Glycemic Patterns Detected by Continuous Subcutaneous Glucose Sensing in Children and Adolescents With Type 1 Diabetes Mellitus Treated by Multiple Daily Injections vs Continuous Subcutaneous Insulin Infusion

Naomi Weintrob, MD; Amir Schechter, MA; Hadassa Benzaquen, CDE; Shlomit Shalitin, MD; Pearl Lilos, BSc; Avinoam Galatzer, MA; Moshe Phillip, MD

Objective: To compare glycemic patterns by mode of therapy in children with type 1 diabetes mellitus using the Continuous Glucose Monitoring System (CGMS).

Design: Open randomized crossover comparing 3½ months of multiple daily injections (MDI) and continuous subcutaneous insulin infusion (CSII).

Setting: Tertiary care, university-affiliated medical center.

Patients: Twenty-three children and adolescents with type 1 diabetes mellitus.

Interventions: The CGMS was applied for 72 hours after 1 month and at the end of each study arm.

Main Outcome Measures: Hemoglobin A1c levels and glucose level profiles were compared between the 2 study arms and the 2 sensor applications for each arm.

Results: The arms were similar for mean (SD) hemoglobin A1c levels (CSII, 8.0% [0.8%]; and MDI, 8.2% [0.8%]) and glucose levels. Areas under the curve were significantly larger during MDI for nocturnal and 24-hour hypoglycemia (P = .01 and .04, respectively) and for postprandial hypoglycemia and hyperglycemia (P = .03 and .05, respectively). The rate of hyperglycemia increased during CSII (P = .03), but 24-hour duration and area under the curve for hyperglycemia were similar. Compared with the first CGMS reading in each arm, the second had a longer mean duration of postprandial within-target glucose levels (P = .04), tendency for lower rate of diurnal hypoglycemic events (P = .1), shorter duration of nocturnal hypoglycemia (P = .05), and smaller 24-hour area under the curve for hypoglycemia (P = .04).

Conclusions: Intensive treatment with CSII seemed to be associated with slightly better prebreakfast, postprandial, and within-target glucose profiles than MDI, as well as a smaller area under the curve for hypoglycemia. Lower hypoglycemia-related variables in the second sensor reading in each arm indicate that the CGMS may serve as an educational tool to decrease the rate and magnitude of hypoglycemia.


The Diabetes Control and Complications Trial (DCCT)1-3 reported that intensive treatment of type 1 diabetes mellitus led to a striking reduction in the development and progression of microvascular complications. During 4 years’ follow-up of the adolescent cohort, the beneficial effects persisted in the initial intensive treatment group compared with the conventional treatment group, despite their similar hemoglobin A1c (HbA1c) levels. These data indicate that less than optimal glycemic control during adolescence has a lasting detrimental effect, even if better glycemic control is established later in the course of the disease. However, strict metabolic control is associated with an increased risk of severe hypoglycemic episodes and significant weight gain.1,2 Indeed, hypoglycemia is the limiting factor in the implementation of intensive insulin therapy in children and adolescents,3 who lead a hectic and an unpredictable lifestyle.2 Furthermore, more than 50% of hypoglycemic events occur at night,3 when glucose levels are usually not measured.

Continuous subcutaneous insulin infusion (CSII) offers the most physiologic mode of insulin delivery available. The pump continuously delivers predetermined basal rates of insulin to meet nonprandial requirements and infuses a bolus dose at mealtimes. A meta-analysis6 of randomized controlled trials comparing CSII with multiple daily injections (MDI) of insulin in patients with type 1 diabetes...
mellitus showed a slight but significantly better percentage of HbA1c (−0.44%) during pump therapy. However, studies comparing the rate of hypoglycemia yielded contradictory results. All these findings were based on self-blood glucose measurements (SBGMs) and patient self-reports. In 1999, the minimally invasive Continuous Glucose Monitoring System (CGMS; MiniMed, Sylmar, Calif) was introduced for clinical use. The system is designed to provide Holter-style rather than real-time continuous measurements of glucose levels in the subcutaneous interstitial fluid in the range of 40 to 400 mg/dL (2.22-22.2 mmol/L). The CGMS was found to detect significantly more hypoglycemic and postprandial hyperglycemic episodes than SBGM.

