3090 (20.3)</td>
<td>9865 (44.2)</td>
</tr>
<tr>
<td>Self-monitoring of blood glucose per day</td>
<td>4.3 ± 1.4 (4.0)</td>
<td>5.2 ± 1.9 (5.0)</td>
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</table>

SDS, standard deviation score.
Plus-minus values are means ± standard deviation (median).
*DCCT reference range 4.05–6.05%, conversion for glycated hemoglobin A1c [mmol/mol Hb] = [HbA1c (%) – 2.15] × 10.929.
†Insulin injection time points per day. All parameters significantly differed between periods (p < 0.001), except sex, p = 0.12 and insulin dose, p = 0.43, based on chi-squared or Kruskal–Wallis tests, respectively.

Table 2. Hypoglycemia rates in type 1 diabetes patients of two different treatment periods

<table>
<thead>
<tr>
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<th>1995–2003 Rate (95% CI)</th>
<th>2004–2012 Rate (95% CI)</th>
<th>p value</th>
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</thead>
<tbody>
<tr>
<td>Severe hypoglycemia</td>
<td>19.18 (17.95–20.48)</td>
<td>15.01 (14.18–15.88)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypoglycemic coma</td>
<td>4.36 (3.83–4.83)</td>
<td>2.15 (1.94–2.39)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CI, confidence interval.
Mean rates per 100 patient-years with 95% CI based on negative binomial regression models adjusted for HbA1c (log-linear term), sex, age, and diabetes duration.

Rates of severe hypoglycemia and coma in different treatment periods

In the period between 1995 and 2003, 3058 episodes of severe hypoglycemia occurred in 1771 patients (11.6% of entire cohort), and 681 events of hypoglycemic coma were observed in 531 patients (3.5%). Between 2004 and 2012, 3459 episodes of hypoglycemia occurred in 1601 patients (7.2%), and 488 coma events were observed in 366 patients (1.6%). Comparison of both treatment periods, comprising 9 yr each, showed that the unadjusted mean rates of severe hypoglycemia were significantly lower in the 2004–2012 period compared to the 1995–2003 period (p < 0.001).
Table 3. Glycated hemoglobin as risk factor of severe hypoglycemia and coma in two different treatment periods

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<tbody>
<tr>
<td>Severe hypoglycemia</td>
<td>1.22 (1.15–1.30)</td>
<td>&lt;0.001</td>
<td>1.06 (1.01–1.12)</td>
<td>0.03</td>
</tr>
<tr>
<td>Hypoglycemic coma</td>
<td>1.27 (1.15–1.40)</td>
<td>&lt;0.001</td>
<td>1.04 (0.94–1.16)</td>
<td>0.41</td>
</tr>
</tbody>
</table>

CI, confidence interval; RR, relative risks.
Results are assessed from negative binomial regression models adjusted for sex, age, and diabetes duration.

*R with 95% CI per 1% lower HbA1c.
†p values are related to RR.

and hypoglycemic coma decreased from 22.40 (95% CI, 21.59–23.24) and 4.94 (95% CI, 4.76–5.12) per 100 patient-years in 1995–2003 to 17.10 (95% CI, 16.51–17.70) and 2.24 (95% CI, 2.17–2.32) in 2004–2012, respectively (p < 0.001). After adjustment for potential confounders, the significant decrease of severe hypoglycemia and coma events between treatment periods persisted (Table 2), indicating a relative risk reduction for severe hypoglycemia of 22% and for coma of 51%.

