Relationship of Fasting and Hourly Blood Glucose Levels to HbA_{1c} Values

Safety, accuracy, and improvements in glucose profiles obtained using a 7-day continuous glucose sensor

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OBJECTIVE — In this study, we evaluated the safety and efficacy of 7-day transcutaneous, real-time, continuous glucose monitoring (CGM) in subjects with insulin-requiring diabetes.

RESEARCH DESIGN AND METHODS — Eighty-six subjects were enrolled at five U.S. centers. Subjects wore a sensor inserted under the skin of the abdomen for 7 days during each of three consecutive periods. Data were blinded during period 1 and unblinded during periods 2 and 3.

RESULTS — Of the 6,811 matched self-monitoring of blood glucose to sensor values prospectively analyzed, 97.2% fell in the Clarke error grid zones A and B, and median absolute relative difference was 11.4%. After unblinding, subjects reduced time spent at <55 mg/dl by 0.3 h/day, reduced time spent at >240 mg/dl by 1.5 h/day, and increased time in the target zone (81–140 mg/dl) by 1.4 h/day ($P < 0.05$ for all three comparisons). Improvements were seen in both types 1 and 2 diabetes and with use of both multiple daily injections and continuous subcutaneous insulin infusion. Modal day graphs were generated in six groups of subjects based on HbA_{1c} (A1C) (≤6, 6–7, 7–8, 8–9, 9–10, and >10%). Mean glucose levels from midnight to 7:00 A.M. (fasting and dawn phenomenon periods) were only normal for subjects with A1C ≤6%. All other groups were hyperglycemic during this and all periods. Reductions in overall mean glucose were achieved for the four highest A1C groupings with unblinded device use.

CONCLUSIONS — This is the first report of a real-time, transcutaneous glucose sensor that functioned for 7 days. The use of CGM in the unblinded phase resulted in improvements in target-range glycemia across all A1C values.

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Large-scale clinical trials have shown that intensive insulin therapy, aimed to achieve glucose control as close to the nondiabetic range as safely possible, decreases the incidence and progression of both micro- and macrovascular diabetic complications (1–4). Moreover, maintaining HbA_{1c} (A1C) at normal or near-normal levels reduces health care costs for adults with diabetes (5). Unfortunately, intensive insulin therapy is also associated with an increased risk of hypoglycemia. Subjects in the intensive insulin treatment arm of Diabetes Control and Complications Trial, for example, experienced a 3.3-fold higher incidence of severe hypoglycemia than the control group despite performing self-monitoring of blood glucose (SMBG) four or more times daily (1).

Preliminary evidence suggests that use of continuous glucose data results in reductions in A1C (6–12), and our previous studies using a 3-day, real-time continuous glucose sensor (STS System; DexCom, San Diego, CA) demonstrated improvements in glycemic excursions, entailing the reduction of time spent in hyperglycemia coupled with a decreased risk of hypoglycemia (13,14). We report, with a new 7-day transcutaneous glucose sensor that was used for three consecutive periods (21 days), that fasting periods contribute substantially to hyperglycemia and that reductions in overall hyperglycemia can be obtained with continuous sensing, especially when used by subjects with higher A1C levels.

RESEARCH DESIGN AND METHODS

— This study included a heterogeneous group of subjects. Eighty-six subjects with insulin-requiring diabetes were enrolled at five centers within the U.S.; 69 (80.2%) had type 1 diabetes and 17 (19.8%) had type 2 diabetes. Thirty-eight (44.2%) were men, and 77 (89.5%) were Caucasian. Subjects were 42.4 ± 13.39 (mean ± SD) years old, with a diagnosis of diabetes for 20.2 ± 12.32 years, and subjects with type 2 diabetes required insulin for 7.8 ± 6.11 years; 43 (50.0%) delivered insulin via continuous subcutaneous insulin infusion (CSII) pumps, and 43 (50.0%) used multiple daily injections (MDI). Height was 170.2 ± 10.50 cm, weight was 84.2 ± 27.14 kg, and BMI was 28.9 ± 8.05 kg/m^2. At baseline, subjects performed SMBG 5.3 ± 2.13 times daily and had an A1C of 7.7 ± 1.27%. Individuals <18 years old and those who were pregnant or lactating or had a contraindication to using the continuous glucose monitor (known allergy to medical adhesives or dermatological conditions that would preclude wearing sensors on unaffected skin) were excluded. The protocol was approved by the institutional review boards of all centers, and all subjects pro-

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Abbreviations: ARD, absolute relative difference; CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections; SMBG, self-monitoring of blood glucose.

