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SYMPOSIUM

Blood Glucose Measurements in Critically Ill Patients

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Abstract

Studies on tight glycemic control by intensive insulin therapy abruptly changed the climate of limited interest in the problem of hyperglycemia in critically ill patients and reopened the discussion on accuracy and reliability of glucose sensor devices. This article describes important components of blood glucose measurements and their interferences with the focus on the intensive care unit setting. Typical methodologies, organized from analytical accuracy to clinical accuracy, to assess imprecision and bias of a glucose sensor are also discussed. Finally, a list of recommendations and requirements to be considered when evaluating (time-discrete) glucose sensor devices is given.

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Introduction

Hyperglycemia is part of the natural stress response of humans.[1] Nevertheless, clinical and scientific interest in the dysregulation of the normal glucose homeostasis has emerged only recently. Before the landmark trial by Greet Van den Berghe and coworkers in 2001, blood glucose (BG) levels were only sporadically measured, mainly in patients with known diabetes mellitus.[2] In patients without established diabetes mellitus, blood hyperglycemia was tolerated to very high levels. Current practice in those days, although poorly documented, would recommend administration of insulin when BG levels would exceed the renal threshold of ±220 mg/dl.[3] But even short-term peaks of over 300 mg/dl were not aggressively treated.

The studies on tight glycemic control (TGC) by intensive insulin therapy abruptly changed this climate of limited interest in and complacency towards the problem of hyperglycemia. In the Leuven proof-of-concept studies, the BG levels were kept tightly between 80 and 110 mg/dl.[2,4] The strategy of TGC decreased mortality and morbidity in surgical critically ill patients and morbidity in medical critically ill patients. Results of the Leuven proof-of-concept studies were swiftly incorporated in international guidelines, and intensive care units (ICU) all over the world started implementing TGC. Most likely, the methodology for TGC, as practiced in the well-controlled Leuven studies, was not ready for worldwide implementation. This became clear with the publication of data from the Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study in 2009.[5] Implementation of TGC in a pragmatic multicenter trial, accepting among others a wide array of BG measurement devices, turned out to increase the mortality risk.[6,7]

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Abbreviations: (BG) blood glucose, (Hct) hematocrit, (ICU) intensive care unit, (ISO) International Organization for Standardization, (NICE-SUGAR) Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation, (TGC) tight glycemic control

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In daily clinical practice, the paradigm suddenly shifted from tolerating a wide range of higher BG levels to actively targeting the narrow normoglycemic range of 80–110 mg/dl. This change in clinical "context" is having a strong impact on the methodology of BG measurements and explains why glucose sensors that were earlier found accurate (in higher glucose ranges) have appeared to be less reliable in these lower "normal" glucose ranges.

General Aspects of Blood Glucose Measurements

For obvious reasons, BG readings from the devices used are the centerpiece of TGC. A BG reading is the result of the integration of different components. Blood is drawn from a patient and subsequently analyzed for glucose concentration in a device. Each may induce variability in the final glucose reading (**Table 1**).[8–10]

Enzymes for Blood Glucose Measurement

The ultimate reference technique to measure glucose levels accurately is mass spectrometry. As this is a labor-intensive and expensive approach, alternative methods have been developed. All time-discrete glucose sensor devices are based on enzymatic reactions in which glucose is a converted value. It is important to realize that these enzymes are used in central laboratory devices, blood gas analyzers, and handheld BG meters. Hexokinase is used only in central laboratory analyzers. Therefore, this method is regarded as the second best reference method for BG measurement. Glucose oxidase and glucose-1-dehydrogenase are the other enzymatic reactions. At the level of the enzymatic conversion of glucose or at the level of the cofactor used herein, interferences may happen. The glucose oxidase reaction requires water and oxygen. Therefore, high oxygen tensions, which may occur in mechanically ventilated patients, could result in falsely lower BG levels in glucose oxidase systems, which use a mediator. Reducing agents, such as ascorbic acid (vitamin C) and acetaminophen (paracetamol), tend to induce underestimation of BG levels.[11] The main advantage of the glucose oxidase enzymatic reaction is its specificity to glucose.

