

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

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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 A_{1c} 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 A_{1c} 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.

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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 A_{1c} (HbA_{1c}) 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,⁴ who lead a hectic and an unpredictable lifestyle.² Furthermore, more than 50% of hypoglycemic events occur at night,⁵ 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

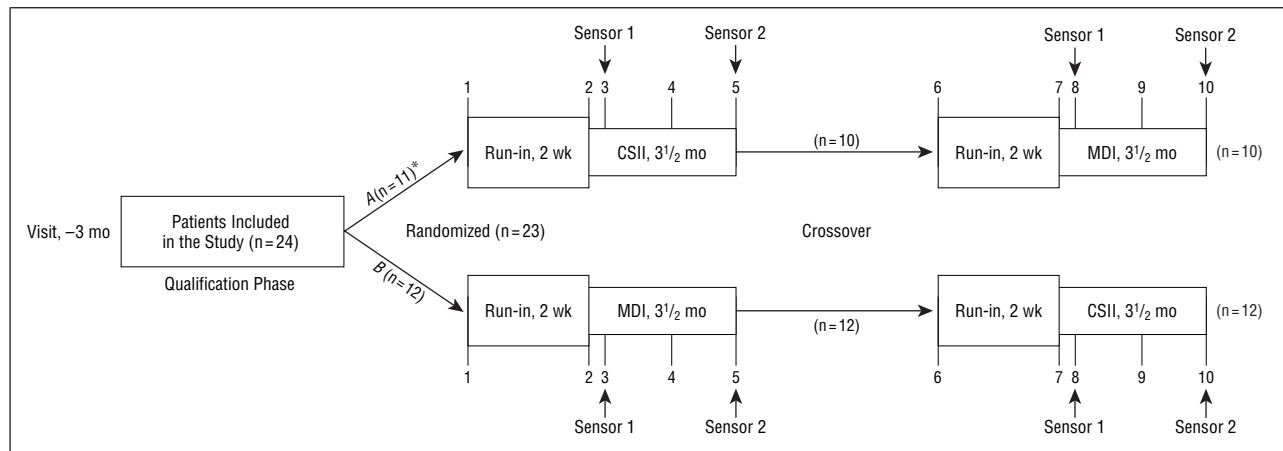


Figure 1. Randomized crossover design comparing 2 methods of intensified insulin therapy (continuous subcutaneous insulin infusion [CSII] and multiple daily injections [MDI]). The sensors were applied for 72 hours 1 month after the start of each arm and at the end of each arm. Visit -3 mo describe the lecture given before the study randomization and the asterisk, one patient who was not randomized due to detected C-peptide levels.

mellitus showed a slight but significantly better percentage of HbA_{1c} (-0.44%) during pump therapy. However, studies^{7,8} 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)⁹ 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.¹⁰⁻¹²

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 9¼ to 13¾ years (median, 11.9 years). The duration of diabetes mellitus was 2½ to 11 years (median, 6.0 years), and the prestudy HbA_{1c} 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 CGMS⁹ 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.¹³ 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.¹⁴ 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

150 mg/dL (>8.3 mmol/L) were corrected with additional insulin given before meals and snacks, using 1 U for every 50 to 100 mg/dL (2.8-5.6 mmol/L) above 150 mg/dL. During pump therapy, the participants were asked to change the infusion site every 3 days and under the following conditions: when blood glucose was greater than 300 mg/dL (>16.7 mmol/L) with positive urinary ketones or when blood glucose was greater than 300 mg/dL (>16.7 mmol/L) and failed to respond to a corrective insulin dose and at any sign of insertion site infection. The patients and their parents were asked to record all adverse events in a daily diary.

Each subject was asked to wear the CGMS 1 month after entering each study arm and at the end of the study arms (total of 4 times), for 72 hours each time. Subjects were trained in the techniques of sensor function and shown how to enter the event markers 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 nA 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 these 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:

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

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

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 A_{1c} 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.¹⁵ 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. $P \leq .05$ was considered significant.

