

The Role of the Independent Variable to Glucose Sensor Calibration

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ABSTRACT

In vivo subcutaneous glucose sensor accuracy depends on the calibration method. Sensor accuracy was assessed during standard oral glucose tolerance tests in six non-diabetic subjects each wearing six subcutaneous glucose sensors (Medtronic MiniMed). Paired blood glucose (B_G) and sensor current readings were used for retrospective sensor calibration using either B_G or sensor current as the independent variable. Sensor accuracy after calibration was assessed using three criteria: linear regression between B_G and sensor glucose (S_G); correlation; and mean absolute difference (MAD), defined as $100 \times |B_G - S_G|/B_G$. Calibration with B_G as the independent variable resulted in unbiased estimates of regression slope (1.02, not different than 1, $p < 0.01$) and y -intercept (-1.06 mg/dL, not different than 0, $p < 0.01$). In contrast, calibration with sensor current as the independent variable resulted in biased estimates of slope (0.76, different than 1, $p < 0.01$) and y -intercept (31.25 mg/dL, different than 0, $p < 0.01$). However, with sensor current as the independent variable, the MAD was lower than the corresponding value for calibration with B_G at the x -axis ($15.00 \pm 0.47\%$ vs. $18.35 \pm 0.63\%$, $p < 0.01$). The Pearson correlation coefficient between B_G and S_G was higher when using sensor current as the independent variable ($R = 0.82$ vs. $R = 0.79$ when using glucose on the x -axis). We suggest that despite the fact that calibration with sensor current as the independent variable leads to a bias in the estimate of B_G , it is a more appropriate calibration method when the primary concern is minimization of the MAD between S_G and B_G .

INTRODUCTION

MONITORING OF BLOOD GLUCOSE (B_G) in patients with diabetes is of paramount importance to the management of the disease. Studies have shown¹⁻³ that intensive glucose management can prevent or delay the onset of complications related to elevated levels of B_G and lead to an $\sim 60\%$ reduction in the risk for diabetic retinopathy, neuropathy, and nephropathy.⁴

Patients typically perform self-monitoring of B_G at home by capillary samples obtained through skin punctures. However, only a small number of blood samples can be drawn daily as skin punctures are both inconvenient and painful. A continuous minimally invasive B_G measurement should substantially contribute to superior management of glycemia and dramatically improve the quality of life of subjects with diabetes. Glucose information provided by continuous glucose monitors has been

shown to adequately track acute changes in plasma glucose⁵ and reveal previously unrecognized nonfavorable glucose patterns^{6–8} lasting from a few minutes to several hours. With continuous glucose monitoring these excursions can potentially be corrected.

For the purpose of continuous glucose measurement, the subcutaneous space is an ideal surrogate for the placement of the glucose sensors, as both patients and physicians can easily and safely access it. However, the small size of the sensor, the abundance of proteins and other nutrients in the interstitial fluid (ISF), and numerous other subject-dependent factors constitute sources of additive noise to the glucose-specific sensor current. Moreover, while the subcutaneous sensor estimates glucose through measurement of the glucose concentration in the ISF, no method for accurate measurement of the ISF glucose concentration is currently available. The use of B_G as a reference for sensor calibration introduces errors to the sensor glucose (S_G) either due to the difference of glucose dynamics between ISF and blood or because of a time-varying gradient between B_G and ISF glucose. Studies^{9–11} on the gradient and dynamic relationship between blood and ISF have reported ISF glucose concentrations to range from 20% to 110% of B_G and that changes in ISF glucose may precede or lag changes in B_G , depending on the specific characteristics of the insertion site (i.e., insulin sensitivity of the tissue surrounding the sensor) and the subcutaneous glucose measurement method. Moberg et al.¹² unveiled different equilibration times between adipose tissue and muscle and suggested that conventional B_G measurements might not be the optimal solution for glucopenia detection. Therefore, further validation of glucose sensors requires extensive understanding of the insertion site characteristics as well as adequate comprehension of the relationship between sensor current and B_G .

For linear amperometric sensors, retrospective calibration of the sensor current to B_G level can be implemented by standard least squares. Calibration factors can be calculated either by using B_G as the reference (x -axis) and sensor current as the dependent variable (y -axis), or vice versa. With B_G on the x -axis, the slope after linear regression yields an estimate

of sensor sensitivity ($\text{nA}/[\text{mg}/\text{dL}]$) to interstitial glucose, while the offset represents both a nonspecific “background” current as well as any transport delay of glucose between plasma and ISF.

The quantity with the higher measurement accuracy is believed to be the best theoretical choice for the independent calibration variable. Measurements of B_G from laboratory analyzers have demonstrated very low measurement error (usually $<2\%$). Nonetheless, the estimates of commercially available home B_G meters have been shown to range within as much as 20% of the actual B_G .¹³ In conclusion, there is no clear answer yet to the question of the choice of an independent variable for retrospective calibration. Thus, the purpose of the present study was to evaluate the impact of using B_G versus sensor current as the independent variable for retrospective calibration of the Medtronic MiniMed subcutaneous glucose sensor.