In the present randomized crossover study, we compared the rate, degree, and duration of hypoglycemia and hyperglycemia and the variability in glucose levels between children and adolescents treated by CSII or MDI. We also sought to determine whether the CGMS can improve glycemic control and glucose patterns.

**METHODS**

**SUBJECTS**

All patients were followed up at the National Center of Childhood Diabetes of Schneider Children’s Medical Center of Israel. Inclusion criteria were age 8 to 14 years, treatment with insulin for at least 2 years, deficient C-peptide secretion (fasting level, <0.6 ng/mL), and absence of other health problems except for treated hypothyroidism or antibody-negative celiac disease controlled with a gluten-free diet. None of the patients had clinical evidence of microvascular complications, mental retardation, or a psychiatric disorder. The study population consisted of the first 23 consecutive patients who met these selection criteria and who were motivated to participate in the study, agreed to perform 4 to 6 SBGMS daily, and had the ability to cope, together with their parents, with the treatment procedures, as judged by the diabetic team. There were 10 boys and 13 girls, aged 9½ to 13½ years (median, 11.9 years). The duration of diabetes mellitus was 2½ to 11 years (median, 6.0 years), and the prestudy HbA1c level was 6.1% to 10.1% (mean [SD], 8.9% [1.0%]). On enrollment, all children were treated with MDIs (≥3) of insulin (Insulatard and Actrapid |Novo-Nordisk, Bagsvaerd, Denmark| or Humulin N and Humulin R [Eli Lilly, Indianapolis, Ind]). The study protocol was approved by the Ethics Committee of Rabin Medical Center, Tel Aviv. Informed consent was obtained from the patients and their parents.

**GLUCOSE SENSOR AND DATA ANALYSIS**

The CGMS has been described before. A computerized program was developed by one of us (A.S.) for calculation of the variables and their comparison between modes of therapy and between the first and second sensor reading in each arm.

**STUDY DESIGN AND PROTOCOL**

A randomized crossover design was used (Figure 1). The 23 children were randomly assigned to start with CSII (group A, n=11) or MDI (group B, n=12) with their prestudy insulin for 3½ months, after which they were switched to the other mode of therapy for another 3½ months, with a 2-week washout period. The MDI protocol consisted of combined neutral protamine Hagedorn (NPH) and regular insulin before breakfast, regular insulin before lunch and supper, and NPH at bedtime. Continuous subcutaneous insulin infusion was delivered with a programmable external pump (MiniMed 508) using lispro (Humalog; Eli Lilly). The regular insulin was given 20 to 30 minutes before meals, and the lispro was given immediately before meals and snacks. The children were asked to perform SBGM 7 times per day (before meals, after meals, and weekly at 3 AM). The target range for glycemia was 80 to 150 mg/dL (4.4-8.3 mmol/L) before meals and at midnight and 120 to 180 mg/dL (6.7-10.0 mmol/L) at 2 hours after meals. During MDI, the patients were instructed to use a fixed caloric amount of carbohydrates for each meal and then adjust the insulin dose according to postprandial glucose values.

Before initiation of CSII, the patients were taught carbohydrate counting and insulin bolus dosing based on the insulin-carbohydrate ratio, using 1 U of insulin per 10 to 20 g of carbohydrate. On transition to CSII therapy, the insulin dosage was determined by decreasing the mean total insulin dosage per day during the preceding 2 weeks by 20%; 50% was given as a basal rate and 50% as premeal boluses and then adjusted according to SBGM. During 1 to 2 hours of physical activity, the patients were asked to stop the pump infusion and to decrease the infusion rate following the activity as necessary, by using the temporary basal rate option. Blood glucose levels above...
Hemoglobin A1c was measured at each sensor insertion using and between the first and second sensor recordings in each arm.

The percentage time during which glucose level variability was traced.

The percentage time during which glucose level variability was defined as unstable (ratio of the standard deviations to the means for each glucose marker into the monitor (all insulin injections or boluses, meals, exercise activities, and symptomatic hypoglycemic reactions). They were also instructed to check the input signal and voltage counter screens twice a day to ensure normal ranges (10-100 mV and 0.4-1.6 V, respectively). While wearing the CGMS, the patients were asked to perform 7 daily SBGM tests (preprandial, postprandial, and weekly at 3 AM) by home glucose meter (Glucometer Elite; Bayer Healthcare, Mishawaka, Ind) and to enter those values into the CGMS for sensor calibration. The same meters were used throughout the study. After each sensor tracing, the findings were discussed with the patient and parents, and the insulin dose was adjusted accordingly.

