Evaluation of Inaccuracies in the Measurement of Glycemia in the Laboratory, by Glucose Meters, and Through Measurement of Hemoglobin A_{1c}

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This article provides clinicians with a framework for the logical analysis of apparent disparities in glucose measurement among laboratory glucose tests, home meters, and hemoglobin A_{1c} (A1C) tests. The accurate measurement of glucose in whole blood, serum, and plasma has achieved increased importance during the past 15 years. The concept that improvement in glucose levels results in reduced diabetes complications took firm hold in 1993 with publication of the Diabetes Control and Complications Trial (DCCT) for type 1 diabetes,[1] and the U.K. Prospective Diabetes Study for type 2 diabetes,[2] and most recently with the follow-up of the DCCT.[3] Targeted goals for fasting, preprandial, and postprandial glucose have become extremely important in achieving desirable A1C values.

Accurate glucose values also play an important role in the diagnosis of diabetes, especially since 1997, when the Expert Committee on the Diagnosis and Classification of Diabetes changed the definition of diabetes by reducing the required fasting plasma glucose (FPG) level from > 140 mg/dl (established with the National Diabetes Data Group in 1979) to > 126 mg/dl.[4] This committee also established a new diagnostic category of diabetes referred to as impaired fasting glucose (IFG), representing glucose values between 110 and 125 mg/dl.

In 2003, the Expert Committee further reduced the definition of the normal FPG level from 110 to 100 mg/dl,[5] making the glucose levels between 100 and 126 mg/dl definitive of IFG. Subsequently, the U.S. Secretary of Health and Human Services coined the term "prediabetes" to represent what had previously been euphemistically called IFG and impaired glucose tolerance (IGT). Accurate laboratory glucose values are paramount in correctly defining patients with pre-diabetes. Failure to diagnose this condition has serious long-term consequences because pre-diabetes carries an increased risk of cardiovascular disease, and its treatment can result in delay or prevention of the onset of type 2 diabetes.[6]

Tight control of plasma glucose is now a mandate for diabetes treatment, with a general goal A1C of < 7%. This, combined with the lower diagnostic criteria for diabetes (> 126 mg/dl FPG) and the new category of pre-diabetes starting at an FPG of 100 mg/dl, our ability to rely on the accuracy of glucose measurement is clearly crucial. Thus, the stage is set for a renewed look at the accuracy of the laboratory values for proper diagnosis, of home glucose monitoring results to guide therapeutic decisions, and of A1C results to measure the success of treatment.

DIAGNOSIS OF DIABETES BY LABORATORY GLUCOSE

Since the report of the National Diabetes Data Group in 1979, plasma has been the testing agent of choice for glucose determination.[7] In 1997, the aforementioned Expert Committee recommended FPG measurement as the diagnostic test of choice because it is easier to perform and more reproducible than the oral glucose tolerance test (OGTT).[4]

The National Academy of Clinical Biochemistry, in its 2002 publication "Laboratory Guidelines and Recommendations for Laboratory Analysis in the Diagnosis and Management of Diabetes Mellitus," established criteria for a proper diagnostic glucose test, including *1*) an accredited laboratory determination, *2*) an FPG drawn in the morning after 8 hours of fasting, *3*) cells and plasma separated within 1 hour, and *4*) blood placed in a tube with a glycolytic inhibitor if immediate separation cannot occur.[8]

The use of home glucose meters for the diagnosis of diabetes is not recommended because of their potential for imprecision.[8] Likewise, the American Diabetes Association considers A1C a method of assessing long-term glucose control but not a method for diagnosis of diabetes.

Although other markers, such as elevated cytokines from visceral fat, may

IN BRIEF

The accurate measurement of glucose is extremely important in the diagnosis of diabetes and pre-diabetes, where the laboratory values are crucial; in the management of diabetes, where glucose meter values are crucial; and in attainment of goals in diabetes, where hemoglobin A_{1c} measurement is crucial. This article reviews pitfalls that may interfere with accuracy of glucose measurement in each of these three areas and how this inaccuracy may be evaluated and managed in the primary care setting. Three case presentations of disparity are discussed.

become a future indicator for earlier diagnosis of diabetes, state-of-the-art diagnosis at this time relies on accurate laboratory glucose measurement.

