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ORIGINAL ARTICLES

Estimates of Total Analytical Error in Consumer and Hospital Glucose Meters Contributed by Hematocrit, Maltose, and Ascorbate

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Abstract

Background:
Patients and physicians expect accurate whole blood glucose monitoring even when patients are anemic, are undergoing peritoneal dialysis, or have slightly elevated ascorbate levels. The objective of this study was to estimate analytical error in two consumer and two hospital glucose meters contributed by variations in hematocrit, maltose, ascorbate, and imprecision.

Method:
The influence of hematocrit (20–60%), maltose, and ascorbate were tested alone and in combination with each glucose meter and with a reference plasma glucose method at three concentrations of glucose. Precision was determined by consecutive analysis (n = 20) at three levels of glucose. Multivariate regression analysis was used to estimate the bias associated with the interferences, alone and in combination. Total analytical error was estimated as $|\%\ \text{bias}| + 1.96\ (\%\ \text{imprecision})$.

Results:
Three meters demonstrated hematocrit bias that was dependent upon glucose concentration. Maltose had profound concentration-dependent positive bias on the consumer meters, and the extent of maltose bias was dependent on hematocrit. Ascorbate produced small but statistically significant biases on three meters. Coincident low hematocrit, presence of maltose, and presence of ascorbate increased the observed bias and was summarized by estimation of total analytical error. Among the four glucose meter devices assessed, estimates of total analytical error in glucose measurement ranged from 6 to 68% under the conditions tested.

Conclusions:
The susceptibility of glucose meters to clinically significant analytical biases is highly device-dependent, and low hematocrit exacerbated the observed analytical error.

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Abbreviations: (CV) coefficient of variation, (IFCC) International Federation of Clinical Chemistry, (ISO) International Organization for Standardization, (PQQ) pyrroloquinoline quinone

Keywords: ascorbate, bias, glucose meters, hematocrit, imprecision, interference, maltose, total error

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Introduction

The inequality of glucose results determined by handheld meters and hospital central laboratories undermined confidence in medical decisions and fostered technological improvements and hundreds of studies on performance in various clinical settings from 1995 to 2010.[1] Several authors have described strategies to assess the discrepancies more consistently.[2–4] Factors that contribute to error with glucose meters include user error, environmental error, and several sources of analytical error.[5] There is ongoing debate comparing the merits of assessing the top-down total analytic error or the bottom-up method uncertainty of clinical laboratory methods,[6] however, both approaches aim to identify method factors and their influence on performance and medical decisions. In our opinion, the total analytic error method is better adapted for research in clinical settings.

Estimates of total analytical error account for sources of inaccuracy, imprecision, and random patient interferences.[2] The Clinical and Laboratory Standards Institute and International Organization for Standardization (ISO) have continued to develop and refine guidelines to assess glucose meter accuracy, for example the documents POCT12-A3 (in preparation as of 2010)[7] and ISO 15197 (published in 2003).[8] In ISO 15197, the minimum acceptable performance expectations for glucose meter performance are that 95% of the individual glucose results shall fall within ±0.83 mmol/liter (15 mg/dl) at low glucose concentration [<4.2 mmol/liter (75 mg/dl)] and within ±20% when glucose concentrations are higher. A recent audit found that only 16 of 27 Conformité Européenne systems met the ISO 15197 expectations.[9]

In a 2009 study, we screened two consumer and two hospital glucose meters for susceptibility to error due to hematocrit, maltose, and ascorbate[10] and developed a linear regression model to assess glucose meter performance.[4] In this study, we extend the analysis of the data collected for the two consumer and two hospital glucose meters using linear regression to predict bias and then compare estimates of total analytical error with ISO 15197 standards.

Methods

Instrumentation

$Meter_1$ is the Nova Biomedical StatStrip® (Waltham, MA) hospital meter that utilizes a modified glucose oxidase-based amperometric test system with hematocrit correction. $Meter_2$ is the LifeScan SureStep® Flexx (Milpitas, CA) hospital meter that uses a photometric glucose oxidase detection system. $Meter_3$, the Roche Diagnostics ACCU-CHEK® Aviva (Indianapolis, IN) consumer meter, uses an electrochemical pyrroloquinoline quinone (PQQ) glucose dehydrogenase amperometric strip and an electrode with hematocrit correction. $Meter_4$ is the Abbott Diabetes Care Precision FreeStyle Freedom Lite® (Alameda, CA) consumer meter that utilizes an electrochemical PQQ glucose dehydrogenase strip. The meter manufacturers were identified in our 2009 study.[10] The hexokinase method for measuring plasma glucose (Roche Hitachi 912, Roche Diagnostics, Laval, Quebec) was used as the comparative method. Hematocrit was determined using a Clay Adams Brand (Becton Dickinson & Company, Sparks, MD) Autocrit Ultra 3® microhematocrit centrifuge.

Within-Run Precision Study

Blood was collected from a healthy adult volunteer on the previous day and permitted to sit overnight to enable glycolysis to lower endogenous glucose concentration. Within-run precision was assessed by adding varying volumes of a glucose-spiking solution (20 g/dl glucose in deionized water) to three aliquots of heparinized whole blood, as described in our 2009 study.[10] The target glucose concentration ranges were 4–5 mmol/liter (low), 9–12 mmol/liter (medium), and 19–22 mmol/liter (high). Blood for each glucose concentration was consecutively measured on each glucose meter (n = 20). To ensure homogeneity and equilibration of intracellular and extracellular glucose concentrations, blood was mixed for 1 hour prior to testing and also mixed between analyses.

Interference Studies

Details regarding the interference studies were described in our 2009 study.[10] Briefly, hematocrit (20–60%), maltose (2.8 and 5.6 mmol/liter), and ascorbate (0.29 and 0.59 mmol/liter) were tested alone and in combination with one another, using two consumer meters, two hospital glucose meters, and the comparative method at three blood glucose concentration ranges (3.9–4.7, 11.3–13, and 20.6–24 mmol/liter). All samples were assayed with each of the meters within 20 minutes and by the hexokinase comparative method within 20 minutes of sample preparation.

Data Analysis

Linear regression was performed using Stata 11 statistical software (StataCorp LP, College Station, TX) as described

in our 2010 study[4] to estimate the bias caused by interferences. Within-run precision was determined by calculating coefficients of variation (CV_a = 100 × standard deviation/mean) for the replicate values. The percent bias of the meters was predicted using the regression models described in the **Appendix** at 10 mmol/liter plasma glucose [% bias = 100(Estimated Meter Glucose – 10 mmol/liter)/10 mmol/liter]. Estimated total analytical error was estimated as % Estimated Total Analytical Error = |% bias| + 1.96 (% CV_a).

