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ORIGINAL PAPERS

- Pharmacodynamics and Stability of Subcutaneously Infused Glucagon in a Type 1 Diabetic Swine Model In Vivo** 135
F.H. El-Khatib, J. Jiang, R.G. Gerrity, and E.R. Damiano
- Type 1 Diabetes Mellitus in Human and Chimpanzee: A Comparison of Kyoto Encyclopedia of Genes and Genomes Pathway** 145
V. Wiwanitkit
- Waist Circumference Identifies Primary School Children with Metabolic Syndrome Abnormalities** 149
V. Hirschler, G. Maccallini, M. Calcagno, C. Aranda, and M. Jadzinsky
- The HealthPia GlucoPack™ Diabetes Phone: A Usability Study** 158
A.E. Carroll, D.G. Marrero, and S.M. Downs
- Relative Accuracy of the BD Logic® and FreeStyle® Blood Glucose Meters** 165
The Diabetes Research in Children Network (DirecNet) Study Group
- Relationship Between Interstitial and Blood Glucose in Type 1 Diabetes Patients: Delay and the Push-Pull Phenomenon Revisited** 169
I.M.E. Wentholt, A.A.M. Hart, J.B.L. Hoekstra, and J.H. DeVries
- Menstrual Cycle Effects on Insulin Sensitivity in Women with Type 1 Diabetes: A Pilot Study** 176
K.K. Trout, M.R. Rickels, M.H. Schutta, M. Petrova, E.W. Freeman, N.C. Tkacs, and K.L. Teff
- Calibration of the Continuous Glucose Monitoring System for Transient Glucose Monitoring** 183
L.M. Lesperance, A. Spektor, and K.J. McLeod
- Pramlintide as an Adjunct to Insulin in Patients with Type 2 Diabetes in a Clinical Practice Setting Reduced A1C, Postprandial Glucose Excursions, and Weight** 191
D. Karl, A. Philis-Tsimikas, T. Darsow, G. Lorenzi, T. Kellmeyer, K. Lutz, Y. Wang, and J.P. Frias

LETTER TO THE EDITOR

- Response to Baum et al. on Meter Miscoding** 200
J. Ellison, D. Price, A.T. Cariski, and C. Davis

Instructions for Authors can be found at the back of the issue and on our website at www.liebertpub.com

Calibration of the Continuous Glucose Monitoring System for Transient Glucose Monitoring

LEANN M. LESPERANCE, M.D., Ph.D., ANNA SPEKTOR, M.S.,
and KENNETH J. MCLEOD, Ph.D.

ABSTRACT

Background: Oral glucose tolerance testing (OGTT) remains the gold standard for diagnosis of diabetes and is used commonly in the research laboratory. The Medtronic MiniMed (Northridge, CA) Continuous Glucose Monitoring System (CGMS[®] Gold[™]), developed for long-term monitoring of glycemic levels, could provide a convenient means for tracking OGTT results during research protocols; however, the sensor demonstrates glucose and time dependencies that preclude direct application of the company-provided conversion algorithm in the first 12–24 h after sensor insertion. Here, we propose an alternative conversion algorithm that permits utilization of the CGMS monitor for glucose monitoring during this time.

Methods: Healthy female participants underwent CGMS monitoring during OGTT or fasting sessions in combination with finger-stick blood glucose measurements. Logarithmic transformations and multiple regression analysis were used to quantify the time and glucose dependence of the sensors.

Results: Sensor performance, as characterized by sensitivity (ratio of sensor current to capillary blood glucose levels), was shown to vary logarithmically with glucose levels as well as time after sensor insertion. A conversion algorithm developed on the basis of these observations was tested on 17 subjects during OGTT. A mean absolute relative difference between capillary blood glucose and CGMS values of $11.6 \pm 6.5\%$ for the new algorithm was seen, compared to $20.6 \pm 5.9\%$ with the Medtronic Solutions version 3.0c algorithm.

Conclusions: Incorporation of the glucose and time dependence in CGMS sensor data yields an improved mean absolute difference between actual and estimated blood glucose values compared to the Medtronic-supplied algorithm in the immediate time period following sensor insertion.