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

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Table 1—*Summary of accuracy measures over sensor life: sensor vs. SMBG*

	No. of paired points	Pearson correlation coefficient	Difference (mg/dl)*	Relative difference (%)†	ARD (%)‡
Overall	6,334	0.899	2.3 ± 32.45 (2.0)	2.9 ± 21.75 (1.6)	15.7 ± 15.34 (11.4)
Day 1	1,041	0.878	5.2 ± 35.97 (3.0)	4.4 ± 24.71 (2.5)	17.9 ± 17.63 (12.9)
Day 2	1,068	0.920	8.3 ± 29.91 (7.0)	6.4 ± 20.56 (4.8)	15.6 ± 14.81 (11.4)
Day 3	994	0.933	8.2 ± 28.63 (7.0)	6.4 ± 20.39 (5.4)	14.8 ± 15.44 (10.7)
Day 4	877	0.904	2.7 ± 31.19 (2.0)	3.6 ± 21.21 (1.4)	15.3 ± 15.14 (10.9)
Day 5	789	0.888	−1.3 ± 33.22 (0.0)	0.7 ± 21.65 (0.0)	15.8 ± 14.79 (11.9)
Day 6	797	0.893	−5.5 ± 32.51 (−4.0)	−1.6 ± 19.33 (−2.6)	14.5 ± 12.84 (11.0)
Day 7	768	0.889	−6.4 ± 32.18 (−4.0)	−2.0 ± 22.10 (−2.8)	15.7 ± 15.62 (11.5)

Data are means ± SD (median).*Calculated as (sensor − SMBG), where for each paired point sensor indicates time-matched continuously measured glucose value. †Calculated as [(sensor − SMBG)/SMBG]. ‡Calculated as the absolute value of [(sensor − SMBG)/SMBG]. Day is defined from the time of sensor insertion (in 24-h increments).

vided witnessed, written informed consent before enrollment.

Subjects were enrolled in June and July of 2005. Baseline A1C was measured within 30 days of participation. Throughout this study, subjects wore a 7-day transcutaneous sensor, a transmitter, and a receiver. Subjects inserted the sensor under clinical staff supervision. The sensor was inserted into abdominal subcutaneous tissue by an introducer needle and applicator and relayed glucose values every 5 min to the receiver by radiofrequency (14). Glucose trend graphs of the preceding 1, 3, or 9 h, alerts for high glucose (>200 mg/dl) and low glucose (<80 mg/dl) levels, and alarms for hypoglycemia (<55 mg/dl) were provided.

Subjects used a calibrated OneTouch Ultra glucometer (LifeScan, Milpitas, CA). This meter was used for continuous glucose monitoring (CGM) calibration and diabetes self-management (fingersticks only; alternate-site testing was not allowed). All SMBG values were uploaded into receivers via a cable.

This study was conducted over three consecutive 7-day periods. At the beginning of the study, clinicians reviewed the principles of diabetes management, including insulin dosing, hypoglycemia treatment, and SMBG. During period 1, subjects wore the device, but receivers were blinded to serve as a control. Two hours after insertion, subjects uploaded two fingerstick values to their receiver to calibrate. Subjects were instructed to upload all subsequent SMBG values but, at minimum, to upload one fingerstick value every 12 h for calibration.

During periods 2 and 3, receivers were unblinded, and subjects were provided with CGM data in real-time. During unblinded use, subjects were instructed to use CGM data as an adjunct to and not as a replacement for SMBG fingersticks. Subjects returned to the clinic on study days 8 and 15 for sensor replacement and on study day 22 for final removal. Adverse events and insertion site assessments were performed at each visit. A telephone call was made 6–10 days after the final sensor removal to screen for late complications. Digital data from all receivers and meters were downloaded to a computer for analysis. Eighty-five of the 86 subjects completed all three periods. One subject withdrew after period 1 for non-safety–related reasons; that subject's data were excluded. Another subject's receiver remained blinded during insertion period 2 because of an oversight; this subject's glucose data from period 2 were excluded, but periods 1 and 3 were included.

