

Anemia causes hypoglycemia in intensive care unit patients due to error in single-channel glucometers: Methods of reducing patient risk*

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Objective: Intensive insulin therapy in the critically ill reduces mortality but carries the risk of increased hypoglycemia. Point-of-care blood glucose analysis is standard; however, anemia causes falsely high values and potentially masks hypoglycemia. Permissive anemia is practiced routinely in most intensive care units. We hypothesized that point-of-care glucometer error due to anemia is prevalent, can be corrected mathematically, and correction uncovers occult hypoglycemia during intensive insulin therapy.

Design: The study has both retrospective and prospective phases. We reviewed data to verify the presence of systematic error, determine the source of error, and establish the prevalence of anemia. We confirmed our findings by reproducing the error in an *in vitro* model. Prospective data were used to develop a correction formula validated by the Monte Carlo method. Correction was implemented in a burn intensive care unit and results were evaluated after 9 mos.

Setting: Burn and trauma intensive care units at a single research institution.

Patients/Subjects: Samples for *in vitro* studies were taken from healthy volunteers. Samples for formula development were from critically ill patients who received intensive insulin therapy.

Interventions: Insulin doses were calculated based on predicted serum glucose values from corrected point-of-care glucometer measurements.

Measurements and Main Results: Time-matched point-of-care glucose, laboratory glucose, and hematocrit values. We previously found that anemia (hematocrit <34%) produces systematic error in glucometer measurements. The error was correctible with a mathematical formula developed and validated, using prospectively collected data. Error of uncorrected point-of-care glucose ranged from 19% to 29% ($p < .001$), improving to $\leq 5\%$ after mathematical correction of prospective data. Comparison of data pairs before and after correction formula implementation demonstrated a 78% decrease in the prevalence of hypoglycemia in critically ill and anemic patients treated with insulin and tight glucose control ($p < .001$).

Conclusions: A mathematical formula that corrects erroneous point-of-care glucose values due to anemia in intensive care unit patients reduces the prevalence of hypoglycemia during intensive insulin therapy. (Crit Care Med 2010; 38:471–476)

KEY WORDS: glucose; insulin; anemia; point-of-care systems; hematocrit; glucose oxidase; critical care; intensive care unit; glucometer; glucose measurement

Inaccuracy of glucometer measurement is an often discussed but poorly understood phenomenon, in part, because of the plethora of variables that can affect performance. Many of these exert effects only under specialized circumstances, and relevance to the majority of intensive care unit (ICU) patients is unknown. Here, we identify the single most

important factor affecting glucometer performance in hemodynamically stable ICU patients and we describe the impact of glucometer error on hypoglycemia.

Glucometer performance is an important issue in the care of ICU patients because, although the demonstrated benefits of intensive insulin therapy (IIT) changed therapy around the world (1, 2), problems

with implementation are generating controversy. Hypoglycemia is a recognized complication of insulin treatment and, as we previously showed, can be related to the effects of anemia on glucometer performance (2). This is not a trivial problem; in severe cases, hypoglycemia can lead to seizures, coma, and death (3, 4). Recent European trials (GLUCONTROL and VISEP) designed to confirm and extend the findings of the original Van den Berghe study were closed before completion due to unacceptable increases in prevalence of hypoglycemia (5, 6).

IIT requires frequent glucose measurement to maintain patient safety; single-channel point-of-care (POC) whole blood glucometers are used almost universally to direct care as they are inexpensive, require small blood volumes, and have rapid response times compared with laboratory analysis (7). Recent studies, however, question whether they are sufficiently accurate and reliable for use

*See also p. 703.

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in critically ill patients (8, 9). According to the American Diabetes Association guidelines (10, 11), error rates in glucose measurement should not exceed 5%, but actual rates >25% have been reported (9, 12, 13). Given the narrow glucose target of 80 mg/dL to 110 mg/dL associated with IIT, this degree of measurement error can have a significant clinical impact.

Error in POC analysis is multifactorial and the literature describing causative factors is extensive; yet, before this study, the relative clinical contribution of individual sources of error was unclear. Reported causes of poor glucometer performance include abnormal hematocrit, low oxygen tension, acetaminophen, uric acid, ascorbic acid, maltose, galactose, xylose, lactose, operator inexperience, age of strips, heat, and humidity. Anemia results in error because the estimated volume of plasma equivalent used to calculate glucose concentrations are based on expected plasma displacement associated with normal erythrocyte content (12, 14). In anemic samples, the degree of displacement is overestimated, the plasma volume is underestimated, and the reported glucose concentration is thus artificially high. Laboratory analyzers are not subject to this error as plasma rather than whole blood is measured.

