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SYMPOSIUM

Modeling of Calibration Effectiveness and Blood-to-Interstitial Glucose Dynamics as Potential Confounders of the Accuracy of Continuous Glucose Sensors during Hyperinsulinemic Clamp

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Abstract

Background:

Models of the dynamics of interstitial fluid-based continuous glucose sensors imply a variable sensor deviation from reference blood glucose (BG), depending on both sensor calibration procedure and BG dynamics. These effects could have a significant effect on the cross-interpretation of nonidentical accuracy studies.

Methods:

Hyperinsulinemic euglycemic and hypoglycemic clamps were performed on 39 subjects with type 1 diabetes wearing the Medtronic Continuous Glucose Monitoring System®. Sensor calibration and interstitial glucose (IG) dynamics were modeled and analyzed as potential confounders of sensor deviation from reference BG.

Results:

The mean absolute deviation (MAD) of sensor data was 20.9 mg/dl during euglycemia and 24.5 mg/dl during descent into and recovery from hypoglycemia. Computer-generated recalibration reduced MAD to 10.6 and 14.6 mg/dl, respectively. Modeling of IG dynamics reduced the MAD further to 10.0 and 10.4 mg/dl (using idiosyncratic parameters) or to 10.6 and 11.5 mg/dl (using model parameters common for all subjects), respectively.

Conclusions:

The sensor MAD from reference is strongly influenced by the choice of calibration points. Thus, cross-experiment comparisons of sensor accuracy are likely to be heavily dependent on the employed calibration procedures. Demanding calibration points substantially differing in value was found to improve calibration effectiveness. Simulation using existing IG models and population parameters reduced the bias resulting from BG–IG dynamics.

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Abbreviations: (BG) blood glucose, (CGS) continuous glucose sensor, (IF) interstitial fluid, (IG) interstitial glucose, (MAD) mean absolute deviation, (SIG) surrogate interstitial glucose, (T1DM) type 1 diabetes

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Introduction

Continuous glucose sensor (CGS) technology has the potential to revolutionize diabetes management by providing patients with ongoing, online feedback about current blood glucose (BG) levels and rate/direction of change, as well as signals to alert for possible dangerous trends, such as rapid decreases that may lead to hypoglycemia.[1] Compared to few self-monitoring blood glucose readings per day, CGS yield detailed time series of BG estimates (e.g., every 5 minutes), allowing for the precise tracking of BG variation—an essential component of glycemic control.[2] It is important, however, to emphasize that most contemporary CGS yield *estimates* of BG not via direct measurement in blood, but via sampling of interstitial fluid (IF). Such estimates are the product of at least two consecutive steps: (1) blood-to-interstitial glucose (IG) transport and (2) deduction of BG values from IG-related electrical current recorded by the sensor. As a result, although CGS technology has made dramatic strides,[1,3,4] the development of accurate and reliable CGS devices continues to face a number of significant challenges in terms of sensitivity, stability, calibration, and the physiological time lag between blood and interstitial glucose concentration, which has been observed in a number of clinical studies and laboratory experiments.[5–10] Such a time lag becomes particularly important in the context of real-time warnings for hypoglycemia or hyperglycemia or in the context of a closed-loop system based on the combination of a CGS, a control algorithm, and an insulin pump (although in the latter case the time lag related to subcutaneous insulin injection is much more pronounced[11]).

While models of IG dynamics have been explored and validated,[12–14] there remains an unanswered question of how these dynamics impact the deviation of CGS readings from reference blood glucose data. In particular, the relative contribution of calibration and BG-to-IG diffusion to the deviation of sensor data from reference BG remains unclear. The evaluation of CGS performance is therefore left with a central difficulty: separating the portion of CGS-BG deviation due to the sensor from that due to the IG–BG gradient. This article models mathematically the two steps of conversion of sensor current to BG reading: calibration and IG dynamics. It then explores their impact on sensor deviation from reference using a standard metric of CGS accuracy, the mean absolute deviation (MAD). Because we intend to view these two steps as potential study biases/confounders, the precision of CGS under different conditions of IG dynamics and simulated recalibration is examined. We utilize CGS results from hyperinsulinemic euglycemic and hypoglycemic clamps in subjects with type 1 diabetes (T1DM) with the premise that the contrasting conditions of steady-state euglycemia, descent into hypoglycemia, and recovery will provide a comprehensive view on IG dynamics. In addition, because IG is difficult to measure directly, we introduce and utilize a model-predicted IG, i.e., surrogate interstitial glucose (SIG).

