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ORIGINAL ARTICLES

Agreement between Glucose Trends Derived from Three Simultaneously Worn Continuous Glucose Sensors

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Abstract

Background:

Sensors detect the rate and direction of glucose trend. They need to be accurate and reproducible as could be evidenced by strong agreement between multiple sensors. We evaluated this relationship through simultaneously worn glucose sensors using several methods of slope analysis.

Methods:

Ten type 1 diabetic, insulin pump-treated subjects were studied while simultaneously wearing three CGMS® Gold sensors each. Sensors were placed in the right abdomen (reference), left abdomen, and left upper arm. Sensors were calibrated and chronologically aligned. Data were only interpreted and included if there were 24 hours of data simultaneously obtained from all three sensors.

Results:

Using a two-point derived slope, increasing the duration of the trend from 5 to 60 minutes improved agreement between sensors. Using a 20-minute rolling average trend (using every 5-minute glucose value during the 20 minutes) improved the agreement to 94.3%. Finally, using whichever of the two comparator sensor rolling average trends was closest to the reference (better of two), the agreement improved to 98.2%. However, for these trend analysis methods, when the absolute reference rate of change was more than 1 mg/dl/min, the agreement decreased. Even with the best analysis approach, at an absolute reference sensor rate of change of >2 mg/dl/min, the agreement between sensors was only 40.0%.

Conclusion:

Despite several methods of analysis, trend agreement from multiple sensors diminishes as the absolute rate of change of reference glucose increases.

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Abbreviations: (CGM) continuous glucose monitoring, (SD) standard deviation

Keywords: closed loop, continuous glucose monitoring, glucose trends, trend analysis

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Introduction

Glucose trends from modern continuous glucose monitoring (CGM) sensors allow prediction of future glucose excursions. Such information may guide the provider or patient to make adjustments in activity, eating, or treatment.[1] It has been the dream of many that CGM would provide the information needed for insulin delivery in a hands-free system, the "closed loop cure."[2] To achieve this objective, sensors must deliver reliable information at various rates of glucose variation encountered in daily living. The purpose of our study was to evaluate methods of trend calculation from data derived from three simultaneously worn glucose sensors.

Methods

Patients

Ten type 1 insulin pump-treated diabetic patients from our clinic population signed an informed consent for this institutional review board (WIRB Protocol # 20051812)-approved study. Subjects were included if they were >17 years of age, had type 1 diabetes for more than 3 months, treated with an insulin pump, and demonstrated adherence to clinic visits and instructions. Subjects were excluded if they were pregnant or nursing. The mean age of the subjects was 46.8 [standard deviation (SD 5.8, range 38–55)] years, mean hemoglobin A1c was 7.8 (SD 0.8, range 6.7–9.5) %, mean body mass index was 32.8 (SD 5.9, range 25.7–43.1) kg/m^2, mean duration of diabetes was 13.4 (SD 8.6, range 6–34) years, and the mean duration of pump therapy was 5.8 (SD 2.7, range 2–10) years.

Methods

For 24 hours subjects simultaneously wore three CGMS® Gold (Medtronic MiniMed, Northridge, CA) sensors: one on the upper left arm, one on the left abdomen, and one on the right abdomen. After insertion and initial calibration of the sensor in the clinic (about 1 hour), each subject was discharged for the remainder of the study to their work or home. The right abdomen sensor was arbitrarily assigned the status of "reference." All three sensors were calibrated simultaneously four times during relatively stable glucose levels (readings at 4 hours after a meal) during the 24-hour period as per the manufacturer's recommendation. Data were only interpreted and included if there were 24 hours of data obtained simultaneously from all three sensors. Spontaneous glucose excursions during each subject's usual diet and activity provided data for the following comparisons.

1. Agreement (within 1 mg/dl/min) between trends of different duration from 5 to 60 minutes using a single point at the start and end of the time period, the "two-point slope," at various reference sensor rates of change.

2. Agreement (within 1 mg/dl/min) between 20-minute trends when determined by a two-point slope, by using all data points of the 20-minute interval (every 5 minutes), the rolling average, and by selecting the comparator sensor trend that was in closest agreement with the reference sensor (better of two). Comparisons were made at various rates of reference sensor rates of change.

Results

Figure 1 shows the three sensor readings on a representative subject with reference glucose measurements made with a meter during the 24-hour period. **Figure 2** demonstrates the degree of each subject's spontaneous glucose excursions. The variation in nearly all subjects exceeded 150 mg/dl. Because these variations occurred during the "normal" day they would provide a "real-life" experience with variation in glucose trends.