MATERIALS AND METHODS

Oral glucose treatment

The study was performed in seven normal glucose-tolerant human subjects. Data acquired from one of the subjects were excluded because of excessive noise in the sensor signal. Each subject wore six Medtronic MiniMed sensors, inserted simultaneously at the abdominal area before the beginning of the experiment. The protocol allowed a “settling in” period of 3 h, followed by a 2-h basal glucose sampling and a 3-h standard oral glucose tolerance test (OGTT) (75 g of glucose). Glucose measurements were obtained throughout the experiment by using the HemoCue[®] system according to a predefined sampling schedule (every $1/2$ h before the start of the OGTT, every 5 min during the first $1/2$ h, every 10 min during the second half of the first hour of the test, and every 15 min thereafter until the end of the test). Subjects had no skin abnormalities or current or concomitant illnesses and were at least 18 years of age.

Glucose sensor

Sensors used in this study are amperometric devices designed and manufactured by Medtronic MiniMed for up to 3 days of continuous subcutaneous use. The sensor is manufactured using semiconductor technology and consists of an electro-enzymatic three-electrode cell in which a constant potential of 0.535 V is maintained between the reference and working electrode. At this potential and under the presence of the glucose oxidase enzyme, glucose is oxidized to hydrogen peroxide, and the current generated is proportional to the glucose concentration in the ISF.^{14–18} The sensor is enclosed in flexible polymer tubing with a side window exposing the active electrode area that is covered by a glucose diffusion limiting membrane. The membrane defines a linear relationship between ISF glucose concentration in surrounding tissues and sensor current in the range of 20–400 mg/dL. The *in vitro* precision of the sensor is within 5% in the range of 50–350 mg/dL and the response time is <1.5 min (τ_{90} ; time to reach 90% steady state). The sensor is embedded in a split (half) 22-gauge needle that is removed after insertion. The sensor connects to a Holter-style continuous glucose monitoring system (CGMS) via a cable where the current data are stored for later calibration and evaluation by the physician. Sensor signals are sent to the monitor every 10 s, with the average value stored in memory every minute. (The commercially available CGMS reports sensor values every 5 min. For this study a modified CGMS was used in order to collect data on a 1-min sampling interval.) No additional processing was applied to the stored sensor current inside the monitor. Glucose sensors were packed individually and sterilized in accordance with the Association for the Advancement of Medical Instrumentation Guideline for Electron Beam Radiation Sterilization of Medical Devices. Components that pass into subcutaneous space or contact the skin meet the appropriate requirements of ISO-10993-1 (Biological Evaluation of Medical Devices).

Calibration analysis

Data were downloaded from the glucose monitor and filtered with a seventh-order finite

impulse response (FIR) filter (see Appendix). The filtered sensor signal was then paired with B_G values acquired at least 4 h after sensor insertion, and calibration was performed with two different methods (Fig. 1) to yield sensor glucose values. The first method used B_G as the independent variable, therefore minimizing the error between the sensor current and the linear regression line, whereas the second method used sensor current on the x -axis and minimized the difference between actual B_G values and the linear regression line. In each case the slope and intercept of the linear regression were used for S_G calculation.

The performance of each method was evaluated by three statistical methods: linear regression of B_G versus S_G ; correlation; and mean absolute difference (MAD), defined as $(|B_G - S_G|/B_G) \times 100$. Linear regression and MAD were used as an index of numerical agreement, whereas the correlation coefficient was used as a measure of the trend accord between the B_G measurements and the sensor readings. Sensor performance in the hyper- ($B_G > 180$ mg/dL) and hypoglycemic ($B_G < 65$ mg/dL) ranges was separately evaluated by calculation of the percent bias of the sensor estimate and by examining the sensor error distribution.

Data analysis and filtering were implemented in MATLAB® and Graph Pad Prizm®. Data are presented as mean $\pm$ SEM unless otherwise stated.

RESULTS

B_G reached a peak value (181.6 ± 7.3 mg/dL) 50 min after glucose administration. The glucose nadir (61.00 ± 1.61 mg/dL) was observed 165 min after initiation of the glucose challenge. The experimentally achieved glucose excursion was 129.8 ± 12.7 mg/dL. Both calibration methods generated sensor glucose that tracked B_G successfully (Fig. 2). Retrospective calibration with B_G on the x -axis (method 1) generated a higher calibration factor than calibration with sensor current on the x -axis [method 2; 6.70 ± 0.48 vs. 4.60 ± 0.32 (mg/dL)/nA, $p < 0.01$]. No statistical difference was observed in the offset (4.39 ± 5.81 vs. -3.10 ± 2.21 nA).