Methods

Subjects

Thirty-nine subjects with TIDM were recruited through regional advertisement. Exclusion criteria were age >65 years, mental retardation, psychological diagnoses, or active substance abuse. The average age of the participants was 42.5 ± 12 years, the average duration of T1DM was 21.6 ± 9.4 years, and the average hemoglobin A1c was 7.4 ± 0.8%; there were 16 males. The study was approved by the University of Virginia Human Investigation Committee. All subjects gave written consent and had a complete physical examination prior to the beginning of the protocol.

Procedure

Subjects were admitted to the University of Virginia General Clinical Research Center in the evening prior to the study, and their BG levels were controlled overnight within the target range of 100–150 mg/dl, preventing hypoglycemia (BG <70 mg/dl). The Medtronic CGMS® (Medtronic, Northridge, CA) was attached to each subject on the evening of admission, approximately 12 hours prior to the initiation of the principal procedure, and was calibrated 2 hours after sensor insertion and before and after the clamp procedure on the next day. The device clock was synchronized with the room clock for subsequent matching of data. The total time of CGMS data recording during the study was approximately 18 hours. All CGMS were inserted in the abdomen. In the morning, a hyperinsulinemic clamp was initiated using a constant insulin infusion rate of 1 mU/kg/min and a variable glucose infusion rate to achieve and maintain BG levels at approximately 110 mg/dl. Subsequently, the glucose infusion rate was reduced to permit a controlled decline in BG of approximately 1 mg/dl/min until BG reached ~50 mg/dl. Glucose infusion was then resumed to allow a recovery to normal glucose levels. The lead-in portion of the clamp study (until achieving BG of 110 mg/dl) varied significantly across the subjects (between 20 and

140 minutes) depending on their morning glucose level. Once stable BG was achieved, euglycemia was maintained for 50–70 minutes, followed by descent into hypoglycemia and recovery. The rates of descent and ascent were quite uniform across the subjects, with a mean rate of descent of 1.15 (SEM = 0.03) mg/dl/min and a mean rate of ascent of 1.73 (SEM = 0.07) mg/dl/min. Arterialized blood was achieved by warming the hand to 50°C and was sampled every 5 minutes for reference BG levels using a Beckman glucose analyzer (Beckman Instruments, Inc., Fullerton, CA).

Data Preprocessing

The first 15 minutes of data after the beginning of infusion were ignored to avoid rapid fluctuations in insulin and glucose levels at the beginning of the study. CGMS readings, recorded at the standard Medtronic CGMS frequency of 5 minutes, were synchronized for each subject with his/her reference BG and other clinical measures with a precision of 30 seconds. This synchronization was strictly of the devices' clocks, without adjustment for any possible time lags. Further, we separated each clamp into two data sets for comparison across subjects: steady-state euglycemic clamp and hypoglycemic descent and recovery by matching data streams across subjects at the moment of BG nadir.

Sensor Recalibration

To test the effect of the spacing across the BG scale of sensor-calibration points, we took a 2-hour time window of each subject's CGMS BG estimates around his/her nadir of BG during hypoglycemia and generated sensor recalibration using two reference BG values chosen to have been different by a given BG gradient. The recalibration used the standard linear calibration function of the CGMS, BG = scale × [current offset]. We also performed an optimal calibration, which used all available reference BG values to estimate the parameters of the sensor calibration function. For the purposes of evaluating the effect of calibration, optimal calibration was performed within a 2-hour time window around the nadir of BG; for the purposes of computing the SIG (next section), optimal calibration was performed using all data from the entire experiment (except the first 15 minutes).

Mathematical Model of IG Changes in Response to BG

Because glucose is a relatively small molecule, it is widely supposed to diffuse freely across the capillary wall.[6] Adipose tissue is highly vascularized, and the IF occupies a relatively thin layer between cells.[12] This means that no volume element is very far from a cell surface, nor is it very far from a capillary wall. Hence, uptake and diffusion of glucose in the IF can be assumed to be relatively uniform, without a significant local gradient. As reported previously,[13–15] the dynamics of glucose diffusion and uptake can be described as

$$\left(\frac{d(IG)}{dt}\right)_{net} = \beta(BG(t) - IG(t)) - \alpha(IG(t)) = k_1 BG(t) - k_2 IG(t) \quad . \quad (1)$$

