Estimated Risk for Insulin Dose Error Among Hospital Patients Due to Glucose Meter Hematocrit Bias in 2020

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• ***Context.***—**Glycemic control requires accurate blood glucose testing. The extent of hematocrit interference is difficult to assess to assure quality patient care.**

Objective.—**To predict the effect of patient hematocrit on the performance of a glucose meter and its corresponding impact on insulin-dosing error.**

Design.—**Multilevel mixed regression was conducted to assess the extent that patient hematocrit influences Roche Accu-Chek Inform II glucose meters, using the Radiometer ABL 837 as a reference method collected during validation of 35 new meters. Regression coefficients of fixed effects for reference glucose, hematocrit, an interaction term, and random error were applied to 4 months of patient reference method results extracted from the laboratory information system. A hospital inpatient insulin dose algorithm was used to determine the frequency of insulin dose error between reference glucose and meter glucose results.**

Results.—**Fixed effects regression for method and hematocrit predicted biases to glucose meter results that met the "95% within ±12%" for the US Food and Drug Administration goal, but combinations of fixed and random effects exceeded that target in emergency and hospital inpatient units. Insulin dose errors were predicted from the meter results. Twenty-eight percent of intensive care unit, 20.8% of hospital inpatient, and 17.7% of emergency department results were predicted to trigger a ±1 insulin dose error by fixed and random effects.**

Conclusions.—**The current extent of hematocrit interference on glucose meter performance is anticipated to cause insulin error by 1-dose category, which is likely associated with low patient risk.**

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Monitoring of blood glucose by glucose meter is common practice for individuals with type 1 and type 2 diabetes and serves as the basis for insulin-dosing protocols in hospitals.[1] The frequency at which patient glucose levels are measured varies from once daily to more than 8 times per day, dependent on the diabetes regimen and patient self-management. As the foundation for insulin-dosing decisions, the accuracy and precision of devices used to measure blood glucose levels are paramount to achieving optimal and safe glycemic control. Given the significant worldwide burden of diabetes and increasing emphasis on achieving optimal glycemic control, assuring accurate and precise glucose measurements from point-of-care glucose meters is essential.

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In hospital or home care settings, diabetic patients may become acutely unwell and rely heavily on clinician decisions predicated upon reliable glucose meters for insulin-dosing decisions. Overwhelming evidence has confirmed that patient-specific factors, such as hematocrit variation, can substantially alter glucose meter results and lead to significant intermeter variability.[2–7] This hematocrit effect may vary across glucose meter brands, leading to a complex spectrum of published glucose meter performance outcomes. While these hematocrit effects are well described in relation to glucose meter values, the downstream effect upon insulin-dosing decisions, the patient-centered and clinically relevant outcome, is seldom considered. This "bench to bedside gap" may compromise safe and effective diabetes care, particularly in acutely unwell and hospitalized patients.

Hematocrit, which refers to the proportion of the red blood cell volume within the total blood volume, is often expressed as a percentage, with normal reported ranges between 40% and 45%. Several mechanisms have been proposed to explain why many glucose meters are susceptible to hematocrit interference, including (1) the "interference" factor and (2) a "failure to correct." The mechanism of "interference" refers to the effect of red blood cells blocking the enzymatic reaction on the surface of the blood glucose test strip, thereby altering the accurate ability to detect glucose in the plasma.[8] The "failure to correct" mechanism relates to the inadequacy of a "1.11 correction factor" used to convert whole blood glucose results to plasma equivalent concentrations that assumes all patients

have hematocrits of 43%. The "failure to correct" mechanism may be reduced by adjusting the 1.11 factor if the patient hematocrit or other factors related to glucose molality are known.[9,10] The combination of these 2 mechanisms, and perhaps others, results in hematocrit interference affecting glucose meter performance.