Figure 3 is a Clarke error grid analysis chart comparing glucose point-to-point agreement between the left

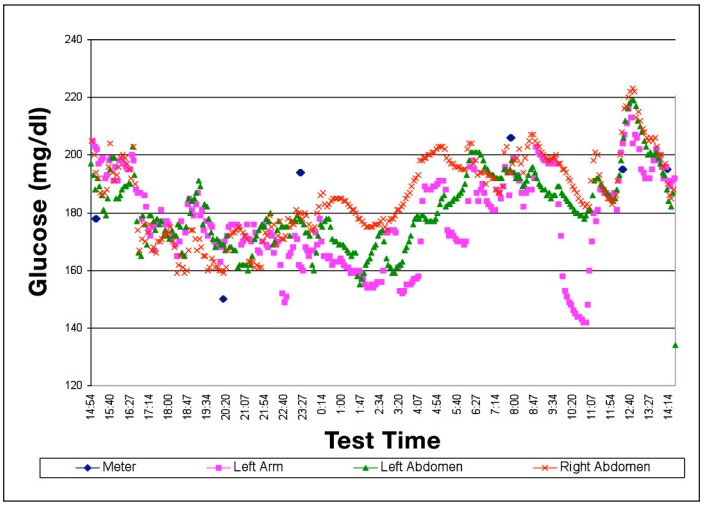

Figure 1. Graph demonstrating the three sensor tracings on Subject 0802 with glucose meter readings collected during the 24-hour period. Sensor traces are from left arm, left abdomen, and right abdomen.

abdomen to the reference sensor, the right abdomen. There was no clinically significant difference between a similar comparison of the left arm sensor results when compared to the reference sensor and therefore data are not shown. The Clarke grid shows that 79% of the readings were in zone A and 93% were in zones A + B. The mean absolute relative difference was 15% and the median was 10%. The correlation coefficient was 0.92.

Figure 4 compares data for the two-point 5-minute trend from the left arm and left abdomen to the reference sensor. **Figure 4** is divided horizontally across by the rate of change of the reference sensor. The vertical axis displays the corresponding rate of change of the comparator sensor. Within each box is listed the percentage distribution of the left arm/left abdomen readings for any reference rate of change. The left arm and left abdomen are clinically similar in agreement to the reference sensor and, therefore, we will report here only on the trend comparison between the left abdomen and the reference sensor. Note that as the absolute rate of change of the reference sensor increases beyond 1 mg/dl/min, the disagreement between sensors increases. Since sensor "noise" may diminish sensor agreement because of the short duration of the analysis period, we then studied the effect of increasing the duration of the trend period.

Figure 5 shows the effect of increasing the two-point trend duration from 5 to 60 minutes on the percentage agreement within 1 mg/dl/min between sensors. When the reference sensor rate of change was minimal (absolute change within 1 mg/dl/min), the agreement between the sensors increased from 50 to 70% as the trend duration increased from 5 to 60 minutes. However, when the reference sensor absolute rate of change was greater than 1 mg/dl/min, the agreement was less.

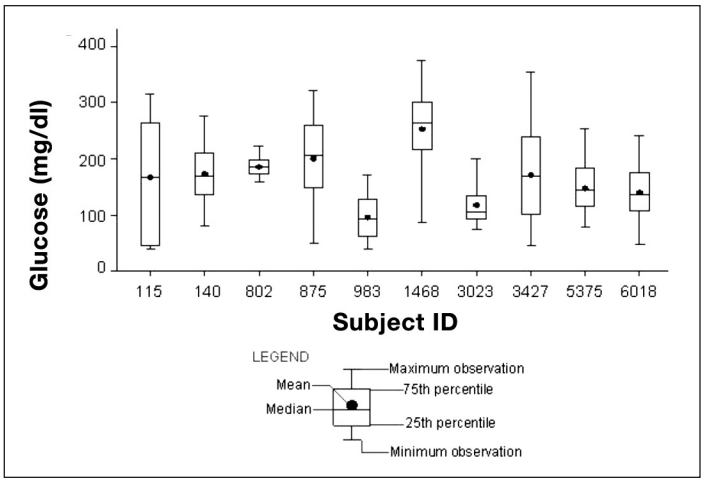

Figure 2. Spontaneous changes in each subject's glucose during the 24-hour period studied.