Equation (1) assumes that the rate of removal of glucose from the interstitial fluid is proportional to IG (with rate parameter α) and that the movement of glucose from the blood to the interstitial fluid (or vice versa) is passive diffusion and hence is proportional to the gradient (with rate parameter β). Because there are no other apparent sources or sinks of glucose in the interstitium, Equation (1) describes the net change in IG via two parameters (α, β). In order to follow the standard representation in the literature, we rearrange the terms of the equation with two parameters (k_1, k_2). The parameters were estimated via numerical integration of Equation (1) using reference BG values and recalibrated sensor readings. The step of numerical integration was fixed at <0.001 minute, a data density not provided by original data. In order to achieve such a data density, original data were interpolated using smooth interpolation curves between the data points. This process identified SIG, a fitted, scaled continuous approximation of each person's IG concentration. Furthermore, because the ratio of k_1 to k_2 affects a change in scale of the integrated solution, allowing k_1 and k_2 to vary independently would essentially recalibrate the result. Hence, in already recalibrated data we required $k_1 = k_2$, which results in one-dimensional parameter space. Having arrived at parameters (equivalent to delay estimates), we used SIG to estimate the impact of that delay.

Results

Sensor Calibration

Figure 1 illustrates the influence of BG differential between two calibration points on the quality of calibration: the *X* axis represents the distance between two simulated calibration points in BG units (mg/dl); the *Y* axis represents MAD of the sensor output, given this two-point calibration with error bars ±SEM of absolute deviation. The MAD was computed within a 2-hour time window encompassing the nadir of BG for each subject. It is evident that MAD is high if the two calibration BGs are close by in value, is decreasing rapidly when the difference approaches 20 mg/dl, and is decreasing slowly after that. Thus, **Figure 1** demonstrates that MAD is very dependent on the choice of points for a two-point calibration. The upper dashed horizontal line in **Figure 1** represents the MAD of the sensor's original calibration (i.e., that created by calibration points in the evening,

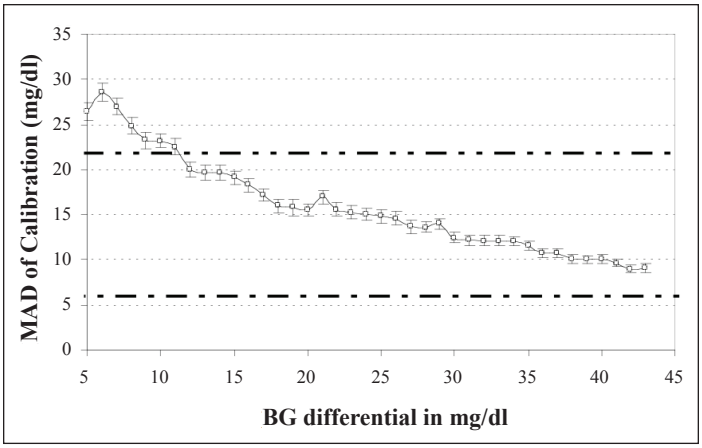

Figure 1. Sensor accuracy against reference of two-point recalibration given forced difference in recalibration point values. Bottom dashed line is optimal all-point calibration; top dashed line is original device calibration.

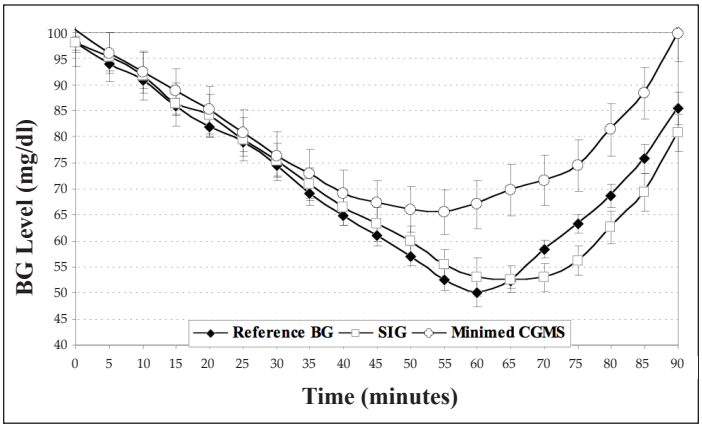

Figure 2. Averaged time courses of CGS, BG, and SIG. Subjects are time matched by nadir of BG.

Table 1. Mean Absolute Deviation

Model	MAD: Steady euglycemic state, N = 1146 data points	MAD: Descent and recovery from hypoglycemia, N = 699 data points
Sensor recalibration		
Original sensor readings	20.9	24.5
Recalibrated	10.6	14.6
BG-to-IG diffusion		
Idiosyncratic-parameter SIG	10.0	10.4
Global-parameter SIG	10.6	11.5

before and after the clamp); the lower dashed horizontal line in **Figure 1** represents the MAD resulting from an optimal calibration using all reference points within the selected time window. It is evident that two calibration BGs >40 mg/dl apart would achieve nearly optimal results.