Hypoglycemia was defined as a capillary blood glucose level or sensor reading of 70 mg/dl (3.9 mmol/L) or less; hyperglycemia, as a capillary blood glucose level or sensor reading of 180 mg/dl (10.0 mmol/L) or greater; and postprandial hyperglycemia, as a capillary blood glucose level or sensor reading of 180 mg/dl (10.0 mmol/L) or greater 2 to 3 hours after a meal. Readings between 7 AM and 10 PM were considered daytime values and those between 10 PM and 7 AM as nighttime values. The rate of hypoglycemia or hyperglycemia was calculated per day or night recordings, and the duration of glucose levels within the target area or above or below was calculated as a percentage of the time recorded. To quantify the extent of glucose excursions outside the patients’ target glycemic thresholds, we calculated the area under the curve (AUC) for hypoglycemia (AUC hypo) and hyperglycemia (AUC hyper) using the following equations, respectively:

\[
(1) \quad \text{Area Above} \left( \frac{\text{mg/dL}}{\text{day}} \right) = \int \left( \text{Measurement [mg/dL]} - \text{Maximum Target Level [mg/dL]} \right) \text{Time Recorded (in Days)}
\]

\[
(2) \quad \text{Area Below} \left( \frac{\text{mg/dL}}{\text{day}} \right) = \int \left( \text{Minimum Target Level [mg/dL]} - \text{Measurement [mg/dL]} \right) \text{Time Recorded (in Days)}
\]

Glucose level variability was determined by calculating the ratio of the standard deviations to the means for each glucose measurement during 1 hour. On the basis of the glucose profiles, variability above 30% was defined as unstable (Figure 2). The percentage time during which glucose level variability was above 30% (excess variability) was calculated for each CGMS tracing.

Variables were compared between the CSII and MDI arms and between the first and second sensor recordings in each arm. Hemoglobin A1c was measured at each sensor insertion using the DCA 2000 analyzer (Bayer Diagnostics, Tarrytown, NY), with a nondiabetic range of 4.3% to 6.3%. The instrument standards are run 6 times annually and have always been in the expected ranges.

### STATISTICAL ANALYSIS

The data were analyzed using BMDP software. Data are presented as mean (SD) or median and range, as appropriate. Analysis of variance (ANOVA) was applied to compare CGMS tracings between modes of therapy. Analysis of variance with repeated measures was used to compare CGMS readings between the first and second sensor recordings in each study arm, by mode of therapy. We also calculated Pearson correlation coefficients between mean glucose levels during CGMS and SBGM. Fisher exact test was applied to compare frequencies. All reported results are 2-tailed. \( P < 0.05 \) was considered significant.

### RESULTS

The adverse events during the 2 modes of therapy in this population were previously described. In brief, there were 3 severe hypoglycemic events during MDI and 1 during CSII. There was no diabetic ketoacidosis. During pump therapy, there were 12 minor infusion set site infections (treated by local antibiotic cream), 16 blockages, and 42 dislodgments.

Twenty-two of 23 patients enrolled completed the study; 1 patient dropped out because he was afraid to insert the sensor. The sensor was well tolerated by the other 22 subjects, and there were no signs of infection or discomfort at the insertion site. Patients entered at least 4 SBGM values every 24 hours for CGMS calibration (mean, 4.4 every 24 hours during both arms). In 2 children, 1 sensor was disconnected prematurely, so that they had only 3 sensor readings; therefore, their data were included only in the between-mode analysis and not in the repeated-measures analysis. Overall, 43 sensor readings were available for each study arm. Analysis of variance with repeated measures could be applied in 20 subjects and was used for comparison between the first and the second sensor reading in each study arm, by mode of therapy. Because means and standard deviations of glucose levels were similar between treatment modes and between the 2 sensors in each arm, we also applied ANOVA for comparison between the 43 tracings of each mode.