RESULTS

The adverse events during the 2 modes of therapy in this population were previously described.¹³ 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 ($n=1062$, $r=0.89$, $P<.001$) and the absolute intra-use difference (18.8% \pm 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]; $P=.23$).

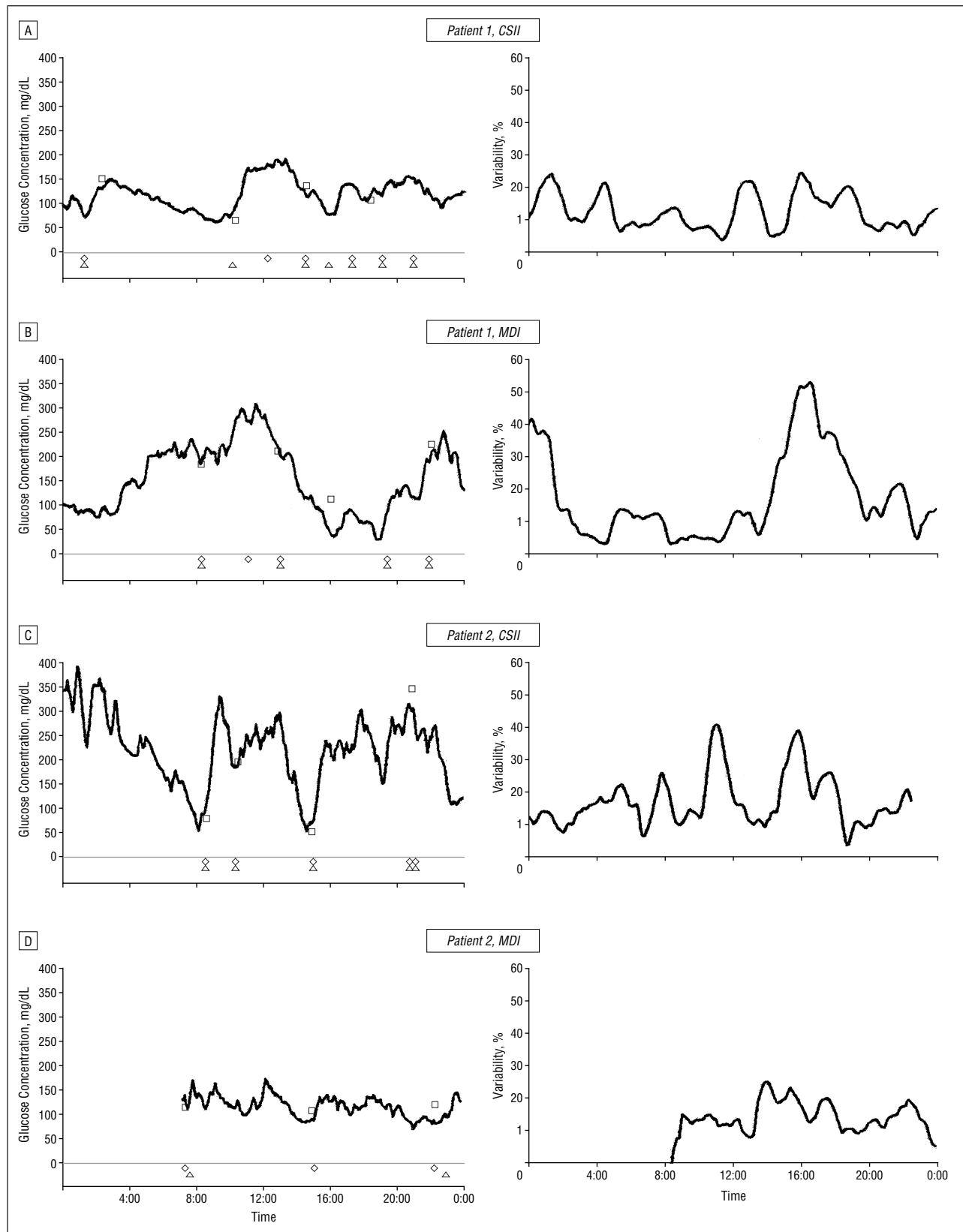


Figure 2. Representative 24-hour glucose sensor tracing obtained from 2 patients during continuous subcutaneous insulin infusion (CSII) and multiple daily injections (MDI). Glucose level variability was calculated by the ratio of the standard deviation to the mean for each glucose measurement for an 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.

