Are Those Glucometer Results Accurate?

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CLINICAL CASE FROM 2009

JF, a 64-year-old man with a 30-year history of type 2 diabetes managed with basal and rapid-acting prandial insulin, started peritoneal dialysis using icodextrin dialysis solution. Since starting dialysis, JF has experienced persistently elevated blood glucose readings (in the high 200 mg/dL to high 300 mg/dL range) using his Accu-Chek Compact glucometer purchased in 2008. In response, JF has been taking higher doses of rapid-acting insulin with meals and for correction, with two-to-three-hour postprandial blood glucose readings persistently elevated (in the high 200s). JF has no fevers, chills, abdominal pain, or other signs/symptoms of infection. Urine ketone testing is negative.

Yesterday, JF's pre-lunch blood glucose registered at 380 mg/dL on his glucometer, and he took a dose of rapid-acting insulin that was double what he would have taken prior to starting dialysis. About 90 minutes after lunch, JF felt weak and diaphoretic and became unresponsive, with seizure-like activity. His wife called the paramedics; when they arrived, JF's fingerstick glucose level was 28 mg/dL (using a One Touch Ultra glucometer).

JF was treated acutely with IV dextrose and then transported to a nearby hospital. During his hospitalization, his blood glucose level was maintained in the mid-100 to high-200 mg/dL range, with approximately 50% lower doses of rapid-acting insulin with meals. Hospital work-up revealed no evidence of secondary causes of hyperglycemia. EEG was negative.

Further investigation determined that JF's Accu-Chek Compact glucometer used GDH-PQQ methodology, which is unable to distinguish between the blood glucose level and the maltose metabolite of icodextrin contained in the peritoneal dialysis solution—leading to falsely elevated glucose results. JF switched to a different glucometer that did not use test strips containing the GDH-PQQ method, allowing for more accurate blood glucose readings and no recurrent episodes of severe hypoglycemia.

BIOCHEMISTRY OF GLUCOSE MEASUREMENTS

In 1964, Ernie Adams invented Dextrostix, a paper strip that developed varying shades of color proportional to the glucose concentration. In 1970, Anton Clemens developed the first glucometer, the Ames Reflectance Meter (ARM), to detect reflected light from a Dextrostix. The ARM weighed 3 lb and cost $650.[1]

Modern glucometers analyze whole blood using both an enzymatic reaction and a detector. The enzyme is packaged in a dehydrated state contained in a disposable strip. The glucose in the patient's blood rehydrates and reacts with enzymes in the strip to produce a detectable product.[1]

The gold standard for measuring glucose is isotope dilution mass spectrometry; however, this is not commonly performed in clinical laboratories. The accuracy of glucometers is most commonly assessed by comparing the glucometer result to a venous plasma sample collected at the same time and analyzed by a clinical laboratory using multi-analyte automated instrumentation.[1]

The two main types of commercially available glucometers are the glucose oxidase (GO) and glucose dehydrogenase (GDH) systems. The GO meters utilize the GO enzyme to catalyze the oxidation of glucose into gluconic acid. The oxidation reaction produces electrons that generate current proportional to the glucose level in the test sample.[1-3]

With GDH glucometers, several different enzymes can catalyze glucose oxidation, including nicotinamide adenine dinucleotide (GDH-NAD), flavin adenine dinucleotide (GDH-FAD), pyrroloquinoline quinone (GDH-PQQ), or mutant glucose dehydrogenase PQQ (Mut Q-GDH).[2,4,5]

Measurement of glucose using the hexokinase enzyme is considered more accurate than both the GO and GDH systems and is commonly used in clinical laboratories. However, the cost of this

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system is more than that of the commercially available glucometers, and thus it is not widely available.[2]

PERFORMANCE REQUIREMENTS FOR GLUCOMETER SYSTEMS

There is no single standard for glucometer accuracy. Per Guideline 15197, issued by the International Organization for Standardization (ISO) in 2013, the minimum criteria for accuracy is at least 95% of blood glucose results within ± 15 mg/dL of the reference value at blood sugar concentrations < 100 mg/dL and within ± 15% at blood sugar concentrations ≥ 100 mg/dL.[6] For OTC glucometers, the FDA has recommended that at least 95% of measurements fall within ± 15% and at least 99% of measurements fall within ± 20% of reference values across the entire claimed range of the glucometer system.[7]

