

A Pilot Study of the Continuous Glucose Monitoring System

Clinical decisions and glycemic control after its use in pediatric type 1 diabetic subjects

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OBJECTIVE — To determine whether the continuous glucose monitoring system (CGMS) (MiniMed, Sylmar, CA) could be used to make clinical decisions and whether it has an impact on glycemia in pediatric type 1 diabetic subjects.

RESEARCH DESIGN AND METHODS — Pediatric subjects were recruited if they had HbA_{1c} >8.0% with management problems ($n = 35$) or episodes of severe or nocturnal hypoglycemia or hypoglycemia unawareness associated with HbA_{1c} $\leq 8.0\%$ ($n = 12$). A total of 47 patients with a mean HbA_{1c} value of $8.6 \pm 1.6\%$ (mean age 11.8 ± 4.6 years, youngest 2.7 years, and diabetes duration 5.5 ± 3.5 years) on three to four insulin injections/day ($n = 24$) or insulin pump therapy ($n = 23$) were followed with the CGMS for a mean of 69.5 ± 28 h. Comparisons were made between the number of high (>150 mg/dl) and low (<70 mg/dl) glucose patterns discerned with the sensor or the logbook, and HbA_{1c} levels were evaluated.

RESULTS — In patients on injection therapy, 30 high or low glucose patterns were discerned with the logbook records and 120 patterns with the CGMS. Specific alterations of the diabetes regimen were made. An overall significant change in HbA_{1c}, from 3 months before wearing the sensor to 6 months after (analysis of variance 0.04), was found in the subjects. Post hoc analysis showed a significant change in HbA_{1c} from $8.6 \pm 1.5\%$ at baseline to $8.4 \pm 1.3\%$ at 3 months (paired Student's t test 0.03).

CONCLUSIONS — The CGMS can be used by pediatric patients to detect abnormal patterns of glycemia. The information that was obtained could be used to alter the diabetes regimen and impact glycemic outcome.

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Abbreviations: ANOVA, analysis of variance; CGMS, continuous glucose monitoring system; CSII, continuous subcutaneous insulin infusion.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

The goal of the management of type 1 diabetes in children and youth is to maintain blood glucose and HbA_{1c} levels as near to normal as possible (1). Although this goal is difficult to achieve for all patients with type 1 diabetes, it is even more challenging for pediatric subjects. Children and adolescents often have fluctuations in blood glucose level, and their activity pattern and food intake are often erratic and unpredictable. In 1998–1999, data from our large, urban center at Childrens Hospital Los Angeles for over 1,000 patients who had received diabetes education and had access to the health team for advice on diabetes management showed that the mean HbA_{1c} level was 8.2%.

The diabetes regimen followed by our patients consisted of taking multiple insulin injections per day or using continuous subcutaneous insulin infusion (CSII) (2). As part of the diabetes regimen, our patients are advised to obtain at least four finger-stick glucose measurements each day. This allows for adjustment of insulin dosage, food intake, and activity level to maintain glycemia within the individualized target range, which is dependent on age, developmental stage, and the ability to recognize hypoglycemia (3). Currently, one of the main obstacles to achieving glycemic control is that blood glucose is intermittently measured. Continuous glucose monitoring would eliminate the fact that finger-stick measurements can only provide information regarding a few minutes of each day and cannot be used to easily identify patterns of abnormal glycemia.

Recently, the MiniMed continuous glucose monitoring system (CGMS), a light-weight, portable, minimally invasive system, was developed (4). This system continuously measures subcutaneous tissue interstitial glucose levels, recording values on average every 5 min within a range of 40–400 mg/dl. Glucose values obtained with the CGMS have been shown to correlate with laboratory mea-

measurements of plasma glucose concentrations (5) and home glucose values (6). With glucose fluctuations, it has been shown that there is a 5-min lag time with the CGMS. This lag time appears to be inconsequential in the present study because it retrospectively evaluates glucose levels.