Multivariate Regression Models

The relationship between hematocrit and glucose determined in whole blood and plasma is shown in **Equation (1)**.[11–13] This equation describes how the molality of glucose in whole blood detected by direct electrodes can be converted into the molarity of glucose in plasma, the consensus reporting unit. The International Federation of Clinical Chemistry (IFCC) consensus paper on reporting whole blood glucose recommends that point-of-care devices multiply detected glucose molality in whole blood by a constant factor of 1.11 to convert the value to glucose molarity, which assumes a constant hematocrit. Based on the relationship shown in **Equation (1)**, the linear models shown in **Equations (2)–(5)** were developed for regression analysis in this report to assess the influence of hematocrit, ascorbate, maltose, and their joint effects on glucose meter performance (see **Appendix: Linear Model Derivations**). All terms were retained in the linear models to generate the graphs depicted in the results section. Tables of the regression coefficients (with 95% confidence intervals and statistical significance) for each model are listed in the appendix to highlight the extent of joint effects among the interference conditions assessed.

Equation (1): The relationship between whole blood glucose molality and plasma glucose molarity.[13] Plasma water (PW), hematocrit (H), red blood cell water (RCW).

$$\text{Glucose}_{\text{plasma,molar}} = \text{Glucose}_{\text{whole blood,molal}} \frac{\text{PW}}{(\text{H} \times \text{RCW}) + ((1 - \text{H}) \times \text{PW})} \quad (1)$$

Equation (2): Model for estimation of conditional means of coefficients that describe the influence of hematocrit on glucose meter results.

$$\text{E}(\text{Glucose}_{\text{meter}}) = \beta_0 + \beta_1\text{Glucose}_{\text{plasma,molar}} + \beta_2\text{H} + \beta_3\text{HGlucose}_{\text{plasma,molar}} \quad (2)$$

Equation (3): Model for estimation of conditional means of coefficients that describe the influence of hematocrit and maltose (M) on glucose meter results.

$$\text{E}(\text{Glucose}_{\text{meter}}) = \beta_0 + \beta_1\text{G} + \beta_2\text{H} + \beta_3\text{M} + \beta_4\text{GH} + \beta_5\text{GM} + \beta_6\text{HM} + \beta_7\text{GHM} \quad (3)$$

Equation (4): Model for estimation of conditional means of coefficients that describe the influence of hematocrit and ascorbate (A) on glucose meter results.

$$\text{E}(\text{Glucose}_{\text{meter}}) = \beta_0 + \beta_1\text{G} + \beta_2\text{H} + \beta_3\text{A} + \beta_4\text{GH} + \beta_5\text{GA} + \beta_6\text{HA} + \beta_7\text{GHA} \quad (4)$$

Equation (5): Model for estimation of conditional means of coefficients that describe the influence of hematocrit, maltose, and ascorbate on glucose meter results.

$$\text{E}(\text{Glucose}_{\text{meter}}) = \beta_0 + \beta_1\text{G} + \beta_2\text{H} + \beta_3\text{M} + \beta_4\text{A} + \beta_5\text{GH} + \beta_6\text{GM} + \beta_7\text{GA} + \beta_8\text{HM} + \beta_9\text{HA} + \beta_{10}\text{MA} + \beta_{11}\text{GHM} + \beta_{12}\text{GHA} + \beta_{13}\text{HMA} + \beta_{14}\text{GMA} + \beta_{15}\text{GHMA} \quad (5)$$

Results

Linear regression of the model in **Equation (2)** was performed for each glucose meter to estimate hematocrit bias and if hematocrit bias was dependent on glucose concentration. **Figure 1A** shows the solid line of equivalence compared to a single dashed line of glucose values predicted for $Meter_1$ derived from the estimated conditional mean values of the regression coefficients (**Appendix, Table A1**). There was no evidence that $Meter_1$ was influenced by hematocrit and meter glucose results had a positive bias of ~5% (β_1 estimate: 1.049, estimates of $\beta_0 = \beta_2 = \beta_3 = 0$, no hematocrit effect) (**Appendix, Table A1**). In **Figure 1B**, $Meter_2$ displayed evidence that glucose concentrations were influenced by hematocrit ($\beta_2 \neq 0$) and that hematocrit bias was dependent on the glucose concentration ($\beta_3 \neq 0$). Dashed lines at various hematocrits predicted for $Meter_2$ derived from the estimated conditional mean values of the regression coefficients (**Table 1**) show that hematocrit bias increases at higher glucose concentration and that low hematocrit values cause a positive bias (and elevated hematocrit causes a negative bias) relative to the solid line of equivalence. The influences of hematocrit were more pronounced with the consumer devices $Meter_3$ and $Meter_4$ (**Figures 1C and 1D**). It is noteworthy that for $Meters_3$ and $Meter_4$, hematocrit modifies glucose measurement ($\beta_3 \neq 0$) and does not directly affect meter results ($\beta_2 = 0$).

The potential bias caused by maltose was assessed with each meter, at different hematocrits and glucose concentrations using the model described in **Equation (3)**. **Figure 2A** depicts a solid line of equivalence and dashed lines of glucose values predicted for $Meter_1$ derived from the estimated conditional mean values of the regression coefficients (**Appendix**, **Table A2**) for a constant hematocrit of 43%, and 0, 2.8, and 5.6 mmol/liter maltose. Neither maltose nor hematocrit altered detection of glucose by $Meter_1$ (**Appendix, Table A2**). Maltose had a small positive influence on $Meter_2$ at elevated glucose concentrations and this positive influence of maltose was increased at low hematocrit. It was clear from the minimal maltose effect in **Figures 2A** and **2B** that maltose was not hydrolyzed into glucose by disaccharidases during the study. The influence of maltose on $Meter_3$ and $Meter_4$ is consistent with reports by Flore and Delanghe[14] and Tsai and colleagues[15] of positive bias from this type of device when used to assess glucose in patients undergoing maltose-based peritoneal dialysis fluid therapy.