Given the effect of anemia on glucometers and their widespread use, implementation of IIT has resulted in a potentially dangerous clinical scenario due to the coincident adoption of restrictive blood transfusion therapies in response to the landmark work of Hébert and colleagues (15). Lower transfusion thresholds have increased the prevalence and depth of anemia in the ICU (15–20), but the impact on glucometer performance is poorly recognized (12, 14). We previously showed that significant error is found in four of the most widely used glucometers and that the error was associated with anemia (2, 6). This study examines causation and seeks to identify the most important source of glucometer error in hemodynamically stable patients. We further studied the effect of glucometer error correction on occult hypoglycemia and hypoglycemia frequency, and its role in preventing excessive insulin administration in anemic patients who receive IIT.

MATERIALS AND METHODS

This study was conducted at Brooke Army Medical Center/United States Army Institute of Surgical Research, Fort Sam Houston, TX.

This study was approved by the Institutional Review Boards from Brooke Army Medical Center and the University of Texas Health Science Center - San Antonio. The risk of study participation was considered minimal and formal consent was waived by the Institutional Review Board, except in the case of healthy volunteers who signed consents before enrollment.

All POC whole blood glucometer measurements were made with the SureStepFlexx glucometer (Lifescan, Milpitas, CA) except as noted, and laboratory glucose values were obtained from plasma samples, using the Vitros Fusion analyzer (Ortho Clinical Diagnostics, Rochester, NY). The intra- and interassay coefficient of variations for the Vitros analyzer range from 0.5% to 1.2% and 1.2% to 3.5%, respectively (21). The POC glucometer uses reflectance-based glucose oxidase technology, as does the laboratory analyzer (14). Glucometer measurements were made, according to manufacturer's specifications on undiluted whole blood. Samples for glucose analysis were sent to the laboratory in additive-free, or sodium fluoride and potassium oxalate-containing evacuated tubes filled with whole blood.

Frequency of Glucometer Error

Our first task was to establish the frequency of systematic glucometer error in ICU patients. To do so, we analyzed glucometer and laboratory glucose (used as the reference in our study) paired by recorded collection time. Data from 19 ICU subjects over 4 consecutive mos were analyzed to determine the prevalence of error. The source of blood could not be determined in this retrospective review. Error rates found in the retrospective data were confirmed with prospective data. POC glucometer glucose measurements from patients in the medical, surgical, and burn ICUs were collected and compared with reference.

Cause of Glucometer Error

Once glucometer error was defined and found to be consistently present, we conducted a literature search, which identified multiple potential sources of error. These included suboptimal environmental and operator-related conditions, sample degradation, interfering substances, and low oxygen tension, which were eliminated as confounders (data not shown).

We assessed hematocrit effect due to anemia as a causative factor by adding time-matched hematocrit values to the retrospective data from the 19 ICU subjects, almost all of whom were anemic. The association of glucometer error with abnormal hematocrit was examined by comparison with data from hospitalized patients over the same time period with normal hematocrits, and confirmed with an *in vitro* model in which five glucose and

three hematocrit concentrations were artificially constructed from the blood of healthy volunteers stored in sodium heparin-containing evacuated tubes. POC glucometer, reference laboratory, and hematocrit analysis was conducted on the resulting samples.

Once anemia was confirmed as a significant cause of glucometer error in our ICU populations, the additional contribution of interfering substances and low oxygen tension was evaluated by comparing results from a traditional single-channel glucometer corrected for error due to anemia alone, with measurement of the same samples using a new, commercially available multi-channel glucometer (StatStrip, Nova Biomedical, Waltham, MA) that corrects for the effects of anemia, low oxygen tension, acetaminophen, uric acid, ascorbic acid, maltose, galactose, xylose, and lactose. Whole blood samples prospectively collected from anemic critically ill patients in the medical, surgical, and burn ICUs were used for testing. Arterial blood was preferentially used unless arterial access was unavailable; in these cases, the research team used careful collection techniques in obtaining venous blood to avoid contamination with glucose-containing intravenous infusions. Capillary blood was not used. Error rates for each meter model were calculated by comparing POC results with reference laboratory values.