The ISO and FDA both recommend that industry test glucometer accuracy using glucose levels ranging from ≤ 50 mg/dL to ≥ 400 mg/dL.[6,7] They also recommend evaluating blood glucose accuracy at different hematocrit levels and assessing accuracy in the presence of interfering substances, such as acetaminophen, ibuprofen, salicylate, sodium, ascorbic acid, bilirubin, creatinine, dopamine, maltose, xylose, galactose, hemoglobin, heparin, L-dopa, methyldopa, triglycerides, cholesterol, sugar alcohols, and uric acid.[6,7] The FDA additionally recommends testing glucometer accuracy in the presence of temperature extremes, humidity, and different altitudes.[7]

Currently, the premarket evaluation of glucometers is a one-time procedure that is typically conducted by the manufacturer. Not all available glucometers currently comply with the less stringent ISO accuracy standards from 2003, and most currently available glucometer systems fail to meet the more stringent accuracy criteria outlined by the ISO in 2013 and the FDA in 2014. Furthermore, there can be inconsistency in the measurement quality between different test strip lots, adding another variable to assessing glucometer accuracy.[6]

VARIABLES AFFECTING GLUCOMETER ACCURACY

Patient and environmental factors

Both patient and environmental factors can interfere with obtaining accurate glucometer results. These include sampling errors, improper storage of test strips, inadequate amount of blood applied to the test strip, improper meter coding, and altitude.[1]

Temperature extremes and humidity can denature, inactivate, or prematurely rehydrate enzymes and proteins within the test strip.[1] GO meters can overestimate glucose levels at low temperatures, while GDH meters can produce unpredictable results in increased humidity.[1] The detector portion of the meter is composed of electronics and should be protected from temperature extremes and excessive moisture as well.[1]

In high altitude, both GO and GDH meters can produce unreliable results, with a tendency to overestimate blood glucose levels.[8] Another variable confounding the accuracy of glucometer readings at high altitude is the potential for secondary polycythemia, which can result in underestimation of glucose levels.[8,9]

Physiologic factors

Physiologic factors that can cause inaccurate glucometer results include hypoxia, abnormal pH, hyperuricemia, jaundice, polycythemia, anemia, peripheral vascular disease, and hypotension resulting in poor perfusion.[1,7,9]

Elevated oxygen tension in patients receiving oxygen therapy can falsely lower glucometer results for GO meters, while hypoxia can falsely elevate glucose results for these meters.[1,3]

Low pH (< 6.95), such as in diabetic ketoacidosis, falsely lowers glucose readings in GO meters, while a high pH falsely elevates glucose readings.[1,10] Elevated serum uric acid (> 10-16 mg/dL) and elevated total bilirubin concentration (> 20 mg/dL) can cause overestimation of blood glucose levels due to electrochemical interaction at the electrode site in GDH-PQQ meters.[11]

Polycythemia can result in underestimation of glucose levels, and glucose levels can be overestimated in the setting of anemia.[9] In anemia, the reduced red blood cell volume results in less displacement of plasma, causing more glucose molecules to be available to react with the enzyme contained in the test strip.[12]

Despite manufacturers' claims

"There is no single standard for glucometer accuracy, although minimum criteria have been established."

that glucometers are reliable to a hematocrit range of 20% to 25%, clinically significant errors of greater than 20% were observed when the hematocrit level dropped below 34%, which can present challenges if glucometers are used in the ICU.[13] Mathematical formulas to correct point-of-care glucometer measurements based on the hematocrit level have been proposed and have demonstrated effectiveness in decreasing the incidence of hypoglycemia in critically ill patients treated with insulin.[12]

> *"Review the product insert for verification of the specific enzymatic methodology used in the test strip."*

Medications

Drugs that most commonly interfere with glucometer measurements include acetaminophen (especially at a serum concentration > 8 mg/dL), ascorbic acid, maltose, galactose, and xylose.[1,11] Acetaminophen and ascorbic acid consume peroxide, resulting in falsely lowered blood glucose readings in GO meters. In GDH meters, direct oxidation can occur at the electrode site in the presence of acetaminophen and ascorbic acid, resulting in falsely elevated glucose levels.[6,9,12]

Maltose, galactose, and xylose are nonglucose sugars found in certain drug and biologic formulations, such as icodextrin peritoneal dialysis solution, certain immunoglobulins (Octagam 5%, WinRho SDF Liquid, Vaccinia Immune Globulin Intravenous [Human], and HepGamB), Orencia, and BEXXAR radioimmunotherapy agent.[14]