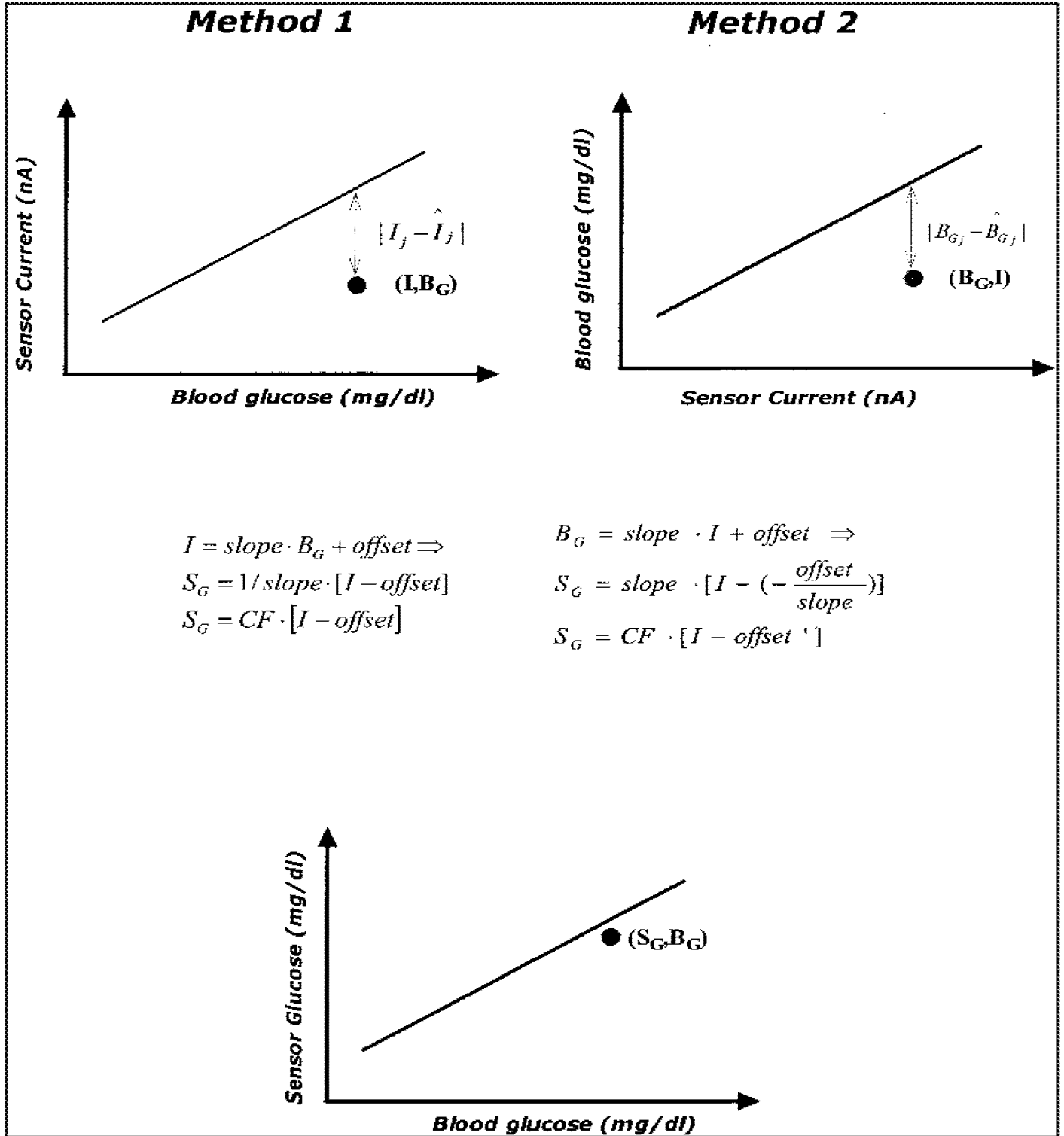


FIG. 1. Schematic of the two proposed ways of calibration. Use of B_G on the x-axis (**top left**) yields a regression line by minimizing the sum of errors $|I_j - \hat{I}_j|$ (difference between the sensor current measurement and the regression line). Conversely, use of sensor current as the independent variable (**top right**) minimizes the sum of errors $|B_{Gj} - \hat{B}_{Gj}|$ (difference between the B_G regression line). Each method results in an S_G estimate (see equations) that can be compared with B_G (**bottom panel**).

