Journal of Diabetes Science and Technology
Volume 3, Issue 4, July 2009

CLINICAL APPLICATIONS

Glucose Meters: A Review of Technical Challenges to Obtaining Accurate Results

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Abstract

Glucose meters are universally utilized in the management of hypoglycemic and hyperglycemic disorders in a variety of healthcare settings. Establishing the accuracy of glucose meters, however, is challenging. Glucose meters can only analyze whole blood, and glucose is unstable in whole blood. Technical accuracy is defined as the closeness of agreement between a test result and the true value of that analyte. Truth for glucose is analysis by isotope dilution mass spectrometry, and frozen serum standards analyzed by this method are available from the National Institute of Standards and Technology. Truth for whole blood has not been established, and cells must be separated from the whole blood matrix before analysis by a method like isotope dilution mass spectrometry. Serum cannot be analyzed by glucose meters, and isotope dilution mass spectrometry is not commonly available in most hospitals and diabetes clinics to evaluate glucose meter accuracy. Consensus standards recommend comparing whole blood analysis on a glucose meter against plasma/serum centrifuged from a capillary specimen and analyzed by a clinical laboratory comparative method. Yet capillary samples may not provide sufficient volume to test by both methods, and venous samples may be used as an alternative when differences between venous and capillary blood are considered. There are thus multiple complexities involved in defining technical accuracy and no clear consensus among standards agencies and professional societies on accuracy criteria. Clinicians, however, are more concerned with clinical agreement of the glucose meter with a serum/plasma laboratory result. Acceptance criteria for clinical agreement vary across the range of glucose concentrations and depend on how the result will be used in screening or management of the patient. A variety of factors can affect glucose meter results, including operator technique, environmental exposure, and patient factors, such as medication, oxygen therapy, anemia, hypotension, and other disease states. This article reviews the challenges involved in obtaining accurate glucose meter results.

J Diabetes Sci Technol 2009;3(4):971-980

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Abbreviations: (ADA) American Diabetes Association, (ARM) Ames Reflectance Meter, (SMBG) self-monitoring of blood glucose, (YSI) Yellow Springs Instrument

Keywords: accuracy, diabetes, glucose meters, glucose testing, self-monitoring, technical performance

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Introduction

Glucose meters are widely used in hospitals, outpatient clinics, emergency rooms, ambulatory medical care (ambulances, helicopters, cruise ships), and home self-monitoring. Glucose meters provide fast analysis of blood glucose levels and allow management of both hypoglycemic and hyperglycemic disorders with the goal of adjusting glucose to a near-normal range, depending on the patient group.

The development of self-monitoring of blood glucose (SMBG) is probably the most important advance in controlling diabetes since the discovery of insulin in the 1920s and provides the ability for diabetes patients to test their own blood glucose and adjust insulin dosage to control their glucose needs. With the universal availability of glucose meters today, it is difficult to imagine that managing blood glucose was once considered impossible. The history of glucose meters started in 1963 when Ernie Adams invented the Dextrostix®, a paper strip that develops a blue color whose intensity was proportional to glucose concentration and could be read by visually comparing the strip color to a color-concentration chart. This method gave an approximation of the blood glucose level. In 1970, Anton H. Clemens developed the first blood glucose meter and glucose self-monitoring system, the Ames Reflectance Meter (ARM), to detect reflected light from a Dextrostix.[1] This ARM weighed 3 lb, cost $650, and was intended for physician office use. Richard K. Bernstein was the first patient to test his blood glucose with an ARM.[2] Medical journals at the time refused to publish this method, so Bernstein had to complete medical school at the age of 45 in order to gain attention for this method from the medical world. The idea of SMBG developed by Bernstein had to travel to Europe and Eastern Asia before it found acceptance here in the United States.[3]

Glucose meters have now found a wide range of applications in medicine both for diagnostic purposes in identifying hypoglycemia and hyperglycemia in the emergency room and physician's office, and for management of tight glycemic control in intensive care units, as well as SMBG at home. Apart from diabetes, hyperglycemia can be stress-related as a result of trauma, stroke, and other acute conditions commonly requiring intensive care management. Hyperglycemia can also be secondary to the use of some medications, for example, steroids. Hypoglycemia, on the other hand, can be caused by a number of acute and chronic conditions. Hypoglycemia can be the result of hyperinsulinism, lack of counter-regulatory hormones (cortisol or growth hormone), inborn errors of metabolism, and alcohol and medication intoxications (sulfonylurea, salicyates, propranolol). Ketotic hypoglycemia, a common condition in pediatrics, may require parents to use a glucose meter in order to avoid hypoglycemia and establish a safe feeding schedule. Hypoglycemia is especially common in small children because of the large size of their brain in proportion to the rest of their body. The brain accounts for 60% of the glucose utilization, so infants and small children have higher glucose utilization rates and are more prone to hypoglycemia.