The CGMS is comprised of four components. The glucose sensor, an electrode impregnated with glucose oxidase, is subcutaneously placed via a flexible catheter that can be easily tolerated for 3 days. Additional sensors can be worn to provide >3 days of data. The sensor is seamlessly connected via a cable to the monitor, which is light-weight and worn on clothing or a belt. The monitor collects and stores the glucose data until it is downloaded into the com-station, where glucose values are displayed. A typical 3-day tracing of the sensor-wear can then be analyzed.

The initial studies on the CGMS were performed in adult subjects (7,8). These studies showed that the system is well tolerated by adult type 1 diabetic patients. Additional research has shown that the information obtained allows the patient and health care team to adjust the timing and dosage of insulin and the nutrition plan to improve glycemic control, resulting in an average decrease in HbA_{1c} from 9.9 to 8.8% after 5 weeks (9). Chase et al. (10) studied continuous glucose monitoring in pediatric subjects to determine whether it could help recognize nocturnal hypoglycemia or lower HbA_{1c}. A small cohort of children ($n = 11$) were randomized to the CGMS or a control group for 30 days, during which time the CGMS group used six 3-day sensors. The CGMS revealed asymptomatic hypoglycemia in study patients, and HbA_{1c} was decreased by $0.36 \pm 0.07\%$ in the CGMS group compared with $0.2 \pm 0.2\%$ in the control group.

The purpose of the present study was to determine whether the CGMS could be used by a larger group of pediatric patients with type 1 diabetes. Children and youth were recruited to use the CGMS to determine whether high and low patterns of glycemia could be identified. The initial subjects chosen for this study were those with less than optimal glycemic control, as determined by HbA_{1c}, or a history of severe hypoglycemia, hypoglycemia unawareness, or nocturnal hypoglycemia. HbA_{1c} levels were measured at 3 months

before continuous glucose monitoring, at placement of the CGMS, and at 3 and 6 months post sensor-wear and compared to see whether adjusting the diabetes regimen with the information obtained from the CGMS led to a change in glycemic outcome.

RESEARCH DESIGN AND METHODS

Patient selection

Fifty pediatric patients with type 1 diabetes were recruited for this study during routine clinical visits to the Comprehensive Diabetes Center at Childrens Hospital Los Angeles during a 6-month period at the end of 1999 and the beginning of 2000. Patients were eligible to enter if they had an HbA_{1c} value >8.0% ($n = 35$) associated with one of the following clinical problems: elevated fasting blood glucose levels or suspected dawn phenomenon; glycemic excursion with exercise; insulin dosage $>1-1.5$ units \cdot kg⁻¹ \cdot day⁻¹ for prepubertal and pubertal children, respectively; widely fluctuating blood glucose levels; or erratic response to blood glucose correction. Subjects with recurrent hypoglycemia, hypoglycemia unawareness, or suspected nocturnal hypoglycemia ($n = 12$) combined with an HbA_{1c} level $\leq 8.0\%$ were also eligible. After being shown the sensor and receiving an explanation as to what a 3-day sensor-wear entailed, all subjects agreed to wear the sensor for a 3-day period. Pump patients were given the option to insert a second sensor. A total of 47 subjects/parents agreed to participate and signed informed consent. The mean age of the subjects was 11.8 ± 4.6 years (range 2.7–29.1). There were 18 male and 29 female subjects. The patients had a mean duration of diabetes of 5.5 ± 3.5 years (range 0.8–20) and a mean baseline HbA_{1c} of $8.6 \pm 1.6\%$ (6.3–12.9). A total of 24 subjects took three to four insulin injections per day, and the remaining 23 subjects used CSII.

Study protocol

Patients and parents were brought to the outpatient clinic at Childrens Hospital Los Angeles for a 2-h training and evaluation session. Sensor placement was done by one of two Certified Diabetes Educators after pretreatment of the abdominal skin where the sensor was placed with EMLA Cream (Astra Pharmaceuticals,

Wayne, PA). Calibration of the sensor was accomplished by following the protocol established and outlined in the MiniMed CGMS manual. Four monitors were used during the study.