To address growing patient and clinician concerns about the safety of both hospital and self-monitoring blood glucose meters, the US Food and Drug Administration (FDA), the International Standards Organization, and the Clinical Laboratory and Standards Institute have revised their level of tolerance for hospital and home glucose meters for inaccuracy.[11–14] For example, the 2018 FDA premarket performance expectations require that at least 95% of glucose results below 75 mg/dL (4.2 mmol/L) fall within ±12 mg/dL (0.67 mmol/L) of laboratory results and within ±12% for values of 75 mg/dL (4.2 mmol/L) or greater. Although the analytic performance and susceptibility to hematocrit interference has been reduced in some glucose meter models, the impact of hematocrit variation in different patient populations is often not evaluated. The objective of this quality assurance study was to predict the effect of patient hematocrit on the performance of glucose meters when glucose level is 75 mg/dL (4.2 mmol/L) or greater and assess the impact of this interference on insulin-dosing error in our local hospitals.

MATERIALS AND METHODS

Patient Data

The University of Saskatchewan Research Ethics Board (Saskatoon, Saskatchewan, Canada) designated this analysis of anonymous patient data a quality assurance study and exempt from full review. Anonymous test results for glucose and hematocrit analyses and the clinical unit associated with patient location were extracted for a 4-month period (n = 21 057) for blood gas and metabolite test panels. Test results from pediatric units were excluded.

Glucose Meters

Accu-Chek Inform II glucose meters (Roche Diagnostics Canada Laval, Quebec, Canada) were used in this evaluation. The manufacturer states this device has reportable glucose range of 11 to 600 mg/dL (0.6–33.3 mmol/L) without influence for hematocrit values of 10% to 65%.[15]

Glucose Meter Validation Protocol

Residual whole blood specimens collected into lithium heparin Vacutainer tubes were analyzed with the Radiometer ABL 837 blood gas analyzer (Copenhagen, Denmark) for reference method glucose and hematocrit results. Subsequently, within 5 minutes, samples were analyzed on Accu-Chek Inform II glucose meters according to manufacturer specifications. Hematocrit was determined by spectrophotometric measurement of hemoglobin and hematocrit was calculated by using the following equation: Hematocrit = 100% (Total Hemoglobin/33.2 g/dL).

Data Analysis

Multilevel mixed regression analysis was conducted with the glucose and hematocrit data using STATA/IC 16.1 (Stata Corp LLC, College Station, Texas) to determine the extent that patient hematocrit and the reference glucose results predict Accu-Chek Inform II glucose results. Equation 1 describes the fixed and random effects model.[16]

$$GM = \beta_0 + \beta_1 G_{ref} + \beta_2 Hct + \beta_3 G_{ref} Hct + \zeta G_{ref} + \varepsilon \qquad (1)$$

GM denotes glucose levels recorded by glucose meters; G_{ref} represents the glucose levels measured by the reference method; *Hct* denotes the hematocrit levels measured with the blood gas analyzers; and G_{ref} *Hct* represents the interaction term. Coefficients β_0 *to* β_3 describe fixed effects, ζ describes the random coefficient at the specimen level for blood gas instrument analyses, and ε represents the unexplained random error.[16]

Prediction of Glucose Meter Hematocrit Bias on Insulin Dose Errors

Consecutive, anonymous blood gas instrument glucose and hematocrit results (n = 21 057) were extracted from the laboratory information system and categorized by patient location as emergency medicine, hospital inpatient, or intensive care. Five hundred and eighty-three results (2.8%) were removed from the dataset to meet the glucose meter performance ranges for glucose and hematocrit. Test results from pediatric units were also excluded. Reference method glucose and hematocrit values were substituted into Equation 1[16] to predict meter glucose results. Insulin doses were determined and compared for reference glucose and predicted meter glucose result pairs, and the differences in insulin dosage were counted as errors. Differences in insulin dose errors by clinical unit or statistical model (fixed effects or combined fixed and random effects) were determined by χ^2 analyses. The subcutaneous insulin-dosing algorithm outlined in the "2018 Diabetes Canada Clinical Practice Guidelines: Insulin Order Sets & In-Hospital Management of Diabetes" was used for this assessment with an insulin dose error assessment (IDEA) grid for this algorithm as outlined by Lyon et al.[17]