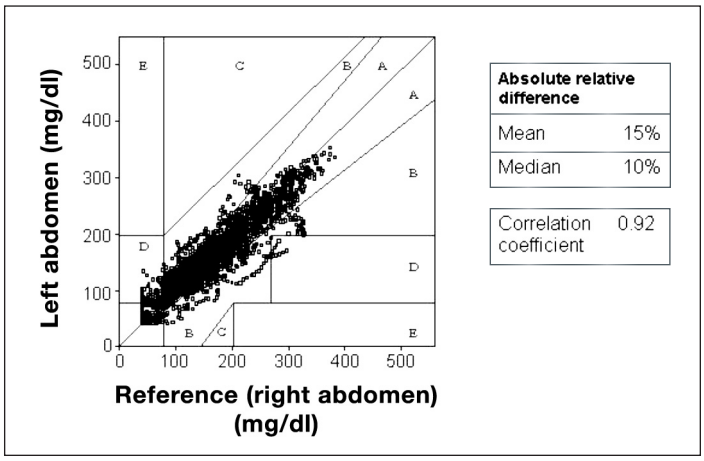

Figure 3. Clarke error grid analysis of glucose sensor point-to-point agreement comparing the left abdomen to the right abdomen (reference) during 24 hours of spontaneous glucose excursions.

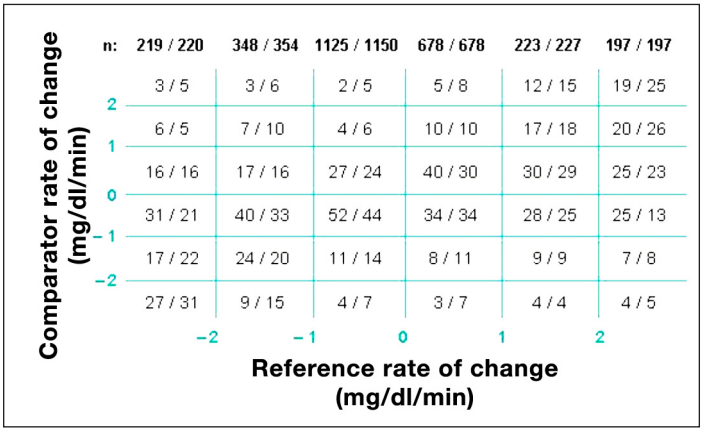

Figure 4. Two-point, 5-minute trend comparison between a comparator sensor (left abdomen and left arm) represented on the vertical axis and a right abdomen sensor (reference) represented on the horizontal axis. The upper horizontal line contains the number of trend observations for each comparator sensor at each reference sensor rate of change bracket. Within each box is the percentage of observations of each comparator sensor within ±1 mg/dl/min of each comparator and reference rate of change.

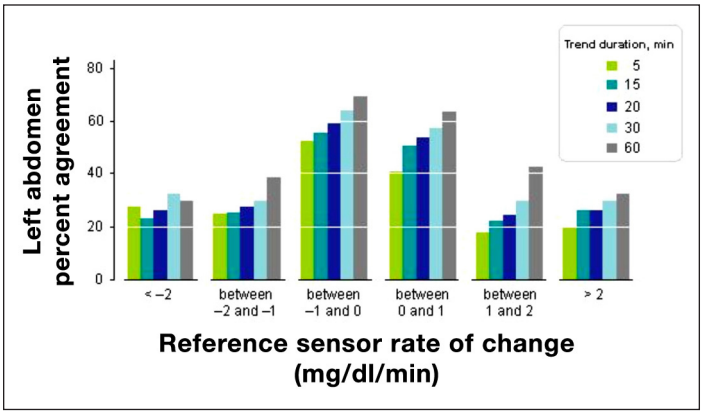

Figure 5. Comparison of agreement among the comparator sensor, the left abdomen, and the reference sensor, the right abdomen, at various duration (5–60 minutes) of two-point determined trends, and at various rates of reference sensor rates of change.

Figure 6 demonstrates the agreement comparison of three ways of determining a 20-minute slope: the two point, the rolling average, and the better-of-two rolling average. There is a progressive improvement moving from the two-point method, to the rolling average, and to the better-of-two determined slopes. The agreement when the reference sensor rate of change was minimal (within 1 mg/dl/min) increased from 85, 90, to 98%, respectively. However, as the reference sensor showed greater rates of glucose excursion, the agreement between sensors decreased. At an absolute rate of change of >2 mg/dl/min, the agreement was only 30, 35, and 40%, respectively. Of course, the number of observations at these higher rates of glucose change was less.

Based on reference readings from the right abdomen, hypoglycemic events were observed in four subjects (one subject had two episodes of hypoglycemia). The hypoglycemic period observed with three sensors is compared for these subjects in tabular form in **Table 1**.