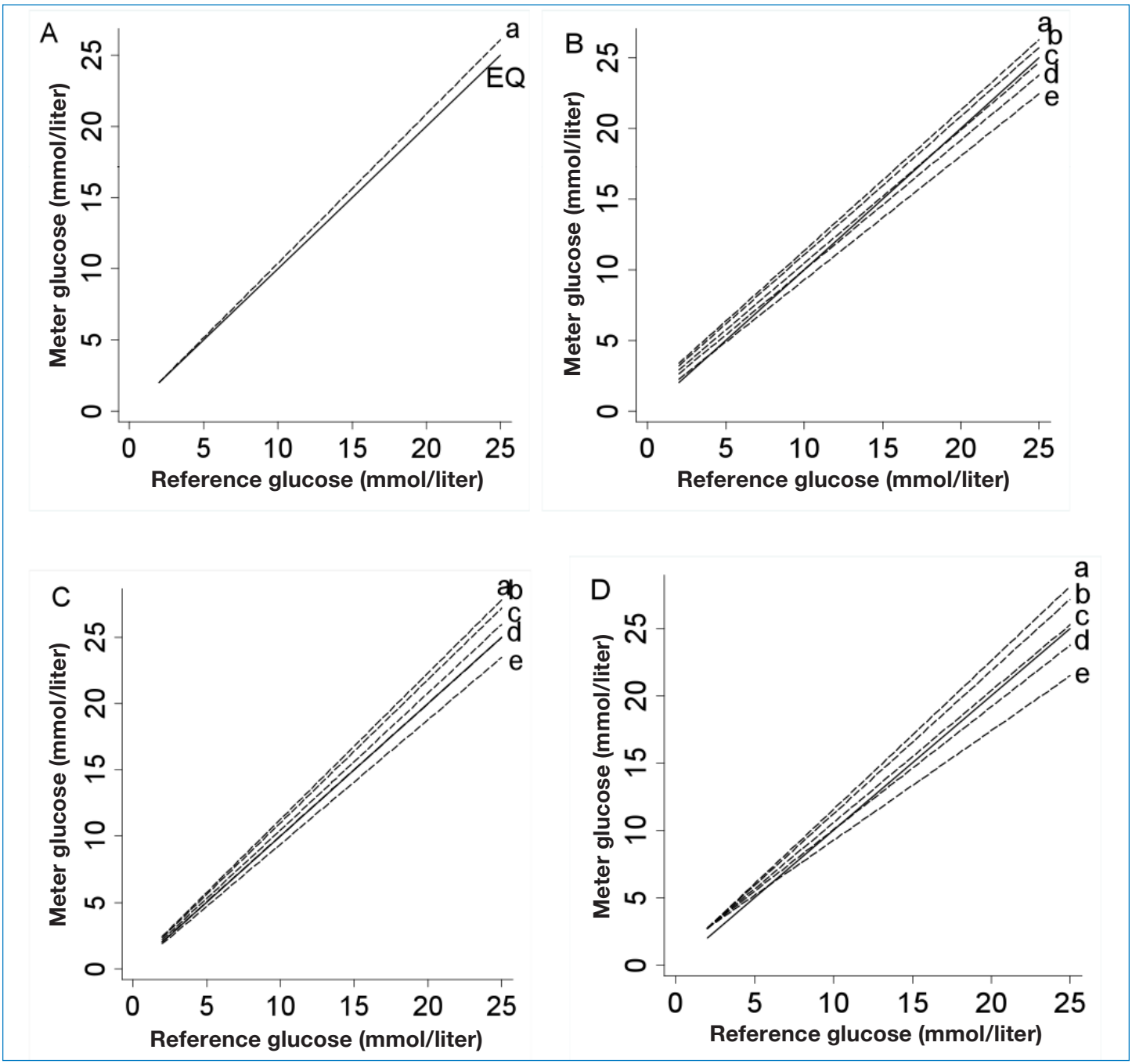

Figure 1. Effect of hematocrit on glucose meter results. Solid lines represent line of equivalence (EQ); dashed lines represent estimated conditional mean values for glucose meters predicted from coefficients derived by linear regression at different hematocrit values. (**A**) $Meter_1$: no variation with hematocrit; (**B**) $Meter_2$; (**C**) $Meter_3$; (**D**) $Meter_4$. Dashed lines: (a) H = 20%, (b) H = 25%, (c) H = 35%, (d) H = 43%, (e) H = 55%.

The regression analysis described how maltose caused a large dose-dependent positive bias in glucose results with $Meter_3$ and $Meter_4$, depicted in **Figures 2C** and **2D** at constant hematocrit. Low hematocrit levels contributed to additional positive bias in a manner dependent on both glucose and maltose concentrations in $Meter_3$ and $Meter_4$.

The bias caused by ascorbate was assessed with each meter at different hematocrits using the model described in **Equation (4)**. The addition of exogenous ascorbate at two or four times the upper limit of its reference range caused small but statistically significant positive or negative biases with the meters, and the bias was often dependent on glucose concentration ($\beta_5 \neq 0$ or $\beta_7 \neq 0$) or influenced by hematocrit (**Appendix**, **Table A3**).

The regression analysis for each meter with **Equation (5)** is shown in **Table A4** (**Appendix**) to depict the extent of associations between biases due to hematocrit, maltose, and ascorbate and their dependency on glucose concentration. This complex analysis clearly shows that each meter has different susceptibilities to interference and that the