INTRODUCTION

THE CONTINUOUS GLUCOSE MONITORING SYSTEM (CGMS[®]) (Medtronic MiniMed, Northridge, CA) detects variations in interstitial glucose values over the course of 3 days and has been shown to be an effective tool in the management of patients with poorly controlled di-

abetes, helping them to lower hemoglobin A1c levels without increasing the incidence of severe hypoglycemia.¹ The CGMS is easy to operate, virtually painless to insert and wear, and requires infrequent calibration with (finger) capillary blood glucose (CBG) measurements. It has been used successfully in inpatient and outpatient settings and in various populations,

Clinical Science and Engineering Research Center, Binghamton University, Binghamton, New York.

including women with gestational diabetes,² patients with type 2 diabetes,³ and children.⁴ All these qualities make the CGMS a potentially valuable research tool, and it has been used to measure glucose in a number of studies.^{5,6}

Research studies utilizing the CGMS, however, suggest difficulties can be encountered during data analysis. The CGMS measures interstitial glucose levels using a disposable glucose oxidase-coated sensor. Medtronic-supplied software (MiniMed Solutions version 3.0c) converts sensor current readings to blood glucose (BG) levels assuming a linear relationship to CBG calibration points, and assuming constant sensor sensitivity within the detection thresholds of 40 mg/dL and 400 mg/dL over the operational lifetime of the sensor (approximately 72 h). In some cases, these assumptions may not be valid. While some studies have reported excellent correlation between CGMS and CBG values ($R^2 = 0.91$, $P < 0.001$) throughout sensor lifetime,⁷ others have identified accuracy, reproducibility, and stability problems in CGMS data. For example, several studies have indicated that while the device demonstrates high accuracy in the normoglycemic and hyperglycemic regions, high error rates occur in the hypoglycemic region (BG <50–70 mg/dL).^{4,8,9} Metzger et al.¹⁰ have questioned the reproducibility of measurements, showing a correlation of 0.74 between CGMS and CBG values in an initial trial and a correlation of 0.93 in a follow-up trial under essentially identical conditions. Nyback-Nakell et al.¹¹ have shown that sensor sensitivity can deteriorate significantly over time, with correlations between plasma glucose measurements and CGMS values dropping from 0.80 after 48 h of operation, to 0.33 after 72 h.

That the CGMS sensors may demonstrate a drift in sensitivity over time and may have variable sensitivity as a function of glycemic levels does not necessarily preclude its use in research. In fact, the high initial sensitivity of the sensors led us to suggest that the CGMS may be useful for short-term monitoring, such as required in oral glucose tolerance testing (OGTT). Here, we report on the results of a study designed to establish a sensor current-to-glucose conversion algorithm for the CGMS that may permit its use in the initial hours following sen-

sor insertion and where wide swings in glucose levels were expected, such as with OGTT.

SUBJECTS AND METHODS

The study was approved by the Binghamton University Human Subjects Committee (Binghamton, NY). Healthy females without diabetes and without hypoglycemia ($n = 28$; mean age 43.6 ± 9.0 years; mean body mass index 29.0 ± 5.0 kg/m²) were recruited. (Females were chosen for convenience of recruiting on campus and for comparison to earlier studies in our laboratory.) In order to confirm the manufacturer's report of rapidly changing sensitivity over the first 24 h of sensor use, one subject completed a 48-h monitoring session. For development of the model, five subjects underwent 4 h of CGMS monitoring in the fasting state, and five subjects underwent 4 h of CGMS monitoring during OGTT. For model testing, an additional 17 subjects were monitored during OGTT.

For OGTT, participants reported to the clinic after an overnight fast (=10 h). The CGMS System Gold™ sensor (Medtronic MiniMed) was inserted into the abdomen following the manufacturer's instructions. At the completion of sensor initialization (60 min), the CGMS was calibrated with a finger CBG measurement using an Accu-Chek® Active portable glucose meter (Roche Diagnostics, Indianapolis, IN). This initial calibration established time zero. Following 30 min of baseline data collection, CBG measurement was repeated, and participants ingested a 75-g oral glucose beverage (Perk Scientific, Yeadon, PA). Data were recorded for another 3 h; CBG measurements were repeated at 90, 150, and 210 min. Participants remained seated for the duration of the test, taking 5-min breaks once every hour. At the end of the test, the sensor was removed, and the sensor current data were downloaded. For the fasting sessions, a procedure identical to the OGTT was used, without consumption of the glucose beverage.

