The Impact of the Diabetes Control and Complications Trial and Humalog Insulin on Glycohemoglobin Levels and Severe Hypoglycemia in Type 1 Diabetes

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OBJECTIVE — This study was performed to determine the effects of the Diabetes Control and Complications Trial (DCCT) report in 1993 and the introduction of Lispro (Humalog) insulin in 1996 on glycemic control and on the number of severe hypoglycemic episodes in type 1 diabetic patients of various ages.

RESEARCH DESIGN AND METHODS — Diabetes care parameters and HbA1c data from 884 subjects with type 1 diabetes were entered into our database at the time of clinic visits from 1993 through 1998. In addition, a questionnaire was sent to all patients to validate the number of insulin injections per day, the incidence of severe hypoglycemic episodes (as defined by the DCCT), and the use of Humalog insulin. Data were divided into four age-groups: <5, 5–12, 13–18, and >18 years of age.

RESULTS — Longitudinal HbA1c levels declined significantly after the DCCT report in 1993–1996 (P < 0.001), but the number of severe hypoglycemic events increased (P < 0.001). A second decline in HbA1c levels was observed after the introduction of Humalog insulin in 1996 (P < 0.001). However, severe hypoglycemic episodes did not change (P = 0.26).

CONCLUSIONS — Administration of Humalog resulted in an additional reduction in HbA1c levels beyond the reduction in HbA1c values after the DCCT report. In contrast to the increase in severe hypoglycemic events after the DCCT results, the number of severe hypoglycemic episodes did not increase after the introduction of Humalog, despite a further decrease in HbA1c values.

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Since the report of the Diabetes Control and Complications Trial (DCCT) in 1993 (1), there has been increased emphasis on lowering HbA1c values to prevent the complications of diabetes. The DCCT aimed for HbA1c values <6.05% (the upper limit of normal) and achieved mean levels of 7.0–7.2% in intensively treated adult patients (1). An American Diabetes Association position statement (2) suggested 7.2% as a reasonable goal in intensively treated adult patients. Tuttelman et al. (3) surveyed pediatricians and found that only 33% believed HbA1c <8% (normal to 7%) was indicated for children younger than 18 years of age. Some pediatric diabetologists recommend different HbA1c levels in patients of different ages, decreasing levels with increasing age, and decreasing ability to recognize and treat hypoglycemia. The recommendations of our clinic for various age-groups are as follows: for children younger than 5 years of age (when the brain is still developing), <9.3%; for children 5 to 12 years of age, <8.5%; for teens aged 13 to 18 years, <7.8%; and for adults, <7.5% (4). Intensively treated teens in the DCCT achieved a mean HbA1c level of 8.1% (5). For this group and for adults up to 39 years of age, the DCCT clearly showed the value of a lower HbA1c in preventing the microvascular complications of diabetes. Similar data are not available for children younger than 13 years of age.

Despite the reduction of microvascular complications, improvement in glycemic control in the DCCT resulted in a significant increase in severe hypoglycemic episodes (6). The intensive management of type 2 diabetes has similarly resulted in reductions of the complications of diabetes, but increases in severe hypoglycemic events (7,8). The purpose of the present study was to determine the impact of the DCCT and the introduction of Humalog insulin on HbA1c values and on the frequency of severe hypoglycemic episodes in a large number of subjects of all ages with type 1 diabetes in a specialty diabetes clinic.

RESEARCH DESIGN AND METHODS — A computerized record system developed at our center was used to identify patients seen from 1 January 1993 through 31 December 1998. All subjects began insulin therapy on the day of diagnosis and remained on insulin thereafter. Most patients were seen every 3 months. The diabetes care parameters included HbA1c values, number of injections per day, use of Humalog insulin, and number of severe hypoglycemic episodes, which were recorded in the computer database at the time of the clinic.
visit. A questionnaire was sent to all patients on one occasion (1998–1999) to validate the computer records of the numbers of insulin injections per day, the month and year of switching to Humalog insulin, and the number of severe hypoglycemic episodes. Patients were included in this trial only if they returned the questionnaire. Because the data were considered unreliable when the questionnaire was not returned, patients who did not return their questionnaires were not included in this study. Clinical care guidelines were similar in subjects who remained on regular insulin, compared with those who were switched to Humalog. Severe hypoglycemic events were defined (as in the DCCT) as any episode characterized by symptoms consistent with hypoglycemia in which the patient required assistance from another person or episodes in which the patient experienced either coma and/or seizure as reported by the patient or another person. Patients who had been diagnosed in the previous 12 months of any year of study were excluded, because they were probably still producing endogenous insulin. Routine C-peptide testing was not performed. The protocol was duly approved by the Colorado Multiple Institutional Review Board. All subjects were followed prospectively from 1993 through 1998 for HbA1c levels, severe hypoglycemic episodes, number of insulin injections per day, date of initiation of Humalog therapy, and use of the insulin pump (continuous subcutaneous insulin infusion). Dietary advice did not change during the period of study. Subjects who switched to Humalog were included only if they had used regular insulin for at least 1 year before initiating Humalog treatment (so comparable data would be available). As of December 31, 1998, 676 subjects were using Humalog and 208 subjects were not using Humalog.

