Improved Glucose Excursions Using an Implantable Real-Time Continuous Glucose Sensor in Adults With Type 1 Diabetes

SATISH K. GARG, MD[1]
SHERWYN SCHWARTZ, MD[2]
STEVEN V. EDELMAN, MD[3]

OBJECTIVE — The capability of emerging glucose sensor technology to continuously monitor glucose levels may provide ways to achieve glycemic targets while reducing hypoglycemia.

RESEARCH DESIGN AND METHODS — A first-generation, long-term continuous glucose sensor (DexCom, San Diego, CA) was implanted subcutaneously in 15 patients with type 1 diabetes. Safety, efficacy, and potential benefits were evaluated during a blinded control period and in a study period during which patients had real-time access to the glucose data.

RESULTS — The bias differences between self-monitored blood glucose (SMBG) and sensor data were <15% at 2.8, 4.4, 5.6, 8.3, and 11.1 mmol/l. No procedure or device-related adverse events were observed. Of 15 patients, 13 (87%) had functional sensors during the 12-h simulated home use study with 96% of points in the A and B regions of the Clarke error grid, an *R* value of 0.88, and a mean absolute relative difference of 16% when retrospectively compared with SMBG. In actual home use, during the blinded control period (50 ± 16 days) data were not displayed to the patient, whereas during the unblinded study period (44 ± 17 days) the data were presented to the patient, and alerts were set at 3.1, 5.6, and 11.1 mmol/l. Patients spent a median of 47% less time below 3.1 mmol/l ($P < 0.05$) and 25% less time above 13.3 mmol/l ($P < 0.05$) during the nonblinded study period compared with the blinded control period.

CONCLUSIONS — The availability of real-time continuous glucose values may help patients reduce their hyperglycemic excursions and lower the risk of hypoglycemia.

Diabetes Care 27:734–738, 2004

Currently, single-point testing with a self-monitored blood glucose (SMBG) device is all that is available for at-home use by most patients. Due to the pain and inconvenience associated with fingersticks, patients usually perform SMBG tests infrequently even though a recent report (1) suggested that the number of blood glucose tests done per day was the most important factor relating to a lower A1c level. Even patients who test four to six times per day have a poor understanding of their glucose profiles over any 24-h period.

The Diabetes Control and Complications Trial (DCCT) demonstrated that intensive diabetes management in people with type 1 diabetes delays the onset and reduces the progression of microvascular complications associated with the disease (2). The intensive insulin treatment group monitored glucose at home at least four times a day.

Although the DCCT study showed improvements in outcomes when considering secondary consequences of diabetes, intensive insulin therapy was associated with an increase in the number of severe hypoglycemic episodes. Subsequent research demonstrated significant improvements in A1c levels when high glucose excursions were reduced through intensive diabetes management. However, these improvements were also complicated by a significant increase in "below the target range (<3.9 mmol/l) glucose" (3). More frequent glucose data, along with recent glucose trend information, is needed so that patients are able to reduce elevated glucose values while avoiding hypoglycemia. Hypoglycemia is the limiting factor in safely achieving euglycemia.

A long-term implantable glucose sensor providing continuous real-time data has been developed by DexCom (San Diego, CA). This study describes for the first time the impact of presenting continuous real-time glucose data at home to 15 adult patients with type 1 diabetes.

RESEARCH DESIGN AND METHODS

— The subjects included 15 adults with type 1 diabetes (9 women and 6 men) with a mean ± SD age and duration of diabetes of 37 ± 11 years and 21 ± 11 years, respectively. Additional demographic descriptions are given in Table 1.

The sensor

The sensor is a small, cylindrical device about the size and shape of an AA battery (Fig. 1*A*). The sensor contains a battery, circuit board, microprocessor, radio-

From the [1]Department of Medicine and Pediatrics, Barbara Davis Center for Childhood Diabetes, University of Colorado Health Sciences Center, Denver, Colorado; the [2]Diabetes & Glandular Disease Research Associates, San Antonio, Texas; and the [3]Department of Medicine, University of California, San Diego, California.

Address correspondence and reprint requests to Satish K. Garg, MD, Barbara Davis Center for Childhood Diabetes, University of Colorado Health Sciences Center, 4200 East 9th Ave., Campus Box B-140, Denver, CO 80262. E-mail: satish.garg@uchsc.edu.

Received for publication 20 August 2003 and accepted in revised form 16 December 2003.