After calibration with method 1, the regression between sensor and B_G (Fig. 3) indicated that neither the slope (1.02 ± 0.03) nor the intercept (-0.91 ± 3.33 mg/dL) was biased

(slope not different than 0 and y-intercept not different than 1, $p < 0.01$). However, calibration with method 2 generated a biased slope (0.76 ± 0.02 , different from 1, $p < 0.05$) and an

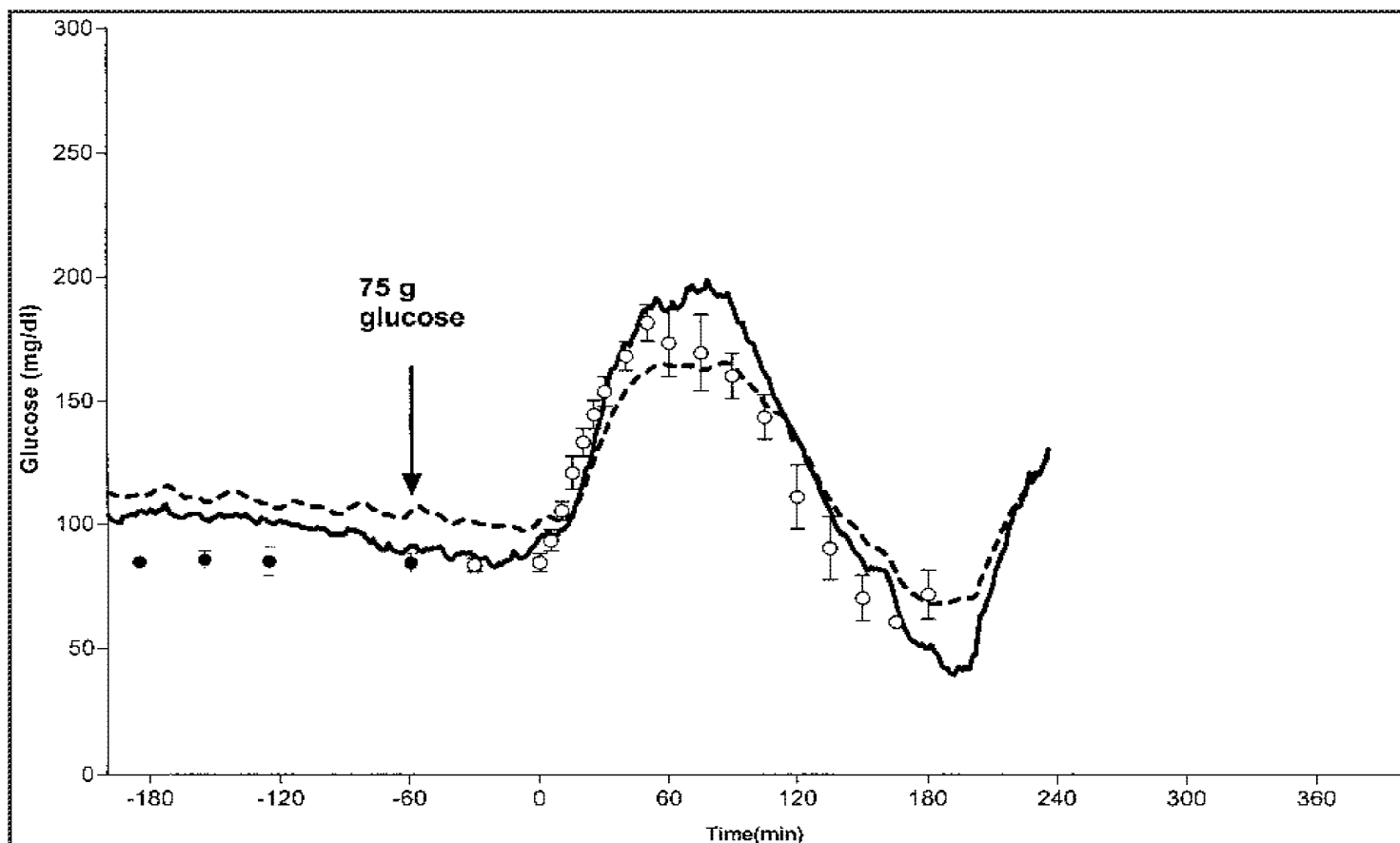


FIG. 2. Average B_G (circles; $n = 6$) and S_G ($n = 36$) after retrospective calibration with B_G (solid line) and sensor current (dotted line) on the x -axis (open circles were used for calibration).

intercept (31.25 ± 2.24 mg/dL, different from 0, $p < 0.05$). Bias in the slope and intercept indicates an underestimation of hyperglycemia and an overestimation of hypoglycemia. This occurs without an overall bias when comparing B_G and S_G throughout the experimentally achieved glucose range ($p < 0.01$). More specifically, while method 1 yielded unbiased S_G estimates in both the hypo- ($B_G < 65$ mg/dL) and the hyperglycemic range ($B_G > 180$ mg/dL) (hypoglycemic range, 56.30 ± 0.67 vs. 50.77 ± 2.52 mg/dL for the sensor, $p > 0.05$; hyperglycemic range, 197.5 ± 1.53 vs. 194.3 ± 3.55 mg/dL for the sensor, $p > 0.05$), method 2 generated overestimation of hypoglycemia (56.30 ± 0.67 mg/dL for reference B_G vs. 67.96 ± 2.43 mg/dL for the sensor, $p < 0.001$) and underestimation of high B_G concentration (178.6 ± 2.58 mg/dL for the sensor vs. 197.5 ± 1.53 mg/dL, $p < 0.001$). Although method 2 generated a biased estimate of B_G , the MAD was lower than the corresponding index from