Hyperglycemia needs to be rapidly diagnosed and managed, as prolonged hyperglycemia can lead to dehydration, metabolic disturbances, and long-term cardiovascular complications. The American Diabetes Association (ADA) recommends SMBG for diabetes patients as a key component of their disease management program.[4] Glycemic control is also increasingly being recognized as a priority in the treatment of critically ill patients. Van den Berghe *et al.* demonstrated a significant reduction in mortality through normalization of glucose levels in patients whose medical intensive care unit stay was >72 h and reduced morbidity in all other intensive care unit patients, regardless of the duration of their stay.[5] Other studies in a variety of inpatient settings report better clinical outcomes associated with improved glycemic control.[6–9] Increasing evidence for the value of tight glycemic control in the management of inpatients with diabetes has led to the ADA target range of 110–140 mg/dl (6.11–10.0 mmol/liter) for critically ill patients[4] and the American Association of Clinical Endocrinologists recommendation of 110 mg/dl (6.11 mmol/liter) as the upper cutoff concentration for glucose in critically ill patients.[10]

Glucose meters are utilized by a diverse population of patients, representing all ages and acuteness of medical conditions. Both patients and doctors need a certain level of confidence in the results of glucose meters. As with any medical device, glucose meters have limitations. Reliability of results can be affected by environmental effects. Operators may inadvertently influence meter results. Patient condition, medication, and other metabolic factors can also impact the quality of results. These preanalytic variables should be taken into consideration when interpreting blood glucose results.[3,11] A preanalytic

variable is any factor that can affect the reliability of a test result occurring before the sample is analyzed. This review discusses the technical challenges to obtaining accurate glucose results and the limitations of current glucose meters.

Principle of Glucose Detection

Glucose meters have two essential parts: an enzymatic reaction and a detector. The enzyme portion of the glucose meter is generally packaged in a dehydrated state in a disposable strip or reaction cuvette. Glucose in the patient's blood sample rehydrates and reacts with the enzymes to produce a product that can be detected. Some meters generate hydrogen peroxide or an intermediary that can react with a dye, resulting in a color change proportional to the concentration of glucose in solution. Other meters incorporate the enzymes into a biosensor that generates an electron that is detected by the meter. There are three principle enzymatic reactions utilized by current glucose meters: glucose oxidase, glucose dehydrogenase, and hexokinase. Each enzyme has characteristic advantages and limitations.

All meters are susceptible to heat and cold, because the enzymes are proteins that can denature and become inactivated at temperature extremes. Although packaged in a dry state, exposure of the enzymes to humidity can prematurely rehydrate the proteins and limit their reactivity when utilized for patient testing. The disposable reagents for glucose meters must therefore be protected from extremes of temperature and humidity. Such conditions could occur when transporting the reagents outside in the heat of summer or cold of winter. Test strips should not be stored in closed vehicles for extended periods and must be protected from rain, snow, and other environmental elements. The detector portion of the meter is composed of electronics, so it must also be protected from extremes of temperature, humidity, moisture, and the elements. Many meters now have internal temperature checks that prevent use of the meter outside of acceptable tolerance by blocking patient results or displaying an error code if the ambient conditions of temperature and humidity are outside manufacturer ranges. Glucose meters must also not be submerged in water when cleaning and must be protected from moisture, as with any electronic device.

Technical Accuracy

Technical accuracy is defined as the measurement closeness of agreement between a measured quantity value and a true quantity of glucose.[12] For glucose, accuracy can be defined by the comparison to a standard analytical method, isotope dilution mass spectrometry.[13,14] Isotope dilution mass spectrometry is performed on a deproteinized sample, but this sample cannot be analyzed by glucose meters and is not common in the clinical laboratory. Frozen serum standards with glucose concentration determined by isotope dilution mass spectrometry are available through the National Institute of Standards and Technology and can be used to determine method accuracy for laboratory instruments that can analyze serum specimens. However, for glucose meters, technical accuracy is rarely determined against the standard isotope dilution mass spectrometry method. Instead, the accuracy of glucose meters is assessed by comparison to a method in routine use in the clinical laboratory. Determining accuracy to a laboratory method establishes meter comparative accuracy but not reference accuracy to a recognized standard.