Outcome measures

Accuracy measures included Clarke error grid (15) analysis, Pearson correlation coefficient, mean/median relative difference, and absolute relative difference (ARD) analyses of paired sensor-SMBG values. Clinical effectiveness was evaluated by comparing blinded and display data from all subjects and within subgroups with various levels of baseline A1C (six groups with A1C ≤6, 6–7, 7–8, 8–9, 9–10, and >10%). Modal day graphs were generated from 24 1-h blocks (midnight to midnight), with average glucose values from all sensors plotted for each time block. These graphs were generated for blinded and display data from each of the six subgroups of A1C. Clinical effectiveness was also assessed by calculating time spent per day with glucose levels <55, 55–80, 81–140, 141–240, and >240 mg/dl for blinded and unblinded data, then comparing the results obtained before and after unblinding.

Statistical analysis

Modal day hourly time point comparisons were made by repeated-measures analysis using the A1C group, hourly time interval, and the interaction between A1C group and hourly time interval as fixed effects and subject as a random effect. For statistical comparison of time spent in various glucose ranges, we used the Wilcoxon rank-sum test. All other end points were summarized using descriptive statistics. All statistical comparisons were conducted at the $\alpha = 0.05$ level of significance using two-tailed tests. Analyses were performed using SAS software (version 9.1.3; SAS Institute, Cary, NC).

RESULTS

Sensor accuracy and stability

Of the 6,811 paired points collected, 6,334 between 40 and 400 mg/dl (range of CGM used in this study) were analyzed for difference statistics. All analyses were prospective, i.e., by using sensor glucose values as displayed to (or blinded from) subjects in real time. Sensor performance was stable across all 7 days of sensor wear (Table 1). There was no appreciable difference in the overall accuracy results; i.e., correlation coefficient, difference, and relative difference were actually slightly better in the analysis including all the paired data points, with minor changes in the ARD. Mean ± SD absolute differences were 12.6 ± 10.02, 20.3 ± 21.59, and 33.1 ± 31.72 mg/dl in the hypoglycemic (<70 mg/dl), euglycemic (70–180 mg/dl), and hyperglycemic (>180 mg/dl) groups, respectively. The low alert used in this study was set at 80 mg/dl. This alert detected hypoglycemia (<70 mg/dl) with 88.0% sensitivity, 91.4% specificity, and 53.8% positive predictive value.