Table 1. Sensor Performance*

Variable	Total	Range	CSII	MDI	P Value†
Correlation, <i>r</i>	0.89 (0.07)	0.70-0.99	0.85 (0.13)	0.88 (0.07)	.30
Absolute difference, %	18.8 (6.0)	9.0-34.0	20.1 (7.8)	18.7 (6.1)	.22
No. of nights recorded‡	2.6 (0.6)	1.0-3.0	2.6 (0.6)	2.6 (0.6)	.44
No. of days recorded	2.6 (0.7)	1.0-3.0	2.7 (0.5)	2.6 (0.7)	.48

Abbreviations: CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections.

*Data are given as mean (SD). Correlation and absolute difference are between point-to-point paired continuous glucose monitoring system and self-blood glucose measurement readings.

†Significance of differences between CSII and MDI.

‡The sensor was applied for 3 consecutive days and nights. Days were defined as 7 AM to 10 PM and nights as 10 PM to 7 AM.

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 HbA_{1c} level (**Table 2** and **Table 3**). Analysis of variance with repeated measures showed a trend toward lower HbA_{1c} 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 HbA_{1c} 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_{hypo} during the 1 hour before breakfast for MDI ($P=.06$). Twenty-four-hour AUC_{hyper} was slightly but not significantly larger during MDI ($P=.15$).

Table 2. Comparison Between CSII and MDI*

Variable	CSII	MDI	P Value
No. of sensors recored	43	43	
HbA _{1c} , %	8.0 (0.8)	8.2 (0.8)	.25
Mean glucose levels, mg/dL			
24 h	187 (36)	191 (45)	.63
Before breakfast	172 (61)	183 (68)	.41
Postprandial	190 (37)	194 (50)	.68
SD glucose levels, mg/dL			
24 h	77 (17)	79 (17)	.44
Before breakfast	55 (25)	60 (31)	.38
Postprandial	64 (22)	67 (20)	.50
Duration of excess variability, 24 h, %	10.0 (5.1)	11.2 (8.7)	.42
Duration of within-target values, %			
24 h	0.33 (0.15)	0.28 (0.11)	.06
Before breakfast	0.27 (0.20)	0.17 (0.16)	.01
Postprandial	0.23 (0.14)	0.22 (0.15)	.85
Hypoglycemia			
No. of events, 24 h	1.1 (0.8)	1.1 (1.0)	.90
Duration, 24 h, %	0.07 (0.06)	0.09 (0.10)	.19
AUC, night, mg/dL per day	198 (300)	433 (544)	.01
AUC, day, mg/dL per day	179 (198)	204 (303)	.65
AUC, 24 h, mg/dL per day	377 (377)	638 (727)	.04
AUC, postprandial, mg/dL per day	24 (42)	64 (113)	.03
AUC, before breakfast, mg/dL per day	16 (32)	36 (58)	.06
Hyperglycemia			
No. of events, 24 h	3.4 (1.2)	2.9 (1.0)	.04
Duration, 24 h, %	0.44 (0.17)	0.47 (0.23)	.57
AUC, 24 h, mg/dL per day	11 479 (5528)	13 368 (6495)	.15
AUC, postprandial, mg/dL per day	1454 (1292)	2282 (2174)	.05
AUC, before breakfast, mg/dL per day	390 (461)	566 (548)	.11

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 given as mean (SD). Duration is expressed as percentage of the total time recorded for the specific variable.

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.