During continuous glucose monitoring, patients/parents were instructed to measure a minimum of four finger-stick blood glucose levels per day and to record glucose values, meals, insulin doses, exercise periods, and symptomatic hypoglycemia in a logbook. They were also instructed on how to code these events into the monitor.

At the completion of the CGMS period, the system was returned and the data downloaded via the com-station to determine glucose patterns. Logbooks were also analyzed for glucose patterns. A high glucose pattern was defined if at least 2 of 3 days or >50% of glucose levels were >150 mg/dl, and a low-glucose pattern was defined if at least 2 of 3 days or >50% of values were <70 mg/dl during one of the eight time periods. The eight time periods were: breakfast, postbreakfast, lunch, postlunch and afternoon snack, dinner, bedtime, midnight, and 3:00 AM. The number of high and low patterns determined by logbooks were compared with the number of high and low patterns seen with the CGMS.

The CGMS patterns were reviewed with the patient/parent, and recommended changes in the diabetes regimen to improve glycemia were discussed. The following nine types of recommendations were made from CGMS analyses: 1) change in one or more bolus or rapid-acting insulin dosage; 2) change in one or more basal or intermediate/long-acting insulin dosage; 3) change in the correction algorithm (3); 4) alteration in the approach to exercise to include change in carbohydrate management (11); 5) reinforcing treatment algorithm for hypoglycemia to include rechecking, adding extra carbohydrate, and protein (11); 6) change in early morning basal rate (pump patients) or bedtime insulin dosage and/or timing (injection patients) due to the dawn phenomenon; 7) increase in meal bolus and timing of injection after the meal (injection patients) or adding square-wave bolus (pump patients) for high-fat meals; 8) increase in meal insulin dosage for high glycemic foods; and 9) referral for counseling to improve adherence with diabetes regimen. Data were analyzed to determine the percentage of

Table 1—Number of high and low patterns for all patients and those on CSII and injections

	Breakfast		Postbreakfast		Lunch		Snack		Dinner		Bedtime		Midnight		3:00 AM	
	Sensor	Log	Sensor	Log	Sensor	Log	Sensor	Log	Sensor	Log	Sensor	Log	Sensor	Log	Sensor	Log
All	26	8	28	3	20	6	26	5	19	9	18	5	22	2	32	3
CSII	8	2	7	0	8	2	10	2	8	4	9	2	9	0	12	0
Injections	18	6	21	3	12	4	16	4	11	5	9	3	13	2	20	3

patients advised to perform each of these nine recommendations. HbA_{1c} levels were obtained with the DCA 2000 (Bayer, Tarrytown, NY) (normal range 3–6%) 3 months before CGMS, at the time of sensor placement, and at 3 and 6 months post sensor-wear.

Descriptive statistical analysis was performed on the sample population. This was done to determine the frequency of sensor findings, differences between information obtained from the CGMS and logbooks, and treatment recommendations. Repeated measures of analysis of variance (ANOVA) were used to evaluate change in HbA_{1c} in subjects. The paired Student's *t* test was used to determine differences in HbA_{1c} levels before and after sensor placement.

RESULTS— All subjects tolerated the CGMS for at least 3 days. The mean duration of sensor-wear was 69.5 ± 28 h (range 29–111). Patients coded a mean of 49 ± 24 events (meals, exercise, and symptomatic hypoglycemia) into the monitor during CGMS use. There was a mean of 18.5 ± 8.0 finger-stick glucose levels recorded in logbooks, resulting in a mean of 4.3 ± 0.7 measurements/day. There was a mean of 1.1 ± 0.9 interruptions in the sensor tracings per subject that were <3 h in duration and did not interfere with data analysis.