The Pearson correlation coefficient

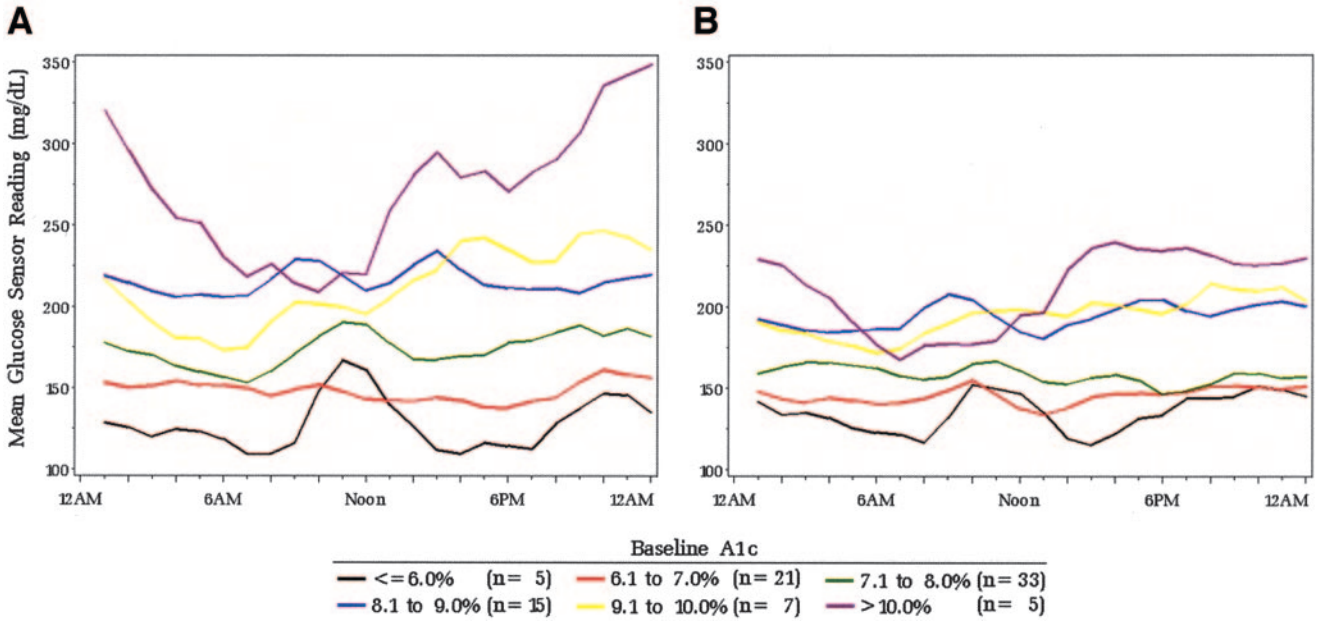

Figure 1—*Modal day by baseline A1C subgroup. Illustrates improvement in glycemic control (blinded versus display). Fasting (midnight to 7:00 A.M.) glucose levels were normal only for subjects with A1C ≤6.0%. Subjects with A1C >10.0% dramatically reduced hyperglycemic exposure. A: Data collected while subjects were blinded to continuous glucose data (insertion period 1).* B: *Data collected while subjects were given real-time access to continuous glucose values, trend graphs, and high/low alerts (insertion periods 2 and 3).*

was 0.899, mean ± SD ARD was 15.7 ± 15.34%, and median ARD was 11.4%. Of 6,811 paired points, 6,619 (97.2%) fell within the clinically acceptable regions A or B of the Clarke error grid (15), with 5,105 (75.0%) in region A and 1,514 (22.2%) in region B; 48 (0.7%) points were in region C, 144 (2.1%) were in region D, and 0 (0.0%) were in region E.

Analyses by baseline A1C

Data were separated into six sets by baseline A1C (≤6, 6–7, 7–8, 8–9, 9–10, and >10%), and modal day plots were generated (Fig. 1) for 7 days of blinded device use (Fig. 1*A*) and 14 days of display use (Fig. 1*B*). Comparison of Fig. 1*B* with Fig. 1*A* shows that all groups had improvements in glycemic profiles. Strikingly, several of the groups, including the 9–10, 7–8, and 6–7% groups, had little variation throughout the day, indicating that the averages were above normal glucose during both postprandial and fasting periods. The >10% group had substantially lower values during the middle of the day than at night and in the early morning hours. There was no preference in reduction during the postprandial period. In fact, one of the most dramatic examples of improvement occurred in the >10% group during the hours between midnight and 7:00 A.M. During the early morning period of midnight to 7:00 A.M, when patients are normally fasting (including the dawn phenomenon during the 4:00–7:00 A.M period), only one of the groups (A1C ≤6%) had average glucose levels in the normal range (Fig. 2*A*). Values for all other groups were above normal all the time, in direct relationship to A1C.

Glycemic excursions

Compared with the control period, the overall study population increased time spent within the target range of glycemia (81–141 mg/dl) by an average of 1.4 h/day (22.6%) during unblinded device use (periods 2 and 3) ($P < 0.0001$). Time spent at <55 mg/dl was reduced by an average of 0.3 h/day (33.3%) ($P = 0.0039$), and time spent at >240 mg/dl was reduced by an average of 1.5 h/day (28.3%) ($P < 0.0001$) (Table 2).

This analysis was repeated on the subgroups of diabetes type, baseline A1C (<7, 7–9, and >9%), and insulin delivery method (MDI or CSII). The pattern of increased time spent in the target range of glycemia while subjects were unblinded, with a concomitant reduction in time spent at both high and low values, was observed in each of these subgroups. There was a linear correlation between reduction in average glucose (blinded versus display) and A1C: the higher the A1C, the greater the reduction of average glucose level (Fig. 2*B*).