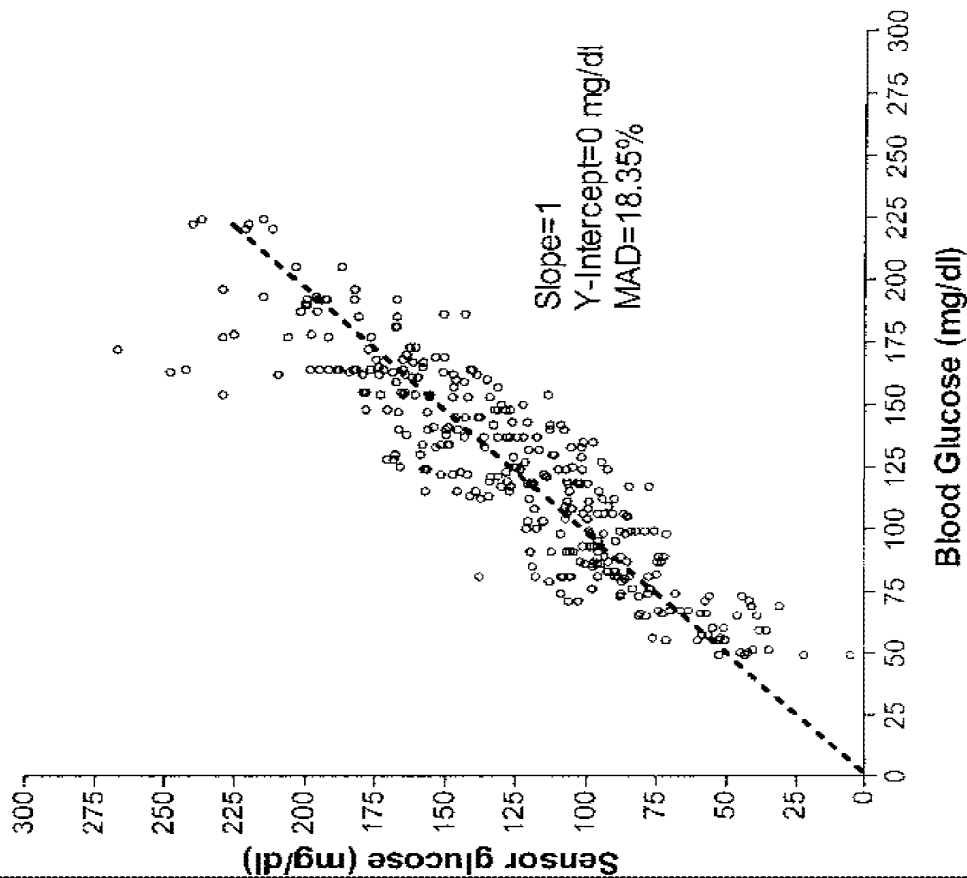
method 1 ($15.00 \pm 0.47\%$ vs. $18.35 \pm 0.63\%$, $p < 0.01$), and the correlation coefficient between S_G and B_G was higher (0.82 vs. 0.79). The trade-off between bias and MAD is a common statistical occurrence¹⁹ and leads to a narrower error distribution around the biased mean in hyper- and hypoglycemia when using method 2 for sensor calibration (Fig. 4), since the mean square error (MSE) is the sum of the variance and bias ($MSE = \text{var} + \text{bias}^2$).

DISCUSSION

The present study investigated the role of the independent variable during retrospective calibration of the Medtronic MiniMed subcutaneous glucose sensor. The goal of the study was to evaluate whether sensor performance is affected by the choice of the independent calibration variable (B_G or sensor current). Our experimental design relied on a well-established

Linear Regression and Mean Absolute Difference between Blood and Sensor Glucose.

Linear regression between sensor and blood glucose after calibration using blood glucose on the x-axis



Linear regression between sensor and blood glucose after calibration using sensor current on the x-axis