Table 1 shows the number of high and low patterns that could be determined using the CGMS as compared with that from the logbook for all subjects and for those on CSII and injection therapy. As shown in Table 1, high and low pattern identification was greater with the CGMS (191 patterns) than with logbook records (42 patterns) for all patients and for those using injection (120 patterns with CGMS and 30 with logbook) and insulin pump therapy (71 patterns with CGMS and 12 with logbook). Overall, there were 1.8 times more abnormal patterns detected for subjects on injection therapy com-

pared with subjects using insulin pump therapy (Table 1).

With the CGMS, a mean of 1.17 ± 1.3 asymptomatic nocturnal hypoglycemic events during the bedtime, night, and early morning time periods were noted per patient, with 83% of subjects having at least one episode. Ten (22%) subjects were found to have an elevation in glucose level during the early morning period that was consistent with the dawn phenomenon. During sensor-wear, 15 (32%) patients were found to have a high breakfast pattern, 15 (32%) had a high lunch pattern, and 12 (25%) had a high dinner pattern, whereas 2 (4%) had a low breakfast pattern, 3 (6%) had a low lunch pattern, and 2 (4%) had a low dinner pattern. In contrast, there were no low postmeal patterns. Eight (17%) patients had a

high postbreakfast pattern, 11 (23%) had a high postlunch/afternoon snack pattern, and 9 (19%) had a high bedtime pattern.

Figure 1 illustrates the percentage of patients with whom a recommendation to alter their diabetes regimen was discussed after using the CGMS. As shown, of the nine types of recommendations of how to alter the diabetes regimen, the most common was to make a change in one or more of the subject's basal insulin dosages for those on CSII and in one or more of the long- or intermediate-acting insulin doses for those taking injections. This was followed by recommendations to change one or more bolus or rapid-acting insulin dose, to change hypoglycemia treatment, and to change the correction algorithm.

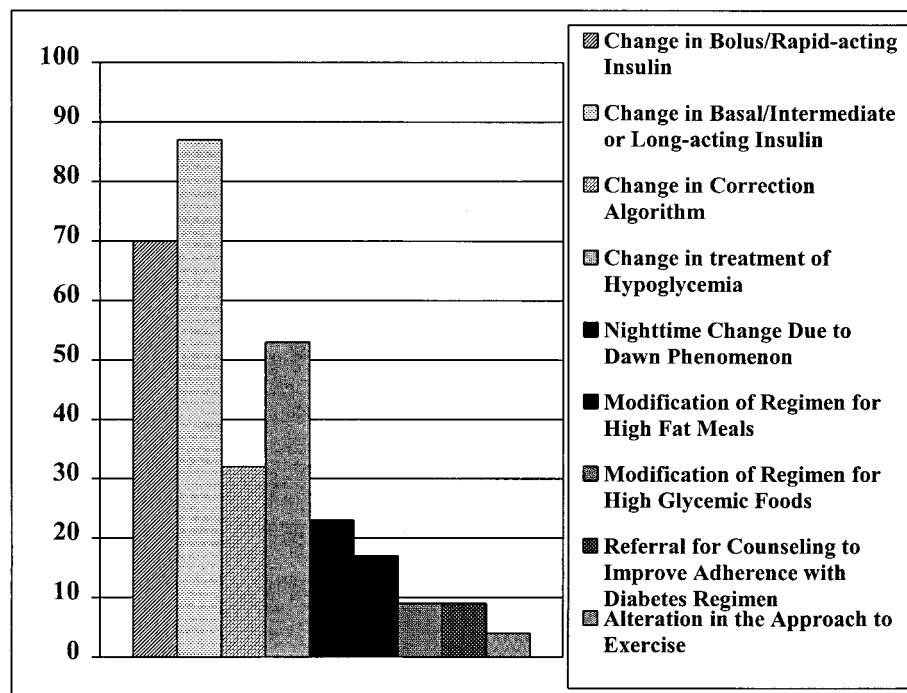


Figure 1—Percentage of patients given each of nine recommendations on how to alter their diabetes regimen.