Safety

Over the 21-day duration of this study, the incidence of sensor insertion site effects was as follows: 32 (12.4%) mild erythema, 2 (0.8%) moderate erythema, 3 (1.2%) mild edema, 6 (2.3%) mild ecchymosis, and 2 (0.8%) moderate ecchymosis. The incidence of sensor adhesive effects was as follows: 67 (26.0%) mild erythema, 2 (0.8%) moderate erythema, 3 (1.2%) mild edema, and 3 (1.2%) mild ecchymosis. Four (4) adverse events were reported study-wide, but none were classified as serious or device related. No sensor insertion site infections or hypoglycemic events requiring assistance were reported.

CONCLUSIONS — This first report on the use of a transcutaneous continuous glucose sensor that lasts for 7 days demonstrates that subjects with an A1C >6% were, on average, hyperglycemic 24 h/day. Through the use of CGM, study subjects with higher A1C levels (e.g., the A1C >10% group) achieved improvements at all hours of the day (Fig. 1). Use of continuous data enforces the fact that patients need to modify their behavior/treatment in such a way that they reduce hyperglycemia throughout the day and night. Access to night-time glucose values and alerts/alarms give patients the opportunity to treat glycemic excursions that they may never be aware of otherwise. Be-

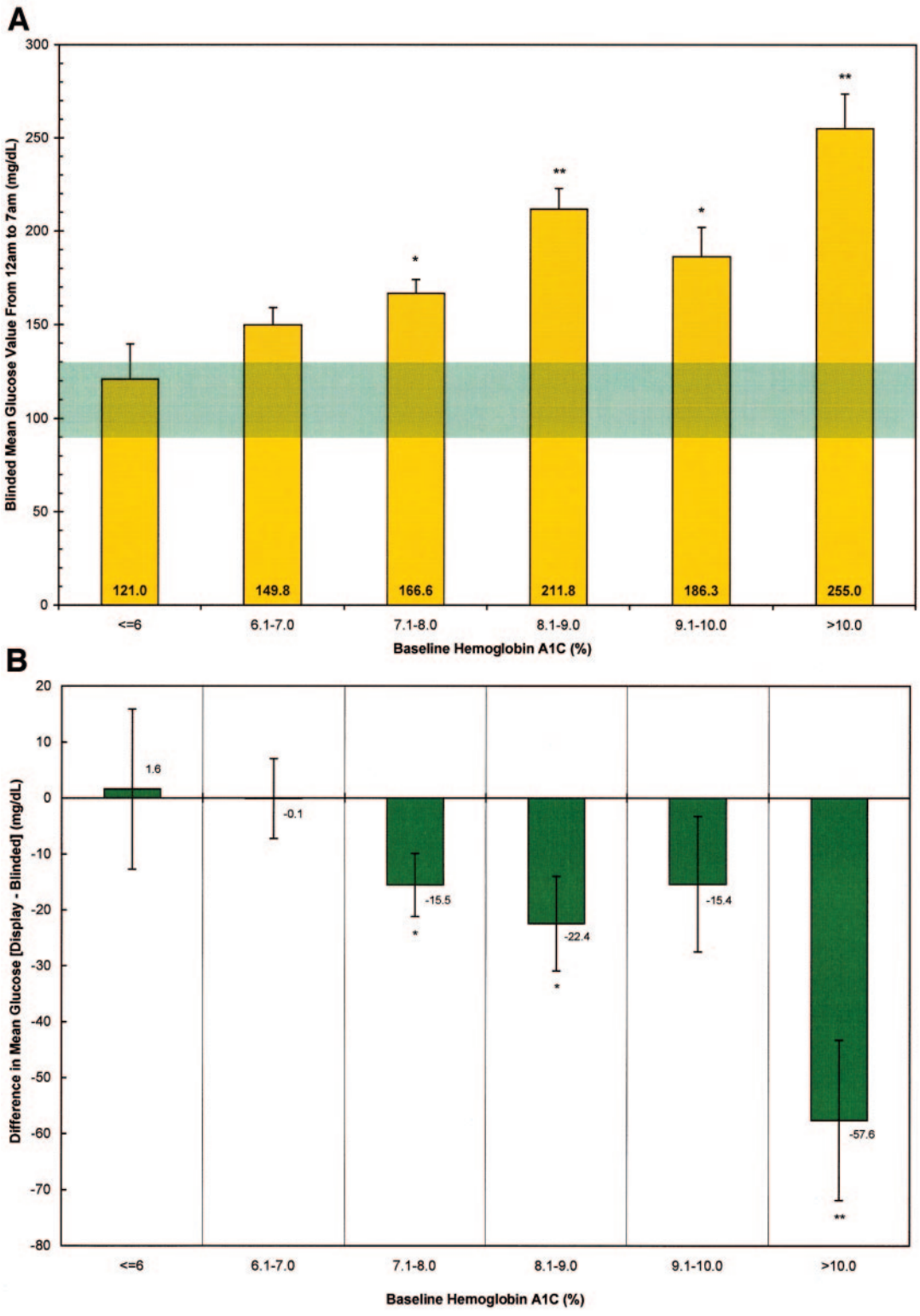

Figure 2—*A: Relationship between blinded mean glucose values (midnight to 7:00 A.M.) and baseline A1C. The green shaded area corresponds to the current American Diabetes Association recommended target range for fasting glucose (90–130 mg/dl). Groups were compared with the A1C ≤6% group: *P < 0.05; **P < 0.001. Error bars indicate SEM.* B*: Relationship between change in mean glucose value in milligrams per deciliter (display − blinded) and baseline A1C. Negative values correspond to a reduction in mean glucose during unblinded device use relative to blinded device use: *P < 0.05, **P < 0.001 for the difference between blinded and display use. Error bars indicate SEM.*