OBSERVATIONS ON ACCURACY

Comparison with a reference gold standard is a common method for assessment of accuracy. The National Institute of Standards and Technology maintains the glucose sample materials that are the gold standard by which instrument manufacturers determine the accuracy of their glucose measurement devices.[9] Clinical accuracy may be less precise but is defined by the fact that the results will lead to the same management decision.[10] Clarke et al.'s grid analysis of glucose is helpful in this regard.[11]

A major problem with the accurate measurement of glucose is that its value continues to decrease in whole blood after specimen collection because of red blood cell glycolysis; processing time is therefore an important variable.[10] The ability of individual patients to effectively become laboratory technicians is a significant variable in assessing total error with glucose meter usage. For example, in a study using five glucose meters, the coefficient of variation with the testing done by a laboratory technician was 2.5–5.9%, but it was significantly worse (7–20%) when testing was carried out by a group of patients.[12]

The measurement of accuracy of continuous glucose monitoring (CGM) devices also presents challenges because the dynamics of the rate of change of glucose need to be assessed, and new techniques are needed to define this kind of accuracy.[13] In addition, glucose levels as measured in interstitial fluid lag behind blood glucose by an average of 17 minutes.[14]

There have been > 20 different methods to measure A1C, which led to different reference ranges and confusion about goals.[8,15] Since the DCCT, however, the National Glycohemoglobin Standardization Program has had a 99% success rate with laboratories in the United States in establishing an A1C testing method cer-

tified as compatible with the DCCT.[15] This allows all clinicians to refer to the same DCCT values when discussing A1C goals with patients.

LABORATORY GLUCOSE MEASUREMENT

Case Presentation

A 51-year-old patient is being screened for type 2 diabetes because of family history. Morning laboratory fasting glucose values are obtained from one blood draw on 12 April 2005 at 8:30 A.M., but the blood is processed in the laboratory in two different tubes with the following results:
- Glucose (comprehensive metabolic panel, serum) 126 mg/dl
- Glucose, plasma 112 mg/dl

Question

What is responsible for the 14-point glucose variation in the same blood sample?

Discussion

One blood sample was drawn into two different tubes, but one was tested as plasma and one as serum. Thus, in this example, the only variation possible is analytical, not biological, because a second sample was not obtained. One possibility is that the plasma sample was not centrifuged quickly enough, resulting in the plasma glucose being markedly reduced by exposure to glycolysis in the red blood cells. Another possibility for the analytical error is that the serum was tested by the hexokinase method, but the plasma was tested by the glucose oxidase method. If we add biological variation by comparing with a next-day sample, the potential total variation would be markedly increased.

Causes of Laboratory Glucose Testing Variability: Analytical and Preanalytical

According to Schwartz et al.,[9] "there is marked variability involved (both preanalytical and analytical) in glucose testing." The preanalytical variation results from intra-individual and inter-individ-

ual variation, whereas analytical variation results from methodology used in measurement of glucose (i.e., use of serum vs. plasma and hexokinase vs. glucose oxidase).[8]

Analytical variation

Serum versus plasma. Serum and plasma are not the same. The word "serum" is a Latin word meaning "whey." In the manufacture of cheese, the whey is the liquid component that separates from curd, the clotted milk portion. Likewise, when whole blood is allowed to clot, the serum (Figure 1) is the remaining liquid component, excluding the fibrin clot.[16]

The requirement that serum samples must be allowed to clot before serum glucose is tested significantly increases turnaround time for glucose results compared with plasma results. Thus, faster laboratory turnaround time is one reason that plasma has become the gold standard for glucose measurement. However, in most laboratory panels (i.e., the comprehensive metabolic panel), serum is the most suitable sample for all other chemistries performed, and so a "panel" glucose is usually a serum glucose.

