

Eight-Point Glucose Testing *Versus* the Continuous Glucose Monitoring System in Evaluation of Glycemic Control in Type 1 Diabetes

The Diabetes Research in Children Network (DirecNet) Study Group*

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Context: Advantages/disadvantages of continuous *vs.* discrete glucose monitoring are not well documented.

Objective: Compare glucose profiles from home meters *vs.* continuous sensors.

Design: Randomized clinical trial conducted by the Diabetes Research in Children Network (DirecNet) to assess the utility of the GlucoWatch G2 Biographer.

Setting: Home glucose measurements.

Patients: Two hundred children (age, 7 to < 18 yr) with type 1 diabetes.

Intervention: At baseline, subjects were asked to wear the continuous glucose monitoring system (CGMS) sensor and perform meter tests at eight prespecified times of the day (eight-point testing) each for 3 d (2 d using both, 1 d eight-point testing only, 1 d CGMS only). Hemoglobin A1c was measured in a central laboratory.

Main Outcome Measure: Six-month hemoglobin A1c. This analysis looked at baseline glucose profiles/hemoglobin A1c.

Results: Only 10% of subjects completed full eight-point testing for 3 d, but median CGMS use was 70 h. Mean glucose was lower when measured by the CGMS compared with eight-point testing (183 ± 37 *vs.* 188 ± 41 mg/dl; 10.2 ± 2.1 *vs.* 10.4 ± 2.3 mmol/liter; $P = 0.009$), especially overnight (2400–0400 h; 174 *vs.* 199 mg/dl; 9.7 *vs.* 11.1 mmol/liter; $P < 0.001$). Associations of hemoglobin A1c with mean glucose were similar for eight-point testing [slope 23 mg/dl per 1% (1.3 mmol/liter); correlation 0.40; $P < 0.001$] and CGMS [slope 19 mg/dl per 1% (1.1 mmol/liter); correlation 0.39; $P < 0.001$]. Postprandial excursions were lower for eight-point testing *vs.* CGMS, especially after dinner (mean excursion -17 *vs.* 63 mg/dl; -1.0 *vs.* 3.5 mmol/liter; $P < 0.001$).

Conclusions: Both methods gave similar mean glucose profiles and associations with hemoglobin A1c. Advantages of the CGMS were higher density of data and better detection of postprandial peaks. However, the CGMS may overestimate the frequency of low glucose levels, especially overnight. (*J Clin Endocrinol Metab* 90: 3387–3391, 2005)

NO SIMPLE TEST currently exists for assessment of glycemic variability in patients with diabetes, especially with respect to the frequency and duration of hyperglycemic and hypoglycemic excursions. The introduction of glycosylated hemoglobin assays in the late 1970s provided a simple and objective means to assess average plasma glucose levels over the past 2–3 months in patients with diabetes. Without this measure, the Diabetes Control and Complications Trial (DCCT) would not have been able to establish the importance of glycemic control on the development and progression of microvascular complications of diabetes.

The use of seven-point glucose profiles with measurements of plasma glucose before and after each main meal and at bedtime to evaluate glycemic control in the home setting was included as a component of the measurement protocol in the DCCT. Such profiles may be useful in identifying patterns of high or low blood glucose levels during the day, but this approach has not been used extensively in pediatric

studies. The method is limited by the number of samples subjects can reasonably be expected to obtain in a day and the number of days that subjects will be willing to carry out such testing. More recently the continuous glucose monitoring system (CGMS, Medtronic MiniMed, Northridge, CA) has been used to evaluate glycemic control in several studies involving children with diabetes (1–3). This retrospective, Holter-style monitoring system has the advantage of measuring interstitial glucose levels every 5 min for up to 3 d, including the overnight period. It may be particularly attractive as an outcome measure for clinical trials in diabetes because the subject is masked to the results. There are limitations, however, on the frequency that subjects are willing to wear the CGMS and several groups, including our Diabetes Research in Children Network (DirecNet) Study Group (4), have described the inaccuracy of the original CGMS sensor (5), especially with respect to glucose values in the hypoglycemic range (6, 7). A modified sensor for the CGMS was introduced in November 2002, which has improved accuracy (4), but this system has not yet been used extensively in clinical trials.