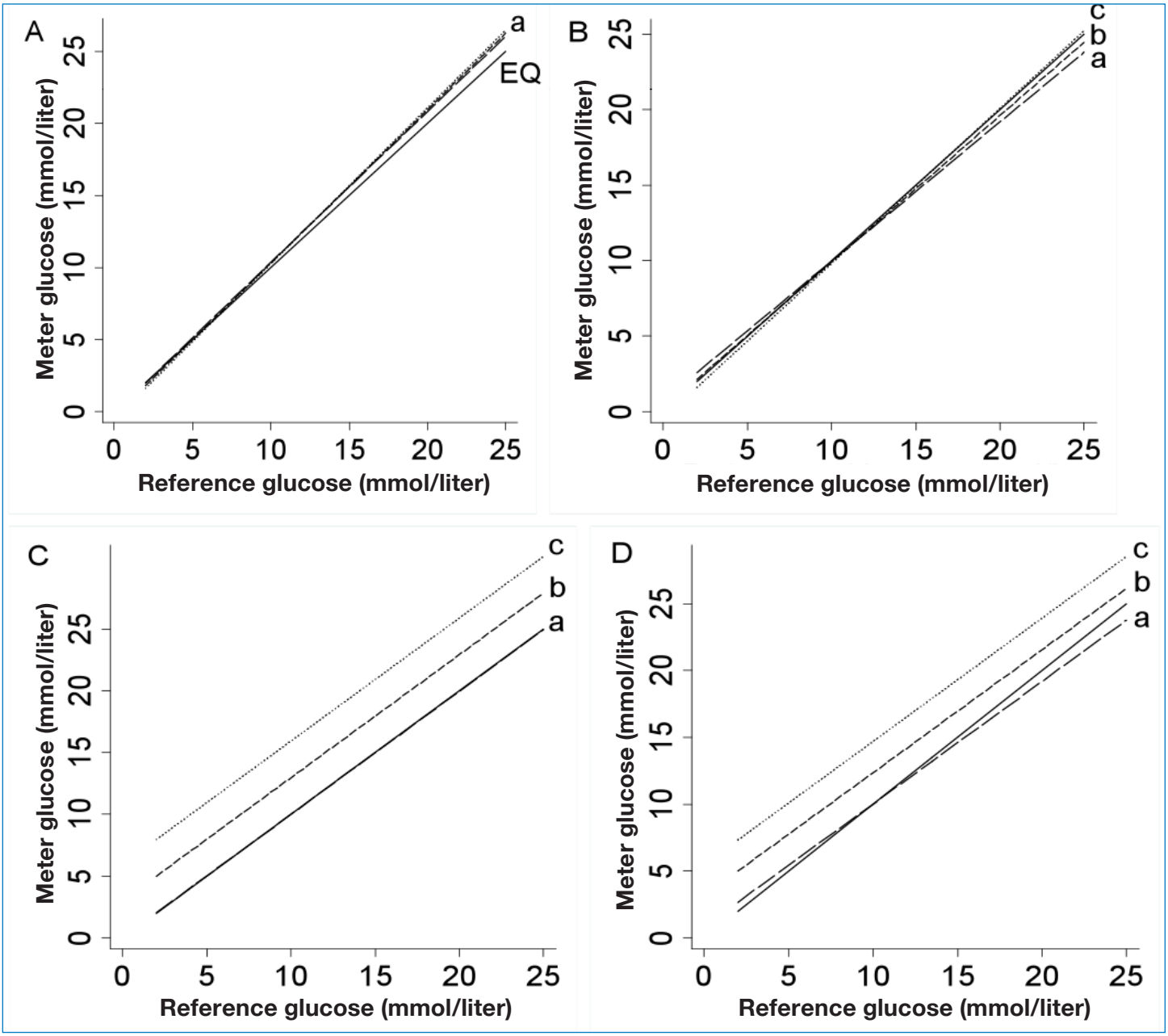

Figure 2. Effect of 2.8 and 5.6 mmol/liter maltose on glucose meter results. Solid lines represent line of equivalence (EQ); dashed lines represent estimated conditional mean values for glucose meters predicted from coefficients derived by linear regression at difference maltose concentrations. (**A**) $Meter_1$, dashed lines for 0, 2.8, and 5.6 mmol/liter maltose (overlapping, labeled 'a'); (**B**) $Meter_2$; (**C**) $Meter_3$; (**D**) $Meter_4$. dashed lines: (a) 0 mmol/liter maltose, (b) 2.8 mmol/liter maltose, and (c) 5.6 mmol/liter maltose.

factors tested often jointly modify glucose measurement, augmenting the bias observed. **Figure 3** depicts the extent of the bias predicted with each meter under selected conditions.

The overall impact of these biases on glucose meter performance was quantitatively assessed by calculating the sum of observed biases and imprecision (**Table 1**) to estimate total analytical error (**Figure 4**). For each device, estimated total error was calculated at 10 mmol/liter plasma glucose for normal, high, and low hematocrit and plotted relative to the analytical goal of ISO 15197 of less than 20% error. It is clear that in the absence of interfering conditions, all four devices meet the standard.