The HbA1c level was determined using the DCA 2000 method (Bayer Diagnostics, Elkhart, IN) with a normal range of 3.2–6.2% throughout the period of this study. Control HbA1c data from 1993 through 1998 is provided in Table 1 to show that results are comparable during this period.

### Statistical methods

Statistical analyses were performed using Microsoft Excel (’97, SR-1, Redmond, WA) and later analyzed using an SAS-Stat program package (SAS Institute, Cary, NC). Descriptive statistics, including mean and SEs, were the primary analytic method. To calculate the mean HbA1c values and the mean number of hypoglycemic events per year, the mean per subject was calculated first, and then the mean of these means was taken. Student’s t tests (Wilcoxon tests where appropriate) were used to compare HbA1c values and hypoglycemic events over time in the same subjects. S-Plus 4.5 software was used. Longitudinal mixed effects models (subject as random effect) were used to assess the effects of intensive therapy and Humalog use on HbA1c values using SAS PROC MIXED (SAS Institute).

### RESULTS

A total of 11,221 visits (and HbA1c values) were analyzed from our computerized record system. Of the 884 subjects, 49.1% were female and 50.9% were male. The mean (± SD) age at diagnosis was 12.8 ± 8.3 years, and the mean (± SD) duration of diabetes at the initial visit was 8.4 ± 8.3 years. The demographics for the four age-groups are shown in Table 2.

Longitudinal HbA1c values showed a significant decline after the DCCT report in 1993 to 1996 (P < 0.001), primarily because of the decrease from 1993 to 1994 (Fig. 1). The decline was significant for all subjects considered together (P < 0.001) and the 5- to 12-year-old (P < 0.04) and the >18-year-old (P < 0.02) age-groups considered individually (Fig. 1). The decline was shown in the adult group only to be significantly related (P < 0.05; mixed effects longitudinal model) to increased use of multiple injections or an insulin pump. The failure of improvement in HbA1c levels from 1995 to 1996 was primarily because of the 13- to 18-year-old group. A second decline in HbA1c levels was observed for all four age-

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### Table 1—Laboratory control data for HbA1c levels (% done at the Barbara Davis Center for Childhood Diabetes and other laboratories)

<table>
<thead>
<tr>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Barbara Davis Center</td>
<td>5.1±0.1</td>
<td>13.9</td>
<td>5.6±0.4</td>
<td>5.5±0.2</td>
<td>12.8±0.4</td>
<td>5.7±0.2</td>
</tr>
<tr>
<td>Other Laboratories</td>
<td>5.0±0.1</td>
<td>13.0±0.4</td>
<td>5.7±0.2</td>
<td>5.7±0.2</td>
<td>12.4±0.4</td>
<td>5.7±0.2</td>
</tr>
</tbody>
</table>

Data are means ± SD. *All Barbara Davis Center for Childhood Diabetes determinations for all years were within the acceptable percentages of allowed deviation; †other laboratories included in CAP analysis ranged from 60 to 150 laboratories.

### Table 2—Demographics at first visit

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>n (total)</th>
<th>Duration (years)</th>
<th>Sex (M/F)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5</td>
<td>103</td>
<td>2.3 ± 0.1</td>
<td>41 2/58.8%</td>
</tr>
<tr>
<td>5–12</td>
<td>414</td>
<td>6.8 ± 0.1</td>
<td>48 8/51.2%</td>
</tr>
<tr>
<td>13–17</td>
<td>202</td>
<td>10.5 ± 0.3</td>
<td>48 5/51.5%</td>
</tr>
<tr>
<td>&gt;18</td>
<td>165</td>
<td>13.4 ± 0.7</td>
<td>55 5/44.5%</td>
</tr>
<tr>
<td>Total</td>
<td>884</td>
<td>—</td>
<td>50 9/49.1%</td>
</tr>
</tbody>
</table>

Data are means ± SEM unless otherwise indicated.
groups considered together ($P < 0.001$), and in the 5- to 12-year-old age-group ($P < 0.05$) considered individually, after the introduction of Humalog in 1996 (Fig. 1 and Tables 3 and 4).