RESULTS

During the previous year, 638 residual whole blood specimens collected into lithium heparin Vacutainer tubes were used to validate the performance of 35 new glucose meters following the local validation protocol. Residual patient specimens were selected to encompass a range of glucose concentrations (11–600 mg/dL) as well as hematocrit levels (10%–65%), as assessed by the reference method. Multilevel mixed regression analysis was conducted to determine the extent to which patient hematocrit and reference glucose concentrations predicted the performance of the glucose meters, using the model depicted in Equation 1.[16] The regression coefficients for this model are shown in Table 1 and indicate no evidence of a fixed bias or intercept and statistical significance ($P < .05$) for the fixed effects coefficients for G_{ref} and $G_{ref}Hct$ and the random effects coefficient for G_{ref}. Plots of the raw validation data (n = 638) comparing reference glucose and meter glucose results and regression-predicted glucose meter results are provided in Supplemental Figure 1, A and B (see supplemental digital content at www.archivesofpathology.org in the October 2020 table of contents).

Consecutive glucose and hematocrit values measured with ABL 837 analyzers were extracted from the laboratory information system during a 4-month period from emergency medicine, hospital, and intensive care (n = 21 057; Figure 1). The central intraquartile ranges and medians of glucose values are similar in the different clinical units (Figure 1, A); however, hematocrit distributions are clearly lower in the intensive care unit and for hospitalized patients than for patients in emergency medicine (Figure 1, B). To predict the influence of hematocrit on glucose meter measurements among patients admitted to the different clinical units, the regression coefficients in Table 1 were applied by using data within the performance specifications for the glucose meter (glucose, 10–600 mg/dL [0.6–33.3 mmol/L]; Hct, 10%–65%). The fraction of glucose meter measurements for the different clinical locations that met the 2018 FDA premarket specifications

Table 1. Regression Coefficients for the Model Outlined in Equation 1 Derived by Multilevel Mixed Regression Analysis of 638 Determinations of Whole Blood Glucose by Meter and by Blood Gas Instrument

Coefficient	Mean ± Standard Error	z Statistic	$P > \|z\|$
β_0	0.0298 ± 4.2894	0.01	.99
β_1	1.104 ± 0.017	64.40	.00
β_2	−0.0460 ± 0.0929	−0.50	.62
β_3	−0.0028 ± 0.0004	−7.10	.00
Coefficient	**Estimate ± Standard Error**		
ζ	14.36 ± 1.05		
ε	7.22 ± 0.22		

Estimates of the standard deviation of ζ and ε are shown.

were determined by using the fixed effects coefficients either alone or in combination with the random effects coefficients (Table 2). When considering only the fixed effects, all glucose meter results were predicted to be within ±12% criteria for glucose values of 75 mg/dL (4.2 mmol/L) or greater from the FDA.[12] However, when both the fixed and random effects were considered, 67.6%, 70.8%, and 76.8% of glucose meter results were predicted to meet the ±12% criteria for emergency, hospital inpatients, and intensive care locations, respectively. The influence of random error in the model is particularly noted at low glucose levels in Supplemental Figure 2.

To evaluate the risk to patients predicted by the fixed and random errors in glucose meter measurements, IDEA analyses of the data were performed. Figure 2 demonstrates an IDEA error grid analysis for the patient data from the intensive care unit for the combined fixed and random effects. The red-shaded squares indicate anticipated overdosing of insulin according to the 2018 Diabetes Canada subcutaneous insulin algorithm and the blue-shaded squares indicate anticipated underdosing of insulin. The predicted glucose meter results are displayed as the dependent variable and blood gas analyzer glucose as the reference method, the independent variable. Using the inpatient specific insulin-dosing algorithm, the frequency of insulin dosage errors, as assessed with the IDEA grid, enabled the errors to be quantified for each clinical unit dataset.