### SENSOR PERFORMANCE

The point-to-point correlation between the simultaneous sensor and SBGM readings (n=1062, \( r=0.89 \), \( P < 0.001 \)) and the absolute intra-use difference (18.8% ± 6.0%) were usually within the acceptable range and similar for both modes of therapy (Table 1). Ninety-four percent of the sensor readings were within 20% of the simultaneous meter values. The mean durations of day and night recordings were similar for the 2 modes of therapy. To rule out the effect of wearing the sensor on glucose levels, we compared the mean values recorded by SBGM during 3 days before sensor insertion with those recorded during sensor wear; no significant difference was found (before, 193±38 mg/dL [10.7±2.1 mmol/L], and during, 199±39 mg/dL [11.0±2.2 mmol/L]; \( P = .23 \)).
Figure 2. Representative 24-hour glucose sensor tracing obtained from 2 patients during continuous subcutaneous insulin infusion (CSII) and multiple daily injections (MDI). Glucose level variability was calculated by the ratio of the standard deviation to the mean for each glucose measurement for an interval of ±1 hour. Glucose level variability above 30% was considered unstable according to the glucose profiles. Glucose level variability is greater during CSII in patient 1 and greater during MDI in patient 2. The triangles in the lower portion of the glucose concentration graphs represent the events (meals, insulin injections, exercise, or hypoglycemic episode) entered and recorded into the glucose monitor during each 24-hour period. The squares represent the self-blood glucose measurement values as measured by the patient with the glucometer and entered into the sensor monitor for calibration. To convert glucose to millimoles per liter, multiply by 0.0555.
Similar results were noted when these values were compared by mode of therapy.

**COMPARISONS BETWEEN CSII AND MDI**

**Measures of Glycemic Control**

No significant differences were noted between the 2 arms in means and standard deviations of glucose levels and mean HbA1c level (Table 2 and Table 3). Analysis of variance with repeated measures showed a trend toward lower HbA1c values during CSII compared with MDI ($P = .08$), which was solely accounted for by the difference at arm initiation. However, there was no significant difference between modes of therapy in the change in HbA1c values over time.

**Rate of Events (Per Day, Per Night, and Postprandial)**

There were more 24-hour hyperglycemic readings during CSII ($P = .03$). The rate of hypoglycemia was similar for the 2 modes.

**Duration of Specific Categories of Glucose Tracings**

There was a trend for a longer duration of glucose readings within the target range (70–180 mg/dL [3.9–10.0 mmol/L]) during CSII than MDI ($P = .06$). This difference reached significance for the 1-hour prebreakfast readings ($P = .01$). The duration of nocturnal hypoglycemia was slightly but not significantly longer during MDI ($P = .14$).

**Area Under the Curve**

Multiple daily injections were associated with a significantly larger AUC for nocturnal and 24-hour hypoglycemia ($P = .01$ and .04, respectively) and for postprandial hyperglycemia and hypoglycemia ($P = .03$ and .05, respectively). There was a trend for a larger AUC for the 1 hour before breakfast for MDI ($P = .06$). Twenty-four-hour AUC hyper was slightly but not significantly larger during MDI ($P = .15$).

**Glucose Level Variability**

The duration of excess glucose level variability was similar between treatment modalities.

**FIRST VS SECOND SENSOR READINGS BY MODE OF THERAPY**

Comparison of the first and second sensor recordings showed that, for both modes of therapy, the second demonstrated a longer duration of tracings for days ($P = .04$) and nights ($P = .03$), a longer duration of postprandial readings within the target range ($P = .04$), a trend for a lower rate of 24-hour hypoglycemic events ($P = .10$), a shorter duration of nocturnal hypoglycemia ($P = .05$), a smaller 24-hour AUC hypo ($P = .04$), and a trend for a smaller postprandial AUC hypo ($P = .07$) (Table 2). There was no difference between the first and the second sensor of each arm for any variable relating to hyperglycemia.
tracings derived from the CGMS together with a sophisticated program developed for CGMS data analysis.