Hematocrit Threshold of Error

The threshold of low hematocrit giving rise to measurable differences in POC and laboratory glucose testing was determined through analysis of a large number of retrospectively collected hematocrit, laboratory glucose, and POC glucose measurements. We plotted the ratio of laboratory/glucometer glucose vs. hematocrit, and filter curve analysis defined the lower limit of the 95% confidence interval where glucometer error reached statistical significance. The percentage of POC glucometer measurements in the burn, surgical, and medical ICUs associated with hematocrit below this level defined the level of risk to patients in each unit. The upper limit was not assessed as polycythemic patients are rare in the ICUs studied and available data were insufficient for meaningful analysis.

Formula Development

Blood samples ($n = 196$ measurements) from ICU patients were collected in evacuated tubes containing sodium fluoride and potassium oxalate and sent for laboratory glucose analysis. Results were matched with complete blood count quantification from evacuated tubes in ethylenediaminetetraacetic acid (EDTA) sent within 12 hrs of glucose sample collection. Additive-free whole blood from the same collection specimen was used simulta-

neously for single-channel POC glucometer measurement. Arterial blood was used preferentially and venous blood was used if arterial access was unavailable. Capillary blood was not used for POC glucose measurements, as several studies have demonstrated that glucometer capillary blood measurement is less reliable than arterial blood (22–25). Glucometer linearity tests were performed, according to manufacturers' instructions, every 24 hrs using high and low glucose control solutions. No glucometer used in the study failed the linearity test at any time. Glucometer analysis was performed by operators trained in the use and maintenance of the device. The mathematical relationship between POC glucometer, laboratory glucose, and hematocrit values was defined, using regression analysis of a logarithmic-based model. The predictive value of the resulting equation was validated, according to the Monte Carlo method (26). Percent error of glucometer data relative to laboratory glucose analyzer results was also tested both before and after correction, using POC glucose values from samples not used in the correction formula derivation.

Effect of Correction on Incidence of Hypoglycemia

The research team initiated a staff education program to disseminate information among intensive care providers regarding the risk of hypoglycemia in ICU patients receiving intensive insulin therapy managed by single-channel glucometers. We analyzed the clinical impact of the model by comparing the incidence of hypoglycemia in the burn ICU before and after formula implementation. Correction was not instituted in the surgical ICU, which provided a negative control. Differences solely reflected the effect of the formula because staff education in both units was similar. Matched sets of glucometer and laboratory glucose measurements were collected over 4-mo periods before and after implementation of the formula, and the delta in hypoglycemic episodes was calculated.

Data Analysis

Data were analyzed, using linear and logarithmic regression analysis. Error was defined as percent deviation in glucometer values from laboratory analyzer quantification of glucose. Quantitative variables were analyzed with Student's *t* test, and qualitative variables were analyzed with the chi-square test. Significance was set at $p < .05$. Variability in sample sets was reported as standard deviation (SD) except where specifically noted.

RESULTS

Frequency of Glucometer Error

We quantified glucometer error in 300 glucometer and laboratory (reference) glucose data pairs from patients admitted to the burn ICU. Glucometer values were on average $21 \pm 16\%$ higher than reference glucose values. The regression equation from a random subset of patients ($n = 9$ subjects, 154 data pairs) was applied to glucometer measurements for the second subset ($n = 10$ subjects, 146 data pairs), correcting the error in the latter group (data not shown). This analysis served to show that the error in this population was systematic, reproducible, and consistently in the direction of glucometer overestimation. Linear models including subject as a random effect revealed no significant variation in the slope ($p = .64$) or intercept ($p = .43$) within subjects. To confirm the findings, glucometer and reference glucose samples were collected prospectively from 41 hemodynamically stable subjects ($n = 196$ samples). Glucometers overestimated the reference value on average by $19 \pm 7\%$, confirming the reproducibility and direction of systematic error.