S.K.G. and S.E. have received consulting fees from DexCom for serving on the advisory board and grant research funds for conducting the study. S.S. has received grant research funds from DexCom for conducting the study.

Abbreviations: DCCT, Diabetes Control and Complications Trial; MARD, mean absolute relative difference; SHU, simulated home use; SMBG, self-monitored blood glucose; YSI, Yellow Springs Instrument.

Table 1—*Demographics*

Sex	
Female	9 (60%)
Male	6 (40%)
Age (years) (n = 15)	37 ± 11*
Race	
Caucasian	12 (80%)
Hispanic	2 (13%)
African American	1 (7%)
BMI (kg/m^2)	24.3 ± 3.8*
Duration of diabetes (years)	21 ± 11*
Baseline A1c (%) (n = 15)	7.41 ± 0.004†
End of the study A1c (%) (n = 14)	7.33 ± 0.003†
Insulin prescription	
Pumps	8 (53%)
Multiple daily injections	7 (47%)

Data are means ± *SD or †SE or *n* (%).

transmitter, and biosensor covered with a multilayered membrane. An analog-to-digital converter translates the data to digital form, and a radio transmitter sends the glucose signal data to the receiver. The sensor determines glucose levels every 30 s in subcutaneous tissue and radio transmits glucose data to the receiver every 5 min.

The sensor was implanted in the subcutaneous tissue of the abdomen by a surgeon in an outpatient procedure under local anesthesia. The surgical technique was designed to assure sensor immobilization after implantation. Patients were instructed to restrict their activities for 72 h and to avoid vigorous physical activity for 2 weeks following implantation.

The receiver

The receiver is an externally worn pager-sized device (Fig. 1*B*). Sensor glucose data are transmitted wirelessly from the sensor to the receiver. After sensor implantation, patients were asked to take a minimum of two SMBG values per day using a One Touch Ultra meter (Lifescan; Johnson & Johnson, Milpitas, CA). The Lifescan blood glucose data are electronically uploaded to the receiver and used to calibrate the transmitted sensor glucose signal.

After the sensor start-up period and calibration, the receiver calculates glucose measurements in mg/dl or mmol/l every 5 min. The data can be displayed to the patient in real time on the receiver as a number (in mg/dl or mmol/l) and as 1-, 3-, and 9-h glucose trend graphs. The receiver also provides vibratory and auditory alerts/alarms when the glucose levels are high or low. For this study, the high and low glucose alerts were set at 11.1 and 5.6 mmol/l, respectively. An additional alarm is triggered when the glucose levels fall below 3.1 mmol/l; this alarm is not changeable.

The sensor-specific receiver is programmed with software that enables the data from the sensor and the SMBG meter to be stored and uploaded to a personal computer at the clinical site equipped with custom software to capture the glucose data stored in the receiver. The data uploaded into the computer application are displayed as trend graphs of the sensor and SMBG glucose values over time and can be viewed by both the health care providers and patients.

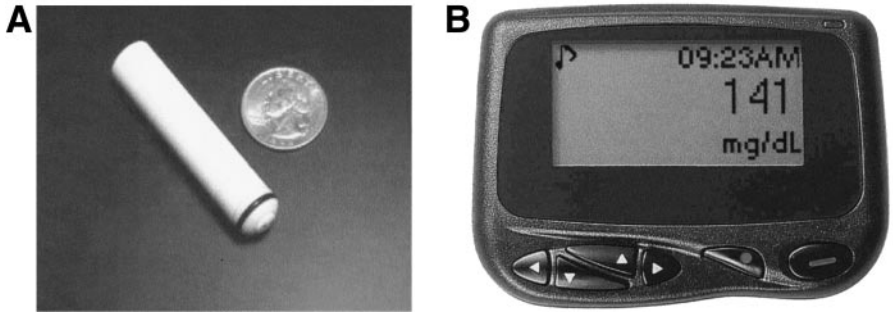

Figure 1—A*: Implantable glucose sensor the size of a AA battery.* B*: The receiver—a pager-like device.*

Study design

The study was conducted at three clinical research sites in the U.S. in three study periods, A, B, and C. Throughout the duration of the study, patients were asked to take a minimum of two SMBG measurements per day and to upload the SMBG meter readings to the receiver by connecting a cable between the two devices.