Glucose meters analyze whole blood. Establishing accuracy of glucose meters is difficult because glucose is unstable in whole blood, and samples may need to be transported to a laboratory for comparison with laboratory methods. Delays in transportation can lead to biases between glucose meters and laboratory methods due to glycolysis. Erythrocytes metabolize glucose, so glycolysis will decrease glucose concentration in a sample at a rate of 5–7% per hour as long as the serum/plasma remains in contact with the red blood cells.[15,16] Glycolysis rates are even higher in leukocytosis or bacteremia. Glycolysis inhibitors (fluoride or iodoacetate) can inhibit glycolysis, but as these are charged molecules, they take 1–2 h to cross cell membranes and become fully effective. Glycolysis will continue during that time. So the use of whole blood samples for accuracy comparisons requires consideration of glycolysis effects and separation of serum/plasma from cells for laboratory analysis within a reasonable period of time, generally within 30 min from whole blood analysis on a glucose meter.

For accuracy determination, glucose levels from the same specimen would ideally be compared by analysis on the glucose meter and by a reference or comparative method. Unfortunately, this is technically challenging due to the small volume of capillary blood that can be obtained from a finger stick. Historically, accuracy comparisons have been conducted by comparing a capillary sample analyzed on a glucose meter against a venous plasma sample collected at the same time and analyzed by a laboratory method. The Yellow Springs Instrument (YSI) analyzer is a laboratory analyzer that can accept whole blood or plasma/serum samples. This analyzer has been

utilized in clinical laboratories and is often employed in the industry to determine calibration factors of glucose meter reagents during manufacturing. The YSI analyzer, however, has been replaced in the clinical laboratory by multi-analyte automated instrumentation, and very few remain for use in accuracy comparisons for glucose meters.

There are physical differences between the glucose concentration in serum/plasma and whole blood as well as venous compared to capillary blood. Glucose equilibrates into the aqueous portion of a blood sample. The concentration of water in serum/plasma differs from the concentration of water in the cellular portion of blood. Erythrocytes contain lipid membranes and high levels of hemoglobin protein that exclude water. So the water content of a specimen will vary based on the hematocrit (erythrocyte percentage). Serum/plasma thus has a higher water content and therefore higher glucose concentration by approximately 11–12% compared to whole blood at a normal hematocrit of 45%.[17] Analytical methods that depend on sample dilution take a quantitative volume of patient sample and mix it with a fixed volume of reagents. A fixed volume of whole blood has less water than the same volume of serum/plasma, and this is a primary reason for whole blood to serum/plasma differences encountered when using an analyzer like the YSI that can analyze both types of specimens or when comparing whole blood lysate to serum/plasma glucose results. Water content of the serum/plasma depends on the concentration of other components as well: lipids, proteins, and, as mentioned, cellular elements such as erythrocytes. Hypertriglyceridemia and paraproteinemias that elevate the concentration of these components in a sample can thus cause a pseudohypoglycemia by water exclusion, increasing the difference between whole blood and serum/plasma results.

Glucose meters vary in their method of analysis. Some meters take a fixed volume of patient whole blood, lyse the cells, and analyze the amount of glucose in that volume of lysate. Other meters utilize a series of absorbent pads to separate the cellular portion of a sample from the serum/plasma portion. This allows only serum/plasma to react with the enzymatic reagents. In order to harmonize glucose results, consensus recommends reporting serum/plasma-based results from glucose meters such that the value will most closely match that of a laboratory method using a serum/plasma sample.[18] Glucose meter whole blood lysate results must therefore be corrected to serum/plasma by either applying a fixed mathematical offset to obtain a "plasma-corrected result" (assuming a normal hematocrit) or correcting the whole blood lysate result using the patient's actual hematocrit. There are meters on the market that use both types of correction. However, it is more common for manufacturers whose meters separate the cellular portion of the sample to set the calibration of the meter against a laboratory method in order to report a "plasma-calibrated" result. The differences between these various calibration and correction functions are one source of variability among the many glucose meter models when analyzing the same specimen. Hematocrits of hospitalized and acute patient populations may not match the assumed normal hematocrits of the samples utilized by manufacturer's to set meter calibration or correction functions, and this can be a source of bias when using glucose meters in these patients.