Plasma (Figure 2) is the cell-free liquid remaining after whole blood is centrifuged. The major difference from serum is that plasma contains the clotting proteins, but serum does not.[16]

Potential analytical problems. If plasma is used, the quickness of separation of the red blood cells from the plasma by centrifugation is a critical element, because it is estimated that plasma glucose levels are reduced ~ 10 mg/dl per hour by consumption of glucose in the red blood cell's glycolytic pathway.[8] Despite the use of coagulation inhibitors in plasma testing, some studies have shown that sodium fluoride takes time to work, so that at the end of the 1st hour, glucose decrease in the plasma is similar regardless of whether sodium floride was used in the tube.[9] Thus, a plasma sample that was immediately centrifuged would be expected to have a significantly different glucose than one centrifuged many hours later.
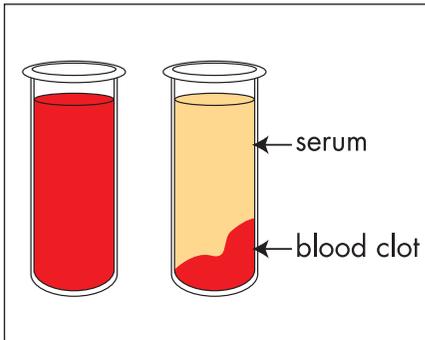
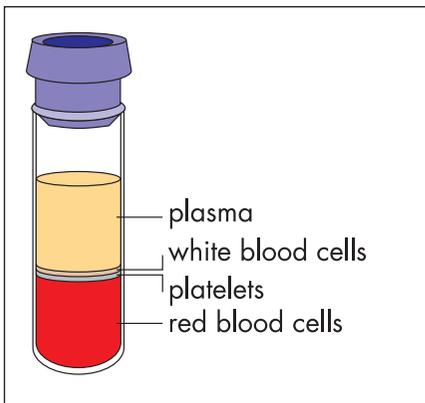*Figure 1. Serum is formed when whole blood clots.*

Figure 2. Plasma is formed when whole blood is centrifuged.

There is also some suggestion of an inherent difference between serum glucose and plasma glucose; serum glucose has been found to be 2–5% higher than plasma glucose (R Gambino, unpublished observations).[9] Either hexokinase or glucokinase enzyme analysis is used in ~ 99% of all laboratories for glucose measurement. These two tests have an intra- and interassay coefficient of variation with a 95% confidence interval < 4%.[8]

Preanalytical variability

Glucose values in the same patient vary from day to day. Ollerton et al.[17] studied 193 newly diagnosed diabetic patients and found that the biological variation (intra- and interindividual) of the FPG on two consecutive mornings was ~ 14%. Thus, a plasma glucose value of 126

Table 1. Potential Variables Altering Laboratory Glucose Measurement
• Fasting samples collected on different days?   → Next day fasting value may vary 14%.
• Morning or afternoon fasting sample?   → Morning is higher.
• Was serum or plasma glucose sampled?   → Serum glucose is usually higher.
• Was plasma centrifugation completed in < 60 minutes?   → Plasma glucose decreases 10 mg/hour.
• Was a glycolytic inhibitor such as floride used in the plasma collection tube?   → Glycolysis lowers glucose, but floride retards glycosylation.
• Was a hexokinase or glucokinase enzyme assay used?   → The difference is < 4%.
• Was glucose determined as part of a comprehensive metabolic panel?   → Panels usually measure serum glucose.

mg/dl on one day could be ± 14% on the next day, or a low of 109 mg/dl and a high of 143 mg/dl for 95% of the time.

If fasting can include both morning and afternoon, this biological variation is even larger, because morning fasting blood glucose is higher than afternoon fasting blood glucose.[18]

It is important for clinicians to consider the analytical and preanalytical variation when evaluating a laboratory glucose level (Table 1). These considerations can be very important in the management and classification of diabetes.

Recommendations for Improvement in Laboratory Testing

The Centers for Disease Control and Prevention and the National Cholesterol Education Program describe the protocol for accurate testing of lipids and maintain the standards by which the nation's chemistry laboratories can compare lipid results. No such oversight is available to define the appropriate requirements for accurate glucose testing, and some believe these standards need to be defined for glucose collection and instrument measurement as they are for lipids measurement.[9]

In its position paper on laboratory

analysis in diabetes,[8] the National Academy of Clinical Biochemistry states that, "no consensus has been achieved on goals for glucose analysis." Its recommendation is "an analytic imprecision < 3.3%, bias < 2.5%, and total error < 7.9%."