Table 2—*Comparison of time spent in various glucose ranges: blinded versus display*

Subgroup	*n*	Hours per day									
		<55 mg/dl		55–80 mg/dl		81–140 mg/dl		141–240 mg/dl		>240 mg/dl	
		Blinded	Display	Blinded	Display	Blinded	Display	Blinded	Display	Blinded	Display
Overall	85	0.9 ± 1.0	0.6 ± 0.9*	1.5 ± 1.3	1.6 ± 1.2	6.2 ± 3.4	7.6 ± 3.1†	9.9 ± 3.4	10.1 ± 2.7	5.3 ± 4.4	3.8 ± 3.3†
Diabetes type											
Type 1	68	1.0 ± 1.0	0.7 ± 1.0*	1.8 ± 1.2	1.8 ± 1.2	6.6 ± 3.1	7.9 ± 2.6‡	9.6 ± 2.9	9.9 ± 2.4	4.6 ± 3.3	3.3 ± 2.5‡
Type 2	17	0.3 ± 0.4	0.2 ± 0.3	0.7 ± 0.9	0.6 ± 0.8	4.4 ± 3.9	6.4 ± 4.6*	10.8 ± 5.0	11.0 ± 3.7	7.9 ± 6.7	5.7 ± 5.2*
Baseline A1C											
<7%	23	1.4 ± 1.3	0.9 ± 1.5*	2.5 ± 1.2	2.3 ± 1.7	8.8 ± 3.5	9.2 ± 3.6	9.5 ± 3.5	8.9 ± 3.6	1.9 ± 1.9	1.7 ± 1.6
7–9%	47	0.8 ± 0.9	0.5 ± 0.5†	1.3 ± 1.1	1.4 ± 0.9	5.5 ± 2.9	7.2 ± 2.7†	10.0 ± 3.4	10.7 ± 2.2	6.0 ± 4.2	4.1 ± 3.3†
>9%	12	0.4 ± 0.6	0.2 ± 0.2	0.5 ± 0.3	0.8 ± 0.6	3.3 ± 1.2	5.6 ± 2.9*	10.3 ± 4.1	10.3 ± 2.4	9.4 ± 4.5	7.1 ± 3.5
Insulin delivery											
MDI	43	0.7 ± 0.9	0.4 ± 0.5*	1.3 ± 1.3	1.5 ± 1.5	5.4 ± 3.5	7.2 ± 3.4†	10.1 ± 4.3	10.4 ± 3.0	6.1 ± 4.9	4.4 ± 3.9‡
CSII	42	1.1 ± 1.1	0.8 ± 1.2	1.8 ± 1.2	1.7 ± 0.9	7.0 ± 3.0	8.0 ± 2.9*	9.7 ± 2.2	9.8 ± 2.4	4.4 ± 3.5	3.2 ± 2.5*

Data are means ± SD. *P* values were calculated using the Wilcoxon rank-sum test: *$P < 0.05$, blinded vs. display; †$P < 0.0001$, blinded vs. display; ‡$P < 0.001$, blinded vs. display.

ing aware of nocturnal glucose values and seeing that nocturnal hypoglycemia was absent probably gave patients enough confidence to increase their nocturnal insulin dose.