Depending on the clinical situation, a variety of sample types may need to be analyzed by a glucose meter, including capillary, arterial, and venous specimens, particularly on hospitalized inpatients. Alternate collection sites, including forearm, leg, and abdomen, have recently become popular, as patients claim these sites are less painful than finger stick collection given the abundance of nerve endings in the fingertips. Arterial blood has higher glucose levels compared to venous blood because arterial blood is being delivered to the tissues where glucose is absorbed as an energy source. In the fasting state, arterial glucose levels are only 5 mg/dl (0.27 mmol/liter) higher than capillary and 10 mg/dl (0.55 mmol/liter) greater than venous concentrations.[19] The difference can be amplified by perfusion difficulties, oxygenation, and pH differences between arterial and venous blood samples. Glucose levels also differ between fasting and postprandial states. During fasting, capillary glucose may be only slightly (2–5 mg/dl) higher than venous glucose. In the postprandial state, however, capillary blood may be 20–25% or greater than venous levels.[20] These differences become a significant concern if accuracy of a glucose meter is assessed using paired capillary and venous samples from a nonfasting individual. Perfusion is another consideration with capillary samples, as blood can pool in the extremities of patients with poor perfusion, such as those in shock, or in patients with disease in a specific limb. Poor perfusion can lead to capillary and venous differences in glucose results and should be a consideration when using paired capillary and venous samples to determine meter accuracy.

Meter Performance Criteria

There is some debate over what constitutes good technical accuracy when comparing glucose meters

against a laboratory method. Standards organizations and professional societies differ on accuracy acceptability criteria (**Table 1**). The ADA has recommended that glucose meters agree to within ±15% of the laboratory method at all concentrations, with a future performance goal of ±5% agreement at all glucose concentration.[21,22] Since meter performance can change across the range of the glucose concentrations, some performance criteria differ between the hypoglycemic range and the hyperglycemic range. For instance, the International Organization for Standardization and the U.S. Food and Drug Administration has set accuracy criteria to ±20 mg/dl (1.11 mmol/liter) for levels <100 mg/dl (5.6 mmol/liter) or ±20% for glucose levels >100mg/dl (5.6 mmol/liter) for at least 95% of results.[13,23] There is thus no single standard to assess the accuracy of a glucose meter, so the determination of accuracy will vary by country and recommendation utilized for the judgment.[24–27]

Table 1.
Meter Performance Criteria for Acceptable Agreement between a Glucose Meter and Results from a Comparative Laboratory Method

Organization or society	Glucose range	Performance criteria
ADA 1987	All levels	±15%
ADA 1994	All levels	±5%
CSA	<45 mg/dl (2.5 mmol/liter)	±25% (CV < 12.5%)
	≥90 mg/dl (5.0 mmol/liter)	±15% (CV < 7.5%)
FDA (95% of data)	<100 mg/dl (5.6 mmol/liter)	±20 mg/dl (1.1 mmol/liter)
	≥100 mg/dl (5.6 mmol/liter)	±20%
ISO (95% of data)	<100 mg/dl (5.6 mmol/liter)	±10 mg/dl (1.1 mmol/liter)
	≥100 mg/dl (5.6 mmol/liter)	±20%
IMSS	<60 mg/dl (3.3 mmol/liter)	±25%
	≥60 mg/dl (3.3 mmol/liter)	±20%
CLSI (C30A)	<100 mg/dl (5.6 mmol/liter)	<15 mg/dl (0.83 mmol/liter)
	≥100 mg/dl (5.6 mmol/liter)	±20%
TNO	<117 mg/dl (6.5 mmol/liter)	±20 mg/dl (1.11 mmol/liter)
	≥117 mg/dl (6.5 mmol/liter)	±15 mg/dl (0.83 mmol/liter) (CV < 10%)

CV, coefficient of variation; CSA, Canadian Standards Association; FDA, U.S. Food and Drug Administration; ISO, International Organization for Standardization; IMSS, Instituto Mexicano del Seguro Social; CLSI, Clinical and Laboratory Standards Institute; TNO, Nederlandse Organisatie voor Toegepast Natuurwetenschappelijk Onderzoek