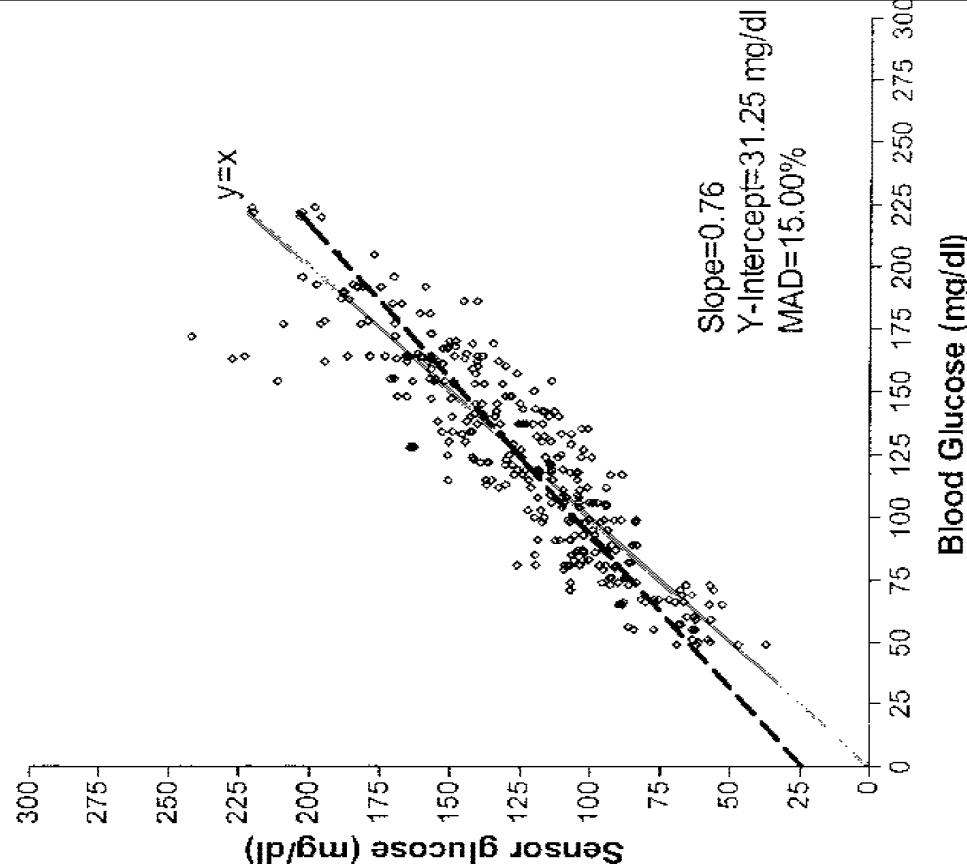


FIG. 3. Linear regression between B_G and S_G after calibration with glucose (left panel) and sensor current (right panel) on the x-axis. Use of sensor current as the independent calibration variable yields a biased estimate of glucose in hypo- and hyperglycemic ranges but generates lower MAD between B_G and S_G .