With CSII, programmed changes can be made in basal insulin delivery to compensate for periods of decreased (such as early night hours) or increased (dawn phenomenon) insulin need.16 Its use also provides more predictable absorption than that of intermediate-acting insulin used with MDI17 and reduces the variability in glucose levels.8,18 Studies8,19 have shown that lispro also has better physiologic kinetics than regular insulin, providing a rapid and short prandial insulin peak. Therefore, we expected smoother glucose sensor tracings during CSII with lispro than during MDI with regular insulin. Despite the lack of significant differences in our between-mode comparison of most of the conventional variables, such as the rate of hypoglycemic events and means and standard deviations of glucose levels, the analysis of the sensor tracings showed a slight advantage for CSII in longer duration of within-target glucose readings, mainly before breakfast, combined with a smaller AUC for nocturnal 24 hours and postprandial hypoglycemia, for the same level of glycemic control. This finding is important considering that hypoglycemia is the limiting factor in the implementation of intensive therapy in chil-

### Table 3. Comparison of the Sensor Tracings Between CSII and MDI and Between the First and Second Sensor Tracings in Each Arm

<table>
<thead>
<tr>
<th>Variable</th>
<th>Times</th>
<th>CSII</th>
<th>MDI</th>
<th>Mode</th>
<th>S1-S2</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c, %</td>
<td>Start</td>
<td>7.9 (0.9)</td>
<td>8.4 (0.8)</td>
<td>.08</td>
<td>.42</td>
<td>.14</td>
</tr>
<tr>
<td></td>
<td>End</td>
<td>8.0 (0.7)</td>
<td>8.1 (0.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean glucose levels, mg/dL</td>
<td>24 h‡</td>
<td>Start</td>
<td>180 (41)</td>
<td>193 (42)</td>
<td>.59</td>
<td>.11</td>
</tr>
<tr>
<td></td>
<td>End</td>
<td>198 (28)</td>
<td>195 (43)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before breakfast</td>
<td>Start</td>
<td>177 (70)</td>
<td>173 (75)</td>
<td>.54</td>
<td>.66</td>
<td>.15</td>
</tr>
<tr>
<td></td>
<td>End</td>
<td>165 (49)</td>
<td>196 (70)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postprandial</td>
<td>Start</td>
<td>184 (48)</td>
<td>193 (45)</td>
<td>.59</td>
<td>.47</td>
<td>.85</td>
</tr>
<tr>
<td></td>
<td>End</td>
<td>192 (27)</td>
<td>196 (44)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of within-target values, %</td>
<td>24 h</td>
<td>Start</td>
<td>0.31 (0.13)</td>
<td>0.27 (0.11)</td>
<td>.14</td>
<td>.59</td>
</tr>
<tr>
<td></td>
<td>End</td>
<td>0.33 (0.16)</td>
<td>0.29 (0.11)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before breakfast</td>
<td>Start</td>
<td>0.28 (0.20)</td>
<td>0.19 (0.18)</td>
<td>.10</td>
<td>.19</td>
<td>.48</td>
</tr>
<tr>
<td></td>
<td>End</td>
<td>0.25 (0.20)</td>
<td>0.12 (0.13)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postprandial</td>
<td>Start</td>
<td>0.17 (0.13)</td>
<td>0.17 (0.15)</td>
<td>.64</td>
<td>.04</td>
<td>.74</td>
</tr>
<tr>
<td></td>
<td>End</td>
<td>0.21 (0.15)</td>
<td>0.24 (0.16)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>No. of events, 24 h</td>
<td>Start</td>
<td>1.0 (0.5)</td>
<td>1.2 (1.0)</td>
<td>.63</td>
<td>.10</td>
</tr>
<tr>
<td></td>
<td>End</td>
<td>0.9 (0.7)</td>
<td>1.0 (1.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration, night*</td>
<td>Start</td>
<td>0.13 (0.14)</td>
<td>0.16 (0.19)</td>
<td>.14</td>
<td>.05</td>
<td>.67</td>
</tr>
<tr>
<td></td>
<td>End</td>
<td>0.06 (0.07)</td>
<td>0.12 (0.12)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration, day*</td>
<td>Start</td>
<td>0.06 (0.05)</td>
<td>0.06 (0.08)</td>
<td>.81</td>
<td>.21</td>
<td>.92</td>
</tr>
<tr>
<td></td>
<td>End</td>
<td>0.05 (0.05)</td>
<td>0.05 (0.06)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration, 24 h*</td>
<td>Start</td>
<td>0.09 (0.07)</td>
<td>0.10 (0.11)</td>
<td>.31</td>
<td>.05</td>
<td>.72</td>
</tr>
<tr>
<td></td>
<td>End</td>
<td>0.05 (0.04)</td>
<td>0.08 (0.08)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC, 24 h, mg/dL per day</td>
<td>Start</td>
<td>504 (457)</td>
<td>756 (856)</td>
<td>.10</td>
<td>.04</td>
<td>.92</td>
</tr>
<tr>
<td></td>
<td>End</td>
<td>292 (260)</td>
<td>518 (565)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of events, postprandial</td>
<td>Start</td>
<td>0.5 (0.5)</td>
<td>0.5 (0.6)</td>
<td>.55</td>
<td>.47</td>
<td>.39</td>
</tr>
<tr>
<td></td>
<td>End</td>
<td>0.3 (0.5)</td>
<td>0.5 (0.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC, postprandial, mg/dL per day</td>
<td>Start</td>
<td>31 (36)</td>
<td>96 (143)</td>
<td>.03</td>
<td>.09</td>
<td>.24</td>
</tr>
<tr>
<td></td>
<td>End</td>
<td>21 (49)</td>
<td>42 (74)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC, before breakfast, mg/dL per day</td>
<td>Start</td>
<td>20 (39)</td>
<td>46 (57)</td>
<td>.14</td>
<td>.29</td>
<td>.31</td>
</tr>
<tr>
<td></td>
<td>End</td>
<td>16 (27)</td>
<td>28 (62)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>No. of events, 24 h</td>
<td>Start</td>
<td>3.5 (1.4)</td>
<td>2.9 (1.2)</td>
<td>.03</td>
<td>.90</td>
</tr>
<tr>
<td></td>
<td>End</td>
<td>3.3 (1.1)</td>
<td>2.9 (0.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration, 24 h*</td>
<td>Start</td>
<td>0.42 (0.19)</td>
<td>0.45 (0.22)</td>
<td>.58</td>
<td>.17</td>
<td>.77</td>
</tr>
<tr>
<td></td>
<td>End</td>
<td>0.49 (0.14)</td>
<td>0.49 (0.22)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC, 24 h, mg/dL per day</td>
<td>Start</td>
<td>10 906 (5217)</td>
<td>13 321 (6396)</td>
<td>.36</td>
<td>.42</td>
<td>.48</td>
</tr>
<tr>
<td></td>
<td>End</td>
<td>12 582 (5507)</td>
<td>13 064 (7132)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC, postprandial, mg/dL per day</td>
<td>Start</td>
<td>1272 (1424)</td>
<td>2382 (1961)</td>
<td>.05</td>
<td>.79</td>
<td>.34</td>
</tr>
<tr>
<td></td>
<td>End</td>
<td>1554 (1160)</td>
<td>1855 (1533)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC, before breakfast, mg/dL per day</td>
<td>Start</td>
<td>394 (507)</td>
<td>468 (532)</td>
<td>.33</td>
<td>.44</td>
<td>.15</td>
</tr>
<tr>
<td></td>
<td>End</td>
<td>358 (379)</td>
<td>649 (557)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AUC, area under the curve; CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections.