The predicted distributions of insulin dose errors for each clinical unit are displayed for the fixed effects only and for the combination of fixed and random effects (Table 3). The prevalence of anemia increases (ie, low hematocrit) with increasing clinical unit acuity, and the frequency of "1 insulin dose error" above/below the appropriate dose increased for both models ($P < .001$). The distribution of insulin dose errors was statistically different between the 2 models ($P < .001$). Very few insulin dose errors greater than 1 dose category were predicted, even when both fixed and random effects were included in this analysis. In earlier studies, Karon et al[18] suggested that patients have greater risk when insulin is administered with a dosing error of 2 or more dose categories. This analysis predicted up to 13% of intensive care unit glucose meter results would be associated with a 1 insulin dose error above/below the appropriate

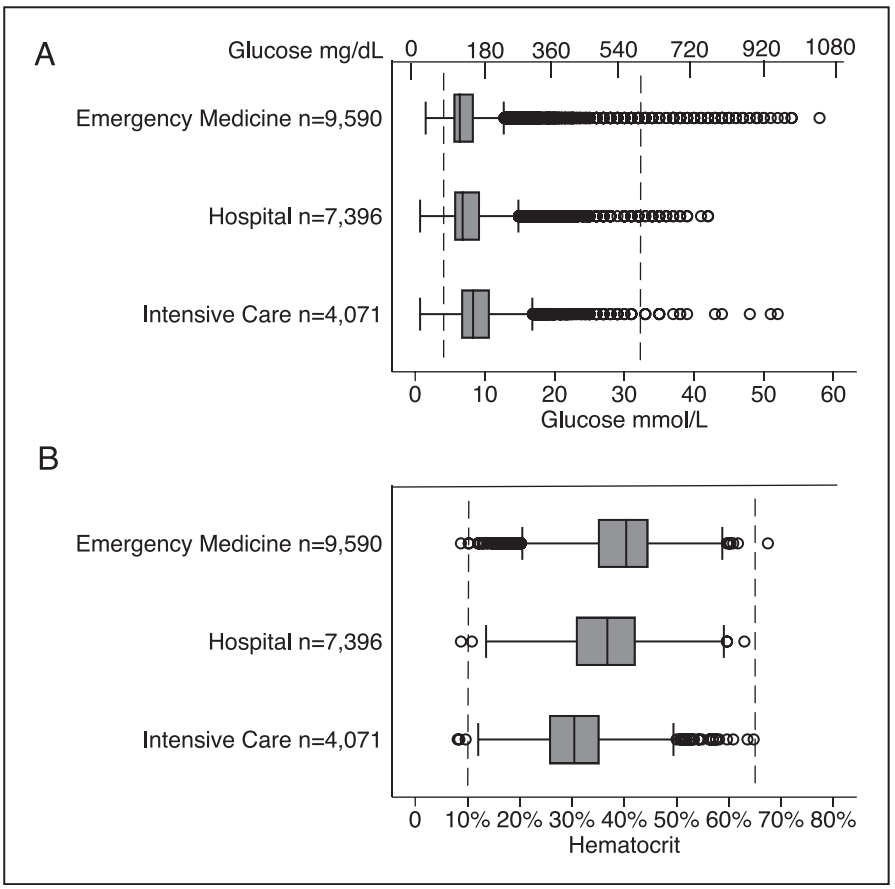

Figure 1. *Distribution of whole blood glucose (A) and hematocrit (B) values among 21 057 pairs of results extracted from the laboratory information system for patients in emergency medicine, inpatient hospital units, or intensive care. The boxes depict the central 2 quartiles and median value, and whisker length represents 1.5 intraquartile range values. The vertical dashed lines represent the reportable range of the glucose meter (10–600 mg/dL or 0.6–33.3 mmol/L), and the manufacturer's range of hematocrit (10%–65%) to avoid interference.*

Table 2. Predicted Glucose Meter Results by Clinical Unit Derived by Mixed Regression			
Unit	Sample Size	Percentage ± 12% for Glucose ≥75 mg/dL Fixed and Random Effects	Percentage ± 12% for Glucose ≥75 mg/dL Fixed Effects Only
Emergency medicine	9288	67.6	100
Hospital	7216	70.8	100
Intensive care	3970	76.8	100

Application of fixed effects (alone) or both fixed and random effects are listed with the percentage of glucose meter results predicted to meet ±12%. The 2018 US Food and Drug Administration criteria for results of 75 mg/dL (4.2 mmol/L) or greater are to have 95% of results within ±12%.

dose, and as such likely represents a low risk to patients, yet high frequency imprecision to patients.