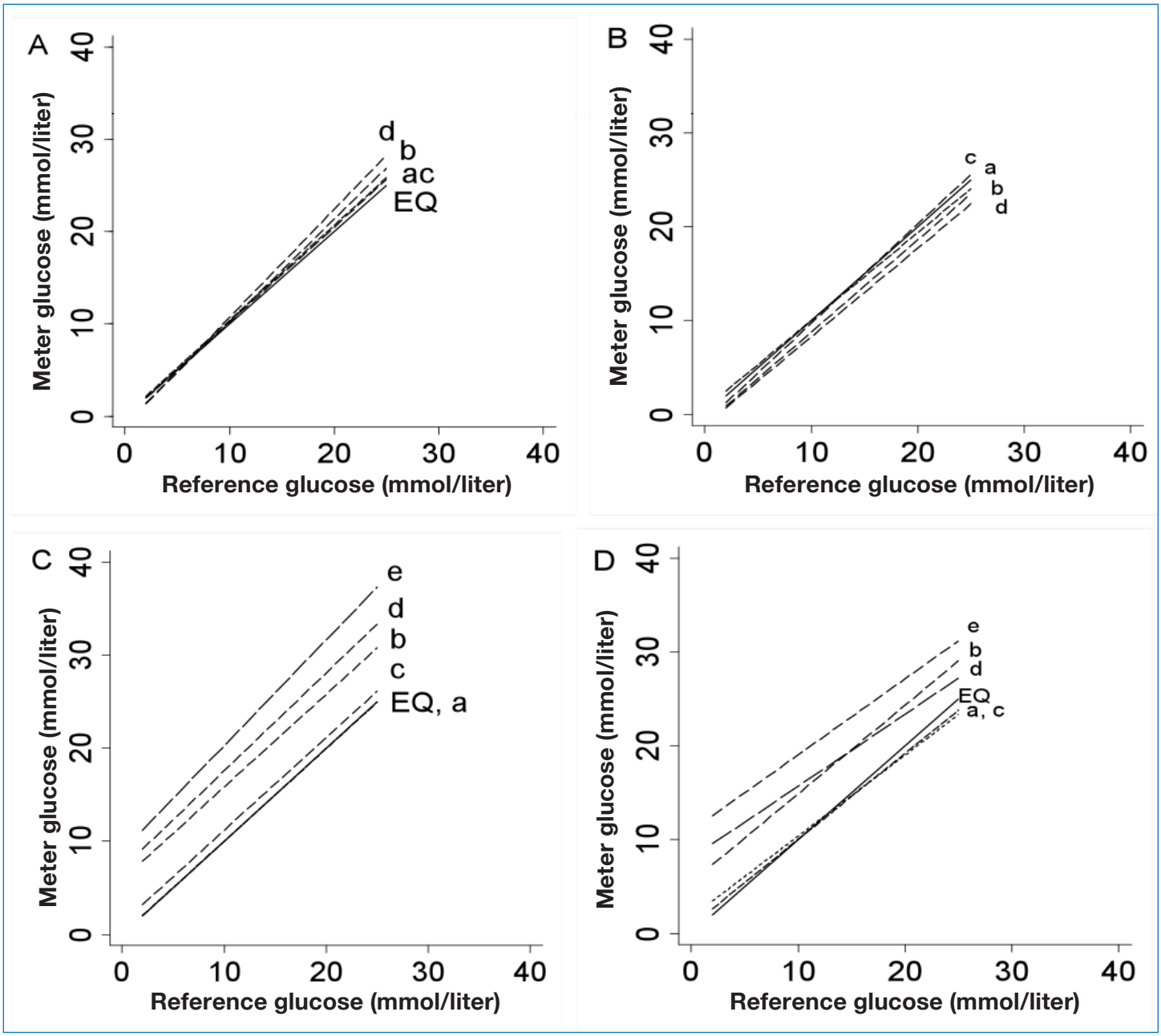

Figure 3. Effect of modifying maltose, ascorbate, and hematocrit on glucose meter results. Solid lines represent line of equivalence (EQ); dashed lines represent estimated conditional mean values for glucose meters predicted from coefficients derived by linear regression. (A) $Meter_1$: (a) untreated, (b) 5.6 mmol/liter maltose, (c) 0.59 mmol/liter ascorbate, and (d) 5.6 mmol/liter maltose and 0.59 mmol/liter ascorbate. (B) $Meter_2$: (a) 0.59 mmol/liter ascorbate, (b) 5.6mmol/liter maltose, 0.59 mmol/liter ascorbate, and H = 43%, (c) 5.6mmol/liter maltose, 0.59 mmol/liter ascorbate, and H = 20%, and (d) 5.6 mmol/liter maltose, 0.59 mmol/liter ascorbate, and H = 55%. (C) $Meter_3$: (a) untreated overlaps with the solid line of equivalence, (b) 5.6 mmol/liter maltose, (c) 0.59 mmol/liter ascorbate, (d) 5.6 mmol/liter maltose, 0.59 mmol/liter ascorbate, and H = 43%, and (e) 5.6 mmol/liter maltose, 0.59 mmol/liter ascorbate, and H = 20%. (D) $Meter_4$: (a) untreated, (b) 5.6 mmol/liter maltose, (c) 0.59 mmol/liter ascorbate, (d) 5.6 mmol/liter maltose, 0.59 mmol/liter ascorbate, and H = 43%, and (e) 5.6 mmol/liter maltose, 0.59 mmol/liter ascorbate, and H = 20%.

However, the susceptibility to interference by maltose and ascorbate is highly device dependent and can be exacerbated by low hematocrit and poor precision.

Table 1.
Within-Run Precision Assessment in Whole Blood. Glucose Mean ± One Standard Deviation in mmol/liter and Percent Coefficient of Variation (n = 20).

Glucose	Low (mmol/liter)	Medium (mmol/liter)	High (mmol/liter)
$Meter_1$	4.14 ± 0.13 (3.08%)	11.18 ± 0.36 (3.19%)	20.70 ± 0.54 (2.59%)
$Meter_2$	4.31 ± 0.13 (3.09%)	9.80 ± 0.17 (1.69%)	19.82 ± 0.18 (0.89%)
$Meter_3$	4.33 ± 0.12 (2.8%)	11.06 ± 0.33 (3.0%)	21.80 ± 0.51 (2.4%)
$Meter_4$	4.39 ± 0.33 (8.0%)	10.09 ± 0.66 (6.6%)	19.53 ± 0.72 (3.7%)

Discussion

The utility of mathematically modeling the relationship between hematocrit, meter glucose, and reference glucose concentrations as a tool for the evaluation of whole blood glucose meters has been reported by Lyon and colleagues.[4] The overall goal of the current study was to estimate the analytical error observed with two consumer and two hospital-grade glucose meters using linear regression models and then assessing whether ISO 15197 performance expectations were met.

In the current study, it was clear that all four glucose meters had observed error that complied with the ISO 15197 guideline so long as there was near-normal hematocrit and no maltose or ascorbate present. This is an important observation and is consistent with reports of excellent analytical performance of glucose meters when patients or samples with normal hematocrits and without exposure to known interferences were evaluated.