During the 48-h monitoring session, the subject initially completed an OGTT, as described above, with CBG taken every 15 min. Following the OGTT, the subject returned to regular daily activities, with the sensor in place. The

subject calibrated the meter every 2–7 h and kept a record of meal times.

MiniMed Solutions version 3.0c software was used to download data from the CGMS and for initial analysis. Data were exported to Microsoft (Redmond, WA) Excel and *Mathematica* version 5.1 (Wolfram Research, Champaign, IL) for subsequent analyses. Statistical analysis was performed with SPSS version 11 (SPSS Inc., Chicago, IL).

In all analyses, sensor performance was characterized by a sensitivity parameter (S), defined as:

$$S = ISIG/CBG \quad (1)$$

where $ISIG$ is the sensor current (in μA), CBG is the CBG (in mg/dL) taken at the corresponding point in time, and S has units of $\mu A/mg/dL$.

RESULTS

Determination of the time dependence of sensor sensitivity

In an initial assessment of sensor performance, a 48-h CGMS monitoring session with OGTT and frequent CBG calibrations was conducted. Consistent with previous reports, sensitivity was observed to decrease significantly over time, most rapidly during the 5–10 h after sensor insertion. With time plotted on a logarithmic scale (Fig. 1A), the decline in sensor sensitivity can be approximated as linear ($R^2 = 0.65$). In addition to the time-dependent decrease in sensitivity, an inverse relationship between serum glucose levels and sensitivity was evident in this initial experiment; sensitivity consistently drops during glucose peaks, and increases during hypoglycemic periods.

To characterize sensor performance as a function of time over the first few hours following sensor insertion while minimizing any effects of glucose variation, 4-h monitoring sessions ($n = 5$) were conducted in the fasting state (Fig. 1B). Glucose levels changed minimally over the course of these fasting studies: initial levels averaged 96 ± 5 mg/dL, while levels at the end of the sessions averaged 80 ± 3.5 mg/dL. Multiple regression analysis confirmed that the glucose variations did not con-

tribute significantly to the change in sensor sensitivity during these tests, but elapsed time from sensor insertion significantly affected sensor sensitivity. Based on the results of the 48-h data recording, we regressed sensitivity against the logarithm of time [$S = A \times \log_{10}(t) + C$], where t is the time from initial sensor calibration (in min) and C is a constant, which produced a good fit ($R^2 = 0.89$; $P = 0.015$). However, over this short time period, a simple linear dependence on time ($S = A \times t + C$) also produced an excellent fit ($R^2 = 0.98$; $P = 0.001$).

Determination of the glucose dependence of sensor sensitivity

We further investigated the dependence of sensor sensitivity on glucose levels by obtaining 4-h recordings during an OGTT, which provided a wide range of glucose levels (Fig. 2). Sensor sensitivity was observed to decrease significantly with increasing glucose levels. This relationship was modeled as linear (i.e., sensitivity decreasing linearly with glucose concentration), as hyperbolic [decreasing as $(1/\text{glucose})$], and as logarithmic (decreasing linearly with log glucose). The best fit to these data ($n = 5$) was obtained by regressing sensitivity against the logarithm of glucose [$S = A \times \log_{10}(CBG) + C$; $R^2 = 0.47$; $P = 0.0001$].

Conversion algorithm

Combining the above two results suggested that a sensor conversion algorithm of the form:

$$S = ISIG/CBG = A \times \log_{10}(t) + B \times \log_{10}(CBG) + C \quad (2)$$

where A , B , and C are coefficients of the model specific to a given sensor, would better describe sensor sensitivity during the early hours after sensor insertion. For this algorithm, at least three CBG calibration points were used to determine coefficients A , B , and C . This expression was then used to convert $ISIG$ values to BG values. Substituting BG for CBG and rearranging Eq. 2 yields:

$$BG = ISIG/[A \times \log_{10}(t) + B \times \log_{10}(BG) + C] \quad (3)$$

Since BG appears on both sides of the equation, it could not be solved for directly and an iter-