It is widely believed that the target patient for early adoption of CGM is the patient already practicing intensive therapy, who has relatively well-controlled glycemic profiles but is at risk of hypoglycemia because of intensive insulin therapy (1). Although these subjects did show improvements in glycemic profiles with reduced risk of hypoglycemia (Table 2), the most dramatic improvements were observed for subjects who had less well-controlled diabetes with high baseline A1C levels. In fact, there was a strong correlation between A1C and glycemic improvements, and much greater improvement was seen in subjects with higher A1C (Fig. 2*B*), a trend that is consistent with the findings of Retnakaran et al. (16,17). These results indicate that patients with poor glycemic control can benefit from the use of a continuous glucose sensor.

Insight into patterns of mean glycemia over time is provided by modal day plots (Fig. 1). In blinded subjects, mean glucose values between midnight and 7:00 A.M. were normal only in subjects with A1C ≤6.0%. Even subjects in the 6–7% A1C group exhibited mean glucose values of ~150 mg/dl during these time periods. Therapies focused on these times of day, in addition to the typical postprandial treatment done throughout the day, may enable patients to achieve target A1C levels as recommended by the American Diabetes Association (18) while reducing the risk of hypoglycemia. The modal day plots also show that subjects at the low end of the A1C spectrum (A1C ≤6%) exhibited midday peaks but normal or near-normal glucose levels throughout the rest of the day. This trend was inverted for subjects with A1C >10.0%, whose mean glucose values were lowest at midday (although still very high, >200 mg/dl) with marked elevations at all other time points, especially in the afternoon and at night. These patterns are in keeping with the findings of Monnier et al. (19) from intermittent SMBG, who showed that postprandial glucose excursions predominate in subjects with low A1C levels, whereas the relative contribution of fasting hyperglycemia increases as glycemic control worsens. The modal day plot of unblinded subjects depicts a substantial reduction in mean glucose throughout the

day for those with A1C >9% and a blunting of mid-day and late-evening peaks for those with A1C ≤6.0%. These improvements in glycemic control were evident after just 14 days, whereas changes in A1C take much longer to become apparent.

Lowering of A1C is desirable if it can be accomplished without increasing the incidence of hypoglycemia (18,20). In this study, the overall subject population, when unblinded to continuous glucose information, experienced a significant increase in time spent in euglycemia and reduced the time spent at <55 and >240 mg/dl (Table 2). Subjects with A1C <7% maintained their time spent euglycemic, but spent 0.5 h/day (35.7%) less time at <55 mg/dl when provided with continuous glucose data ($P = 0.0083$). Subjects with A1C >8% had significant reductions in average glucose levels (Fig. 2*B* and Table 2), accompanied by a significant decrease in the time spent at <55 mg/dl (Table 2). These data provide evidence that individuals with poorly controlled diabetes can use the added information from a continuous sensor to significantly improve target-range glycemia without an increased risk of hypoglycemia. The patient with well-controlled diabetes can also continue to maintain glycemic control while using a continuous sensor but with a reduced risk of hypoglycemia. All subject subgroups in this study, including those with types 1 and 2 diabetes, those receiving MDI insulin therapy, and those using insulin pumps, experienced significant improvements in glycemia (Table 2).

We conclude that use of this 7-day continuous glucose monitor was safe and well tolerated. Sensor performance was stable for 7-day periods of wear without a late decline in accuracy. Data provided in the form of real-time glucose values, trend graphs, and hyperglycemia/hypoglycemia alerts, enabled users to significantly improve both high and low glucose excursions. This study also suggests that CGM, with added attention to fasting and evening hyperglycemia and the period of the dawn phenomenon, may help patients, especially those with poor glycemic control, achieve lower A1C levels.

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