DISCUSSION

Glucose tests are among the most frequent in-hospital biochemical assessments performed, and awareness of the limitations of glucose meter performance is critical for clinicians in the hospital setting to assure safe and optimal patient management. The technologies and devices involved in care of patients with diabetes continue to evolve and adapt. In this study, we evaluated the clinical risk of hematocrit interference with the Accu-Chek Inform II glucose meter in current local hospital practice. We translated these "bench findings" of predicted glucose meter bias into "bedside outcomes" by predicting the impact of bias on insulin dose decision-making to make the information clinically relevant and useful to providers and patients.

The influence of hematocrit on measurement and reporting of glucose levels by point-of-care testing devices has been an important focus of clinicians, laboratorians, international standards organizations, and medical device manufacturers for the past 20 years.[2–8,19,20] The decision to convert whole blood measurements into plasma equivalent glucose concentrations, rendering point-of-care device results more consistent with central laboratory results,[9] was clinically pragmatic, but analytically cryptic. A hematocrit mean level of 43% is anticipated in many healthy populations. Among hospital inpatient or home care settings of acutely or chronically unwell patients, a range of hematocrit values well above or below the 43% threshold is observed, raising concerns about the accuracy of whole blood point-of-care testing devices in those settings. For example, in 2011, Lyon et al[10] reported median hematocrit levels of 42%, 39%, and 28% among community patients, hospital inpatient populations, and adult intensive care patients and risk of glucose meter error, respectively.[10] In this study, we aimed to predict the extent of hematocrit influence on the Inform II glucose meter measurements in 2020 among adult patients with a range of hematocrit levels by using validation data gathered during evaluation of 35 new meters throughout 2019.

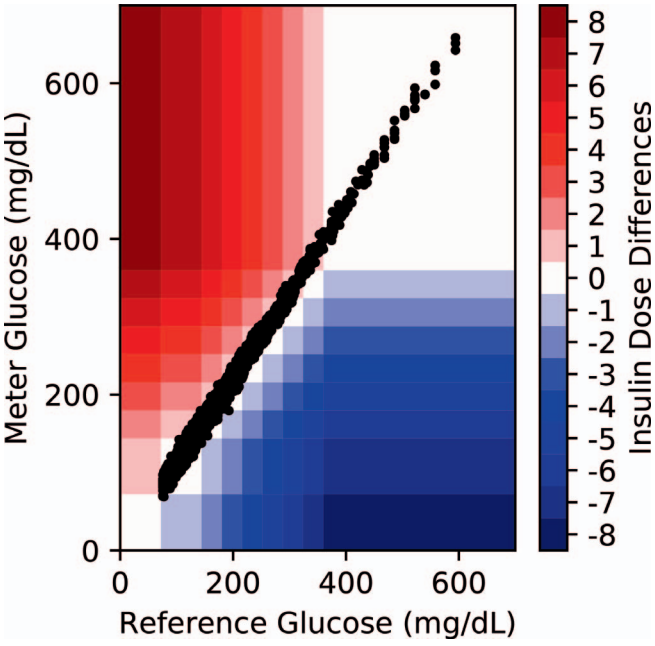

Figure 2. *Insulin dose error assessment error grid analysis example for intensive care results (n = 3970) with fixed and random error effects. The axes indicate the reference glucose and meter glucose concentrations. The red-shaded squares indicate predicted overadministration of insulin as positive insulin dose errors. The blue-shaded squares indicate predicted underadministration of insulin as negative insulin dose errors.*