The National Institutes of Health (NIH)-funded multicenter DirecNet has conducted a randomized trial to assess the merits of the GlucoWatch G2 Biographer (Cygnus Inc., Redwood City, CA) in 200 children aged 7–17 yr with type 1 diabetes. To provide baseline assessments of glycemic control and frequency of hypoglycemia, patients underwent 3 d

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* A listing of the DirecNet Study Group appears in the Appendix.

Abbreviations: A1c, Hemoglobin A1c; CGMS, Continuous Glucose Monitoring System; DCCT, Diabetes Control and Complications Trial; DirecNet, Diabetes Research in Children Network; MAGE, mean amplitude of glycemic excursions.

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of eight-point self-monitoring of blood glucose using the One Touch UltraSmart meter (LifeScan, Milpitas, CA), (before and after each main meal, bedtime, and a nighttime sample) and a 3-d CGMS profile was obtained. Subjects were instructed to overlap the two methods of glucose monitoring on at least 2 d of the 3 d. Hemoglobin A1c (A1c) level was measured in the DirecNet Central Laboratory at the University of Minnesota. The purpose of the present report was to examine and compare the effectiveness of eight-point testing with CGMS use as means of evaluating glycemic control in children with type 1 diabetes enrolled in a clinical research study.

Subjects and Methods

The DirecNet Data and Safety Monitoring Board and the institutional review boards at each of the DirecNet centers approved the study protocol, informed consent, and assent form. A parent or guardian gave written consent for each subject, and subjects gave written assent before protocol entry.

Enrollment, baseline testing, and randomization

The main eligibility criteria for the study included: 1) age between 7 and 18 yr, 2) clinical diagnosis of type 1 diabetes mellitus with use of insulin for at least 1 yr, 3) screening A1c in the range of 7.0–11.0% measured locally using the DCA2000 (Bayer Inc., Tarrytown, NY), and 4) a consistent insulin regimen (either a pump or at least 2 injections per day, and not switching from one treatment modality to another) for the past 2 months. Eligibility was assessed by medical history, physical examination, and local measurement of A1c. At the time of the local A1c measurement, a second fingerstick blood sample was obtained, refrigerated, shipped as whole blood to the DirecNet Central Laboratory at the University of Minnesota, and measured by the Tosoh A1c 2.2 Plus glycohemoglobin analyzer method using cation-exchange HPLC methodology (8). Only the central lab A1c measurements were used in the data analyses. Two hundred children and adolescents met the study eligibility criteria and were enrolled in the GlucoWatch G2 Biographer randomized clinical trial.

During the run-in period, before randomization, a CGMS sensor was inserted and the subjects were provided with a One Touch UltraSmart meter and test strips. The subjects were asked to complete three eight-point (before and 2 h after each meal, before bed, and overnight between 2400 and 0400 h) glucose profiles using the One Touch UltraSmart meter. Research from DirecNet has shown the One Touch Ultra meter to be very accurate (median relative absolute difference 6%) (9). The postmeal eight-point testing value was defined as the value obtained within 2 h after the premeal glucose value. Subjects were not asked to keep diet records. Use of the CGMS was requested for 3 d, and families were told they would need to repeat the CGMS if there were not at least 2 d of values.

To be included in the analysis as a valid eight-point testing day, at least 6 of the requested eight-point tests including the overnight measurement had to be completed. To be included in the analysis of CGMS testing, at least 40 h of use averaging three or more calibrations per 24 h was required. The 40-h cut-off was intended to capture 2 d of CGMS data, including at least one night.

Statistical methods

A mean glucose value from eight-point testing was calculated for each subject separately giving equal weight to each of the eight points (results were similar when calculating area under the curve using the trapezoid rule). A preprandial mean was calculated for each subject weighting each of the prebreakfast, prelunch, and predinner means equally. An analogous method was used to calculate the postprandial mean. The percentage of tests in the target range (61–180 mg/dl) was calculated for each subject in a similar manner. Percentages were first calculated for each of the eight points separately and then averaged weighting each point equally. A uniform target range was chosen to be consistent with how data are routinely obtained in the outpatient setting with proprietary software provided by the manufacturers of home glucose meters.