Period A, the start-up period, consisted of the time from sensor implantation to sensor initiation (calibration). During this time, the biointerface vascularizes and stabilizes. A proprietary algorithm calculates a sensor-based glucose value using the SMBG values that are uploaded into the receiver. A stable interface in conjunction with the minimum algorithm requirements is required for the continuous sensor to be in calibration and provide continuous glucose measurements (in mmol/l or mg/dl).

Period B, after sensor initiation, was the blinded control period of the study. During period B (50 ± 16 days), the calibrated sensor calculated sensor glucose measurements, and the values were stored in the receiver memory. However, during this phase of the study, the readings were not made available at any time to the physician or patient. Patients continued to obtain SMBG values (a minimum of two times per day) and to treat with insulin as advised by their health care providers.

Accuracy of the sensor data were evaluated near the end of period B. A 12-h in-clinic simulated home use (SHU) study was performed at the three research sites between days 51 and 58 after implant. During these in-clinic study days, patients spent 12 h eating normal meals and had a blood glucose sample drawn through a peripheral venous line every 20 min for Yellow Springs Instrument (YSI) glucose determinations. During the SHU study, the patient monitored his or her blood glucose, treated his or her diabetes as usual, and ate as he or she would during a typical day. Both patients and health care

Table 2—*Bias

Glucose value (SMBG) (mmol/l)	2.8	4.4	5.6	8.3	11.1
Bias end point requirement (mmol/l)	<0.80	<0.80	<0.84	<1.24	<1.66
Sensor results (mmol/l)	0.32	0.14	0.23	0.27	0.58

*Null hypothesis was rejected using Deming linear regression.

providers were blinded to sensor data during the 12-h study day. Upon completion of the SHU study, the venous blood samples for each patient were sent to a core lab for analysis.

Period C (study period lasting on average 44 ± 17 days) followed period B and lasted until explantation of the sensor. In period C, the receiver display was activated so that patients and their health care providers could see real-time glucose values and glucose trend graphs for the previous 1, 3, or 9 h. Alerts that produced vibratory and auditory signals were also activated at 3.1, 5.6, and 11.1 mmol/l. Patients were asked to confirm all alerts and alarms with an SMBG test and were instructed not to make any therapeutic adjustments solely on sensor data during the unblinded study period.

Primary safety and efficacy end points were procedure- and device-related adverse events and bias, respectively. The bias end point between SMBG and sensor data had to be <0.8 mmol/l at 2.8 and 4.4 mmol/l and <15% at 5.6, 8.3, and 11.1 mmol/l (Table 2). The bias end point was calculated from the Deming linear regression as described in statistical analysis.

Statistical analysis

Paired values (n = 3,097) from the sensor and the SMBG meter in the home setting were compared using Deming regression. The Deming method takes into account the error in the comparative meter measurement by using a variance ratio between the sensor and SMBG meter (4). The variance ratio was determined by estimating the variance between blood glucose measurements, the YSI and clinical fingerstick (One Touch Ultra meter) measurements, and the variance between the YSI and continuous sensor measurements at the same time points. From these estimations, the variance ratio of sensor to SMBG meter was calculated to be 3. This variance ratio was then applied to calculate the Deming regression of the home use data. The R value results reported for the SHU study were calculated from a least squared regression correlation coefficient.

The SHU study was performed to determine the relative accuracy of the sensor compared with a laboratory standard (YSI analyzer). The 12-h sensor and YSI measurements were retrospectively calibrated per patient, least squares regression correlation coefficient, mean absolute relative difference (MARD), and the percentage of points in the A, B, C, D, and E regions of the Clarke error grid were then calculated on the matched sensor glucose and YSI measurements across all patients (5). The same analyses were performed comparing the in-clinic One Touch Ultra values with the sensor values obtained on the in-clinic day.

To assess the effect of providing real-time glucose information to the patients, the time spent per day for each patient in different glucose ranges was compared between the blinded and unblinded study periods. The glucose ranges analyzed were 2.2–3.1 mmol/l, 3.1–4.4 mmol/l, 4.4–7.8 mmol/l, 7.8–13.3 mmol/l, and 13.3–22.2 mmol/l. For each glucose range, the median glucose value and interquartile range were calculated across all patients. A one-sided Wilcoxon's signed-rank test was performed on the median difference of time spent in a given glucose range to test for differences between the unblinded and blinded phases.

RESULTS — No serious or unanticipated device-related or procedure-related adverse events occurred even though patients were unblinded to their real-time glucose values.

The bias was calculated using the Deming linear regression. As seen in Table 2, the bias was less than the predefined cutoff for all five clinically relevant glucose levels.