Table 2—HbA_{1c} for all subjects and those on CSII and injections

Time from baseline (months)	All	CSII	Injections
-3	8.7 ± 1.6	8.5 ± 1.6	8.9 ± 1.6
0	8.6 ± 1.5	8.4 ± 1.7	8.8 ± 1.4
+3	8.4 ± 1.3	8.2 ± 1.3	8.5 ± 1.3
+6	8.3 ± 1.3	8.1 ± 1.3	8.5 ± 1.4

Data are means ± SE. Repeat measures of ANOVA: type III sum of squares = 4.509; df = 2.185; mean square = 2.064; $F = 3.262$; $P = 0.038$.

There was a mean of 3.3 ± 0.8 recommendations per patient.

Table 2 shows the HbA_{1c} results 3 months before, at baseline, and 3 and 6 months post-CGMS for all patients and those using CSII and injection therapy. Repeated measures of ANOVA showed significance in HbA_{1c} at these intervals ($P = 0.04$). Post hoc analysis showed a significant change between time of sensor placement and 3 months post-CGMS as in table 2 ($P = 0.03$, paired Student's *t* test). Comparing HbA_{1c} levels at the time of sensor placement and at 3 months, 27 patients (25 with HbA_{1c} >8.0% and 2 with HbA_{1c} ≤8.0% at baseline) had a reduction in HbA_{1c} by a mean of 0.66%. These subjects had a mean baseline HbA_{1c} of $9.08 \pm 1.1\%$. Sixteen subjects (seven with HbA_{1c} >8.0% and nine with HbA_{1c} ≤8.0% at baseline) had an increase in HbA_{1c} by a mean of 0.43%. Their mean baseline HbA_{1c} was $7.88 \pm 0.9\%$. In four children (three with HbA_{1c} >8.0% and one with ≤8.0% at baseline), there was no change in HbA_{1c} between 3 months before and 3 months after continuous glucose monitoring.

CONCLUSIONS—This study showed that the CGMS was well tolerated and beneficial in pediatric type 1 diabetic patients. Patients, some of whom were very young, were able to wear the sensor without problems, and events such as meals, exercise, and symptoms of hypoglycemia were coded in the sensor during daily activities as advised. The glucose tracings derived from the CGMS enabled diabetes care providers as well as patients and their families to discern distinct patterns of abnormal glycemia regardless of whether they were using CSII or insulin injection therapy. The information obtained led to recommendations for adjustment of the diabetes regimen. Follow-up studies determined that these alterations led to im-

proved glycemic control as assessed by mean HbA_{1c} levels. Although HbA_{1c} levels were statistically unchanged when retrospectively compared 3 months before and at the time of CGMS placement, these values were improved at 3 months post-CGMS and sustained at 6 months. Because HbA_{1c} levels had been previously correlated with the number of finger-stick glucose levels obtained in a French study that evaluated 2,579 children with type 1 diabetes (12), it was anticipated that the larger number of glucose measurements done with the CGMS would improve the glycemic outcome of pediatric subjects.

The CGMS revealed that one or more basal, bolus, and correction insulin dosage was not optimal in a large number of patients. At least one-quarter to one-third of subjects were found to have a high premeal pattern (at one or more premeal time periods), and 17–23% were found to have a high postmeal pattern (at one or more postmeal time periods). These findings necessitated increasing one or more basal and bolus insulin dosage in 87 and 70% of subjects, respectively, as well as increasing the dose of insulin used to correct a high glucose level outside of the target range in 32% of patients. It is likely that these recommendations on how to decrease the large number of high pre- and postmeal patterns positively impacted on the follow-up HbA_{1c}. At the present time, it is controversial whether fasting or postprandial glycemia has more impact on diabetes control (13). With follow-up sensor-wear, it might be possible to determine the relative importance of pre- versus postmeal glucose levels on diabetes outcome. Therefore, the CGMS might prove to have a role in clinical diabetes research that is aimed at addressing areas of controversy in diabetes management.