To fully characterize the utility of CGMS profiles, data from days in

which no eight-point testing was done were also included in analysis. Analysis also included CGMS data obtained beyond 72 h of use. Results were similar when analysis was restricted to the first 72 h of CGMS use (data not shown). To give uniform weight throughout the 24-h day, a separate mean was first calculated for each hour (2400–0100 h, 0100–0200 h, etc.). The overall CGMS mean then gave equal weight to each hour. Percentages of CGMS measurements in target range were calculated for each subject analogously giving equal weight to each of the 24 h of the day.

To investigate whether the sampling times of the eight-point testing were representative of the full 24-h day, we paired each eight-point test with the closest concurrent CGMS value within ± 15 min accounting for a 2.5 processing lag for the CGMS (99% were within 5 min). Mean concurrent CGMS values were compared with overall CGMS values using the paired *t* test.

The sensor glucose values provided every 5 min by the CGMS may give a more robust estimate of meal-related glycemic excursions than the single-point, postprandial value obtained during eight-point testing. To evaluate this question, meal-related glucose excursions were evaluated during days with concurrent eight-point and CGMS testing. The meal-related glycemic excursion during eight-point testing was calculated as the difference between the pre- and postmeal glucose value. The meal-related glucose excursion during CGMS monitoring was calculated as the difference between the premeal CGMS glucose value corresponding to the time of the eight-point test and the peak sensor value within the 3 h after the premeal eight-point test (or the next premeal test, whichever came first).

The 5-min sampling interval provided by the CGMS also allowed the investigators to estimate overall glycemic variability. Two methods were examined in our subjects: the standard deviation score and the mean amplitude of glycemic excursions (MAGE) (10). The SD score of CGMS values was determined by calculating the variance of the glucose values for each day. These variances were then averaged for each subject and the square-root of this average was taken to be the subject's SD score.

All mean eight-point and CGMS glucose values and percentages in target range were calculated, weighting each subject equally regardless of the number of available data points. Spearman correlations with A1c values were calculated for both eight-point and CGMS glucose means. Slopes of the eight-point and CGMS glucose means against A1c were calculated by least squares regression.

Comparisons of eight-point testing vs. CGMS values for mean glucose, percentage of values below target, and postprandial excursions were done using the paired *t* test based on the paired differences from each subject.

Results

Compliance with glucose testing

A minimum of at least 1 d with six points or more including the overnight test was completed by 165 of the 200 subjects (83%). At least seven points were completed by 19% of subjects for all 3 d, 30% for 2 d, 22% for 1 d, and 30% had no days of seven-point testing. Only 10% of the 200 subjects fully complied with 3 d of full eight-point testing. In contrast, the median (25–75th percentiles) hours of CGMS use was 70 (62, 75) among the 200 subjects, and 96% of these subjects completed 48 h or more. At least 40 h of CGMS use averaging at least three calibrations per 24 h were completed by 194 subjects (97%).

Our analysis included 161 subjects who met the minimum criteria for both eight-point testing and CGMS use (*i.e.* overlap between the $n = 165$ and $n = 194$ noted above). Demographic and clinical characteristics of these 161 subjects were similar to those of the 39 excluded subjects (data not shown). The 161 subjects had a mean age of 12.4 yr (range 7–17 yr); 86% were Caucasian and 47% female. Mean duration of diabetes was 5.5 ± 3.3 yr. About half (47%) of the subjects were using insulin pumps. The mean A1c value was 7.9% with 58 subjects (36%) having a value less than 7.5%, 61

subjects (38%) 7.5 to less than 8.5%, and 42 subjects (26%) 8.5% or more. Thirty-seven subjects (23%) were at Center A, 36 (22%) at Center B, 35 (22%) at Center C, 28 (17%) at Center D, and 25 (16%) at Center E.