COMMENT

We compared the glucose patterns between CSII with lispro and MDI with a combined regimen of regular and intermediate-acting insulin, in children and young adolescents with type 1 diabetes mellitus. We used glucose

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

Variable	Times	CSII	MDI	P Value†		
				Mode	S1-S2	Interaction
HbA _{1c} , %	Start	7.9 (0.9)	8.4 (0.8)	.08	.42	.14
	End	8.0 (0.7)	8.1 (0.8)			
Mean glucose levels, mg/dL	Start	180 (41)	193 (42)	.59	.11	.38
	End	198 (28)	195 (43)			
24 h‡	Start	177 (70)	173 (75)	.54	.66	.15
	End	165 (49)	196 (70)			
Before breakfast	Start	184 (48)	193 (45)	.59	.47	.85
	End	192 (27)	196 (44)			
Postprandial	Start	0.31 (0.13)	0.27 (0.11)	.14	.59	.95
	End	0.33 (0.16)	0.29 (0.11)			
Duration of within-target values, %	Start	0.28 (0.20)	0.19 (0.18)	.10	.19	.48
	End	0.25 (0.20)	0.12 (0.13)			
24 h	Start	0.17 (0.13)	0.17 (0.15)	.64	.04	.74
	End	0.21 (0.15)	0.24 (0.16)			
Hypoglycemia	Start	1.4 (0.9)	1.2 (1.0)	.63	.10	.57
	End	0.9 (0.7)	1.0 (1.1)			
No. of events, 24 h	Start	0.13 (0.14)	0.16 (0.19)	.14	.05	.67
	End	0.06 (0.07)	0.12 (0.12)			
Duration, night*	Start	0.06 (0.05)	0.06 (0.08)	.81	.21	.92
	End	0.05 (0.05)	0.05 (0.06)			
Duration, day*	Start	0.09 (0.07)	0.10 (0.11)	.31	.05	.72
	End	0.05 (0.04)	0.08 (0.08)			
AUC, 24 h, mg/dL per day	Start	504 (457)	756 (856)	.10	.04	.92
	End	292 (260)	518 (565)			
No. of events, postprandial	Start	0.5 (0.5)	0.5 (0.6)	.55	.47	.39
	End	0.3 (0.5)	0.5 (0.7)			
AUC, postprandial, mg/dL per day	Start	31 (36)	96 (143)	.03	.09	.24
	End	21 (49)	42 (74)			
AUC, before breakfast, mg/dL per day	Start	20 (39)	46 (57)	.14	.29	.31
	End	16 (27)	28 (62)			
Hyperglycemia	Start	3.5 (1.4)	2.9 (1.2)	.03	.90	.84
	End	3.3 (1.1)	2.9 (0.9)			
No. of events, 24 h	Start	0.42 (0.19)	0.45 (0.22)	.58	.17	.77
	End	0.49 (0.14)	0.49 (0.22)			
Duration, 24 h*	Start	10 906 (5217)	13 321 (6396)	.36	.42	.48
	End	12 582 (5507)	13 064 (7132)			
AUC, 24 h, mg/dL per day	Start	1272 (1424)	2382 (1961)	.05	.79	.34
	End	1554 (1160)	1855 (1533)			
AUC, postprandial, mg/dL per day	Start	394 (507)	468 (532)	.33	.44	.15
	End	358 (379)	649 (557)			

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.

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} Studies^{8,19} 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 dur-

ing 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-

dren and adolescents.⁴ Furthermore, the presence of recurrent mild events of hypoglycemia predisposes patients to hypoglycemia unawareness, thereby placing them at increased risk of severe hypoglycemia.²⁰ The smaller AUCs for hypoglycemia during CSII in the present study might explain the significant decrease in the rate of severe hypoglycemia over long-term CSII therapy found in previous studies.^{21,22} Our results also suggest that the duration and the AUC might better replace the concrete number of events as a tool by which to measure and compare glycemic patterns.