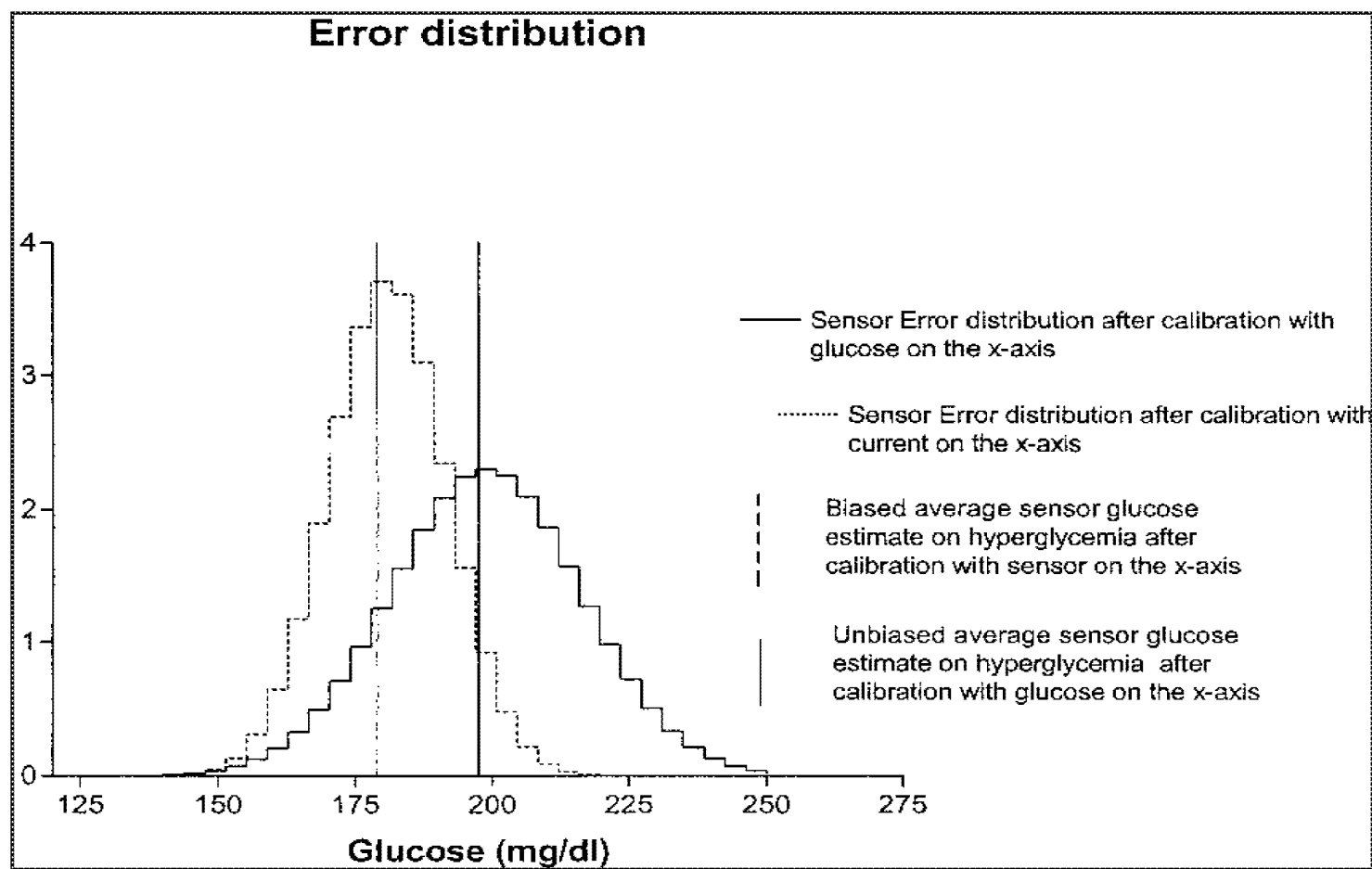


FIG. 4. Error distribution (%) and S_G average values in hyperglycemic ranges after using the two proposed methods of calibration. Use of B_G as the independent calibration value gives an unbiased estimate of glucose but yields a wider error distribution. Conversely, use of sensor current on the x-axis during calibration provides a biased estimate of S_G but yields a much narrower error distribution around the average of the biased estimate.

protocol that facilitated evaluation of the sensor performance during rapid, yet physiological, changes in B_G , in both the hypo- and hyperglycemic range. Results indicated that the estimate of sensor sensitivity is contingent upon the choice of independent variable. Use of sensor current as the independent variable generated a lower calibration factor (higher sensor sensitivity, $p < 0.01$) and a lower offset. With this method, MAD was lower, but the sensor values were biased.

The bias in S_G was only apparent when the hypo- and hyperglycemic regions were assessed individually; comparison between B_G and S_G throughout the experimentally achieved glucose range indicated the values were not different ($p > 0.05$). The bias was $\sim 21\%$ in the hypoglycemic region and $\sim 10\%$ in the hyperglycemic range and is indicated by a regression slope less than 1 (Fig. 3, right

panel). The use of B_G on the x-axis for calibration provided an unbiased estimate throughout the glucose range ($p > 0.05$; Fig. 3, left panel) but generated a higher MAD ($18.35 \pm 0.63\%$ vs. $15.00 \pm 0.47\%$ when compared with current on the x-axis, $p < 0.01$). MAD is widely accepted as a measure of sensor accuracy. Sensor current as the independent variable also resulted in a narrower error distribution in hyperglycemic and hypoglycemic regions. Therefore, S_G is closer to the actual B_G value throughout the range of its values when current is used as the independent calibration variable.

The population correlation coefficient (i.e., the correlation for the pooled data across all subjects) was also higher when sensor current was used as the independent calibration variable. Correlations were not averaged across individuals in that for a single subject the corre-

lation is independent of the choice of axis. If S_G is calculated as a linear expression of sensor current (true in both methods of retrospective sensor calibration) the correlation is identical.^{20,21}

The overestimation of hypoglycemia, together with the underestimation of hyperglycemia, that occurs when calibrating with sensor current as the independent variable is of concern. Specifically, the reported range of S_G values will be narrower than the actual B_G range and could affect reporting of hypo- and hyperglycemia. This problem can, however, be countered by embodying the bias effect into the sensor alarms. In such a case the glucose monitor hypoglycemia alarm would be set at a slightly higher level, and the hyperglycemia alarm would be set at a lower level. These changes could be imposed by software so as to be transparent to the user. The alarm values could be triggered using the rate of change of S_G so as to provide an advanced warning of impending hypoglycemia. With this scheme, the glucose monitor would combine the benefits of smaller error associated with current as the independent variable, and maintain the user-desired alarm levels. Validation of this technique will, however, require a separate study on a larger population of individuals with type 1 diabetes.

The present study provides a solid theoretical base for choosing the independent calibration variable. The two methods presented here represent two extremes: With glucose on the x -axis, errors in sensor current are minimized, and the resulting calibration is unbiased; with current on the x -axis, errors in S_G are minimized, but the result is biased at low and high glucose. A balance between these two extremes could be obtained by use of Deming regression, which minimizes both errors.²² This method requires the user to specify the relative weights of the two error components (ideally the inverse of the variance). Deming regression results in MAD and bias that varies between the two extremes reported here (data not shown). Ultimately, the method of choice may depend on the desired performance specifications and intended use.

Results from the present study also provide insight into the choice of offset for a one-point

calibration. That is, in the simplest real-time calibration algorithm the offset is fixed, and the most recent B_G measurement is used to estimate the calibration factor. The choice of offset is important and directly linked to sensor performance. Our results indicate that a low offset value would contribute towards underestimation of the peak-to-peak B_G sensor estimate of B_G but give better MAD and improved correlation between S_G and B_G (across the population). Increasing the offset would lead to an improved (less biased) estimate of peak-to-peak glucose but would result in an elevated MAD and lower correlation.