This is the chief problem with glucose dehydrogenase systems, which may detect nonglucose sugars such as maltose, mannose, and xylose. A well-known example is the glucose dehydrogenase with the cofactor pyrroloquinoline quinone, which overestimates BG levels in patients on peritoneal dialysis with icodextrin, a maltose polymer. A mutant of the glucose dehydrogenase appears to be selective for glucose.[12] Glucose dehydrogenase-based systems are, on the other hand, generally less vulnerable (than glucose oxidase-based systems) to interferences for nonsugar medications and oxygen.

Table 1.
Important Components of Blood Glucose Measurements and Their Interferences

Enzyme	Specimen	Interferences
Hexokinase	Arterial	Anemia
Glucose oxidase	Capillary	Medication
Glucose dehydrogenase	Venous	Operator

Arterial, Capillary, and Venous blood

The source of the sample and the specimen matrix in which BG levels are measured has attracted much attention in the debate on TGC. In healthy humans, fasted arterial glycemia is already 5 mg/dl higher than capillary and 10 mg/dl higher than venous glycemia.[8,12] In critically ill patients, it is questionable whether capillary blood reflects the blood or the interstitial fluid compartment. The interstitial fluid compartment often dramatically increases when the patient becomes edematous. Therefore, it may no longer reflect the glucose levels in the blood. While interstitial glycemia may still correlate with arterial BG levels, the absolute glucose concentrations may strongly differ. The response time of changes in BG concentrations in the interstitial compartment may also be slower than in the arterial blood. This lag time became more apparent when subcutaneous *near-continuous* BG sensors, measuring the interstitial glycemia, were compared with arterial BG levels.[13] Reliable trending may suffice in clinical practice, e.g., in cardiac output measurements, as one can easily correlate the cardiac output with markers of organ perfusion (such as blood lactate concentrations). However, for BG control, one can only rely on the measurements themselves as clinical signs of hypoglycemia are masked by the sedation of critically ill patients.[14]

Venous blood may be a good alternative to arterial blood. In daily practice, this blood is drawn from a deep venous catheter as frequent vena punctures are impossible in those patients. However, there is a risk of glycemia overestimation if highly concentrated dextrose solutions are administered through the same multiple lumen catheter.

Interferences

Blood glucose levels measured in plasma or serum are 1.11 times higher than measurements in whole blood,

provided that the patient has a hematocrit (Hct) of 40–45%. This is explained by the higher water content, which contains the glucose, in plasma. Most glucose meters nowadays are calibrated to report plasma glucose levels. Before embarking on TGC, one has to verify that the BG meter to be used incorporates the whole blood plasma factor. However, the aforementioned conversion factor is only valid when the patient has a normal Hct. Since the 1990s, anemia is widely tolerated in critically ill patients due to restrictive transfusion policies.[15,16] As a result, the average Hct in critically ill patients is often between 25% and 30%, which has been shown to strongly increase the error in BG measurements.[17,18] Anemia mainly results in overestimation of glycemia, leading to over-treatment with insulin and finally inducing hypoglycemia. A mathematical correction for anemia may prevent these measurement and treatment errors.[18] The rise in mortality rate in patients on intensive insulin therapy in the NICE-SUGAR study may be related to the use of inaccurate BG meters in critically ill patients.[6,7] Other interference factors that hinder accurate and reliable glucose measurements are the administration of medication (such as ascorbic acid and paracetamol), varying oxygen levels (particularly high levels of pO_2), and acidosis. Finally, the operator error is presumably a large, important factor in erroneous BG readings but unfortunately hard to quantify.[19]

Assessment of Imprecision and Bias

Inaccurate BG measurements can be attributed to bias (average error) and imprecision (variability of repeated/reproduced measurements of a sample). Needless to say that interference gives rise to imprecision in the BG measurements. This imprecision generally goes unnoticed to the user, which only amplifies the risk of making wrong treatment decisions, particularly overdosing the insulin dosage. This may eventually lead to hypoglycemia, which may still go unnoticed as the BG meter may give falsely elevated readings. Karon and colleagues[20] have shown by simulation modeling for TGC that a frequency of 4% large dosing errors may occur when an imprecision of 20% is accepted. Conversely, when imprecision is kept below 10%, dosing errors are virtually avoided. This modeling was done on a database of BG concentrations from critically ill patients on TGC with two different protocols. Nevertheless, already 10 years before, it was shown that to provide 95% of the right insulin dose, both imprecision and bias should be less than 2%.[21]