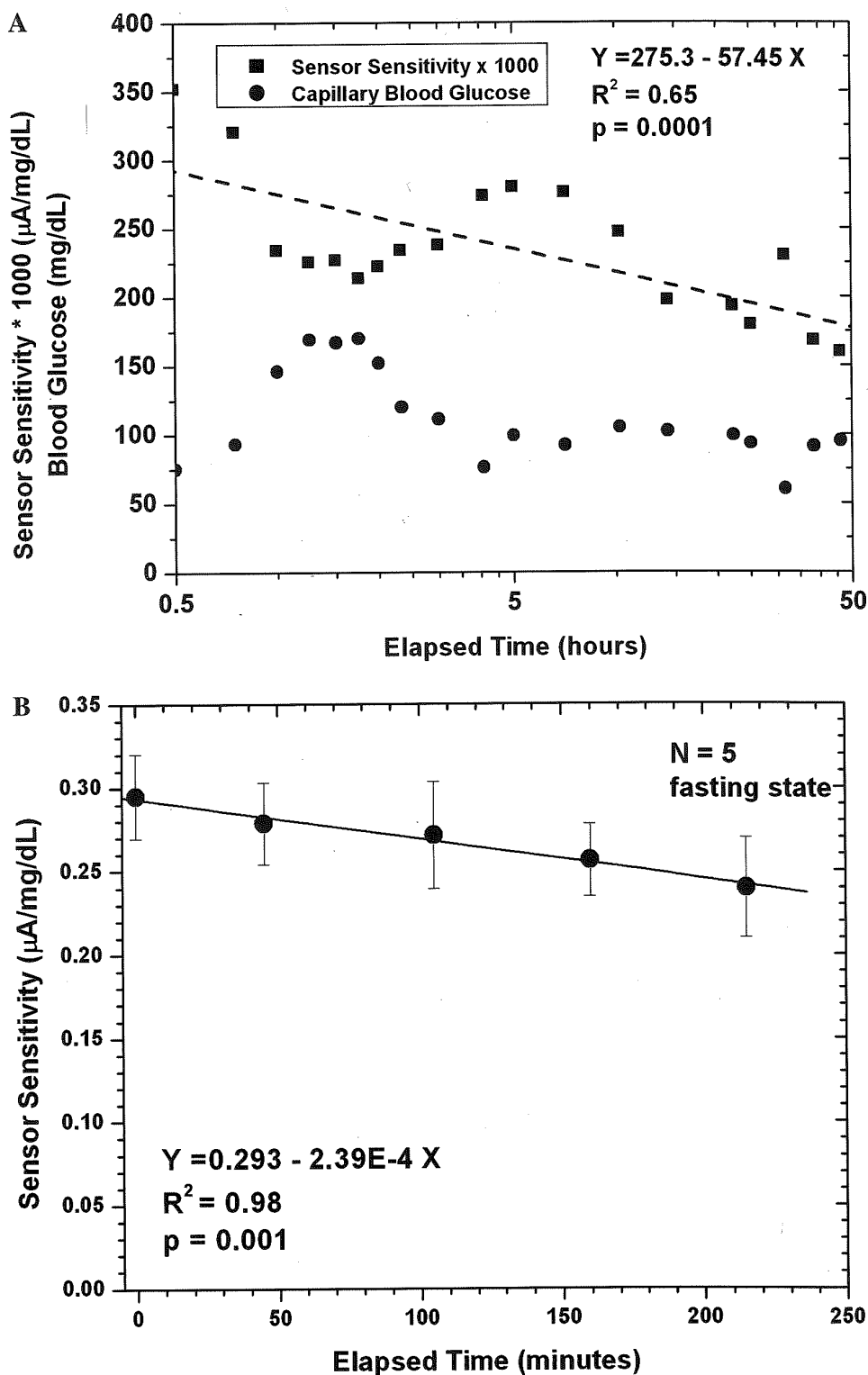


FIG. 1. Sensor sensitivity declines as a function of time after insertion. (A) Sensitivity profile for a 41-year-old woman without diabetes over 48 h with frequent finger capillary blood samples for calibration. The subject underwent an OGTT starting at the 30-min time point. The linear fit to the sensitivity data on a logarithmic time scale indicates an exponential decay in sensitivity over long time periods. An inverse relationship between glucose levels and sensor sensitivity is also evident. (B) Sensitivity profile over 4 h in five fasting subjects, which minimizes temporal glucose variations, shows a 19% decline in sensitivity over the first 4 h. A linear fit of the data explained 98% of the time-dependent behavior, indicating that, for short time periods, linear decay sufficiently represents the sensor's logarithmic dependence on time.