HbA$_{1c}$ values for the subjects were arbitrarily divided, as previously discussed (4), into four age-groups: <5, 5–12, 13–18, and >18 years of age (Fig. 1). Although the decrease in HbA$_{1c}$ values was similar across all four age-groups, the average HbA$_{1c}$ values varied between groups. Subjects whose ages ranged from 13 to 18 years had the highest average HbA$_{1c}$ values during the study period. Subjects older than 18 years had the lowest average HbA$_{1c}$ values during the same period.

A total of 676 subjects were switched to Humalog after it was introduced in September 1996. The remaining 208 subjects were not switched to Humalog after it was introduced in 1996; however, there was no corresponding increase in the number of severe hypoglycemic events ($P = 0.26$). The duration of diabetes increased during the study period and did not have an effect on the HbA$_{1c}$ levels.

When the results from the two methods of data collection regarding hypoglycemia (computerized record system versus family questionnaires) were compared, they matched almost exactly for seizures and unconscious episodes. However, episodes requiring assistance were reported as higher in the family questionnaires (which were used in this report). However, this is a difficult question, for families of young children, in which all episodes require assistance by another individual. Families of young children were asked to report requirement of help only if the child was not lucid during the episode.

**CONCLUSIONS** — The DCCT and other studies proved the importance of good blood glucose control in preventing eye, kidney, and nerve complications in people with both type 1 (1) and type 2 diabetes (7,8). Unfortunately, when the DCCT results were released, the only way to achieve better glucose control was more daily injections associated with

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**Table 3—HbA$_{1c}$ levels in subjects receiving Humalog or regular insulin**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>1996 HbA$_{1c}$</th>
<th>1997 HbA$_{1c}$</th>
<th>Change in HbA$_{1c}$</th>
<th>1998 HbA$_{1c}$</th>
<th>Change in HbA$_{1c}$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Humalog</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–4</td>
<td>8.10 ± 0.44</td>
<td>8.19 ± 0.22</td>
<td>0.09 ± 0.46</td>
<td>7.87 ± 0.20</td>
<td>−0.23 ± 0.60</td>
</tr>
<tr>
<td>5–12</td>
<td>9.03 ± 0.26</td>
<td>8.54 ± 0.10</td>
<td>−0.53 ± 0.26</td>
<td>8.33 ± 0.08</td>
<td>−0.70 ± 0.34</td>
</tr>
<tr>
<td>13–18</td>
<td>9.05 ± 0.25</td>
<td>9.02 ± 0.10</td>
<td>0.03 ± 0.24</td>
<td>8.52 ± 0.09</td>
<td>−0.53 ± 0.24</td>
</tr>
<tr>
<td>&gt;18</td>
<td>8.23 ± 0.20</td>
<td>8.38 ± 0.13</td>
<td>0.15 ± 0.22</td>
<td>7.98 ± 0.09</td>
<td>−0.25 ± 0.20</td>
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<tr>
<td><strong>Regular</strong></td>
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</tr>
<tr>
<td>0–4</td>
<td>8.59 ± 0.17</td>
<td>8.41 ± 0.21</td>
<td>−0.18 ± 0.25</td>
<td>8.80 ± 0.80</td>
<td>0.21 ± 0.81</td>
</tr>
<tr>
<td>5–12</td>
<td>8.69 ± 0.08</td>
<td>8.70 ± 0.14</td>
<td>0.01 ± 0.15</td>
<td>8.50 ± 0.34</td>
<td>−0.19 ± 0.33</td>
</tr>
<tr>
<td>13–18</td>
<td>9.19 ± 0.12</td>
<td>9.05 ± 0.19</td>
<td>−0.14 ± 0.21</td>
<td>8.46 ± 0.43</td>
<td>−0.73 ± 0.40</td>
</tr>
<tr>
<td>&gt;18</td>
<td>8.45 ± 0.13</td>
<td>8.35 ± 0.18</td>
<td>−0.10 ± 0.21</td>
<td>8.14 ± 0.33</td>
<td>−0.31 ± 0.32</td>
</tr>
</tbody>
</table>