SI Conversion: To convert glucose to millimoles per liter, multiply by 0.0555.

*Data are presented as mean (SD). Duration is expressed as percentage of the total time recorded for the specific variable.

†Mode, between CSII and MDI; S1-S2, between the first and second sensor for each arm tracing; Interaction, between Mode and S1-S2 difference.

‡When results of day, night, and 24-hours are similar, only the 24-hour data are shown.
The comparisons of glycemic patterns in young patients between MDI and CSII have been conflicting with regard to rate of hypoglycemia and blood glucose fluctuation. In the present randomized crossover study, we used the CGMS to evaluate the duration and degree of within-target hypoglycemia and hyperglycemia in children and adolescents using these treatment regimens.

There was a longer duration of within-target glucose profiles, a smaller AUC for nocturnal hypoglycemia, and a higher rate of hyperglycemic episodes during pump therapy compared with MDI, with the same glycemic control. These findings indicate that the advantages of pump therapy are modest and that both modalities are equally efficient for achieving tight metabolic control in this age group.

The 2 frequently “missed” findings by conventional glucose monitoring (SBGM) were nocturnal hypoglycemia and postprandial hyperglycemia. During the second sensing, the variables relating to these variables were better, with the same level of glycemic control, indicating that the CGMS may have an educational effect in terms of hypoglycemia and postprandial glycemic control.