In this study, a multivariate mixed regression model was selected that could distinguish fixed effects by hematocrit on glucose meter performance and method bias as well as random effects (Table 2). Unexplained random error is inherent imprecision when any 2 measurements are performed and when this additional variation was added to the fixed effects, the model predicted that approximately 8.5% of emergency results would exceed ±12% of the reference glucose method, whereas the FDA target was less than 5%. However, as depicted in Figure 1, B (supplemental digital content), the anticipated analytic errors are not large. This prediction is consistent with a recently published postmarket assessment of glucose meters in acute care.[20]

To assess the clinical impact of the predicted glucose meter error, we assessed the impact on predicted insulin-dosing decisions. The IDEA grid is a relatively new error grid that depicts glucose meter performance by assessing the frequency and extent of insulin dose category errors as a direct consequence of glucose measurements.[17] The IDEA grid provides the clinical outcome (positive or negative) directly linked to the performance of the glucose meter in detecting the reference blood glucose result. We applied the IDEA grid to assess the impact of the predicted Accu-Chek Inform II glucose meter results, anticipated from the combined effect of fixed and random effects, by using a nationally accepted, inpatient insulin algorithm.[1] Twenty-eight percent of intensive care unit results, 20.8% of hospital inpatient results, and 17.7% of emergency department results were predicted to trigger a 1-category insulin dose error above/below the appropriate dose (Table 3). This result is statistically significant and is related to the prevalence of low hematocrit levels, but because only errors of a single insulin dose category are predicted, we anticipate this to be

Table 3. Comparison of the Predicted Insulin Dose Errors (%) for Fixed Effects Alone and in Combination With Random Effects by Clinical Unit										
	Fixed Effects Only					Fixed and Random Effects				
Insulin dose error category	−2	−1	0	1	2	−2	−1	0	1	2
Emergency medicine, n = 9288	0%	3.1%	96.0%	0.8%	0%	0.05%	10.8%	82.2%	6.9%	0.05%
Hospital, n = 7216	0%	2.7%	95.3%	2.0%	0%	0%	10.9%	79.1%	9.9%	0.1%
Intensive care, n = 3970	0%	1.5%	92.7%	5.8%	0%	0.1%	10.8%	71.8%	17.2%	0.1%

Fixed effects comprise hematocrit and method biases, while random effects include a random bias in addition to hematocrit and method biases. Insulin dose errors were projected for emergency, hospital inpatients, and intensive care clinical units. The χ^2 analyses demonstrated statistical differences in errors between clinical units ($P < .001$) and between the fixed effects and combined fixed and random effects models ($P < .001$).

a low risk to adult patients. While each individual dose error may confer "low patient risk," the cumulative effect of dose errors does greatly impact long-term patient care outcomes. Given the number of factors that contribute to glycemic variability, the addition of yet another source of insulin dose error, glucose meter inaccuracy, will affect glycemic control in chronically managed patients. For a patient with diabetes, insulin-dosing decisions may be made anywhere from 1 to 6 or more times per day. In the event of hematocrit bias on glucose meter accuracy, this could lead to several single-category dose errors per day or tens to hundreds of dosing errors over a year span. As those with diabetes strive to mitigate all known and potential sources of variation that impact their glycemic control, the "low risk" yet cumulative effect of insulin dose error from hematocrit bias contributes yet another recurrent factor impeding their attempts to achieve optimal glycemic control.

We acknowledge this study has several limitations: (1) the study evaluated only 1 brand of glucose meter; (2) the study used glucose values obtained during evaluation of arterial or venous blood gas and metabolite profiles from clinical units as representative of patients in each clinical unit; and (3) the study used whole blood glucose measurements by a blood gas analyzer as a reference method rather than a definitive glucose method.

In summary, this quality assurance study predicted the extent that hematocrit bias, method bias, and variation influence glucose meter performance and the downstream decision of insulin dosing. Although the extent of the fixed effects met the 2018 FDA performance expectations of 95% of results within ±12% (for results ≥75 mg/dL [4.2 mmol/L]), when fixed and random effects were considered, 28% of intensive care unit analyses were predicted to result in a 1-category insulin dose error above/below the appropriate dose. The impact of this anticipated insulin-dosing error likely represents a low risk for patients.

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