We used regular insulin in the MDI arm of therapy. The choice was based on the observation that, for optimal premeal and bedtime glycemic control during MDI therapy, a small amount of NPH needs to be added to each premeal lispro injection.²³ As the children preferred to use insulin pens for premeal shots, we decided to continue with the regular insulin during MDI. In view of the recent study²⁴ comparing insulin analogue with regular insulin in children treated with MDI, in which glycemic control and rate of hypoglycemia were found to be similar in the 2 groups, we assume the difference in insulin types did not have a major effect on the results.

Recently, glargine, a new longer-acting, peakless insulin analogue, was introduced as a basal insulin for MDI. Investigations have suggested that glargine therapy is associated with less nocturnal hypoglycemia and better glucose levels on awakening than NPH insulin.²⁵ However, results comparing CSII with MDI using glargine and rapid-acting insulin analogue are conflicting, with one study showing that glargine is better than NPH and equally effective as the pump²⁶ and the other reporting a better effect of the pump.²⁷ In addition, in many countries, insulin glargine is not available or is not covered by health insurance companies.

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^{8,18} 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,²⁸ who showed that with CSII the duration of therapy is the

What This Study Adds

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.

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, AUC_{hyper} and AUC_{hypo} were larger during MDI using regular insulin compared with CSII using lispro. These results confirm previous studies^{24,25} 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.¹⁰ 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 accuracy²⁹ and reproducibility³⁰ 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 study³⁰ 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 glargine²⁶ 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.