To achieve this goal, it may be necessary for an expert committee to determine more specific guidelines for laboratory glucose testing, similar to those of the National Glycohemoglobin Standardization Program.

HOME GLUCOSE MONITORING VARIATION

Case Presentation

A 56-year-old type 2 diabetic patient presents for 3-month follow-up. His medications include metformin, 1 g twice daily; rosiglitazone, 8 mg per day; and NPH insulin, 20 units at bedtime. His A1C performed yesterday is 8.1% (in accordance with the National Glycohemoglobin Standardization Program), and two recent laboratory FPG values are 158 and 152 mg/dl. Home blood glucose monitoring results show consistent fasting values of 115–120 mg/dl (within the target range).

Question

What would explain this apparent discrepancy in the home glucose monitoring results?

Discussion

This patient is using an older model glucose meter, which reports the glucose as measured in whole blood but does not correct to the corresponding plasma value. Thus, the comparable plasma glucose would be 10–15% higher. In addition, a demonstration of the patient's technique for application of capillary blood shows that an insufficient amount was placed on the test strip because the patient smears the blood. These two problems could cause the falsely low glucose meter readings. Appropriate corrections result in readings within 15% of the plasma glucose value. On the basis of the home monitoring, this patient took no action. With the correction of the home readings, the bedtime insulin this patient is taking is appropriately increased, fasting glucose is then in the target range, and A1C becomes 6.9%. A newer model glucose meter is recommended for this patient.

Accuracy Goals for Home Glucose Monitors

The 1987 and revised 1994 American Diabetes Association consensus statements on self-monitoring of blood glucose[19,20] recommended that glucose meter values should vary by < 15% from the reference laboratory. With the good news of the DCCT, a 1996 revision[21] recommended an analytical performance goal for glucose meters such that results should vary < 5% from the reference laboratory.

The goals for glucose meter accuracy have been quite variable. Clarke et al.[11] proposed an accuracy grid to establish a more expansive set of goals for glucose meter usage taking into account clinical accuracy, which was defined as within 20% of the laboratory glucose. For glucose levels > 75 mg/dl, the International Organization for Standardization recommends a goal for glucose meter error of within 20% when compared with a reference glucose sample, but for glucose levels < 75 mg/dl, the goal is for 95% of readings to be within 15 mg/dl of the reference.[15] The U.S. Food and Drug Administration goal for glucose meters is within 20% of the reference value when glucose is > 100 mg/dl and within 20 mg/dl when glucose is < 100 mg/dl.[10]

Multiple Variables Affecting Glucose Meter Usage

Preanalytical variables

A number of preanalytical variables can potentially cause inaccuracy in glucose meter measurements: hematocrit, temperature, hypoxia, humidity, severe hypo- or hyperglycemcia, low systolic blood pressure, elevated triglycerides, and some drugs, such as ascorbic acid.[8,15] The technique of the user of the glucose meter usually is responsible for more inaccuracy than the glucose meter itself.[22,23] Error of the machine results from improper calibration and inadequate maintenance in addition to the specific techniques used to measure glucose: photometric versus electrochemical, as well as the type of enzyme used (hexokinase vs. glucose oxidase vs. glucose dehydrogenase).

Glucose meter sample: whole blood or interstitial fluid?

The major component of measured glucose is located outside of the red blood cell. Because a significant component of the volume of whole blood consists of red blood cells, the plasma glucose is thus diluted in the presence of whole blood, such that whole-blood glucose values are 10–15% lower than values obtained from plasma alone.[24] Most modern glucose meters will automatically convert the capillary whole-blood measurements to the respective plasma reading, but it is important for patients to know the type of reading their meter provides.