Cause of Glucometer Error

To examine the effect of anemia on glucometer accuracy, we reanalyzed the initial retrospective data set with regard to hematocrit and compared percent error from ICU samples with that from non-ICU patients with normal hematocrit ($n = 56$, 75 data pairs). Percent error was correlated inversely with hematocrit (Fig. 1); effects of

polycythemia were not assessed due to insufficient data. Average hematocrit in the ICU group was $25 \pm 7\%$ compared with $42 \pm 2\%$ in the non-ICU group (selected for normal hematocrit). Hematocrit analysis yielded similar results in the prospectively collected sample set (data not shown). Anemia was confirmed to be a significant source of error by reproducing it in an *in vitro* model that tested the effect of different hematocrit concentrations on glucometer performance. As expected, low hematocrit resulted in inappropriately high glucometer values (data not shown).

The effects of interfering substances (acetaminophen, uric acid, ascorbic acid, maltose, galactose, xylose, lactose) and low oxygen tension were eliminated as significant contributors to error by comparison of glucometer results corrected for anemia alone with those from a new four-channel glucometer, which corrects for hematocrit effect and all substances listed above. The average hematocrit for samples tested was $26.6 \pm 5.2\%$. Uncorrected single-channel glucose measurement error was $22 \pm 9.4\%$ compared with reference; however, correction improved the error to levels similar to that from the multi-channel device ($4.36 \pm 5.6\%$ vs. $-4.25 \pm 5.3\%$, $p = .88$). The two analyzers were within the set zone of indifference of $\pm 5\%$ (-0.67% , 95% confidence interval = $-1.79-0.45$). The demonstrated noninferiority between methods is evidence that contributions to single-channel glucometer error were primarily due to the effect of anemia.

Hematocrit Threshold of Error

A very large retrospective data set ($n = 12,800$ measurements) was analyzed

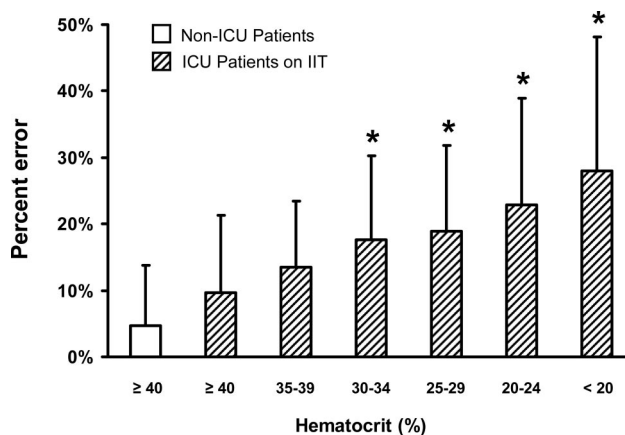


Figure 1. Percent error in glucometer measurements (reference = laboratory glucose) inversely correlated with degree of anemia in intensive care unit (ICU) patients; the lowest hematocrit group, significantly different from that of normal hematocrit in non-ICU patient samples collected during same time period ($p < .001$). IIT, intensive insulin therapy.

to determine the level of hematocrit at which correction for anemia becomes necessary. The laboratory/glucometer glucose ratio was plotted against hematocrit; error was significant at hematocrit levels of <34% ($p = .05$). A subanalysis of measurements from ICU patients undergoing frequent glucose quantification revealed that 64%, 79%, and 92% of glucometer measurements in the medical, surgical, and burn ICUs were associated with a hematocrit <34% threshold, posing a significant risk of hematocrit error and occult hypoglycemia to patients in those units.

Formula Development

Samples were collected prospectively from 41 hemodynamically stable ICU subjects ($n = 196$ measurements), using hematocrit measurement within 6 hrs of phlebotomy for analysis. POC glucometer error rates \pm SD in the prospective data were $19 \pm 7\%$ (average hematocrit = 25%). This was similar to error found in the retrospective samples ($21 \pm 16\%$ error \pm SD, average hematocrit = $25 \pm 7\%$). The linear equation derived from regression analysis was:

$$LG_p = 0.21(\text{POCG}) \times \text{LN}(3.32 \times \text{HCT}) - 11.39, (r^2 = 0.97)$$

where LG_p is the laboratory glucose predicted by correction, POCG is the whole blood glucose measurement before correction, LN is the natural log, and HCT is the hematocrit. The predictive validity of the formula was tested with randomly extracted subsets of data; the formula reduced average error to $-0.02 \pm 4.78\%$. Corrected POC glucometer data were highly correlated with laboratory glucose measurements ($r^2 = .97$) and conformed closely to the line of identity. An additional 205 prospectively collected, matched glucometer and reference values (average hematocrit = $23 \pm 5\%$) were used to test adequacy of correction. Application of the formula improved the error rate in this data set from $29 \pm 13\%$ ($p < .001$) to $5 \pm 11\%$, resulting in corrected glucometer values that did not differ statistically from laboratory analysis ($p = .43$). Bland-Altman analysis revealed negligible measurement size effect on error after correction (Fig. 2).