Glucose profiles

In the 161 subjects, the average number of CGMS readings per subject (859) was 45 times greater than the average number of glucose readings by eight-point testing (19/subject). The overall mean (\pm SD) plasma glucose level with eight-point testing was higher than that measured by CGMS (188 ± 41 vs. 183 ± 37 mg/dl; 10.4 ± 2.3 vs. 10.2 ± 2.1 mmol/liter; $P < 0.001$; Table 1) with a larger discrepancy overnight (199 ± 69 vs. 174 ± 57 mg/dl; 11.1 ± 3.8 vs. 9.7 ± 3.2 mmol/liter). Results were similar when restricting the CGMS to times concurrent with eight-point testing [concurrent CGMS values 180 ± 40 mg/dl (10.0 ± 2.2 mmol/liter) overall and 177 ± 68 mg/dl (9.8 ± 3.8 mmol/liter) overnight vs. 188 ± 41 (10.4 ± 2.3 mmol/liter) and 199 ± 69 (11.1 ± 3.8 mmol/liter), respectively, by eight-point testing]. Glucose values did not vary meaningfully by clinical center (data not shown).

As shown in Table 1, the overall percentages of glucose values within and above the target range of 61–180 mg/dl (3.4–10.0 mmol/liter) were similar with eight-point testing and CGMS, and they varied as expected with increasing A1c values. The percentage of glucose values below the target range was similar with both methods and did not correlate significantly with A1c levels. However, during the overnight period (2400–0400 h), the CGMS found 8% of glucose values to be 60 mg/dl or less (3.3 mmol/liter), whereas only 2% of eight-point glucose values were low ($P < 0.001$).

Eight-point testing and CGMS mean glucose values had nearly identical correlations with A1c (Fig. 1). With eight-point testing, the overall mean had a stronger correlation with A1c than did any of the individual points (Spearman correlation with overall mean, 0.40; preprandial, 0.31; postprandial, 0.32; bedtime, 0.26; overnight, 0.24). Similar results were obtained with the CGMS (Spearman correlation with overall mean, 0.39; preprandial, 0.23; postprandial, 0.30; bedtime, 0.22;

overnight, 0.20). As shown in Fig. 1, each 1% change in A1c levels was associated with a 23 mg/dl (1.3 mmol/liter) change in overall mean glucose by eight-point testing and a 19 mg/dl (1.1 mmol/liter) change by CGMS testing.

Glycemic excursions (as defined in *Subjects and Methods*) after breakfast and lunch were 2- to 4-fold greater when measured by the CGMS than by eight-point testing (Fig. 2). The mean eight-point glucose testing was actually lower after dinner than it was before dinner (mean excursion, -17 mg/dl; -1.0 mmol/liter; $P = 0.06$), whereas the postdinner rise in glucose was 63 mg/dl (3.5 mmol/liter) with the CGMS. Excursions were greater after breakfast, compared with after lunch ($P = 0.07$ and < 0.001) and after dinner (both $P < 0.001$) by both eight-point testing and CGMS, respectively. The timing of postprandial CGMS peak excursions occurred more than 15 min before the Ultra peak in 75, 65, and 72% of cases for breakfast, lunch, and dinner, respectively. The CGMS peak occurred within ± 15 min of the Ultra peak in 13, 13, and 8% of cases, and more than 15 min after the Ultra peak in 13, 22, and 21% of cases for breakfast, lunch, and dinner, respectively.

The frequent sampling provided by the CGMS also allowed us to determine other indices of overall glycemic variability, including the standard deviation score and the MAGE value. As shown in Table 1, both of these indices tended to increase with increasing A1c values, but the absolute differences between A1c categories were modest.

Discussion

This is the first report to compare eight-point testing with the CGMS as a means to evaluate glycemic control. Despite the much larger number of measurements with the CGMS than with eight-point testing, the overall mean glucose levels were nearly identical. With both methods, the percentage of glucose values above the target range increased and the percentage of values within the target range decreased as A1c levels rose. Nevertheless, rising A1c levels did not protect the subjects from biochemical hypoglycemia because the frequency of low glucose values did not differ as a function of A1c with either method.