Clinical Accuracy

While technical accuracy refers to the analytical result agreement of a glucose meter to a comparative laboratory method, clinical accuracy compares the medical decisions based on the test results. The same or different clinical decisions may be made despite apparent analytical differences in results, depending on how the result will be utilized in patient care: screening, diagnosis, or management. For example, analytical acceptability criteria allow ±20 mg/dl (±1.11 mmol/liter) for glucose levels <100 mg/dl (<5.56 mmol/liter). Clinically, this means that, if a patient's glucose measured by a meter is 50 mg/dl (2.8 mmol/liter), then the laboratory glucose could be severely hypoglycemic at 30 mg/dl (1.7 mmol/liter) and present a risk of seizures or, on the other hand, could be 70 mg/dl (3.89 mmol/liter), just within the normal range. Confusion can also present in the hyperglycemic range, where glucose meter measurements of 400 mg/dl (22.2 mmol/liter) could be ±20% or 320 mg/dl (17.8 mmol/liter) versus 480 mg/dl (26.7 mmol/liter). There would be differences in insulin dosage based on glucose levels of 320 mg/dl (17.8 mmol/liter) or 480 mg/dl (26.7 mmol/liter). For patients and clinicians, it is important to ensure that glucose meter accuracy criteria provide sufficient stringency to allow the same clinical decisions to be made no matter which analytical method is utilized for analysis.

Clarke and associates tried to address clinical agreement by developing an error grid analysis method that evaluates the clinical significance of the glucose meter result against a comparative method.[28] The Clarke error grid has 5 accuracy zones. A mild discrepancy between the glucose meter result and the comparative method falls within zones A or B and would lead to no change in clinical decision. On the contrary, larger differences between the glucose meter and laboratory comparative method would fall in zones C, D, or E, with unnecessary corrective action or potentially dangerous failure to detect hypoglycemia or hyperglycemia. Parkes *et al.* modified the Clarke error grid to avoid discontinuities between risk zones where small changes in blood glucose levels can result in dramatic changes in risk.[29] Error grid analysis remains an important tool for evaluation of glucose meter accuracy.

Clinical accuracy of the instrument also depends on how the obtained information will be used: screening, diagnosis, or management.[30] A significant positive bias of >10% was seen in more than a third of glucose results from three new plasma-calibrated blood glucose meters

(Abbott Precision Xceed, Bayer Ascensia Contour, and Roche Accu-Chek Aviva) when compared to venous plasma measurements on the Dade Behring RXL analyzer (Hexokinase method). The number of values in zones B (altered clinical action with little to no clinical effect) or C (altered clinical action with likely effect on clinical outcome) in the Parkes error grid for Abbott, Bayer, or Roche was 13%, 8.7%, and 10.4%, respectively. The study concluded that these meters should therefore not be used to diagnose diabetes but could be suitable for patient monitoring and insulin management.[31] Since the late 1970s, advances in glucose meter technology have resulted in significant improvement of accuracy and precision of meters. Solnica and colleagues tested the Accutrend, Glucotrend, Precision QiD, One Touch, and Glucocard II in an outpatient setting and demonstrated good analytical performance with a bias <10% from the comparative method.[32] These studies have thus shown the clinical accuracy of current glucose meters and have concluded that the meters are sufficiently reliable for clinical decision making.

Glucose meter variability or precision also contributes to differences in glucose meter analytical and clinical agreement.[33–35] One study, a Monte Carlo simulation model, evaluated the clinical significance of glucose meter precision.[36] In this study, pairs of "meter-measured" and "true-laboratory" glucoses were randomly generated based on a mathematical model of total glucose meter error. Paired-differences were assessed for clinical accuracy against an algorithm for insulin dosing. With a glucose meter analytical variability of only 5%, clinical insulin doses varied in 8–23% of cases, depending on the glucose concentration when compared against dosage based on the laboratory result. A glucose meter total variability of 10% led to different insulin dosage in 16–45% of cases, and a glucose meter variability of >10–15% led to a two-fold or greater discrepancy in insulin dosage. The study concluded that a glucose meter total precision of <1–2% was required to ensure similar insulin dosage compared to the laboratory methods more than 95% of the time. Unfortunately, none of the current glucose meters available on the market are capable of providing this level of precision.