SHU study results (period B)

Fifteen patients participated in the SHU study. Accuracy data are shown in Table 3. The sensor data were retrospectively calibrated using both SMBG and the YSI. For the YSI analysis, 3 of the 15 patients were removed from the analysis, two sensors were not functioning appropriately, and the third patient's YSI blood glucose values were lost. For the SMBG analysis, two patients' data were removed from the analysis due to the same sensor issues as the YSI analysis. The percentages of data points in the A and B regions of the Clarke error grid were 96 and 97%, respectively, for the sensor compared with SMBG and the YSI. When SMBG was used for calibration, the R value was higher and MARD was lower compared with a retrospective calibration with YSI (R = 0.88 vs. 0.82 and MARD = 16 and 25%, respectively, for SMBG and the YSI).

Additional glucose values

The median (interquartile range) glucose values (in mg/dl) recorded by the sensor and SMBG were 8.8 mmol/l (5.8–13.6) and 8.3 mmol/l (5.5–12.5), respectively, in the blinded period and 8.8 mmol/l (5.8–13.6) and 7.9 mmol/l (5.3–11.1), respectively, in the unblinded period. Patients took an average of 4.1 ± 2.4 SMBG values per day in period B and 4.2 ± 2.5 SMBG values per day in period C.

Glucose data from period B (blinded) were compared with those from period C (unblinded) to see if glucose patterns were changed. The glucose ranges were defined as the hypoglycemic zone (blood glucose values <3.1 mmol/l), the euglycemic zone (glucose values between 4.4 and 7.8 mmol/l), and the hyperglycemic zone (glucose values >13.3 mmol/l).

The amount of time per day patients spent in the hyperglycemic range, in the hypoglycemic range, and in the euglycemic range was analyzed (Fig. 2). Patients spent 47% less time per day in the hypoglycemic range ($P < 0.05$) and 25% less time per day in the hyperglycemic range

Table 3—*Accuracy of sensor when calibrated and compared using SMBG and YSI*

Calibration and comparison	Clarke A & B	Clarke C	Clarke D & E	R	MARD
SMBG* (n = 13)	96%	0%	4%	0.88	16%
YSI† (n = 12)	97%	0%	3%	0.82	25%

*Two devices did not function appropriately during the 12-h SHU study. †In addition, laboratory YSI glucose measurements from one patient during the SHU study were not available because the blood samples were lost.

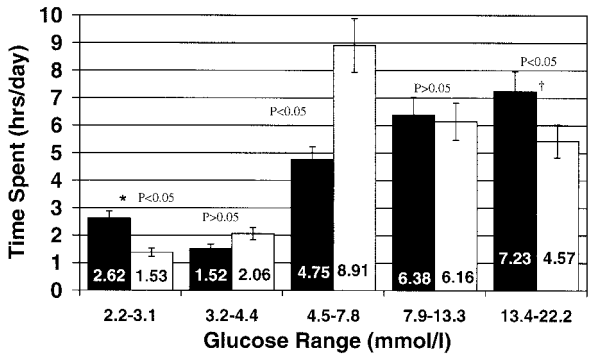

Figure 2— *Comparison of time spent (per day) in various glucose ranges during period B (■) vs. period C (□). *47% decrease in time spent below 3.1 mmol/l. †25% less time spent per day in the hyperglycemic zone (>13.4 mmol/l).*

($P < 0.05$) during period C compared with period B. This was accompanied by substantially more time per day (88%) spent in the euglycemic zone of 4.4–7.8 mmol/l ($P < 0.05$).

CONCLUSIONS — The availability of an accurate real-time continuous glucose monitor led to the question can real-time, prospective, long-term continuous monitoring decrease time spent in the hyperglycemic range and increase time spent in the desired range without increasing the time spent in the hypoglycemic range? Previous data obtained in an intensive therapy study using SMBG for glucose monitoring (3) demonstrated that there is a strong correlation between A1c levels and a reduction of "above the target region" glucose values. The reference study demonstrated a reduction of 28% of the glucose values in the high region and a 1.5% improvement in A1c values (from 8.5 to 7.0%). However, this change also resulted in a 50% increase in hypoglycemia (<70 mg/dl and <3.89 mmol/l). One explanation was that the relatively infrequent SMBG measurements in the reference study provided insufficient information to the patient to warn of impending hypoglycemia. The present study allowed patients to observe glucose values and trends in real-time over long periods for the first time.