Risks of severe hypoglycemia and coma related to hemoglobin A1c in different periods

From 1995–2003 to 2004–2012, the relative risk for severe hypoglycemia per 1% lower HbA1c decreased from 1.22 to 1.06 (Table 3), corresponding to a 13% decline in the relative risk per 1% lower HbA1c (RR 0.87, 95% CI, 0.80–0.94, p < 0.001). Likewise, the relative risk for hypoglycemic coma per 1% lower HbA1c decreased from 1.27 to 1.04 (Table 3), corresponding to an 18% decline in the relative risk per 1% lower HbA1c (RR 0.82, 95% CI, 0.72–0.95, p = 0.007). In 2004–2012, glycated hemoglobin was no longer a risk factor of hypoglycemic coma (p = 0.41, Table 3). The substantial decrease of severe hypoglycemia and coma risk from 1995–2003 to 2004–2012 persisted after additional adjustment for different insulin regimens (categorized as 1–3, or ≥4 injection time points per day, or pump therapy), p < 0.001.

Rates of severe hypoglycemia and hypoglycemic coma for each period were examined per glycated hemoglobin category. Severe hypoglycemia rates (Fig. 1A) only decreased in patients with HbA1c levels of 6–6.9% and 7–7.9% from 21.85 (95% CI, 18.92–25.23) and 25.06 (95% CI, 22.32–28.13) per 100 patient-years in 1995–2003 to 15.31 (95% CI, 13.49–17.36) and 15.88 (95% CI, 14.42–17.49) in 2004–2012, respectively (p for comparison between periods <0.001), while hypoglycemia rates remained unchanged in patients with HbA1c ≥8% (p ≥ 0.45). Hypoglycemic coma rates (Fig. 1B) decreased in all HbA1c categories, but the most prominent decline was observed in patients with HbA1c of 6–6.9% and

Table 4. Relative risks for severe hypoglycemia and coma per glycated hemoglobin category in 2004–2012 compared to 1995–2003

<table>
<thead>
<tr>
<th>HbA1c</th>
<th>Severe hypoglycemia</th>
<th>p value</th>
<th>Hypoglycemic coma</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>RR (95% CI)</td>
<td></td>
<td>RR (95% CI)</td>
<td></td>
</tr>
<tr>
<td>6–6.9</td>
<td>0.70 (0.58–0.85)</td>
<td>&lt;0.001</td>
<td>0.43 (0.31–0.60)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>7–7.9</td>
<td>0.63 (0.55–0.74)</td>
<td>&lt;0.001</td>
<td>0.38 (0.29–0.48)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>8–8.9</td>
<td>0.93 (0.78–1.12)</td>
<td>0.45</td>
<td>0.56 (0.42–0.75)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥9</td>
<td>0.93 (0.78–1.12)</td>
<td>0.46</td>
<td>0.69 (0.50–0.96)</td>
<td>0.03</td>
</tr>
<tr>
<td>All</td>
<td>0.78 (0.72–0.85)*</td>
<td>&lt;0.001</td>
<td>0.49 (0.43–0.57)*</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CI, confidence interval; RR, relative risks.
Results are assessed from negative binomial regression models adjusted for sex, age, and diabetes duration. RR with 95% CI. p values for comparison between periods.

7–7.9%, decreasing from 4.84 (95% CI, 3.88–6.03) and 6.06 (95% CI, 5.11–7.18) to 2.09 (95% CI, 1.65–2.65) and 2.27 (95% CI, 1.90–2.71), respectively (p for comparison between periods <0.001). In effect, predominant risk decline in lower HbA1c categories from 1995–2003 until 2004–2012 resulted in flattening of regression curves for severe hypoglycemia (Fig. 1A) and hypoglycemic coma rates (Fig. 1B) in relation to HbA1c.

From 1995–2003 to 2004–2012, there was a risk reduction for severe hypoglycemia of 30% and 37% in patients with HbA1c of 6–6.9% and 7–7.9%, respectively (Table 4). Strikingly, from 1995–2003 to 2004–2012, a risk reduction for hypoglycemic coma of 57% and 62% was observed in individuals with HbA1c of 6–6.9% and 7–7.9%, respectively (Table 4).