There is a consensus among clinical chemists and the Food and Drug Administration that current BG meters have to be improved for use in the ICU in the context of TGC.[22,23] However, to what extent and by which criteria this improvement should be measured is still unclear. Methodologies for analyzing the performance of BG meters can be organized in two groups. The first group measures analytical accuracy using common statistical techniques, whereas the second group assesses the direct clinical implementation.[24]

Analytical Accuracy Methods

Probably, the most widely used statistical technique for evaluating BG meters is the correlation coefficient. However, it must be noted that the computation of the correlation between two variables does not give any information on the accuracy of the sensor device under study. Regression (or correlation) measures the strength of the relation between two variables, which is different from the numerical agreement. A strong relation (and a high correlation coefficient) between two sensor devices that measure the exact sample is obvious and expected, but gives no guarantee that the effective measurement error is small.[25] In addition, correlation coefficients can be easily augmented by enlarging the measurement range or by increasing the number of samples, as also shown in the following example. The correlation coefficients of two handheld BG meters were > 0.94 when tested against a blood gas analyzer across all BG levels in critically ill patients.[26] However, in the TGC range of 80–110 mg/dl, the correlation coefficient fell below 0.67. Also in the low BG range (<80 mg/dl), the correlation coefficient was unacceptably low. Computing the mean absolute or relative difference is another rather simple technique for approaching analytical accuracy but is not favored as skewness in the data can easily mislead the analysis.

More sophisticated methods estimate total error. This numerical value is the result of approaching different types of errors: bias, short-term imprecision (repeatability), long-term imprecision (reproducibility), and random (non-controllable) user interferences. This is elegantly described by Krouwer and Cembrowski.[27] Computation of total error is not straightforward when taking into account random (user) interferences that are typically noncontrollable. When considering only the bias and the imprecision, total error can be computed with the Westgard equation (% total error = % average bias + 1.96 ∗ coefficient of variation) as used in a study on the performance of BG meters in the context of diabetes during pregnancy.[28] Another known technique to approach total error was developed by Bland and Altman.[29–31] In this graphical method, the differences of the paired measurements are plotted against the average of the two values. Next, the limits of agreement (i.e., mean difference ± 1.96 ∗

standard deviation) show the 95% confidence intervals. An important side effect of these more sophisticated, parametric analyses is the normality condition (data are normally distributed) on which these techniques are founded. Important deviations from this assumption may lead to wider real confidence intervals and, subsequently, to wrong assessments of the glucose sensor. The Bland–Altman analysis has been used for evaluation of BG meters in the context of TGC. Because of the practice of TGC, the meters were tested in a clinical context of median glycemia of 108 mg/dl. In two independent studies, the 95% confidence interval of the tested meters was larger than the TGC target range of 30 mg/dl (= 110 mg/dl − 80 mg/dl).[26,32] The study by Karon and colleagues[33] tested a handheld BG meter in the context of moderate glycemic control (median BG of 149 mg/dl), comparing capillary, arterial, and venous blood. While the median bias for capillary blood (+2.5 mg/dl) was much lower than the median bias for arterial and venous blood (+15 mg/dl), the 95% confidence interval for venous (±85 mg/dl) and capillary blood (±55 mg/dl) were considerably higher than for arterial blood (±35 mg/dl). This could mean that arterial blood sampling in a handheld BG meter gives a constant overestimation of the actual BG level but may result in a better analytical precision.

Another drawback, present with all standard analytical accuracy measures, is the equal severity of error for the entire glucose range, which can lead to an underestimation of measurement errors in the hypoglycemic range. Indeed, a specific deviation in the hypoglycemic zone may lead to severe clinical decision errors, whereas the same deviation in the hyperglycemic zone would not lead to different clinical treatments. A different evaluation of two seemingly equal measurement errors may be appropriate. In general, we can conclude that statistical methods may lack clinical interpretation while focusing on the analytical accuracy.

Clinical Accuracy Methods

Standards describing the requirements for glucose sensor devices used for self-monitoring by patients with diabetes were set in the past by international organizations. Most known and used are the International Organization for Standardization (ISO) criteria.[34] These criteria can be summarized as follows:

1. For real or "reference" glucose values ≤75 mg/dl, the value resulting from the BG meter under study must fall within ±15 mg/dl limits
2. For reference values >75 mg/dl, target variability is defined as ±20%.