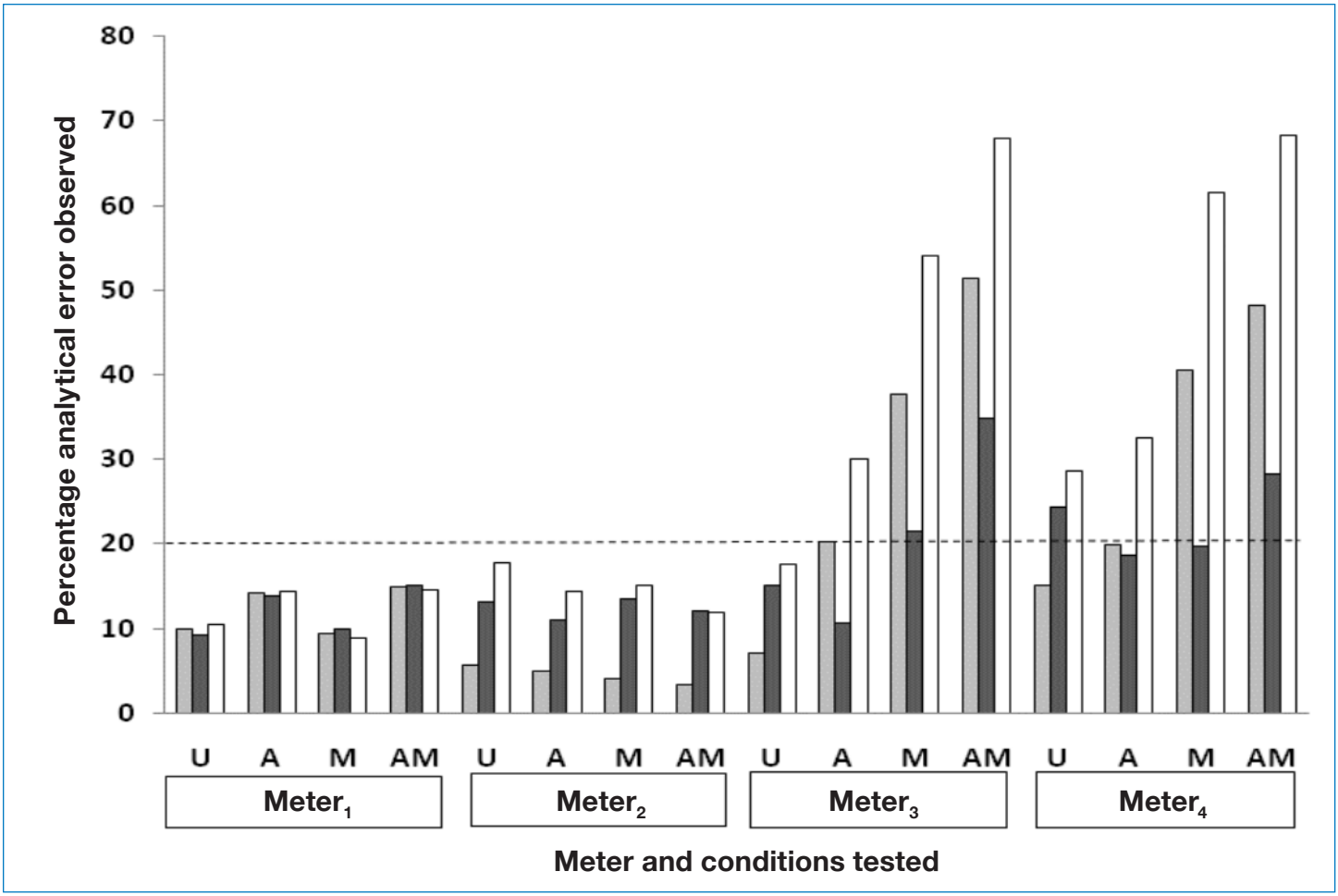

Figure 4. Estimates of total analytical error at 10 mmol/liter glucose. Each glucose meter is denoted by a number (1, 2, 3, and 4). U is untreated; A has 0.29 mmol/liter ascorbate; M has 2.8 mmol/liter maltose; and AM has both ascorbate and maltose. For each glucose meter and interference condition, the first column (light shading) represents the 40% hematocrit specimen, the second column (dark shading) illustrates the 60% hematocrit, and the third column (no shading) represents the 20% hematocrit specimen.

However, few studies have rigorously evaluated the influence of hematocrit variation or interfering substances like maltose or ascorbate. Ample evidence exists to demonstrate that hematocrit values in both hospitalized and ambulatory patients can deviate significantly from near-normal levels[16–18] and for variability in serum ascorbate levels.[19,20] When the glucose meters were assessed under more challenging conditions like 20% hematocrit and 0.29 mmol/liter ascorbate, the estimated total analytical error approached 30% for both consumer meters evaluated. In general, the hospital-grade meters (glucose oxidase-based technologies) tended to have less estimated analytical error than the consumer meters (PQQ glucose dehydrogenase-based technologies).

Fatalities among peritoneal dialysis patients have been partly attributed to maltose interference with specific glucose meter devices and subsequent inappropriate treatment.[21] Regression analysis enabled the assessment of device susceptibility of glucose meters to maltose interference. It was clear that the glucose oxidase-based hospital devices tested were not prone to maltose interference and had less susceptibility to ascorbate bias. In contrast, the total analytical error for the consumer devices tested was magnified in maltose-exposed specimens beyond ISO 15197 criteria, particularly those with abnormal hematocrit or increased levels of ascorbate. In clinical practice, it is expected that only a minor population of patients would be exposed to maltose and other therapeutic agents known to bias glucose measuring devices.[22] Nevertheless, it is incumbent upon us in the clinical laboratory to evaluate the performance of devices used in both the hospital and community settings to avoid inaccurate results and to assure reliable results will be available for all patient populations.[23,24]

Conclusions

- Interference susceptibility is highly device dependent.
- The total analytical error for glucose meters intended for hospital use was superior to consumer meters.
- The extent of glucose bias due to hematocrit is often dependent on glucose concentration.
- With the consumer meters assessed, the profound positive bias in the presence of maltose was exacerbated by low hematocrit and presence of ascorbate.

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Appendix: Linear Model Derivations

Linear Model Development

A descriptive narrative to explain the derivation of the regression models.

Equation (A1)

The relationship between plasma glucose (mmol/liter of plasma) and whole blood glucose (mmol/kg water in whole blood). Direct-reading glucose meters detect the molality of glucose in whole blood by sensing chemically active glucose dissolved in water. The volume of whole blood largely consists of plasma volume and red blood cell volume (and hematocrit is the fraction of blood volume occupied by red blood cells). Converting whole blood molality to plasma molarity requires multiplication by a fraction that consists of a numerator stating the available volume of water in plasma for glucose to dissolve and a denominator describing the volume of water in whole blood (the sum of volumes of water in red blood cells and plasma). This equation was developed and was well described in the IFCC consensus statement: the average volume of plasma water (PW) consisting of water is 93%, the average volume of packed red blood cells consisting of water (RCW) is 71%, and the average hematocrit (H) is 43%.[11–13] Plasma proteins occupy approximately 7% of the volume of plasma, while approximately 27% of the volume of red blood cells is occupied by hemoglobin.

$$\text{Glucose}_{\text{plasma,molar}} = \text{Glucose}_{\text{whole blood,molal}} \frac{\text{PW}}{(\text{H} \times \text{RCW}) + ((1 - \text{H}) \times \text{PW})}$$

$$\text{Glucose}_{\text{plasma,molar}} = \text{Glucose}_{\text{whole blood,molal}} \frac{0.93}{(\text{H} \times 0.71) + ((1 - \text{H}) \times 0.93)} \quad \text{(A1)}$$

Equation (A2)

Assuming the hematocrit is 43%, the volume fraction in **Equation (A1)** has a value of 1.11, a proposed constant factor to convert whole blood molality to the equivalent plasma glucose molarity.[13]

$$\text{Glucose}_{\text{plasma,molar}} = \text{Glucose}_{\text{meter}} = (1.11)\text{Glucose}_{\text{whole blood,molal}} \quad \text{(A2)}$$

This equation shows that whole blood glucose molality detected needs to be increased by a factor of 1.11 to generate plasma equivalent molarity when the hematocrit is 43%. Based on these known relationships, we created a model that describes how glucose values will be reported by meters when the hematocrit varies.

Taking **Equation (A2)** as

$$\frac{\text{Glucose}_{\text{meter}}}{1.11} = \text{Glucose}_{\text{whole blood,molal}}$$

and taking **Equation (A1)** as

$$\text{Glucose}_{\text{whole blood,molal}} = \text{Glucose}_{\text{plasma,molar}} \frac{(\text{H} \times 0.71) + ((1 - \text{H}) \times 0.93)}{0.93}$$

then combining **Equation (A1)** and **(A2)** and gathering terms:

$$\frac{\text{Glucose}_{\text{meter}}}{1.11} = \text{Glucose}_{\text{plasma,molar}} \frac{(\text{H} \times 0.71) + ((1 - \text{H}) \times 0.93)}{0.93} \quad \text{(A3)}$$

Equation (A3)

Equation (A3) shows the expected algebraic relationship between glucose meter results reported and the plasma glucose molarity as hematocrit is varied (and plasma water is assumed to be 93% and red blood cell water is assumed to be 71%). Note that in this example when the hematocrit is 43%, the glucose meter reports a value equal to the plasma glucose molarity.

This algebraic relationship forms the basis of the linear regression model between glucose meter results, plasma glucose concentration, and hematocrit, as shown in **Equation (A4)**. The model consists of a constant, β_0, a term for plasma glucose, a joint effect term glucose × hematocrit. The term for hematocrit is added to make the model hierarchically well formulated.