Data are means ± SEM. The reduction in HbA$_{1c}$ from 1996 to 1997 or 1998 was statistically significant ($P < 0.05$; paired Student’s t test) only for the 5- to 12-year group receiving Humalog. There were no significant changes in HbA$_{1c}$ for 1997 or 1998 for subjects receiving regular insulin. In comparing the two treatment groups, statistical significance ($P < 0.05$; Student’s t test) was present only for the 1998 Humalog versus regular insulin in the >18-year groups. *Change in HbA$_{1c}$ is in comparison with the 1996 value.
more daily blood glucose tests, or the use of an insulin pump-delivery system. To the best of our knowledge, this is the first report to show a decline in HbA1c values in a general diabetes clinic after the DCCT report. The decline in HbA1c was most dramatic in teenagers and adults in the first year after the DCCT. These were the age-groups in which the DCCT data were shown to be applicable. Unfortunately, values leveled off between 1994 and 1996. In this study, the decline in HbA1c values from 1993 to 1996 in adults was significantly related to the use of intensive therapy. As described in the DCCT (1), and as found in this study, the incidence of severe hypoglycemic events increased. The increase continued in 1995 and 1996, even though HbA1c levels stabilized, presumably due to the continued attempts to lower values and the occurrence of “hypoglycemia-unawareness” with the greater duration of tighter control. The realization of the need for improved glycemic control, associated with a two- to threefold increase in severe hypoglycemic episodes, led to displeasure from both diabetes care providers (9) and patients.

Our study showed that the introduction of Humalog insulin made it possible to obtain the goal of improved blood glucose control without any further increase in severe hypoglycemic episodes. Alternative explanations for these outcomes might be the patient cohort changing during the study period, advances in glucose monitoring, insulin administration, increased familiarity with intensive diabetes management, and educational strategies. Humalog insulin resulted in lower postprandial blood glucose levels in every study in comparison with values after regular insulin (10–13). This was primarily because of higher insulin levels 30 to 90 min after injection, which closely matched food absorption. Many studies also showed a decline in severe hypoglycemic episodes (10–14), particularly during the nighttime. In addition, the frequency of hypoglycemic events in people using insulin pumps declined when Humalog was used in the pump rather than regular insulin (15–18).

Although the U.S. Food and Drug Administration initially approved Humalog only for children older than 12 years of age and adults, we and most others began using it in patients of all ages (19,20). Humalog was particularly helpful in children younger than 5 years of age with variable appetites. In toddlers with type 1 diabetes, postprandial administration of Humalog showed lower postprandial glucose excursions when compared with preprandial human regular insulin (20). In the current trial, the major reasons for not changing to Humalog insulin were the physician’s choice, insurance companies not willing to reimburse the cost of Humalog, and lower socioeconomic status.

The decline in HbA1c levels after the introduction of Humalog occurred without an increase in the number of severe hypoglycemic episodes. Instead, a decrease in the number of severe episodes was found. This result is particularly important in young children, in whom severe episodes may result in brain damage (21,22). Patients and health care providers are more likely to accept intensive insulin therapy if it does not result in a greater risk for severe hypoglycemia (which can result in death).

As described in the DCCT (5), the 13- to 18-year age-group had the highest level of HbA1c values. Increased insulin resistance in this age-group is one possible cause for such values (23,24). It is likely that behavior (including food choices) and psychological issues may also contribute to the higher HbA1c values in teens. The 5- to 12-year age-group probably had lower HbA1c values because puberty and insulin resistance were not yet present and because parents have more control and influence over diabetes care during this period. Although we only recommend HbA1c values <9.3% in toddlers, when the brain is still growing and hypoglycemia can often not be recognized, their HbA1c values were not as high as might have been anticipated. Clearly, the adult group consistently had the best HbA1c values, probably because of lack of insulin resistance and better understanding of diabetes.

In conclusion, HbA1c levels declined in all four age-groups after the DCCT. Unfortunately, in concurrence with the findings of the DCCT, the number of severe hypoglycemic episodes increased. However, a second significant decline in HbA1c values occurred with the introduction of Humalog insulin. Fortunately, the incidence of severe hypoglycemic episodes did not increase after Humalog therapy. It will be important with future changes in care (e.g., introduction of continuous glucose monitoring) to document changes in HbA1c levels as well as in the incidence of severe hypoglycemic events in diabetes clinic populations of all ages.

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References
3. Tuttleman M, Lipsett L, Harris MI: Attitudes and behaviors of primary care physicians regarding tight control of blood glucose in IDDM patients. Diabetes Care