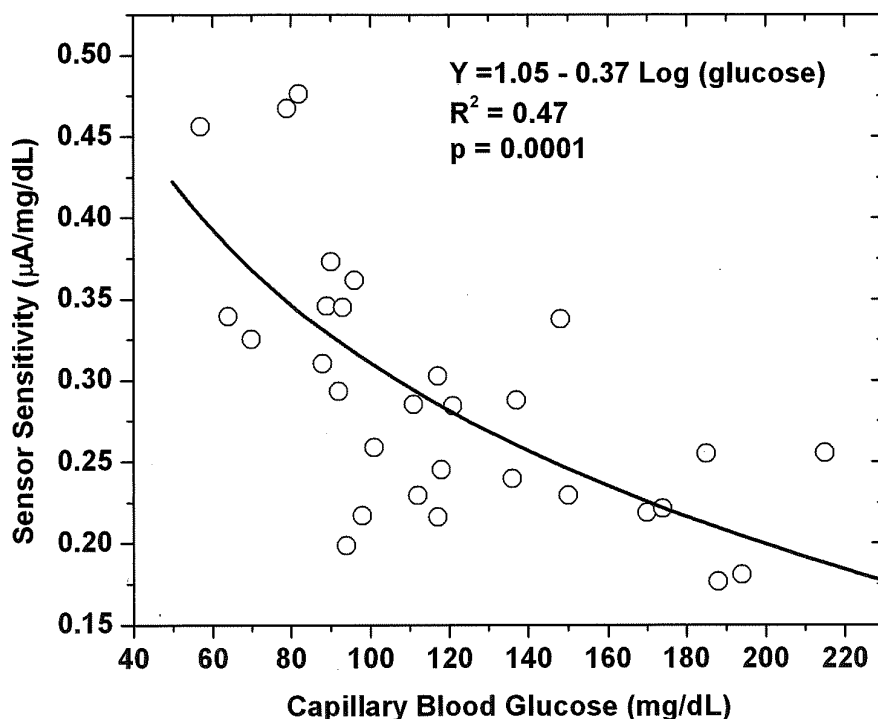


FIG. 2. Sensor sensitivity depends strongly on glucose concentration. Sensor sensitivity as obtained from 4-h recordings of five subjects during OGTT. Data have been corrected for the sensor time dependence. A strong inverse dependence of sensor sensitivity on glucose concentration is evident. This dependence can be modeled as a logarithmic function of glucose concentration.

ative solution was used. A typical glucose response obtained during OGTT using our algorithm is shown (Fig. 3), with glucose values calculated using the MiniMed Solutions version 3.0c algorithm included for comparison. The decreasing sensitivity of the sensor with time and glucose concentration is clearly evident in the values obtained by the Medtronic algorithm. A progressive decline in blood glucose levels appears to be occurring, even though a 75-g glucose bolus was consumed at $t = 30$ min. In addition, the Medtronic algorithm substantially underreports the peak glucose level, consistent with the decreased sensitivity at high glucose levels. Of the five calibration points in this data set, the Medtronic algorithm significantly over- or underestimated four of the five values. Conversely, the modified conversion algorithm demonstrates a typical glucose tolerance response, with a distinct peak approximately 1 h after glucose administration, and a return to baseline after approximately 3 h.¹² The mean absolute relative

difference (MARD)¹³ between CBG and Solutions version 3.0c-converted values for this data set is 24.8%, while MARD for the modified conversion algorithm is only 9.9%.

The modified conversion algorithm was tested on data collected from 17 additional women without diabetes during OGTT. For this data set, the average values for the three regression coefficients in the conversion algorithm were as follows: A (time coefficient) $= -0.031 \pm 0.021 \mu\text{A}/\text{min}/(\text{mg}/\text{dL})$; B (glucose coefficient) $= -0.217 \pm 0.10 \mu\text{A}/(\text{mg}/\text{dL})^2$; and C (constant) $= 0.704 \pm 0.226 \mu\text{A}/\text{mg}/\text{dL}$. Overall MARD for the 85 CBG values was $20.6 \pm 5.9\%$ for MiniMed Solutions version 3.0c calibration and $11.6 \pm 6.5\%$ for the modified conversion algorithm.