Modeling of IG Changes in Response to BG

Figure 2 presents the three signals considered in this article (averaged across all subjects): reference BG, model-predicted surrogate IG, and recalibrated sensor current, with error bars ±SEM. It is evident that the SIG trace is much closer to reference BG than original sensor data.

The parameters of the diffusion model were fitted for each individual subject, as well as globally across all subjects. The median best-fitted parameters of the SIG fitted individually to each subject were k_{eu_id} = 0.12/min (SEM = 0.06/min) for euglycemia and $k_{hypo\ id}$ = 0.17/min (SEM = 0.13/min) for the hypoglycemic descent. The global best-fit parameters were k_{eu_gl} = 0.10/min for euglycemia and k_{hypo_gl} = 0.09/min for the hypoglycemic descent. **Table 1** displays the MAD computed under the following circumstances: original sensor readings, recalibrated readings using all reference data points during the study, SIG using idiosyncratic parameters fitted separately to each subject, and SIG using global parameters.

Table 1 shows that the recalibration accounts for a large portion of the sensor deviation from reference BG. It is also evident that the difference between individually fitted and global parameters is minimal.

Discussion

Calibration

It is intuitively clear that the accuracy of sensor calibration depends on the rate of BG change and perhaps on the BG value at the moment of calibration. Assuming that calibration is performed at a steady BG level (a condition generally required by sensor manufacturers), it is also reasonable to expect that if two calibration points are taken at about the same BG level, the quality of calibration would be *lower* than if these points were taken at different BG levels. The reason behind this premise is that a calibration function would perform better if its input has certain variance, as opposed to two repeated calibrations at the same BG level, as demonstrated by **Figure 1**. This dependency means that when comparing CGS accuracy results across studies, a strong bias can emerge if the method and timing choices of calibration points are not identical. For example, in our study calibration was

performed in the evening and then in a steady state before and after hypoglycemia, with little BG gradient between the calibration points. This resulted in the original sensor trace in **Figure 2**, which deviates significantly from reference during induced hypoglycemia. In an otherwise identical study with the second calibration point taken in hypoglycemia, the MAD would have been over 50% less. The clinical message therefore is that sensors (particularly those with a current offset, such as the CGMS) need to be calibrated at points with a sufficient difference between the glucose levels, e.g., >30 mg/dl.

Surrogate Interstitial Glucose

The dynamics of SIG in **Figure 1** reflects the basic features of IG profiles reported in studies using euglycemic/hypoglycemic clamp and CGS: a low bias during stable BG values and during BG descent and a delayed recovery following BG nadir.[5] This indicates that the proposed mathematical model is capable of describing quantitatively IG dynamics during hyperinsulinemic clamp. In general, the BG-to-IG dynamics is idiosyncratic and the diffusion equation [Equation (1)] is solved individually using the trace of each person, assigning idiosyncratic parameters specific to that person. It appears, however, that the computation of SIG dynamics with global parameters is possible and does not increase the deviation of the IG trace significantly (the last two lines of **Table 1**). Because SIG based on global parameters effectively eliminates the influence of any particular sensor, it is not dependent on sensor mechanical performance. In that sense, SIG represents the "ideal sensor" that reflects IG dynamics free of engineering limitations.

Using SIG as an intermediate component in the analysis of sensor deviation from reference BG, **Table 1** shows that descent vs steady-state deviations differ only in terms of their physiological component and are virtually identical in terms of mechanical sensor error. Thus, it appears that the time lag between BG- and IG-based sensor readings is mostly because of IG consumption and glucose diffusion between the two compartments—blood and interstitium.

The computation of SIG is relatively uncomplicated and can be done with idiosyncratic estimation of a rate constant from reference BG data or using "global" population estimates of this parameter. As presented in **Table 1**, the differences, in terms of accuracy, between idiosyncratic and global rate constants are minimal. Thus, future studies could establish SIG as a bias-correction tool when seeking to compare results across accuracy experiments. The utility of that tool may seem limited: many studies are designed precisely to bypass this confounder by putting multiple sensors on the same patients and calibrating them the same way. However, in a growing marketplace of sensors such demanding comparisons may become infeasible. In addition, such a tool would allow data combination from multiple studies to increase their power.