The glucose sensor under study is found acceptable if these ISO criteria are met in 95% of the individual paired glucose measurements. A drawback of these criteria is the strict differentiation between "accurate" and "not accurate". No requirements are given concerning the glucose values that fall outside the "accuracy" limits. The 5% of the glucose values that may fall outside this target zone may lead to clinically wrong decisions and potential danger for the patient. For example, undetected hypoglycemia (which is wrongly monitored as hyperglycemia) can lead to an increase of the insulin infusion and subsequently to a further decrease of the blood glucose.

The first authors to use ISO criteria in the context of TGC were Kanji and colleagues.[35] They divided the reference range of the ISO error grid in three areas (hypoglycemia <80 mg/dl, normoglycemia 80–145 mg/dl, hyperglycemia >145 mg/dl) and used the 20% allowed error across the entire glycemic range. They elegantly showed that when using a blood gas analyzer for BG measurements, only 1% of the data fell outside the 20% allowed error zone. The proportion of data points outside the ISO-acceptable target zone rose to 12% when using a handheld BG meter measuring arterial blood and to 27% when capillary blood was used for the handheld BG meter. Furthermore, the majority of the measurements outside the 20% error target zone were overestimations of glycemia, which may lead to overtreatment with insulin. Certainly, the 9% of capillary BG levels that overestimate in the hypoglycemia zone when using the handheld BG meter hold the risk of failure to detect and treat hypoglycemia. When working in the context of BG control with a BG target between 81 and 135 mg/dl, 5.9% of the BG readings were outside the ISO target range when whole arterial BG values were converted to serum values.[36] Unconverted, only 90.4% of the BG values were within the ISO target range. This really highlights the importance of knowing whether a BG meter (handheld or blood gas analyzer) reports serum-converted BG levels.

Another acknowledged criterion was set by the American Diabetes Association[37] in 1996, wherein, a target variability of preferably less than ±5% (analytical error) and, at the most, ±10% (total error) was recommended for all glucose concentrations between 31 and 400 mg/dl. This requirement may have been too powerful as *in vitro* relative standard deviations obtained for handheld BG meters typically vary from 3% to 10% (or higher)

depending on the presence of proteins in the solution.[38] It is clear that *in vivo* variability is higher due to the influence of biological parameters related to the patient, the blood sample, etc.

A methodology often considered as standard for analyzing a time-discrete glucose sensor is the Clarke error grid analysis.[39–41] Kovatchev and associates[42] reformulated this assessment technique toward a method to evaluate near-continuous glucose monitoring systems, whereas Parkes and colleagues[43] presented an alternative consensus error grid (for time-discrete glucose sensors). The advantage of these methods lies in the simplified clinical evaluation of the sensor device under study. Paired glucose measurements are visually plotted in areas that interpret the clinical severity of the error. The number of errors per region indicate the acceptability of the device (e.g., for Clarke error grid, a glucose sensor is acceptable if at least 95% of the measurements fall in zone A, maximum 5% of the measurements lie in zone B, and 0% of the measurements are in zone C, D, and E[41]). The error grid technique, however, lacks statistical interpretation and has a low degree of robustness.[44–46] Slight deviations from a measured value by the sensor under study can lead to a shift of the plotted reference–test observation point to a different area and, subsequently, to a potentially different clinical interpretation and analysis of the test sensor. In the context of glycemic control in critically ill patients, error grids were used in combination with Bland–Altman plots by Slater–Maclean.[47] Analogous results were obtained for both analyses, but there is, unfortunately, no certainty as observed by Vlasselaers and colleagues.[26]

In general, we can conclude that clinical accuracy methods analyze BG readings in terms of clinical use while ignoring statistical fundamentals. Clinical accuracy methods are also sensitive to the measured observations as slight deviations may shift the assessment (no robust techniques).