Because acute tight control of glucose in critically ill patients has improved outcomes, point-of-care testing glucose meters are frequently used in many intensive care units (ICUs).[25] A 2005 Mayo Clinic ICU study compared > 800 point-of-care glucose meter measurements to simultaneous plasma glucose measurements in the clinical laboratory and reported an important finding: "for the individual patient, bedside glucose meter measurement gives an unreliable estimate of plasma glucose."[26] This is most likely related to the conditions frequently found in ICU patients that have been known to cause inaccurate results in glucose meters, including hypoxia, low hematocrit, and low systolic blood pressure.[27]

With CGM devices, interstitial fluid is extracted from subcutaneous tissue by electric current, and glucose is then measured in the interstitial fluid but without a disruption of the intact skin.[14] A 2004 study of two CGM systems by the Diabetes Research in Children Network concluded that that they are unreliable at hypoglycemia detection.[28] Nevertheless, these devices make a major contribution by demonstrating trends in blood glucose levels over time.[29]

Alternate site testing

Traditionally, capillary blood from the fingertip is the preferred testing sample. Because of the pain of a finger stick, alternate sites have been tested, including the forearm, where fewer sensory nerve endings are located. If glucose levels are changing rapidly, such as after a meal or during sudden hypoglycemia, the fingertip glucose reflects these changes quicker than the forearm and is the preferred sampling site.[30] Forearm glucose testing sites are comparable to fingertip capillary blood when glucose levels are stable, such as before meals.[31] Newer glucose meters allow additional testing sites, including the upper arm, thigh, and calf.

Recent studies of glucose meter accuracy

A 2005 study by the Diabetes Research in Children Network[32] compared laboratory-tested glucose values in venous blood samples with simultaneous

glucose meter readings from two "newer generation" glucose meters. Both glucose meters were highly accurate and showed a median difference of 5% from the reference laboratory values. The ability to detect hypoglycemia was > 96%.

A 2005 report by Clarke et al.[33] compared two CGM systems to reference glucose as tested by the Beckman Glucose Analyzer. Using a new method called "continuous glucose error grid analysis," Clarke et al. determined that both of these devices were clinically accurate during euglycemia (70–180 mg/dl), with ~ 88–89% of the values in zones A and B, where A is defined as "clinically accurate," and B is "usually within 20% of reference but probably not resulting in deleterious decision making." With hypoglycemia (< 70 mg/dl), one device was in zones A and B 82% of the time, whereas the other was in these zones only 62% of the time.

Variables affecting glucose meter usage are summarized in Table 2.

A1C VARIATION

Case Presentation
A 46-year-old African-American man was diagnosed with type 2 diabetes 6 months ago. The laboratory fasting glucose values consistently average 200 mg/dl, and before-supper glucose is an average of 190 mg/dl. During this 6-month period, the A1C values have been measured at 6.8 and 6.7%.

Question
Why is there a discrepancy?

Discussion
This case demonstrates a disparity between A1C and the apparent mean plasma glucose level. If an estimate of 240 mg/dl is made for the mean plasma glucose in this case, this should correlate to an A1C of ~ 9%, according to Rohlfing et al.[34] An evaluation of this patient shows a normal hemoglobin electrophoresis, but a hemolytic anemia is discovered, thus shortening the life

span of the red blood cell and making the A1C measurement inaccurate and falsely low.

A1C Variables
The problems resulting in A1C measurement not accurately reflecting mean plasma glucose values fall into two main categories: *1*) hemoglobinopathies and *2*) a decrease in the life of the red blood cell. In addition, uremia can produce a chemically abnormal carbamylated hemoglobin, resulting in a falsely high A1C.[15] By interfering with glycosylation, vitamins C and E have been suggested to produce falsely low A1Cs.[15] Even the season can be blamed for high A1Cs, with a Veterans Administration study of 285,705 veterans showing that A1C values were higher in the winter.[35]

Red blood cell life span
The Amadori reaction responsible for glycation is an irreversible process.[36] Thus, a condition such as hemolytic anemia or bleeding, which may reduce the normal life of red blood cells from 120 to 60 days, would reduce the potential for glycosylation because most glycosylation occurs in the last month of red cell life. Studies have shown a nonlinear relationship of glycosylation, with 50% of the A1C reflecting mean glucose in the last 30 days of red cell life, and only 25% of the A1C reflecting the glucose in the first 60 days of red cell life.[15] Laboratory studies such as serum haptoglobin, recticulocyte count, and Coombs tests may be helpful in detecting hemolysis. Conversely, conditions such as aplastic anemia, which increase the life span of the red blood cell by slowing production, may falsely increase A1C.[15]

Hemoglobinopathies
Normally, hemoglobin A makes up 97% of hemoglobin.[36] With hemoglobinopathies, such as the common sickle cell trait HgAS (found in 8% of African Amercians) and the hemoglobin C trait HgAC (found in 2.3% of African Americans), the resulting A1C value may be falsely high or low, depending

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Table 2. Potential Variables Altering Home Glucose Measurement

- Was the capillary whole-blood sample converted into the corresponding plasma glucose by the glucose meter?
  - → Whole blood has a glucose concentration that is ~ 15% lower than plasma. Most modern glucose meters will automatically make the conversion, but some older glucose meters do not.