Conditional means of the coefficients will be determined by fitting actual glucose meter results to plasma glucose values as hematocrit is varied with multiple regression. The mathematical contribution of individual coefficient values to the equation is self explanatory. Alternatively, when coefficient values are not significantly different than zero, there is no evidence that that term contributes to the observed glucose meter results [e.g., in **Equation (A4)**, when β_2 and β_3 equal zero, there is no evidence that hematocrit influences the glucose meter results].

Equation (A4)

Model for estimation of conditional means of coefficients that describe the influence of hematocrit on glucose meter results.

$$E(Glucose_{meter}) = \beta_0 + \beta_1 Glucose_{plasma,molar} + \beta_2 H + \beta_3 HGlucose_{plasma,molar}$$

The models depicted in **Equations (A5)–(A7)** add terms to allow assessment of the joint effects of maltose and ascorbate on glucose meter results in addition to the hematocrit.

Equation (A5)

Model for estimation of conditional means of coefficients that describe the influence of hematocrit and maltose on glucose meter results.

$$E(Glucose_{meter}) = \beta_0 + \beta_1 G + \beta_2 H + \beta_3 M + \beta_4 GH + \beta_5 GM + \beta_6 HM + \beta_7 GHM$$

Equation (A6)

Model for estimation of conditional means of coefficients that describe the influence of hematocrit and ascorbate on glucose meter results.

$$E(Glucose_{meter}) = \beta_0 + \beta_1 G + \beta_2 H + \beta_3 A + \beta_4 GH + \beta_5 GA + \beta_6 HA + \beta_7 GHA$$

Equation (A7)

Model for estimation of conditional means of coefficients that describe the influence of hematocrit, maltose, and ascorbate on glucose meter results.

$$E(Glucose_{meter}) = \beta_0 + \beta_1 G + \beta_2 H + \beta_3 M + \beta_4 A + \beta_5 GH + \beta_6 GM + \beta_7 GA + \beta_8 HM + \beta_9 HA + \beta_{10} MA + \beta_{11} GHM + \beta_{12} GHA + \beta_{13} HMA + \beta_{14} GMA + \beta_{15} GHMA$$

Table A1.
Evaluation of Hematocrit Bias on Glucose Meters by Linear Regression [Equation (A4)]. Estimated Conditional Mean Values of Coefficients with 95% Confidence Intervals Listed with the Wald Test Probability That the Coefficient Value is Equal to Zero.

Device	Coefficient	Estimated value	95% Confidence interval	$p > \|t\|$
$Meter_1$	β_0	0.035	-0.657 to 0.728	0.919
	β_1	1.049	1.000 to 1.096	0.000
	β_2	-0.003	-0.018 to 0.012	0.672
	β_3	0.000	-0.001 to 0.001	0.957
$Meter_2$	β_0	1.904	0.849 to 2.959	0.001
	β_1	1.064	0.992 to 1.135	0.000
	β_2	-0.026	-0.049 to -0.003	0.027
	β_3	-0.003	-0.005 to -0.002	0.000
$Meter_3$	β_0	0.377	-0.523 to 1.278	0.408
	β_1	1.198	1.137 to 1.258	0.000
	β_2	-0.007	-0.026 to 0.012	0.486
	β_3	-0.005	-0.523 to -0.003	0.000
$Meter_4$	β_0	0.175	-0.633 to 0.983	0.668
	β_1	1.270	1.215 to 1.324	0.000
	β_2	0.017	-0.000 to 0.034	0.540
	β_3	-0.008	-0.632 to 0.983	0.000

Table A2.
Evaluation of Hematocrit Bias and Maltose Bias on Glucose Meters by Linear Regression [Equation (A5)]. Estimated Conditional Mean Values of Coefficients with 95% Confidence Intervals Listed with the Wald Test Probability That the Coefficient Value is Equal to Zero.

Device	Coefficient	Estimated value	95% Confidence interval	$p > \|t\|$
$Meter_1$	β_0	-0.037	-0.603 to 0.528	0.896
	β_1	1.050	1.011 to 1.088	0.000
	β_2	-0.002	-0.014 to 0.010	0.735
	β_3	-0.159	-0.362 to 0.044	0.124
	β_4	0.000	-0.001 to 0.001	0.923
	β_5	0.006	-0.009 to 0.020	0.431
	β_6	0.002	-0.0025 to 0.006	0.405
	β_7	0.000	-0.0003 to 0.0003	0.944
$Meter_2$	β_0	1.765	0.917 to 2.612	0.000
	β_1	1.073	1.016 to 1.131	0.000
	β_2	-0.024	-0.042 to -0.006	0.011
	β_3	-0.482	-0.785 to -0.179	0.002
	β_4	-0.003	-0.005 to -0.002	0.000
	β_5	0.039	0.018 to 0.061	0.000
	β_6	0.006	-0.0003 to 0.013	0.062
	β_7	-0.0005	-0.0009 to 0.000	0.046
$Meter_3$	β_0	0.358	-0.558 to 1.274	0.442
	β_1	1.200	1.139 to 1.263	0.000
	β_2	-0.007	-0.026 to 0.013	0.485
	β_3	1.431	1.102 to 1.760	0.000
	β_4	-0.005	-0.006 to -0.003	0.978
	β_5	-0.0003	-0.024 to 0.023	0.978
	β_6	-0.009	-0.016 to -0.002	0.013
	β_7	0.00004	-0.0004 to 0.0005	0.870
$Meter_4$	β_0	0.070	-0.654 to 0.793	0.849
	β_1	1.269	1.220 to 1.318	0.000
	β_2	0.0179	0.002 to 0.033	0.024
	β_3	1.784	1.525 to 2.044	0.000
	β_4	-0.008	-0.009 to -0.007	0.000
	β_5	-0.046	0.0643 to -0.027	0.000
	β_6	-0.022	-0.028 to -0.017	0.000
	β_7	0.001	0.0007 to 0.0015	0.000

Table A3.
Evaluation of Hematocrit Bias and Ascorbate Bias on Glucose Meters by Linear Regression [Equation (A6)]. Estimated Conditional Mean Values of Coefficients with 95% Confidence Intervals Listed with the Wald Test Probability That the Coefficient Value is Equal to Zero.