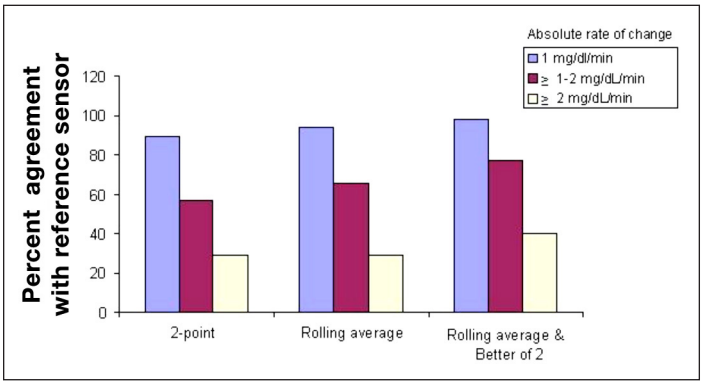

Figure 6. Comparison of agreement (within ±1 mg/dl/min) among the comparator sensor, the left abdomen, and the reference sensor, right abdomen, when the 20-minute duration is determined by two-point, rolling average, or the comparator sensor trend closest to the reference sensor (better of two) for varying rates of the reference sensor.

Discussion

Hirsch[1] suggested that rate of change and trend information should provide a guide to the patient/provider in altering the insulin delivery. Many plan to utilize this trend information to drive insulin delivery without having the patient intercede and to allow, at last, a true "hands-free" system for controlling glucose. Reliable sensor information thus is at the center of these program developments.

Utilizing two simultaneously worn CGM sensors, Metzger and colleagues[3] showed a poor correlation between the point-to-point glucose information. Since then, there have been advancements in sensor technology and interpreting software to improve these analyses. The sensor point-to-point comparison of our data demonstrates better agreement compared to this earlier study and compares favorability to other published median absolute differences of 10%.[4–6]

Our study indicates that sensor placement in the upper arm yields clinically similar results to the abdomen. While using the FreeStyle Navigator® continuous glucose monitoring system sensors Weinstein *et al.*[5] came to the same conclusion. In a multiple sensor site study, Vriesendorp and associates[7] found better accuracy when sensors were placed on the shoulder rather than on the upper thigh. Before recommendations of comparable sensor sites can be made, more comparative studies will need to be done.

Using the better-of-two and rolling average trend information for comparison to a reference sensor, agreement within 1 mg/dl/min was achieved in nearly 100% of analyzes. However, when the baseline glucose was changing more rapidly the percent agreement declined. A greater rate of change leading to greater disagreement has been reported by others.[5]

Table 1.
All Periods in Which Any of Three Simultaneously Worn Sensors Recorded Hypoglycemia (<70 mg/dl) in All Nine Subjects

Subject	Hypoglycemic period		
	Right abdomen	Left arm	Left abdomen
115	2:21 am to 6:00 am	2:21 am to 6:00 am	All readings above 70 mg/dl
3427	9:08 am to 11:08 am	9:48 am and 11:03 am (only two points)	9:08 am to 10:53 am
875	8:00 pm to 9:10 pm	8:05 pm to 8:45 pm	8:00 pm to 9:10 pm
983_1 (first time)	7:15 pm to 8:55 pm	All readings above 70 mg/dl	All readings above 70 mg/dl
983_2 (second time)	10:25 pm to 7:15 am	10:25 pm to 7:15 am	12:30 am and 2:15 am to 4:15 am

There are several explanations for the lack of agreement between sensors during increase rates of glucose change. Because the sensors were employed during the first 24 hours of insertion, there may have been variation in their "bedding down," leading to discrepant results.[5] Other discrepancies can result due to variability in walling off of the sensor as a consequence of fluid or inflammatory mass[8] about the electrode. Further, hyperemia of the area could result in less lag time between blood glucose and its more rapid changes compared to interstitial glucose.[9]

Ward and colleagues[8] have suggested using a multiple sensor array of four or more sensors to combat the variation in agreement between sites. Using a four sensor array in mice, his group demonstrated a closer agreement with a laboratory standard using a "voting" method. This method mathematically excludes sensor readings that deviate significantly from the median and the results more closely follow a laboratory standard. We look forward to studies in humans testing the mathematical analysis at high rates of glucose change.

Our study could be criticized since the glucose changes were not created externally to obtain the full range of glucose point values, especially in the hypoglycemic range. However, our results were in a more "real-life" setting of glucose rates of change for which sensor performance can be judged. As this was not a study of sensor accuracy, we also did not compare the sensors to an external laboratory glucose measurement. Nevertheless, when comparing any of the three sensors used, all sites appeared to behave with the same degree of agreement.

Within small perturbations in resting glucose the single sensor seems to provide accurate reflection in glucose trends, especially when using the rolling-average method and trend duration of 20 minutes. With more rapid absolute changes, e.g., >1 mg/dl/min, our results and those of others[5] demonstrate increasing disagreement between sensors. Such results point to the difficulty in creating closed loop sensor-pump systems with the ability to quickly interpret rapid glucose changes accurately.

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