A methodology that may combine the best of both worlds is the recently developed GLYCENSIT procedure.[48] This tool considers the evaluation of a BG meter from three different perspectives. First, the persistency of the measurement errors, grouped in a hypo-, normo-, or hyperglycemic zone, is studied. Over- and under-estimation of the reference sensor may depend on the magnitude of glycemia. Though nonpersistent measurement behavior is not favored, the device can be reprogrammed afterwards, aiming at more consistent measurement errors (e.g., by subtracting/adding the mean difference computed for each glycemic range). Second, the accuracy of the device is evaluated by analyzing the number of violations against ISO criteria.[34] Instead of counting this number of violations (as done in the classical clinical accuracy methods described earlier), Van Herpe and colleagues selected a statistically sound bootstrap technique. Finally, the reliability of the sensor is studied by estimating tolerance intervals that indicate the range in which the reference value would lie for new test glucose readings.

The advantages of the GLYCENSIT tool can be summarized as follows. First, this methodology is based on (non-parametric) statistics that return statistically reliable conclusions that are clinically interpretable. Next, the severity of error is made independent of the magnitude of the BG as all measurement errors are transformed using a normalization function.[48] Finally, GLYCENSIT enables the user to review the data from three different perspectives. As a drawback, it must be noted that GLYCENSIT is a guide rather than a strictly defined "accurate/nonaccurate" sensor evaluation methodology. The required active contribution of the user may hinder widespread use of the tool. The GLYCENSIT procedure is therefore implemented as a web tool aiming to reduce this hurdle (*http://www.esat.kuleuven.be/GLYCENSIT*). A thorough GLYCENSIT analysis revealed several characteristics for two bedside glucometers applied in the ICU.[26] Statistical results showed a high accuracy level for one sensor, whereas the second sensor had more persistent (but less accurate) measurement behavior.

To conclude, statistical tests are only meaningful when sufficient amounts of data are available. From a statistical point of view, as many data as possible should be considered in a statistical test, whereas in a clinical environment, however, clinical and financial restrictions may be present. At the GLYCENSIT Web site, the probability level as a function of the statistical significance and the number of paired observations is visualized. Though the graphs are intentionally designed for use in the third phase of the GLYCENSIT analysis, they can be consulted as an approach to the number of paired samples required when designing sensor evaluation studies. Finally, all glucose measurements are ideally spread over the full glycemic range and sampled from different patients from the population of the intended use.

Conclusions

Studies on TGC have led to a shift from tolerating a wide range of (high) BG levels toward strictly controlling glycemia within narrow target limits. This change of clinical context reopened the discussion on accuracy

and reliability of glucose sensor devices. This article has described our perspectives on BG monitoring and the corresponding requirements. The ten most important aspects and recommendations are listed in **Table 2**.

Table 2.
List of Recommendations and Requirements for Time-Discrete Glucose Sensor Devices

Patients	1. The sensor device must be tested under real-life conditions, similar to its use in clinical practice (in order to take into account most random interferences). 2. The sensor device must be tested in a population of the intended use (i.e., similar patient group as target patient population, e.g., diabetes of pregnancy vs TGC in critically ill patients). 3. Sufficient number of patients and sufficient number of measurements per patient are required for statistical reasons.
Blood glucose range	4. Glucose measurements should be spread over the full glycemic range. 5. The median and interquartile ranges of the glucose measurements must be reported to clarify the clinical context and compared with the patient's target glucose range.
Glucose sensing in the ICU	6. Sampling of arterial blood is a prerequisite when applying TGC in the ICU. In noncritically ill patient populations, the use of venous/capillary blood is accepted, assuming physiological features (e.g., lag time) typical of the sampling compartment are understood.
Evaluation methodology	7. Glucose sensor performance should be evaluated both for the full glycemic range as well as for the individual hypo/normo/hyperglycemic range. 8. Limits of agreement (e.g., Bland-Altman analysis) should be smaller than the difference of the patient's target zone (e.g., 110 mg/dl – 80 mg/dl = 30 mg/dl in the context of TGC in critically ill patients), preferably over the entire glycemic range, in case of nonpersistent measurement behavior for each individual hypo/normo/hyperglycemic range. 9. Sensor accuracy should be computed with respect to clinically defined criteria, preferably statistically based (e.g., GLYCENSIT Phase 2 for the ISO criteria). 10. Overestimation measurement behavior in the hypoglycemic range may lead to clinically wrong treatment decisions and should be avoided accordingly.

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Disclosures:

Tom Van Herpe is a postdoctoral researcher at the Katholieke Universiteit Leuven. Dieter Messoten is an associate professor at the Katholieke Universiteit Leuven.

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