TABLE 1. Glucose profiles (mg/dl)^a by A1c

	Overall (n = 161)	Stratified by A1c (%)			Association with A1c	
		<7.5 (n = 58)	7.5 to <8.5 (n = 61)	≥ 8.5 (n = 42)	Spearman correlation	P value
Mean glucose ^b						
Eight-point testing	188 \pm 41	174 \pm 30	184 \pm 33	213 \pm 51	0.40	<0.001
CGMS	183 \pm 37	170 \pm 28	181 \pm 34	203 \pm 44	0.39	<0.001
In target range ^c						
Eight-point testing	50%	55%	51%	39%	-0.38	<0.001
CGMS	49%	54%	49%	42%	-0.33	<0.001
Above target range ^c						
Eight-point testing	47%	41%	46%	57%	0.38	<0.001
CGMS	46%	40%	46%	55%	0.36	<0.001
Below target range ^c						
Eight-point testing	3%	4%	2%	4%	-0.08	0.30
CGMS	5%	6%	5%	4%	-0.17	0.04
Glucose variability (CGMS only)						
SD score ^b	70 \pm 16	67 \pm 14	69 \pm 16	75 \pm 18	0.25	0.001
MAGE ^b	150 \pm 42	147 \pm 44	150 \pm 40	156 \pm 40	0.12	0.12

^a Divide by 18 to convert mg/dl to mmol/liter.

^b Mean \pm SD. SD based on between-subject variation.

^c Target range defined as 61–180 mg/dl.

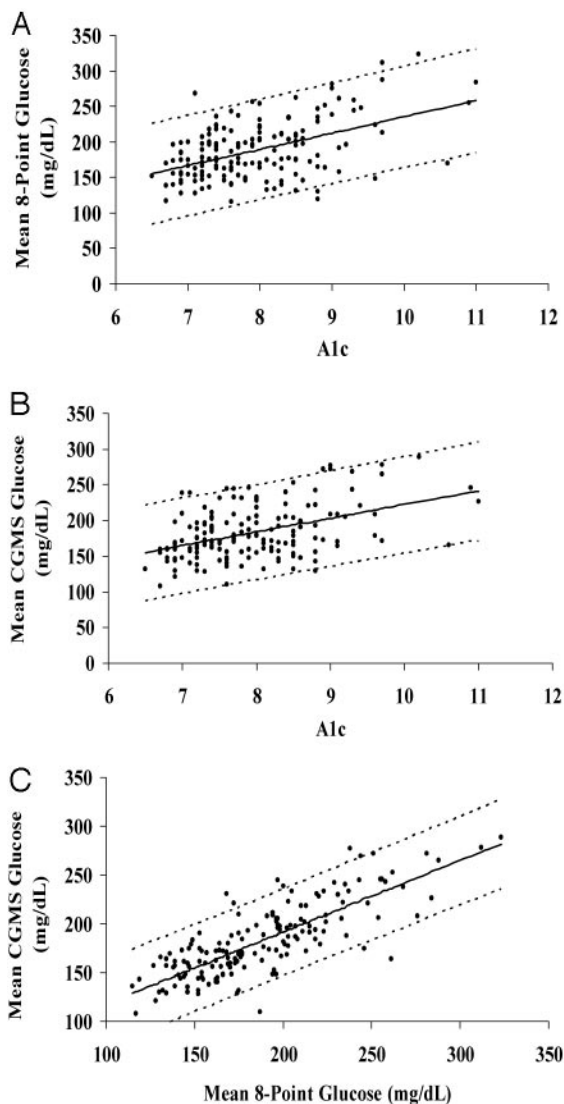


FIG. 1. Correlations of mean glucose with A1c values. Regression line and 95% confidence limits are given for eight-point testing vs. A1c (A); CGMS vs. A1c (B); and CGMS vs. eight-point testing (C). Measures included: slope = 23 mg/dl (1.3 mmol/liter) per 1.0% change in A1c, Spearman correlation = 0.40, $P < 0.001$ (A); slope = 19 mg/dl (1.1 mmol/liter) per 1.0% change in A1c, Spearman correlation = 0.39, $P < 0.001$ (B); Spearman correlation = 0.79, $P < 0.001$ (C).