The rate of the 24-hour hyperglycemic patterns was higher during CSII. This finding might be secondary to the frequent catheter blockade or dislodgment encountered in our children, reflecting the limitation of current pump technology. However, duration and AUC hyper were similar, suggesting prompt correction of the hyperglycemic events by the patients.

The standard deviation of glucose levels has been used to estimate the degree of glucose variability. The similar means and standard deviations of the sensor-derived glucose levels between the 2 modes in our study differed from other studies in adults, which found a lower standard deviation during CSII than MDI. Therefore, we further analyzed the glucose tracings to define a cutoff point for glucose variability and then compared the duration of excess variability between the arms. Again, no differences were noted. This finding suggests that inconsistent meals and boluses, a common behavior among children and adolescents, might counterbalance the advantage of the better basal and insulin replacement offered by CSII with lispro. Another possibility is that the duration of the arms was too short, especially for the CSII, which was a new therapeutic modality for the children. We speculate that, had the arms been longer, some significant differences would have emerged. This was suggested by the meta-analysis of Weissberg-Benchell et al., who showed that with CSII the duration of therapy is the most important factor determining the improvement in glycemic control.

Our postprandial results are interesting in that, while the means and standard deviations of glucose levels were similar, AUChyper and AUChypo were larger during MDI using regular insulin compared with CSII using lispro. These results confirm previous studies showing better postprandial glucose levels using lispro compared with regular insulin and suggest again that the AUC might differentiate between treatment modalities when means and standard deviations are similar.

During the second application of the CGMS (at the end of each study arm), the duration of within-target postprandial glucose readings was significantly longer, and the duration and AUC hypo (mainly nocturnal) were lower for both modes of therapy, with the same level of glycemic control. Indeed, when we discussed the sensor glycemic patterns with the patients and parents, the 2 frequently “missed” findings by conventional glucose monitoring (SBGM) were nocturnal hypoglycemia and postprandial hyperglycemia, in agreement with previous findings. This suggests that the CGMS may have an educational effect in terms of hypoglycemia and postprandial glycemic control. However, during the second sensing, all patients were more experienced with their mode of therapy, which may also have affected these results.

Few recent studies have challenged the accuracy and reproducibility of the CGMS. The first showed that glucose levels were 15% to 20% lower with the sensor than plasma glucose levels measured during hyperinsulinemic clamp, following abrupt changes in insulin levels during intravenous administration. However, these differences were clinically modest and could be prevented by sensor calibration. The second study compared the glucose tracings of paired sensors applied con-
comitantly to the same subject. Thirty-five percent of the paired glucose readings were discordant by clinical category (high, within target, or low). This difference is similar to the 34% discrepancy between our simultaneous sensor and SBGM measurements (data not shown). Nevertheless, we believe that these limitations do not deter our use of this device to compare different methods of therapy, assuming a similar error rate.

In summary, we compared the CGMS tracings of children and adolescents with type 1 diabetes mellitus treated in a crossover manner using CSII with lispro or MDI with a combination of NPH and regular insulin. Only a modest advantage for CSII was revealed, mainly longer duration of glucose readings within the target range and a smaller AUC hypo. Whether these findings have clinical implications for the rate of severe hypoglycemia and long-term complications remains to be elucidated. To further evaluate these potential advantages of CSII, a longer experiment is needed to prevent the effect of subject adjustment factors on the results. In addition, further research is needed to determine if the use of glargine in combination with rapid-acting insulin analogue in the MDI regimen abolishes the modest advantage shown for CSII in the present study. Other significant findings were the decreased duration and degree of hypoglycemia and the increased duration of within-target postprandial glucose levels, at no cost of glycemic control, on the second sensor application, suggesting an educational role for sensor use with regard to hypoglycemia and postprandial glycemic control.

Accepted for publication March 11, 2004.

This study was supported by MiniMed and Agentek, Tel Aviv.

We are grateful for the editorial and secretarial help of Gloria Ginzach and Melanie Kawe, to Michal Kasher and Alon Klein for their help with the figures, and to Noa Gur-Arieh for her help with the revision.

Correspondence: Naomi Weintrob, MD, Institute for Endocrinology and Diabetes, National Center of Childhood Diabetes, Schneider Children’s Medical Center of Israel, 14 Kaplan St, Petah Tiqva 49202, Israel (nweintrob@clalit.org.il).

REFERENCES


©2004 American Medical Association. All rights reserved.