Device	Coefficient	Estimated value	95% Confidence interval	$p > \|t\|$
$Meter_1$	β_0	0.210	-0.657 to 1.077	0.632
	β_1	1.033	0.975 to 1.092	0.000
	β_2	-0.005	-0.024 to 0.013	0.569
	β_3	1.245	-1.610 to 4.101	0.388
	β_4	0.0001	-0.001 to 0.001	0.835
	β_5	-0.169	-0.357 to 0.019	0.077
	β_6	-0.014	-0.076 to 0.047	0.644
	β_7	0.002	-0.002 to 0.006	0.307
$Meter_2$	β_0	1.680	0.467 to 2.892	0.007
	β_1	1.103	1.022 to 1.185	0.000
	β_2	-0.020	-0.046 to 0.005	0.119
	β_3	-2.233	-6.228 to 1.760	0.269
	β_4	-0.004	-0.006 to -0.002	0.000
	β_5	-0.105	-0.368 to 0.157	0.428
	β_6	0.008	-0.077 to 0.094	0.845
	β_7	0.004	-0.002 to 0.009	0.208
$Meter_3$	β_0	0.424	-0.649 to 1.498	0.434
	β_1	1.177	1.105 to 1.249	0.000
	β_2	-0.009	-0.032 to 0.014	0.458
	β_3	3.842	0.306 to 7.377	0.034
	β_4	-0.004	-0.006 to -0.002	0.000
	β_5	-0.245	-0.478 to -0.012	0.039
	β_6	-0.032	-0.108 to 0.044	0.406
	β_7	0.005	0.00006 to 0.010	0.047
$Meter_4$	β_0	0.165	-0.851 to 1.180	0.748
	β_1	1.282	1.214 to 1.351	0.000
	β_2	0.017	-0.005 to 0.038	0.132
	β_3	0.820	-2.524 to 4.163	0.627
	β_4	-0.008	-0.009 to -0.007	0.000
	β_5	-0.111	-0.331 to 0.109	0.319
	β_6	0.018	-0.054 to 0.090	0.616
	β_7	0.0003	-0.004 to 0.005	0.886

Table A4.
Evaluation of Bias Contributed by Hematocrit, Maltose, and Ascorbate on Glucose Meters by Linear Regression [Equation (A7)]. Estimated Conditional Mean Values of Coefficients with 95% Confidence Intervals Listed with the Wald Test Probability That the Coefficient Value is Equal to Zero.

Device	Coefficient	Estimated value	95% Confidence interval	$p > \|t\|$
$Meter_1$	β_0	0.125	-0.612 to 0.861	0.738
	β_1	1.036	0.986 to 1.086	0.000
	β_2	-0.004	-0.020 to 0.011	0.585
	β_3	-0.204	-0.473 to 0.065	0.137
	β_4	1.247	-1.215 to 3.710	0.319
	β_5	0.0001	-0.0009 to 0.001	0.812
	β_6	0.011	-0.008 to 0.030	0.266
	β_7	-0.158	-0.320 to 0.004	0.056
	β_8	0.002	-0.004 to 0.008	0.496
	β_9	-0.015	-0.068 to 0.038	0.568
	β_{10}	-0.365	-1.106 to 0.375	0.331
	β_{11}	0.000	-0.0004 to 0.0004	0.993
	β_{12}	0.002	-0.001 to 0.006	0.236
	β_{13}	0.003	-0.012 to 0.019	0.672
	β_{14}	0.063	0.012 to 0.113	0.015
	β_{15}	-0.0006	-0.002 to 0.0004	0.236
$Meter_2$	β_0	1.535	0.541 to 2.529	0.003
	β_1	1.111	1.044 to 1.179	0.000
	β_2	-0.019	-0.040 to 0.002	0.082
	β_3	-0.360	-0.723 to 0.003	0.052
	β_4	-2.127	-5.449 to 1.194	0.208
	β_5	-0.004	-0.006 to -0.003	0.000
	β_6	0.022	0.003 to 0.048	0.090
	β_7	-0.127	-0.345 to 0.092	0.254
	β_8	0.004	-0.004 to 0.012	0.322
	β_9	0.007	-0.064 to 0.079	0.842
	β_{10}	-0.070	-1.069 to 0.929	0.890
	β_{11}	-0.0002	-0.0007 to 0.008	0.495
	β_{12}	0.004	-0.001 to 0.006	0.096
	β_{13}	0.005	-0.016 to 0.027	0.634
	β_{14}	0.016	-0.052 to 0.085	0.633
	β_{15}	-0.0008	-0.002 to 0.0006	0.273
$Meter_3$	β_0	0.430	-0.788 to 1.649	0.486
	β_1	1.180	1.097 to 1.262	0.000
	β_2	-0.010	-0.036 to 0.016	0.452
	β_3	1.450	1.000 to 1.895	0.000
	β_4	3.941	-0.132 to 8.014	0.058
	β_5	-0.004	-0.006 to -0.002	0.000
	β_6	0.006	-0.025 to 0.038	0.705
	β_7	-0.233	-0.501 to 0.035	0.088
	β_8	-0.009	-0.018 to 0.001	0.067
	β_9	-0.035	-0.122 to 0.053	0.434
	β_{10}	-0.156	-1.381 to1.069	0.802
	β_{11}	-0.0001	-0.0008 to 0.005	0.673
	β_{12}	0.005	-0.0008 to 0.011	0.092
	β_{13}	-0.002	-0.028 to 0.025	0.900
	β_{14}	0.046	-0.038 to 0.130	0.278
	β_{15}	-0.0004	-0.788 to 1.649	0.486

Table A4 (continued).
Evaluation of Bias Contributed by Hematocrit, Maltose, and Ascorbate on Glucose Meters by Linear Regression [Equation (A7)]. Estimated Conditional Mean Values of Coefficients with 95% Confidence Intervals Listed with the Wald Test Probability That the Coefficient Value is Equal to Zero.

Device	Coefficient	Estimated value	95% Confidence interval	$p > \|t\|$
$Meter_4$	β_0	-0.094	-0.880 to 1.069	0.848
	β_1	1.283	1.218 to 1.349	0.000
	β_2	0.017	-0.004 to 0.038	0.113
	β_3	1.863	1.507 to 2.220	0.000
	β_4	1.062	-2.196 to 4.321	0.520
	β_5	-0.008	-0.010 to -0.007	0.000
	β_6	-0.042	-0.067 to -0.017	0.001
	β_7	-0.106	-0.320 to -0.109	0.331
	β_8	-0.024	-0.031 to -0.016	0.000
	β_9	0.012	-0.059 to 0.082	0.729
	β_{10}	0.867	-0.113 to 1.847	0.083
	β_{11}	0.001	0.0005 to 0.0016	0.000
	β_{12}	0.0002	-0.004 to 0.004	0.920
	β_{13}	-0.0009	-0.030 to 0.012	0.421
	β_{14}	-0.052	-0.119 to 0.015	0.130
	β_{15}	0.0009	-0.0006 to 0.002	0.241