Glucose Meter Potential Interferences in the Outpatient Setting

A variety of factors can affect glucose meter results (**Table 2**). Skill of the user, not the technical specifications of the instruments, is the most significant source of blood glucose errors, especially in outpatient settings. Approximately 91–97% of overall inaccuracies are operator dependent.[11,37] Studies comparing the accuracy of results obtained by a patient against a medical laboratory technician find that patients have substantially poorer performance.[38,39] The most common reasons for the discrepancies are mechanical stress applied to the strips, failure to clean the site for testing, dirty meters, and sample issues like specimen clots, bubbles, and failure to apply an adequate amount of blood to the test. Recent advances in meter technology have focused on reducing operator interaction. Current meters have eliminated the need to time reactions and wipe test strips before reading results. New meters also require less blood for testing. Data management functions allow meters to store patient results, connect to a computer, and display result graphs and charts.

Calibration is one potential source of glucose meter error. Some glucose meters require the patient or operator to insert a calibration code based on the lot of test strip utilized for analysis. Baum and associates conducted a study to estimate the importance of proper meter coding on the meter results and clinical decisions.[40] This study revealed deviations of greater than ±30% (-31.6% to +60.9%) when results were obtained with miscalibrated meters. For some miscoded meter and test strip combinations, error grid analysis showed >90% of results falling within clinical accuracy zones that would lead to altered clinical action. Such inaccuracies were not found with the SMBG devices having an automatic calibration or coding feature.

Apart from inadequate patient education on the testing procedure and storage conditions, patient compliance remains the key problem, especially in certain patient groups such as teens or socially challenged families. Patients can sometimes present "good numbers" during

Table 2.
Glucose Meter Potential Interferences

Environmental • Air, exposure of strips • Altitude • Humidity • Temperature	Physiologic • Hematocrit • Prandial state • Hyperlipidemia • Oxygenation • pH
Operational • Hemolysis • Anticoagulants • Generic test strips • Amniotic fluid/animal • Arterial and catheter • Volume of sample • Reuse of strips	Drugs • Maltose • Acetaminophen • Ascorbate • Mannitol • Dopamine

an office visit by testing various body fluids or other solutions in order to please the medical care provider and demonstrate that they have been compliant with treatment goals between visits. Data obtained from even the most sophisticated instruments can be misleading if, for example, the date and time of meter is incorrect. In one study, only 40% of the patients had their meters programmed with a date and time within one hour of the actual time.[41] These findings stress the importance of education to accurate glucose results. Improving glucose meter accuracy can be achieved by periodic observation of patient testing technique, inquiry regarding storage of strips, teaching the necessity of proper calibration, and periodic testing of control solutions (provided with the glucose meter) to verify technique and reactivity of meter and test strip reagents. If any doubt persists regarding the meter accuracy, the glucose meter can be checked against a meter of known accuracy or by comparing a specimen against a laboratory method.

Both clinicians and patients should be aware of test strip performance under various environmental conditions.[42,43] Meters utilizing glucose oxidase can overestimate glucose at high altitudes and low temperatures. Glucose-dehydrogenase-based meters can give unpredictable results if the tests strip is exposed to increased humidity. In one study comparing performance of glucose meters at different temperatures and altitudes, three meters were taken to Mt. Kilimanjaro, Tanzania, where they read 50, 214 and 367 mg/dl on the same sample.[44] This confirms that unpredictable results can be obtained when the meter technology is stressed under extreme environmental conditions. Meters should be protected during transport and not stored in vehicles where the meter or test strips are exposed to the heat and humidity of summer or cold of winter.

Glucose Meter Potential Interferences in the Inpatient Setting

For inpatients, hospital meters have advanced computerization and data management features that enhance the quality of test results. Lock-out functions ensure the analysis of controls at defined time periods, prevent patient testing if controls fail, and prevent untrained operators from using the meters. Newer meters have barcode readers that reduce typographical errors when entering test strip and control lot numbers or patient identification. Some meters can store admissions and discharge data and compare patient identification against active admissions to positively identify the patient and data entry. Hospital glucose meters can store hundreds of results and, when downloaded, can send those results to a laboratory or hospital information system, automating the test resulting and billing functions involved with point of care testing. These computerized data also provide a regulatory compliance record linking the date, time, meter serial number, and patient result to the operator, the test strip lot number, and the quality control performed on that meter and lot of test strips. These quality features on hospital meters provide an additional layer of checks on the test result since inpatient measurements are often performed on the most acute of patients, leading to immediate changes in medical management.