Study results showed that presenting real-time glucose values to patients was associated with a decrease in the time spent in the hyper- and hypoglycemic ranges while increasing the time spent in the euglycemic range. There were concerns about allowing continuous data to be viewed by the patient because they might be confused by the data or might rely on the data for therapeutic decisions, leading to misdosing with insulin. No special training was given to the patients, but their progress was tracked closely with biweekly visits to the clinic. No device- or procedure-related adverse events were reported during any part of the study, including the unblinded period.

Approximately 50 days after implantation, the continuous glucose sensor measurements were comparable to the SMBG and the YSI measurements.

The results clearly document an improvement in glucose profiles when the patients were able to see the data compared with the blinded period. During the unblinded period, patients reduced the time spent in hyperglycemia by 25%. This decrease in hyperglycemia was not offset by an increase in hypoglycemia, as seen in previous studies using SMBG (1). In contrast, the patients in the present study spent 47% less time in the hypoglycemic region, i.e., below 3.1 mmol/l. The decrease in hypo- and hyperglycemia led to a significant increase of 88% more time spent in the euglycemic region.

Potentially, the changes in glycemic levels observed could be attributed to a study effect due to the high frequency of visits (weekly) required for the study compared with routine patient care. However, during the study, patients visited the clinic with the same frequency during both the blinded and unblinded phases, which suggests that the patients' improvements in glycemic control were more likely due to the real-time viewing of continuous glucose data and trends in the unblinded phase compared with the blinded phase. Furthermore, no additional special instructions were provided to the patient on how to utilize the continuous glucose information during the unblinded phase, and investigators did not make major therapeutic changes based on the data due to the investigational nature of the device.

Decreasing glucose excursions may be beneficial to the quality of life and complications of diabetes, as previously described from DCCT subanalysis (6). Even in the intensively treated group in the DCCT, over the study period there was a group of patients with higher A1c values with lower risk of diabetic retinopathy onset and/or progression compared with conventionally treated groups (6), thus concluding that "A1c values may not be the complete picture and glucose excursions may be responsible for diabetes complications."

To the best of our knowledge, these were the first patients to use data from a long-term, implanted, real-time continuous glucose sensor in home use. Patients improved their glycemic profiles while reducing the risk of hypoglycemia, suggesting that more information about glucose data may improve patient outcomes. To confirm these findings and to potentially obtain additional significant clinical outcomes, such as reductions in A1c levels, larger studies over longer times are needed.

Acknowledgments— This study was sponsored primarily by DexCom, San Diego, California, in part by The Children's Diabetes Foundation in Denver, Colorado, and by grants M01 RR000069 from the General Clinical Research Centers Program and P30DK57516 (DERC Grant) from the National Centers for Research Resources, National Institutes of Health, Bethesda, Maryland.

Presented in part at the 63rd American Diabetes Association meeting in New Orleans, June 2003.

The authors would like to thank the DexCom Team (Andy Balo, Jim Brauker, Eric Koehler, Apurv Kamath, and Amy Leptien) for designing the protocol and helping in the data analysis and preparation of the manuscript. We would also like to thank Kelly Peters, Dawn White, Mary Voelmle, Halsley Hoff, Peter Chase, and George Eisenbarth for their help in the preparation of this manuscript.

References

1. Levin BS, Anderson BJ, Butler DA, Antisdel JE, Brackett J, Laffel LMB: Predictors of glycemic control and short-term adverse outcomes in youth and with type

1 diabetes. *J Pediatr* 139:197–203, 2001
2. The 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-dependant diabetes mellitus. *N Engl J Med* 329:977–986, 1993
3. Brewer KW, Chase PH, Owen S, Garg SK: Slicing the pie: correlating HbA_{1c} values with average blood glucose values in a pie chart form. *Diabetes Care* 21:209–212, 1998
4. Deming WE: *Statistical Adjustment of Data* (reprint). New York, Dover, 1964
5. Clarke WL, Cox DC, Conder-Frederick LA, Carter W, Pohl SL: Evaluating the clinical accuracy of systems for self-monitoring of blood glucose. *Diabetes Care* 10: 622–628, 1987
6. The Diabetes Control and Complications Trial Research Group: The relationship of glycemic exposure (HbA_{1c}) to the risk of development and progression of retinopathy in the Diabetes Control and Complications Trial. *Diabetes* 44:968–983, 1995