

Glycemic Markers: A Review of the Tools We All Love, Perhaps Too Dearly?

Preface

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Much is made of the understanding that medicine is an art as well as a science. Although interpretation of this understanding can vary, the challenge that it tries to address is an understandable one: that science is just not enough for all clinical situations. Although we all strive to practice within the confines of what is considered evidence-based medicine, that framework often leaves more questions than answers and just does not fit every patient if treatment goals are to be construed. Yet, if we were to have no direction, no guidelines, then medicine would be chaotic. So, as clinicians, we strive to recognize the exceptions, while trying to practice within the boundaries of such standards.

Certainly, one standard is the measurement of glycemic control in the management of patients with diabetes. This *Diabetes Spectrum* From Research to Practice section reviews the various tools for measuring glucose control in diabetes management, from self-monitoring of blood glucose (SMBG) with meters to A1C testing to the concept of glycemic variability, with particular attention to the utility and limitations of each.

First, from Richard Hellman, MD, FACP, FACE (p. 135), we learn that, despite significant improvements in the nearly 50 years of use of SMBG, challenges remain with this widely used tool. As an example, Dr. Hellman notes glucose values obtained with different meters may differ by as much as 50–70 mg/dl.¹ Although glucose meter manufacturers are also held to standards, one study² found that 41% of the 27 meters reviewed did not conform to basic minimal standards, and many were not accurate or precise,

especially within the hypoglycemic range, when accuracy is most crucial.

The inability of meters to reliably measure blood glucose levels stems from clinical variables that are not always taken into account or necessarily even recognized. In the NICE-SUGAR (Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation) study,³ specific manufacturing lots of the glucose meter strips used varied considerably in their susceptibility to loss of accuracy caused by variation in hematocrit. This led investigators to the hypothesis that some actual blood glucose levels in the hypoglycemic range may have been missed because of falsely elevated point-of-care (POC) glucose meter readings.

In addition to meter-specific error, or “analytic error,” as defined by Dr. Hellman, there is also the challenge of user error. This can occur when patients do not use strip coding for a new lot of strips in meters that require coding or when patients do not periodically use the reference glucose concentration to check for possible drift in their meter’s accuracy. Just a 5% rate of analytic error alone, as considered by Bruns and Boyd in a computer-simulated model,⁴ led to an error rate of 8–23% in choosing insulin doses from an algorithm based on glucose level. A total analytic error rate of 10% led to an error rate of 16–45%. Error rates of 20%, even in the absence of interfering substances or conditions, could lead to unacceptably large errors in clinical decision-making.

POC glucose meters also may provide values called “outliers,” which are so far removed from patients’ true blood glucose level that they can cause medical errors by patients, their fam-

ily members, or their care providers, with potentially catastrophic consequences.⁵ And yet, current regulatory standards allow up to 5% of the values obtained by a POC meter to be outliers. This has raised concerns by many experts, who have vigorously urged regulatory bodies to tighten POC meter standards for precision and accuracy and limit the occurrence of outliers to rare events.⁶

In our second article (p. 141), authors Lorena Alarcon-Casas Wright, MD, and Irl B. Hirsch, MD, discuss the limits of another measurement tool that is considered a standard of care: A1C testing. Who among us has not had the dubious pleasure of receiving from an insurance carrier, a clinic metrics management group, or even an employer insurance benefits/health management oversight group a letter announcing that a patient's A1C has not been measured within some defined period of time. Interestingly, such letters rarely include a response space for providers to explain why this test might have been deliberately omitted.

From Drs. Wright and Hirsch, we learn about clinical situations in which A1C testing does not provide an accurate estimate of average glycemic control during the previous 3 months. Red blood cells that have a short lifespan secondary to destruction (i.e., hemolytic anemia,⁷ destruction through the passage of abnormal heart valves,⁸ or splenomegaly) will result in a low A1C result independent of the mean serum glucose. Additional factors to consider are hemoglobinopathies, use of iron supplementation, and use of erythropoietin-like pharmacological agents—none of which is rare in the diabetic population.^{9,10} Even ethnicity can play a role in our ability to accurately interpret an A1C value.

Drs. Wright and Hirsch propose and review the potential advantages and clinical pitfalls of alternative markers of glycemic control, including 1,5-anhydroglucitol, fructosamine, and glycated albumin. Certainly a major concern with these markers is

the lack of standardization for how to correlate their results to glucose measurement. The authors review the important concept of glycation gap as an index of the variance in A1C determined by processes in both the intra- and extracellular compartments compared to those unique to the extracellular space.¹¹ Glycation gap can refer to the mismatch seen between the expected glucose average from downloaded glucose meter values and the A1C value obtained.

Next, an article from Tracy S. Tylee, MD, and me (p. 149), provides insight into a concept of glycemic control that is not yet widely used but is gaining recognition: glycemic variability. Measurement of glycemic variability can be obtained through various models as shown in the table on p. 150. We review both the concept of glycemic variability and the complications that have been associated with it. This concept is important in understanding the importance not only of average glycemic control, as measured by A1C, but also of glycemic highs and lows. Although more study is needed to give glycemic variability the attention accorded to A1C, this concept does provide perspective on the differing rates of retinopathy seen in the Diabetes Control and Complications Trial¹² among patients achieving the same A1C results through conventional versus intensive therapy. In addition, there is evidence showing an effect of glycemic variability on patients' emotional well-being.¹³

I hope you enjoy this research section and find it a thought-provoking challenge of the norm in diabetes care. Medicine can never be one-size-fits-all; our ability to tailor treatments should be complemented by an ability to recognize the limits inherent in glucose measurements, whether by meter, A1C testing, or tracking of glycemic variability.

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