DISCUSSION

The limitations of glucose oxidase sensors, such as those used with the CGMS, are com-

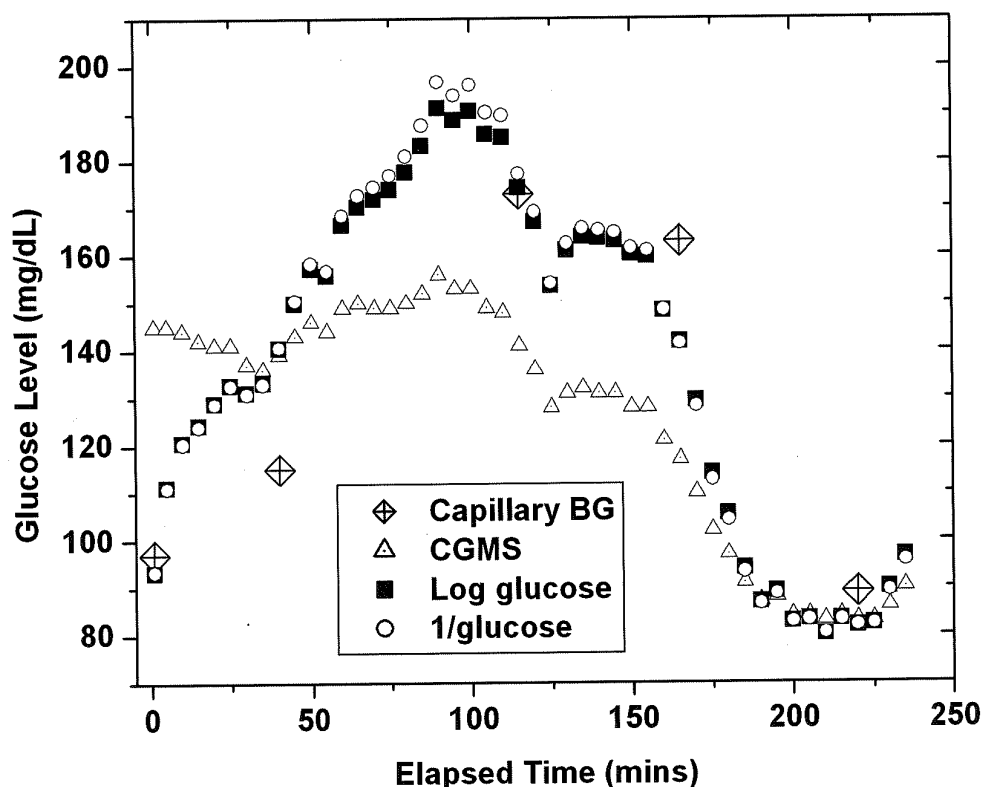


FIG. 3. OGTT profiles using MiniMed and enhanced conversion algorithms. Corrected OGTT profiles (filled squares) for one subject were obtained using a conversion algorithm incorporating corrections for time since sensor insertion and glucose levels: $S = ISIG/BG$ and $S = A \times \text{Log}(t) + B \times \text{Log}(BG) + C$, with coefficients calculated by multiple regression using five calibration CBG values (diamonds). For this individual, $A = -0.059$, $B = -0.081$, $C = 0.451$. The OGTT profile for the same dataset using the Minimed Solutions version 3.0c conversion software is shown for comparison (open triangles). In addition, corrected values using $(1/\text{glucose})$ to approximate $\text{Log}(\text{glucose})$ are shown (open circles).

mon to most biosensors.¹⁴ Biofouling (adsorption of plasma proteins and inflammatory cells due to an inflammatory response) has been shown to contribute to the decrease in sensor sensitivity through a decrease in the available surface area over time.¹⁵ In addition, reaction-diffusion dynamics limit conversion rates at high substrate concentrations, leading to non-linear behavior over the operating range of the device. Both phenomena were observed with the CGMS sensor in the early stages of implantation, consistent with previous reports.¹⁶ For this reason, the manufacturer suggests caution when using the sensor in the first 12–24 h after insertion (D. Wesley, Medtronic MiniMed, personal communication). However, to make optimal use of this glucose monitoring technology in the research setting, it would be beneficial to have data that accurately reflect the temporal dynamics and range of glucose values, starting

shortly after sensor insertion. We found that we could improve results through a relatively simple change in sensor current data conversion.