Discussion
In this study, the risk of severe hypoglycemia and hypoglycemic coma related to glycated hemoglobin levels was compared in two large cohorts of children and adolescents with type 1 diabetes treated during the last two decades. We observed a marked decline of severe hypoglycemia and coma risk per 1% lower HbA1c in the 2004–2012 period compared with the 1995–2003 period. Risk reduction was mainly due to declining hypoglycemia rates in individuals with HbA1c values between 6% and 7.9%. Specifically, from the 1995–2003 period until the 2004–2015 period, the risk of severe hypoglycemia in individuals with HbA1c levels of 6.0–6.9% and 7.0–7.9% declined by 30% and 37%, respectively, and the risk of coma declined by 57% and 62%, respectively. Thus, low glycated hemoglobin was no longer associated with a high risk of severe hypoglycemia and hypoglycemic coma in 2004–2012 in these patients, as depicted by a flattened regression curve of HbA1c-related hypoglycemia risk.

This observation is in accordance with a report of young type 1 diabetes patients in Denmark (12, 23). Possible explanations for the decreased hypoglycemia risk in individuals with low HbA1c include the more frequent use of insulin pumps and insulin analogs in recent years (15, 23–26), increased frequency of self-monitoring of blood glucose (12, 24), more intensive diabetes education (27), better availability of multi-professional diabetes teams, and participation in collaborative quality improvement programs (28). Our data suggest that factors other than anti-hyperglycemic therapy itself (i.e., insulin) are now the major determinants of hypoglycemia risk, including quality and intensity of diabetes counseling. However, as our study was not designed to address the influence of treatment-related variables on hypoglycemia no inferences as to potential causes of hypoglycemia risk reduction can be made.

Mean rates of severe hypoglycemia in both treatment periods of our study were lower than in previous center-based studies (15, 17) but similar to recent findings in multicenter randomized clinical trials (29, 30). Coma rates observed in both treatment periods of our analysis were lower than in other studies (15, 17, 19, 23) but comparable to former population-based reports from Finland (31) and Western Australia (10). Different rates of severe hypoglycemia and coma between populations might be explained by distinct study approach or patient inclusion criteria. The decrease of mean rates of severe hypoglycemia and coma during time periods observed in this study is in accordance with other center-based and population-based studies (13, 15, 24, 28). In addition, the striking reduction of coma rates by half in pediatric type 1 diabetes populations in our study corresponds to similar observations of other studies (13, 24).

Our study has some limitations. Potential determinants of hypoglycemia such as enhanced physical exercise, preceding episodes of severe hypoglycemia,
or participation in educational programs were not recorded. In addition, owing to the non-interventional character of the study, no cause-effect relation can be established. Strengths of our study include its nationwide coverage (encompassing more than 80% of pediatric type 1 diabetes patients in Germany and Austria), long observation periods, large patient cohorts, and prospective and constant data acquisition. Thus, our study outcomes may be considered typical of a pediatric type 1 diabetes population in a ‘real-world’ setting.

Our findings may have clinical relevance, since glycemic control within optimal HbA1c targets may now be feasible without increasing the risk for severe hypoglycemia in children and adolescents with type 1 diabetes. In the past it has been assumed that lower HbA1c inadvertently increases hypoglycemia risk in type 1 diabetes patients (2, 3, 9, 10). For concern of severe hypoglycemia higher HbA1c targets have been advocated particularly for younger children (11). In the light of our observations it now appears that lower HbA1c targets may be safely achieved in young type 1 diabetes patients in the context of adequate self-management education and support, in line with recent recommendations (32–34). As it remains unresolved how glycemic control within optimal HbA1c targets may be safely achieved in young type 1 diabetes patients in the context of adequate self-management education and support, in line with recent recommendations (32–34). As it remains unresolved how glycemic control within optimal HbA1c targets may be safely achieved in young type 1 diabetes patients in the context of adequate self-management education and support, in line with recent recommendations (32–34). As it remains unresolved how glycemic control within optimal HbA1c targets may be safely achieved in young type 1 diabetes patients in the context of adequate self-management education and support, in line with recent recommendations (32–34).

Acknowledgements

HbA1c and hypoglycemia risk

The authors declare that they have no conflicts of interest relevant to this article.

References


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