Bland-Altman Plot

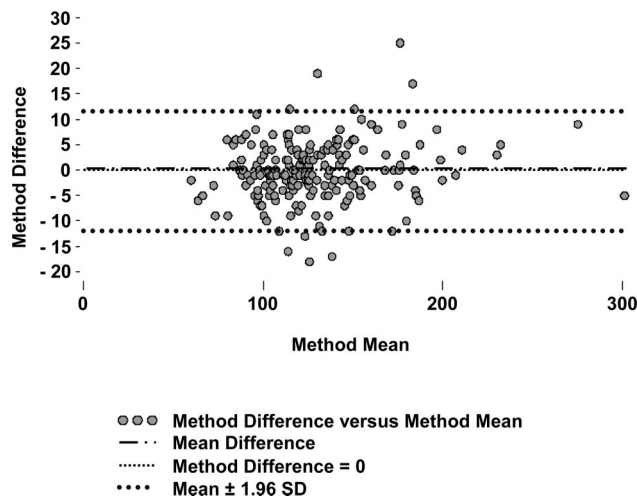


Figure 2. Bland-Altman plot with laboratory glucose as the reference measurement and corrected glucometer glucose as the test measurement. Units on the x and y axes are mg/dL.

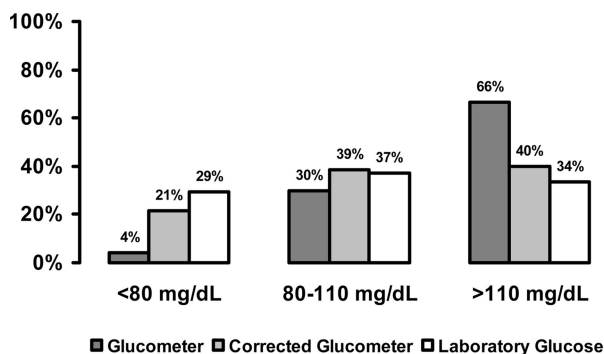


Figure 3. Percent measurement of glucose values below, in, and above the glucose target as measured by glucometer, corrected glucometer, and laboratory analysis. Glucometer measurement significantly underestimates glucose below target compared with laboratory measurement ($*p < .001$), but improves with correction. Data were collected before implementation of the glucometer correction formula.

Effect of Correction on Prevalence of Hypoglycemia

Uncorrected glucometer analysis underestimated the number of glucose values below target (80–110 mg/dL) in the above data set by 86% and overestimated those above target by 93%, undoubtedly leading to excessive insulin infusion (Fig. 3). To determine whether correction of glucometer results decreased the frequency of low glucose measurements, we reviewed data from 4-mo periods before and after the formula was implemented in the burn ICU. The surgical ICU served as a control in this analysis. Laboratory measurements in the low (<80 mg/dL) and hypoglycemic (<60 mg/dL) glucose ranges were reduced by 58% (Fig. 4) and 78%, respectively in the burn ICU ($p < .001$), but not in the surgical ICU.

DISCUSSION

Anemia is common in the ICU, and low hematocrit significantly affects the accuracy of POC glucose measurement (8, 22, 27). In our study, hematocrit effect was the overriding cause for glucometer error, and the false results masked hypoglycemia. Furthermore, we demonstrated that a mathematical formula corrects this error within clinically acceptable limits. Finally, application of this formula decreased significantly the prevalence of hypoglycemia in critically ill patients treated with insulin.