There is an increasing volume of evidence that maintaining as close to normal glucose as possible in hospitalized patients, especially those in intensive, surgical, and critical care units, can significantly improve outcomes, decreasing both morbidity and mortality.[5] Despite sophisticated data management features in hospital glucose meters, critically ill patients whose homeostasis is severely compromised are likely to encounter extreme physiologic conditions that can challenge glucose meter limitations, complicating the interpretation of results. Intensive care patients can present with hyperglycemia secondary to stress or medications, or these patients can present with hypoglycemia when the body reserves and regulatory mechanisms are compromised and unable to respond appropriately. Hypoglycemia is especially dangerous in patients with altered mental status since the symptoms may go unrecognized. Clinicians must be able to rely on the glucose meter results but also understand those situations when glucose meters are unreliable.

In the intensive care unit, patients may have multiple medical problems that can affect glucose meter readings such as hypotension, anemia or polycythemia, and acidemia.[37] Hypotension leads to poor perfusion, blood stagnation, and lower glucose levels because of ongoing tissue metabolism. Hypotension can potentially enhance discrepancies between capillary and venous blood glucose samples collected at the same time for meter accuracy evaluation. Similar perfusion problems can occur in trauma and patients in shock.

High oxygen tension in patients receiving oxygen therapy can falsely depress glucose meter results for glucose-oxidase-based meters, while hypoxia can falsely elevate glucose results. Glucose levels can be underestimated in patients with high hematocrit, such as in neonatal intensive care unit infants.[30] On the other hand, in patients with anemia secondary to any

reason like cancer, chemotherapy, blood loss, and as commonly seen in postsurgical recovery period, glucose levels can be overestimated.[45] Rao and coworkers tested a new glucometer that simultaneously measures and automatically corrects for the patient's hematocrit and concluded that this meter provides improved accuracy over meters without hematocrit correction.[46]

Critical patients often have indwelling catheters, and collection of samples through lines can pose a risk of sample contamination with intravenous fluids. Special care must be taken to provide adequate flushing of catheters or preferably collect glucose specimens from the opposite limb. Specimens should never be collected by finger stick below a catheter, especially in patients with poor perfusion or edema.

Low pH (<6.95) falsely depresses glucose readings, while high pH increases meter readings for meters utilizing glucose oxidase. In diabetic ketoacidosis, glucose readings obtained by all meters can be affected and display falsely decreased results. Diabetic ketoacidosis is a common limitation in the package insert of all glucose meters.

Medications taken by a patient may interfere with their glucose meter reading.[45] Tang and associates studied the interference of 30 drugs with glucose meter readings.[47] Significant interference was noted with acetaminophen, ascorbic acid, dopamine, and mannitol use. Glucose-oxidase-based meters were affected most frequently, possibly because of the peroxide reduction detection method utilized by these meters. Acetaminophen and ascorbic acid consume peroxide, which results in lower blood glucoses. Newer amperometric meters with a third electrode minimize this interference. Glucose-dehydrogenase-based meters show less interference with those medications, but direct oxidation at the electrode can result in higher glucose levels. Dopamine can affect glucose results on glucose-dehydrogenase-based meters. Mannitol interferes with some glucose-oxidase-based meters. Icodextrin, commonly used as an osmotic agent for peritoneal dialysis, can be metabolized to maltose that cross-reacts as glucose, falsely increasing results on some glucose dehydrogenase based meters.[48]

There are thus a variety of factors that can interfere with the accuracy of glucose meters. Clinicians need to be aware of the potential for interferences in all patients, especially hospitalized patients with extreme physiologic conditions, and interpret glucose results based on meter limitations.

Summary

Establishing glucose meter accuracy is challenging. Glucose meters only accept whole blood, but existing standards are serum based. Glucose as an analyte is unstable in whole blood, and the process of stabilizing glucose through glycolysis inhibitors can interfere with some glucose meters. Technical accuracy for glucose meters is defined by comparing meter results against clinical laboratory methods that use plasma/serum-based samples. There is no consensus among standards organizations and professional societies, however, for acceptable performance criteria. While technical accuracy defines meter performance, clinical accuracy establishes how treatment decisions agree between meter results and laboratory glucose results. Glucose meters should be evaluated before use, and the specific meter model selected should be based on technical and clinical performance in the intended patient population. A number of factors can affect the accuracy of glucose meter results, including operator technique, environmental exposure, and patient physiologic and medication effects. Clinicians need to consider the variety of factors that can affect meter accuracy and interpret glucose meter results with regard to the potential for meter interference, questioning glucose meter results whenever the results do not match the clinical scenario.

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