The GDH-PQQ meters cannot distinguish between glucose and nonglucose sugars, resulting in either undetected hypoglycemia or a falsely elevated glucose result (up to 3 to 15 times higher than corresponding laboratory results), which can lead to inappropriate medication dosing that results in potential hypoglycemia, coma, or death.[14] Laboratory-based blood glucose assays, the GO, and most GDH-FAD, GDH-NAD, Mut Q-GDH, and hexokinase test strips do not have the potential for cross-reactivity from sugars other than glucose.[4,14]

It should be noted that in the United States, most GDH-PQQ test strips are no longer manufactured for home glucose testing. However, it is important to review the product insert contained in the test strip box for verification of the specific enzymatic methodology used in the test strip.[4,5]

CONCLUSION

Multiple factors affect the accuracy of currently available glucometers. Consideration of patient comorbidities, medication use, operational technique, and the conditions under which test strips are stored is important when utilizing glucometer data to make medication adjustments in diabetes management. It is important to refer to specific glucometer and test strip manufacturer device labeling to help select the appropriate glucometer for a particular patient.

The case presentation from 2009, involving falsely elevated blood glucose readings in a patient using a GDH-PQQ meter while receiving icodextrin peritoneal dialysis solution, highlights the importance of background knowledge of glucometer operational mechanisms. For a full list of test strips that are compatible with icodextrin peritoneal dialysis solution, please see the Country-Specific Glucose Monitor List at www.glucosesafety.com.[5]

Examples of specific GO meters include the OneTouch Ultra, iBGStar, and ReliOn meters. Although the GO meters do not cross-react with icodextrin, these meters should be avoided in patients receiving supplemental oxygen, due to the potential for falsely lowered readings.

The GDH-FAD, GDH-NAD, and Mut Q-GDH test strips may be used in patients receiving icodextrin peritoneal dialysis solution and those receiving supplemental oxygen.[3,5] Examples of GDH-FAD meters include most currently available FreeStyle meters, Bayer Contour meters, and One Touch Verio meters. The Precision Xtra meter uses GDH-NAD test strips. Most Accu-Chek meters currently use Mut Q-GDH test strips. **CR**

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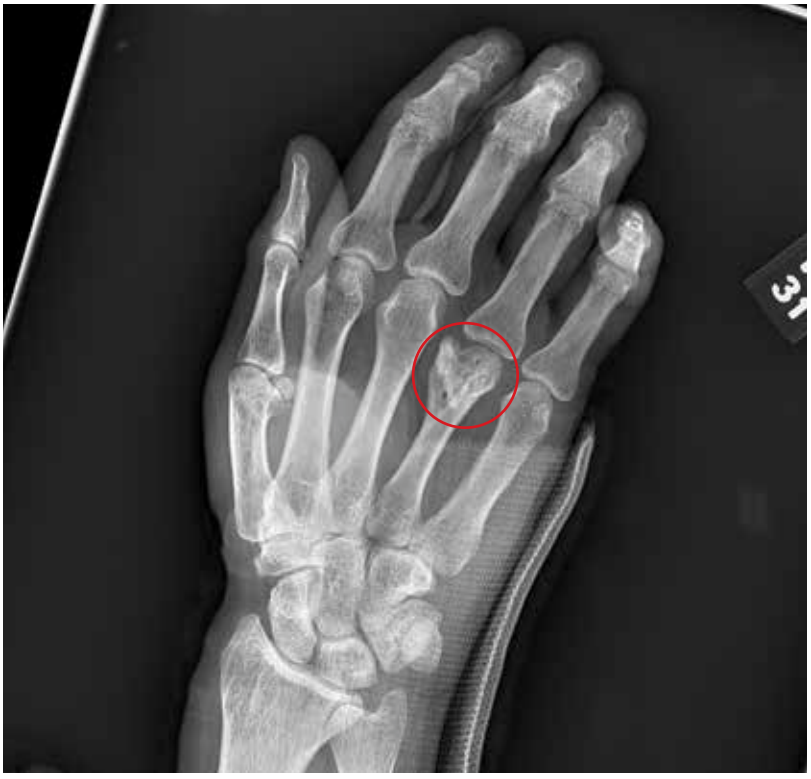
ANSWER

The radiograph shows a slightly displaced fracture of the distal fourth metacarpal head. No other injuries are present.

The patient's hand was left in the splint, and orthopedic evaluation was obtained. **CR**



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