Previous studies cautioned critical care specialists on the risks of using glucometers for IIT (4, 8, 9); however, a low-cost, practical alternative offering ease of testing and minimal blood volume was not available. When institutions simultaneously adopted IIT and restrictive

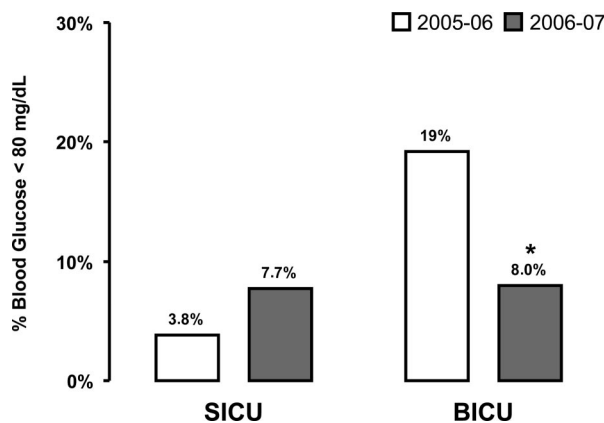


Figure 4. Difference in percent measurements requiring a reduction or discontinuation of intravenous insulin infusions (<80 mg/dL) before and after implementation of the glucometer correction formula (burn intensive care unit, * $p < .001$) compared with no implementation of glucometer correction (surgical intensive care unit, $p = \text{NS}$). *SICU*, surgical intensive care unit; *BICU*, burn intensive care unit.

transfusion strategies (1, 3, 15), the likelihood of concomitant hypoglycemia and anemia increased. Glucometer error drives glucose to a lower range by reporting glucose concentrations that are higher than actual. The likely result is an increase in administered insulin. Hypoglycemia is associated with higher mortality and other complications in the ICU, and its association with IIT is increasingly recognized (4, 28). Our low-cost mathematical formula produces results equivalent to those from a multi-channel glucometer. Regardless of the method used, eliminating low hematocrit error improves patient safety by reducing hypoglycemia and its attendant risks.

This study had several limitations. Patient diagnosis and the percentage of samples derived from arterial vs. venous blood were not evaluated, and these are variables that can affect POC measurements. The level of oxygenation was not recorded; however, no significant difference was found between results from a four-channel glucometer that corrects for low oxygen levels and the single-channel glucometer/mathematical correction method. This finding suggests that low oxygen levels are not a significant source of error in hemodynamically stable ICU patients, such as those in our study. Retrospective data were used to identify potential causes of error; however, because all findings were confirmed with prospective and *in vitro* data, this is not considered a limitation of the study.

The focus in this paper is not to advocate one method over the other but rather to highlight the prevalence of anemia in ICU patients receiving IIT and emphasize the risk of glucometer error in

this population. In a previous paper, we showed that anemia is a significant cause of glucometer error (2). Here, we further demonstrate for the first time that anemia is the primary cause of glucometer error in hemodynamically stable adult ICU patients and that eliminating hematocrit error decreases the frequency of hypoglycemia.

Hypoglycemia can cause severe injury or death and the association with strict glucose control has become a major source of concern (9, 29). Given that impact of anemia on glucometer performance (Fig. 3) remains largely unaddressed, the true prevalence of hypoglycemia in patients treated with IIT is likely even higher than generally feared. We previously quantified error in four widely used POC glucometers and found that error rates between models were comparable (2), and thus concluded that glucometer error likely poses a risk to anemic patients receiving IIT at multiple institutions besides our own.

The emphasis of the work described here was to raise clinician awareness that single-channel glucometers currently in use do not correct for hematocrit, with the consequence that the data used to drive patient care overestimate the actual glucose concentration and may contribute to the higher rates of hypoglycemia associated with IIT. Hematocrit effect may be the reason why the GLUCONTROL and VISEP studies reported high rates of hypoglycemia (5, 6), eventually leading to the discontinuation of both trials. The inability to reproduce the benefits reported by Van den Berghe and associates has been widely discussed, and the root cause may lie in glucose measurement error due to anemia. In this study, we

found that four-channel glucometers, which use proprietary software to correct hematocrit error before reporting a result, perform at least as well as our correction formula. Critical care providers should be aware of the potential for unrecognized hypoglycemia with the use of single-channel glucometers, and that four-channel glucometers do not pose the same risks to anemic patients.

CONCLUSIONS

Anemia is the major cause of glucometer error in ICU patients receiving IIT, and correction with a mathematical formula decreased the frequency of low glucose values. This provides evidence that low hematocrit indirectly results in hypoglycemia, which if severe could reduce or even negate the known benefits of IIT. Clinicians should be aware that the use of single-channel glucometers is contraindicated in anemic patients and they should consider using mathematical correction or multi-channel analyzers to manage IIT in this patient population.

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