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REFERENCES

- Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin dependent diabetes mellitus. *N Engl J Med.* 1993;329:977-986.
- Diabetes Control and Complications Trial Research Group. Effect of intensive diabetes treatment on the development and progression of long-term complications in adolescents with insulin-dependent diabetes mellitus: Diabetes Control and Complications Trial. *J Pediatr.* 1994;125:177-188.
- Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Research Group. Beneficial effects of intensive therapy of diabetes during adolescence: outcomes after the conclusion of the Diabetes Control and Complications Trial (DCCT). *J Pediatr.* 2001;139:804-812.
- Becker DJ, Ryan CM. Hypoglycemia: a complication of diabetes therapy in children. *Trends Endocrinol Metab.* 2000;11:198-202.
- Bergada I, Suissa S, Dufresne J, Schiffrin A. Severe hypoglycemia in IDDM children. *Diabetes Care.* 1989;12:239-244.
- Pickup J, Mattock M, Kerry S. Glycemic control with continuous subcutaneous insulin infusion compared to intensive insulin injections in patients with type 1 diabetes: meta-analysis of randomized controlled trials. *BMJ.* 2002;324:1-6.
- Kaufman FR, Halvorson M, Kim C, Pitukcheewanont P. Use of insulin pump therapy at nighttime only for children 7-10 years of age with type 1 diabetes. *Diabetes Care.* 2000;23:579-582.
- Hanaire-BROUTIN H, Melki V, Bessieres-Lacombe S, Tauber JP, Study Group for the Development of Pump Therapy in Diabetes. Comparison of continuous subcutaneous insulin infusion and multiple daily injection regimens using insulin lispro in type 1 diabetes patients on intensified treatment. *Diabetes Care.* 2000;23:1232-1235.
- Mastrototaro J. The MiniMed Continuous Glucose Monitoring System (CGMS). *J Pediatr Endocrinol Metab.* 1999;12(suppl 3):751-758.
- Boland E, Monsod T, Delucia M, Brandt CA, Fernando S, Tamborlane WV. Limitations of conventional methods of self-monitoring of blood glucose. *Diabetes Care.* 2001;24:1858-1862.
- Chase HP, Kim LM, Owen SL, et al. Continuous subcutaneous glucose monitoring in children with type 1 diabetes. *Pediatrics.* 2001;107:222-226.
- Kaufman FR, Gibson LC, Halvorson M, Carpenter S, Fisher LK, Pitukcheewanont P. A pilot study of the Continuous Glucose Monitoring System. *Diabetes Care.* 2001;24:2030-2034.
- Weintrob N, Benzaquen H, Galatz A, et al. Comparison of continuous subcutaneous insulin infusion and multiple daily injection regimens in children with type 1 diabetes: a randomized open crossover trial. *Pediatrics.* 2003;112:559-564.
- Rohlfing CL, Wiedmeyer HM, Little RR, England JD, Tennill A, Goldstein DE. Defining the relationship between plasma glucose and HbA_{1c}. Analysis of glucose profiles and HbA_{1c} in the Diabetes Control and Complications Trial. *Diabetes Care.* 2002;25:275-278.
- Dixon WJ, ed. *BMDP Statistical Software.* Los Angeles: University of California Press; 1993.
- Koivisto VA, Yki-Jarvinen H, Helve E, Karonen SL, Pelkonen R. Pathogenesis and prevention of the dawn phenomenon in diabetic patients treated with CSII. *Diabetes.* 1986;35:78-82.
- Lauritzen T, Pramming S, Deckert T, Binder C. Pharmacokinetics of continuous subcutaneous insulin infusion. *Diabetologia.* 1983;24:326-329.
- Wredling R, Hannerz L, Johansson UB. Variability of blood glucose levels in patients treated with continuous subcutaneous insulin infusion: a pilot study. *Practical Diabetes Int.* 1997;14:5-8.
- Zinman B, Tildesley H, Chiasson JL, Tsui E, Strack T. Insulin lispro in CSII: results of a double-blind crossover study [published correction appears in *Diabetes.* 1997;46:1239]. *Diabetes.* 1997;46:440-443.
- Cryer PE. Hypoglycemia: the limiting factor in the glycaemic management of type 1 and type 2 diabetes. *Diabetologia.* 2002;45:937-948.
- Bode BW, Steed RD, Davidson PC. Reduction in severe hypoglycemia with long-term continuous subcutaneous insulin infusion in type 1 diabetes. *Diabetes Care.* 1996;19:324-327.
- Boland EA, Grey M, Oesterle A, Fredrickson L, Tamborlane WV. Continuous subcutaneous insulin infusion: a new way to lower risk of severe hypoglycemia, improve metabolic control, and enhance coping in adolescents with type 1 diabetes. *Diabetes Care.* 1999;22:1779-1784.
- Lalli C, Ciofetta M, Del Sindaco P, et al. Long-term intensive treatment of type 1 diabetes with the short-acting insulin analog lispro in variable combination with NPH insulin at mealtime. *Diabetes Care.* 1999;22:468-477.
- Deeb LC, Holcombe JH, Brunelle R, et al. Insulin lispro lowers postprandial glucose in prepubertal children with diabetes. *Pediatrics.* 2001;108:1175-1179.
- Lepore M, Pampanelli S, Fanelli C, et al. Pharmacokinetics and pharmacodynamics of subcutaneous injection of long-acting human insulin analog glargine, NPH insulin, and Ultralente human insulin and continuous subcutaneous infusion of insulin lispro. *Diabetes.* 2000;49:2142-2148.
- Lepore G, Dodesini AR, Nosari I, Trevisan R. Both continuous subcutaneous insulin infusion and a multiple daily insulin injection regimen with glargine as basal insulin are equally better than traditional multiple daily insulin injection treatment. *Diabetes Care.* 2003;26:1321-1322.
- Boland E, Weinzimer S, Ahern JA, Steffen A, Tamborlane W. Randomised, prospective trial of CSII vs MDI with glargine in children: a preliminary report [abstract]. *Diabetes.* 2003;52(suppl 1):192.
- Weissberg-Benchell J, Antisdel-Lomaglio J, Seshadri R. Insulin pump therapy: a meta-analysis. *Diabetes Care.* 2003;26:1079-1087.
- Monsod TP, Flanagan DE, Rife F, et al. Do sensor glucose levels accurately predict plasma glucose concentrations during hypoglycemia and hyperinsulinemia? *Diabetes Care.* 2002;25:889-893.
- Metzger M, Leibowitz G, Weinstein J, Glaser B, Raz I. Reproducibility of glucose measurements using the glucose sensor. *Diabetes Care.* 2002;25:1185-1191.