In summary, each of the proposed calibration methods possesses desirable properties but also contributes towards statistically unwanted characteristics of sensor glucose. The adoption of sensor current as the calibration variable generates more accurate S_G values,

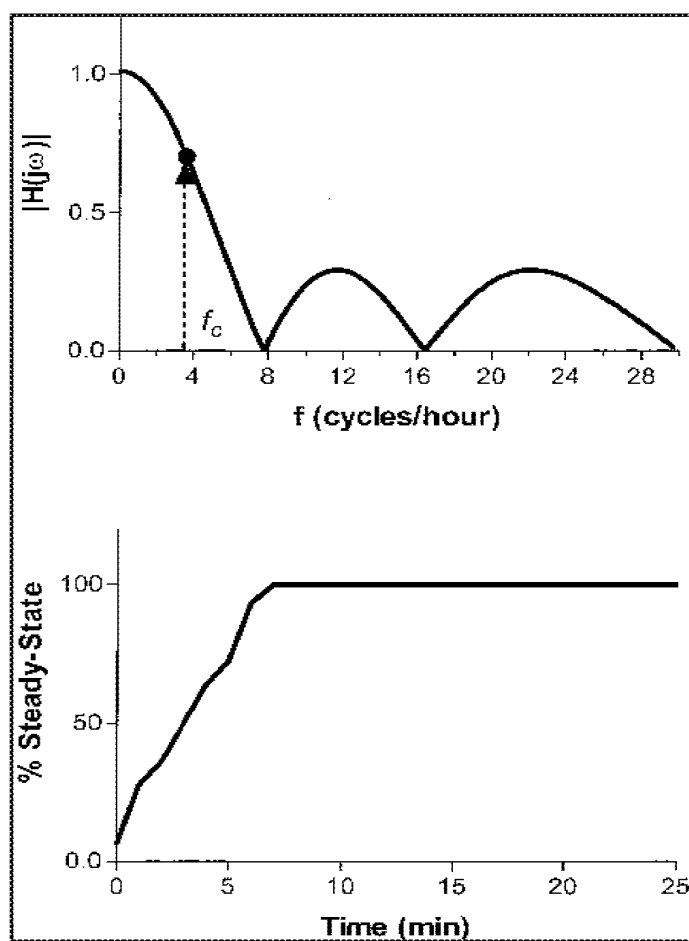


FIG. 5. Amplitude (top panel) and step (bottom panel) response of the seventh-order FIR filter used to reduce the effect of noise to the sensor. The filter has a cutoff frequency of 3.58 cycles/h and a rolloff of 7.94 db/octave.

provides a higher population correlation between S_G and reference glucose, but introduces a bias at low and high glucose values. We suggest that despite the fact that calibration with sensor current as the independent variable leads to a bias in the estimate of low and high B_G , it is a more appropriate calibration method when the primary concern is minimization of the MAD. For situations in which eliminating bias is more important than minimizing MAD sensors would be more appropriately calibrated with glucose on the x -axis.

APPENDIX

The effect of noise to the sensor can be reduced by use of standard FIR or infinite impulse response (IIR) digital filter. The choice of the type of filter—IIR or FIR—as well as the selection of a filter order and a design method are issues that relate to the bandwidth of the input signal as well as the desired properties of the filter output. In general, successful design of a filter requires knowledge of the spectral properties of the input signal, the spectral density of the additive noise, elimination of unwanted effects on the filter output (ripple, stability, delays, gain over frequency), as well as ease of implementation. In our case, we only considered FIR filters since they are simpler to design yet satisfy all requirements set for the intended use. Most importantly, they introduce the same delay to every frequency component (linear phase) of the original signal and are inherently stable.

Until today, limitations related to the volume of blood to be drawn and the minimum time intervals between samples have not favored the use of a sampling rate adequately fast to unveil more information on glucose bandwidth. The emergence of glucose sensor technology is a reliable alternative towards this direction, providing frequent glucose measurements for consecutive days under varying conditions of diet and physical activity.

In the present study, a seventh-order FIR filter was used [Cutoff frequency was 3.58 cycles/h and was chosen empirically after examination of sensor profiles. The filter has a group delay of 3.5 min, and filter rolloff was of

7.94/octave (Fig. 5)]. It is important to note that use of any filter adds delay on top of the intrinsic sensor delay and the delay between B_G and ISF glucose. During the calibration process, delays between B_G and sensor current emerge as errors in the S_G and fundamentally decrease the performance of any glucose monitoring system.²³ Nonetheless, provided that both the gradient and the delays are constant, digital filters can be used for delay correction.²⁴ Also, application of any low-pass filter to the sensor current affects the calibration parameters assessed after linear regression. More specifically, application of a filter increases the calibration offset (in nA), the correlation coefficient between sensor current and B_G , and the MAD.

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