As recently described by Bode et al. (14), during sensor-wear, nocturnal hy-

poglycemia and the dawn phenomenon are frequently found but are not apparent with finger-stick monitoring alone because finger-sticks are rarely done at those times. In our patients, the CGMS confirmed what has been described in previous research studies, which showed a high occurrence of asymptomatic nocturnal hypoglycemia in pediatric subjects who measured nighttime blood glucose levels as part of a research protocol (15,16). In our subjects, the finding of nighttime hypoglycemia led to the recommendation to decrease basal insulin rates during the night for pump patients and evening intermediate-acting insulin for patients on injection therapy. Reducing insulin dosages might have helped decrease further episodes of hypoglycemia by ameliorating hypoglycemia unawareness, which results in part from recurrent low blood glucose (17).

We were surprised by the number of recommendations that were made to alter the diabetes regimen in addition to changing insulin dosages. Over one-half of our subjects did not appropriately manage hypoglycemia. This could be discerned when hypoglycemia was detected by a finger-stick glucose measurement and then subsequent glucose levels were evaluated by the CGMS. Approximately 30% of subjects did not recheck to insure that hypoglycemia had been resolved. In addition to this pattern of persistent hypoglycemia, at least one-quarter of the time, a recurrent episode of hypoglycemia occurred after treatment.

The CGMS data also revealed the frequent occurrence of hypoglycemia associated with exercise in many of our subjects. Some subjects experienced hyperglycemia after the completion of exercise as a result of excess carbohydrate ingestion at the time of hypoglycemia or as a result of disconnecting the insulin pump during exercise. The CGMS data indicated that if glycemic control is to be optimized in the future, patients/families must consider whether the food that is being ingested is high in fat or carbohydrates in order to appropriately alter insulin doses and insulin delivery to account for meal composition. Finally, it should be noted that fewer abnormal patterns were detected in subjects using insulin pumps compared with those taking insulin injections. This suggests that better glycemic control might be achieved

with CSII compared with multiple-injection therapy.

Although there was a significant change in HbA_{1c} over the time intervals, the mean decrease for our study population was modest (0.2 and 0.3% at 3 and 6 months, respectively). These findings were similar to those of Chase et al. (10). This can be explained by the fact that one-quarter of the subjects entered the study with HbA_{1c} values ≤8.0%. Many subjects in this group had either a small rise ($n = 9$) or no change in HbA_{1c} ($n = 1$) after 3 months, presumably due to a decrease in hypoglycemia. On the other hand, 25 patients with elevated baseline HbA_{1c} levels >8.0% (mean 9.08%) had a decrease in HbA_{1c} after the diabetes regimen was altered (mean decrease 0.66%). It is difficult to be sure that the overall improvement in HbA_{1c} and diabetes management in our subjects that was apparent at 3 months post-CGMS and still evident at 6 months post-CGMS was due to instituting the recommendations that came from sensor-wear itself. Our subjects showed no change in HbA_{1c} over the 3-month time period before sensor use despite undergoing a multidisciplinary clinic visit that was focused on altering the diabetes regimen to improve glycemic control. However, they did experience improvement in HbA_{1c} after a self-management counseling session in which the CGMS was used. This suggests that using the sensor and altering each subject's diabetes regimen as a result of the information obtained from the sensor tracing was an effective method for decreasing HbA_{1c}.

The data provided by the CGMS for 3 days should be used to help optimize glycemia in pediatric patients with type 1 diabetes. The wealth of information obtained showed pre- and postprandial glucose levels, incidence and timing of hypo- and hyperglycemia, and the effect of exercise and food composition. These data were used to make specific recom-

mendations that improved HbA_{1c} values in subjects for a 3- to 6-month time period. Whether a more prolonged benefit will be appreciated or repeat continuous glucose monitoring will be required needs to be investigated.

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