An important difference between the CGMS and eight-point testing was that mean glucose levels during the night were lower and the percentage of nighttime values in the hypoglycemic range was greater with the CGMS. It is likely that these differences are related to a tendency of the CGMS to overreport hypoglycemia during the night. Indeed, in designing this study, an overnight sample was added to the DCCT seven-point profile because previous studies from our group indicated that many of the episodes of nighttime hypoglycemia reported by the CGMS were not confirmed by simultaneous laboratory glucose levels (6). In contrast, performance of the Ultra meter in measuring low glucose levels compared favorably with laboratory methods, even during acute insulin-induced hypoglycemia (9). Moreover, the discrepancies between nighttime CGMS and Ultra meter values

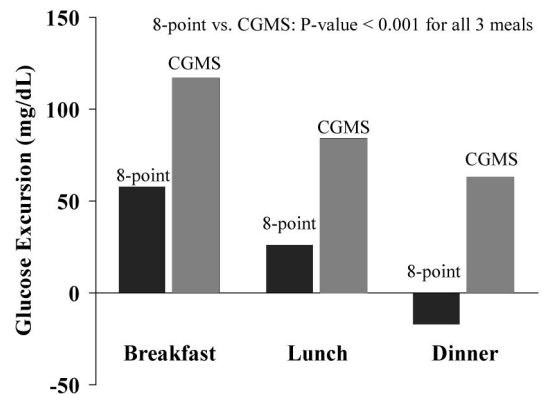


FIG. 2. Mean postprandial glycemic excursions measured by eight-point testing vs. maximum postprandial CGMS glucose values.

cannot be explained by differences in sampling frequency, because the same differences were observed between concurrent CGMS and nighttime Ultra readings.

The DCCT established that overall glycemic control of diabetes, as reflected by A1c levels, is a surrogate biomarker for the risk of microvascular complications of diabetes. It has been suggested but not proven that variations in plasma glucose, especially postprandial hyperglycemic excursions, are an independent risk factor for vascular complications even in the face of similar A1c levels (11). A major obstacle to answering this question has been the lack of a practical way to measure such hyperglycemic excursions. Thus, it is particularly noteworthy that the 5-min sampling provided by the CGMS showed a more marked rise in glucose after each meal than the single postmeal glucose sample during eight-point testing, with the most dramatic differences being in the postdinner period (Fig. 2). Whereas differences in glucose excursions could be related to technical differences between the methods, we speculate that our findings are most likely related to more frequent sampling with CGMS. Boyne *et al.* (12) previously demonstrated similar peak postprandial excursions by CGMS and YSI (Yellow Springs Instruments, Yellow Springs, OH) glucose measurements obtained every 5 min for 3.5 h after a liquid meal.

CGMS profiles also demonstrated that there was very little difference in overall glycemic lability, as assessed by SD scores and MAGE values, across the range of A1c values. Lowering A1c levels without reducing the magnitude of glycemic excursions may be one of the reasons that strict metabolic control of type 1 diabetes in youth has been associated with an increased risk of hypoglycemia (13).

We anticipated that eight-point testing using the Ultra meter would have practical advantages over the CGMS because self-monitoring of blood glucose was part of the subjects' diabetes management. Surprisingly, the opposite was true. There was little problem in obtaining nearly complete CGMS profiles in almost all subjects, whereas compliance to eight-point testing was much poorer than expected. Because the CGMS was not available for individual home use, our study was limited in the ability to assess long-term subject compliance with CGMS.

With both methods of monitoring, there was a very similar direct linear correlation between overall mean glucose and

A1c levels ($r = 0.39$ and 0.40), and a 1% change in A1c levels was associated with approximately a 20 mg/dl (1.1 mmol/liter) change in overall mean glucose levels. The slope and correlation of glucose with A1c observed in our study were considerably lower than those observed in the DCCT trial [36 mg/dl (2.0 mmol/liter) per 1% change in A1c; correlation 0.82] (14). This is possibly due to the fact that the DCCT analysis regressed the mean glucose from multiple time points over several years for each subject against the mean A1c value over those same time points. The prediction of long-term average glucose based on long-term average A1c is a different statistical problem than the prediction of mean glucose at a single time point based on a single A1c value. The two analysis techniques may therefore give different slopes and correlations.

This study has demonstrated that there are strengths and weakness associated with both the CGMS and eight-point testing in their ability to assess glycemic control in children with type 1 diabetes who are enrolled in clinical trials. Both methods provide similar results with respect to overall mean blood glucose values that correlate well to A1c levels, but eight-point testing may provide a more accurate means to assess hypoglycemia. Compliance was better with the CGMS, and this method appears to provide a more robust measure of meal-related glycemic excursions and indices of overall glycemic variability.

Appendix

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