During the development of SIG methodology we have experimented with different, including nonlinear, forms of the model, incorporating features such as (i) glucose uptake controlled by nonlinear kinetics, (ii) flow-limited rate of glucose transfer, (iii) active transport models of glucose transport across the microvasculature, (iv) gradient corrections for large interstitial compartments, and (v) use of state space models and filters for estimation.[16] So far, we have no compelling results showing any of the aforementioned as superior to the minimal assumptions outlined in our methodology. However, continued experiments are needed, particularly regarding the application of SIG methodology to nonclamp field data where the parameters likely vary in time and may have much higher variance than in our relatively small study in a well-controlled environment. In addition, we recognize that some of these different forms may be more appropriate to different interstitial locations. For example, the blood–brain barrier controlling cerebrospinal fluid is thought by many to use active transport[17] and would likely be a large compartment. Alternatively, fluid compartments with high glucose values may be better described by nonlinear uptake kinetics. Further developments of SIG methodology would also account for the ways in which factors, such as body mass index or insulin resistance, can be used to produce more accurate population parameters.

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References:

1. Klonoff DC. Continuous glucose monitoring: roadmap for 21st century diabetes therapy. Diabetes Care. 2005 May;28(5):1231-9.
2. Hirsh IB, Brownlee M. Should minimal blood glucose variability become the gold standard of glycemic control? J Diabetes Complications. 2005 May-Jun;19(3):178-81.
3. Gross TM, Bode BW, Einhorn D, Kayne DM, Reed JH, White NH, Mastrototaro JJ. Performance evaluation of the MiniMed continuous glucose monitoring system during patient home use. Diabetes Technol Ther. 2000 Spring;2(1):49-56.
4. Feldman B, Brazg R, Schwartz S, Weinstein R. A continuous glucose sensor based on wired enzyme technology–results from a 3-day trial in patients with type 1 diabetes. Diabetes Technol Ther. 2003;5(5):769-79.

5. Cheyne EH, Cavan DA, Kerr D. Performance of continuous glucose monitoring system during controlled hypoglycemia in healthy volunteers. Diabetes Technol Ther. 2002;4(5):607-13.
6. Boyne MS, Silver DM, Kaplan J, Saudek CD. Timing of changes in interstitial and venous blood glucose measured with a continuous subcutaneous glucose sensor. Diabetes. 2003 Nov;52(11):2790-4.
7. Pickup J. Sensitive glucose sensing in diabetes. Lancet. 2000 Feb 5;355(9202):426-7.
8. Gerritsen M, Jansen JA, Lutterman JA. Performance of subcutaneously implanted glucose sensors for continuous monitoring. Neth J Med. 1999 Apr;54(4):167-79.
9. Stout PJ, Racchini JR, Hilgers ME. A novel approach to mitigating the physiological lag between blood and interstitial fluid glucose measurements. Diabetes Technol Ther. 2004 Oct;6(5):635-44.
10. Kulcu E, Tamada JA, Reach G, Potts RO, Lesho MJ. Physiological differences between interstitial glucose and blood glucose measured in human subjects. Diabetes Care. 2003 Aug;26(8):2405-9.
11. Hovorka R. Continuous glucose monitoring and closed-loop systems. Diabet Med. 2006 Jan;23(1):1-12.
12. Schoonen AJ, Wientjes KJ. A model for transport of glucose in adipose tissue to a microdialysis probe. Diabetes Technol Ther. 2003;5(4):589-98.
13. Steil GM, Rebrin K, Hariri F, Jinagonda S, Tadros S, Darwin C, Saad MF. Interstitial fluid glucose dynamics during insulin-induced hypoglycaemia. Diabetologia. 2005 Sep;48(9):1833-40.
14. Rebrin K, Steil GM. Can interstitial glucose assessment replace blood glucose measurements? Diabetes Technol Ther. 2000 Autumn;2(3):461-72..
15. Rebrin K, Steil GM, van Antwerp WP, Mastrototaro JJ. Subcutaneous glucose predicts plasma glucose independent of insulin: implications for continuous monitoring. Am J Physiol. 1999 Sep;277(3 Pt 1): E561-71.
16. Palerm CC, Bequette BW, Desemone J, Willis J. Hypoglycemia prediction and detection using optimal estimation. Diabetes Technol Ther. 2005 Feb;7(1):3-14.
17. Nielsen JK, Djurhuus CB, Gravholt CH, Carus AC, Granild-Jensen J, Orskov H, Christiansen JS. Continuous glucose monitoring in interstitial subcutaneous adipose tissue and skeletal muscle reflects excursions in cerebral cortex. Diabetes. 2005 Jun;54(6):1635-9.