We observed the strongest sensor dependence on BG levels. This was best modeled as a decrease in sensitivity with the logarithm of glucose, consistent with many studies on reaction rates at surfaces, where substrate diffusion and adsorption is followed by product desorption.¹⁷ The presumption of a linear relationship tends to overestimate glucose levels at low glucose concentrations and underestimate at high levels, resulting in a smoothing of variations in reported values. Interestingly, this issue was apparently addressed in the development of MiniMed's Solutions version 3.0c software, which, according to company literature, was focused on dampening the large swings in glucose levels, keeping more readings in the target glucose range of 80–170 mg/dL.

Calculation of BG levels using $\log(BG)$, however, is not trivial since the conversion algorithm requires an iterative solution. This computation is easily performed with technical software packages such as *Mathematica* or "R" (public domain), but not in spreadsheet applications such as Microsoft Excel. If necessary, a first order approximation of $\log(BG)$ may be used (i.e., $1/BG$), wherein the expression for sensitivity would become:

$$ISIG/BG = A \times \log_{10}(t) + B \times (1/BG) + C \quad (4)$$

In this case, BG can readily be solved in closed form:

$$BG = (ISIG - B)/[C - A \times \log_{10}(t)] \quad (5)$$

While in many instances this approximation produced a good fit to CBG levels (Fig. 3), in some cases it gave glucose values that were unrealistically large (on the order of 10^4), or even negative; therefore it was not pursued further.

A dependence of CGMS sensitivity on time was also observed. The decrease in sensitivity seen in the 48-h monitoring study is consistent with Medtronic's claim that after 24 h the dependence on time is much reduced. The change in sensitivity with time over the first 3–4 h of sensor life was less pronounced. While we found that a linear relationship with time actually fit our short-term data better than a logarithmic relationship, in the calculations in this paper we have used a logarithmic factor since it did not complicate calculations and permits extension to longer time periods. Therefore, while treating sensor sensitivity as logarithmically dependent on time is necessary for long-duration recordings, modeling sensitivity as decaying linearly with time could be sufficient for at least the first few hours of sensor use.

The conversion algorithm proposed here provides a close fit to the CBG values of normoglycemic adults undergoing OGTT, with an MARD of 11.6% in the first 3 h after sensor insertion. The accuracy of the converted data, however, is a function not only of the algorithm, but also of the calibration data. In this study, calibration data were obtained with an over-the-counter CBG meter, as recommended by Medtronic, but such meters have, on aver-

age, a 15% measurement error relative to laboratory BG assays. It is reasonable to believe that more accurate glucose values would be obtained with this algorithm if we were to use laboratory glucose values for calibration of CGMS. Another approach to improving the accuracy of the conversion algorithm would be to increase the number of calibration points. While only three calibration points are required for this algorithm, we used five points over 4 h of testing. A greater number of calibration points would tend to cancel out the errors in the CBG measurements and should, in principle, lead to more accurate BG estimates. Given the ready availability of statistics software, it is equally convenient to obtain redundant calibration tests and use multiple regression to provide a best estimate of the parameters A , B , and C . However, requiring a large number of invasive measurements negates one benefit of the CGMS.

In summary, incorporation of glucose- and time-dependent factors in a conversion algorithm for the Medtronic's CGMS monitor provides an improved estimation of the variations in glucose in normal subjects undergoing OGTT in the first few hours after sensor insertion. Further studies are necessary to test whether this conversion algorithm can be used in the evaluation of other subjects, where CGMS portability would be of benefit, but it is not practical to wait 24 h before obtaining accurate data.

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Address reprint requests to:

Leann M. Lesperance, M.D., Ph.D.
Department of Bioengineering
Watson School of Engineering
and Applied Science
Binghamton University
Binghamton, NY 13902-6000

E-mail: llespera@binghamton.edu