- Was the whole blood sampled from the fingertip or an alternate site?
  - → For rapidly changing glucose, such as postprandial or during acute hypoglycemia, the fingertip more accurately reflects the current glucose level. Otherwise, many newer glucose meters now give equivalent results at alternate sites, such as the forearm.

- How accurate are the "newer generation" of glucose meters?
  - → A 2005 study showed the values were within 5% of the reference plasma value.

- Should point-of-care glucose meters be used in an ICU setting?
  - → Glucose meters should be used with caution in an ICU setting because the variables of hypoxia, low hematocrit, and low systolic blood pressure, which can affect the accuracy of these devices, are more often found in the ICU population.

- How are continuous monitors best utilized?
  - → These devices have limitations in that the interstitial glucose levels they report lag behind the actual blood glucose, and they may be less reliable in detecting hypoglycemia. They are most useful in providing a daily map of trends in glucose levels.

Table 3. Important Variables Altering A1C Measurement

- Is there a disparity between A1C and the mean patient home glucose monitoring values? What is the first step?
  - → First, check glucose meter accuracy by simultaneously obtaining laboratory plasma glucose and home monitoring glucose values. If these agree, the false A1C will need investigation. This evaluation would include an evaluation for anemia, hemoglobin electrophoresis looking for hemoglobinopathies, and tests that may reflect shortened red blood cell life span, such as reticulocyte count and haptoglobin levels.

- My patient has an A1C of 18%. What is the cause?
  - → With very high or very low A1Cs in diabetic patients, a workup that evaluates the type of red blood cell hemoglobin, in addition to the red cell life span, is in order.

- My patient has a hemoglobinopathy that precludes useful A1C measurement. Are other options available?
  - → Fructosamine is another measurable glycosylated protein that looks back ~ 2–3 weeks, but its relationship to the A1C goals are not established.

- My patient has chronic renal failure and is undergoing dialysis. Is there a precaution when interpreting A1C?
  - → Yes, uremia may increase the carbamylation of hemoglobin, leading to potentially false increases in A1C. In addition, dialysis can shorten the life of red blood cells.

on the test method used (even with high-performance liquid chromatography).[15] With the homozygous variants HgSS and HgCC, "all glycated hemoglobin methods are inadequate for assessment of long-term glycemic control,"[36] and alternate assessments, such as fructosamine, should be measured. Manual inspection of a chromatographic pattern becomes important in detecting some abnormal hemoglobins.[8] A hemoglobin electrophoresis is recommended with A1Cs > 15% or when the A1C and the mean plasma glucose do not correlate.

The variables related to A1C measurement are summarized in Table 3.

The future for A1C

Now, virtually all laboratories in the United States measuring A1C use a standardized method that is applicable to the DCCT method of high-performance liquid chromatography and has a coefficient of variation of < 4%.[15] By using electrophoresis and spectroscopy, the International Federation of Clinical Chemistry has developed a very accurate and apparently more specific measure of A1C.[37] This may result in global unity when talking about A1C, with due care taken to tie any newer methods to

the DCCT numbers (< 7% goal) that physicians and patients have come to know through the years.

SUMMARY

The diagnosis and management of diabetes requires accurate assessment of glucose values by laboratories, glucose meters, and by A1C. This article has summarized factors providers should assess when suspicious circumstances of accuracy arise, as highlighted in the three case studies. The importance of attaining an A1C goal has achieved great recognition, not only for patients, but also for physicians, whose reimbursement is now being tied to successful A1C goal attainment as well as quality of care.[38] If there seems to be a disparity in a patient's glucose numbers, this article offers a framework with which to search for a logical explanation.

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