# When the Blood Glucose and the $HbA_{1c}$ Don't Match: Turning Uncertainty Into Opportunity

A central principle in science and medicine is that the more independent pieces of evidence there are that agree, the more convincing it is that a hypothesis—or diagnosis—is valid. The opposite is also true: discordant information leads to uncertainty. Unfortunately, it is not uncommon for clinicians caring for people with diabetes to encounter individuals in whom $HbA_{1c}$ and blood glucose simply do not match. Sometimes, there is an obvious explanation such as hemolytic anemia. But when it occurs in people with reliable blood glucose records and ostensibly normal peripheral blood and reticulocyte counts, without evidence of hemoglobinopathy, hemolytic disorder, blood loss/transfusion, or nutritional deficiency such as iron, folate, or vitamin B12, we are left with the questions of how the discordant information should be treated and what it means for patient care.

Part of the challenge is that even the best characterization of the association between $HbA_{1c}$ and blood glucose shows an imperfect relationship in populations. For example, at an $HbA_{1c}$ of 6.0%, the mean blood glucose has a 95% CI ranging from 100 to 152 mg/dL. This overlaps with the 95% CI for the mean blood glucose at an $HbA_{1c}$ of 7.0%, which is 123–185 mg/dL (1). Such wide variation reinforces the notion that $HbA_{1c}$ and blood glucose are not exactly equivalent. Moreover, it raises the question of whether a binary cut point for $HbA_{1c}$ in the diagnosis of diabetes, such as 6.5% (2), is an adequate representation of blood glucose and suggests that reliance only on $HbA_{1c}$ could miss persons with diabetes and falsely diagnose those without (3,4). But, if we obtain both glucose measurements and $HbA_{1c}$, we are left with what to do with discordant information.

Three explanations are commonly advanced to explain the spread in the glucose-$HbA_{1c}$ data. The first suggests that any discordance or mismatch in the two measurements is due to the glycemic excursions not captured in a small number of measurements of glucose. The second is the technical measurement variability in either glucose or $HbA_{1c}$, particularly attributable either to self- or point-of-care measurements or to limits on assay standardization. The third explanation takes an alternative approach: that apparent differences between glucose and $HbA_{1c}$ are at least partly real and result from some other physiologic mechanism apart from fluctuations in plasma glucose. This category does not preclude either of the other two. It does, however, expose an opportunity to improve our understanding of the biological basis of the relationships among blood glucose, $HbA_{1c}$, and diabetes complications. There is an increasing body of evidence to support this third explanation as a factor in addition to measurement error and glycemic excursions.

An example of evidence supporting an explanation based in physiology is the number of reports of a consistent difference in the relationship between $HbA_{1c}$ and glucose tolerance between persons of different races, most notably African Americans and Caucasians (3,5–10). Such consistent and reproducible differences cannot be accounted for by random error in blood glucose measurement. The recent, equally unexpected, and seemingly opposite finding that African Americans may have a lower $HbA_{1c}$ threshold for retinopathy than Caucasians has multiple potential explanations, but none have been proven (11). Twin studies have shown that $HbA_{1c}$ has a heritable component of variability, which would be inconsistent with an exact relationship between blood glucose and $HbA_{1c}$ that does not have any interindividual variability (12–15). There is now evidence for sufficient differences between people in erythrocyte life span to result in different $HbA_{1c}$ in two individuals with the same blood glucose (16,17). In this issue of *Diabetes Care*, Rodríguez-Segade et al. (18) add to the growing evidence in support of the contention that there is more than simply random measurement error contributing to discordances between blood glucose and $HbA_{1c}$.

Several investigators have proposed metrics that quantify discrepancies between $HbA_{1c}$ and blood glucose in the form of glycation "gaps" or "indices" (13,19–26). While the metrics differ subtly between reports, they all typically use either integration of multiple blood glucose measurements or one or several glycated serum or plasma protein concentrations to predict what the $HbA_{1c}$ should be, assuming a direct relationship, and then compare the prediction with the measured $HbA_{1c}$ in some way. If the discordance were simply a result of measurement error, these metrics would not be repeatable within individuals. Rodríguez-Segade et al. (18) report the stability of one such metric: a form of glycation gap. In a large population with stable glycemic control, they show that their gap measurement is highly repeatable. This concurs with a 2011 report in which Nayak and colleagues demonstrated the repeatability of an alternative gap measurement, although, we note, with greater variability, perhaps because stable glycemic control was not an entry criterion for the study (26). Both findings strongly support that the discordance between $HbA_{1c}$ and blood glucose is not a result of random measurement error but that there is some systematic deviation that is stable within individuals over time and that suggests a physiologic basis for the disagreement.

Given that we are faced with a measurement that is repeatable and apparently representative of some biological system, it is incumbent on us to take the opportunity to understand the mechanisms involved. In doing so, we must very clearly understand what these metrics represent. As Lachin and colleagues correctly describe, these measurements are not independent of the $HbA_{1c}$ or the blood glucose. They cannot be, as these variables are part of the formulae by which the metrics are derived (27,28). These metrics also cannot be a quantification of measurement error, since measurement error simply propagates through the equation. We contend that

the various metrics are a quantification of one or more biological processes that affect the glycation and turnover of hemoglobin; i.e., they partition the information contained in the $HbA_{1c}$ into information about glucose exposure (blood glucose) and information about the processes by which $HbA_{1c}$ is formed (the metric). These processes are impacted by factors such as erythrocyte life span, iron handling, and glucose distribution across the erythrocyte membrane and perhaps as-yet undiscovered mechanisms (16,29–32). The gap and index metrics describe the interindividual differences in these processes. Recognizing that the metrics reported in the literature represent the balance of multiple mechanisms affecting either $HbA_{1c}$ or the comparator protein or both presents an opportunity to better understand interindividual differences in how glucose exposure, glycemic control, glucose metabolism, and erythrocyte physiology interact. Moreover, some of the mechanisms affecting these gap and index metrics might shed light on mechanisms contributing directly to diabetes complications. The emphasis placed by the National Institutes of Health on adequate inclusion of minorities led to the opportunity for discovery of interracial differences in the glucose-$HbA_{1c}$ relationship, which could theoretically inform the answer to the question of why there are disparities in outcomes (33). The substantial progress on "harmonization" of $HbA_{1c}$ measurement techniques across technologies, manufacturers, and individual laboratories around the globe that David Sacks describes in this issue of *Diabetes Care* (34) is another key step toward better understanding. Reducing interlaboratory variation in the measurement of $HbA_{1c}$ as a source of controversy in the debate over the glucose-$HbA_{1c}$ relationship will permit, for example, meta-analyses and pooled analyses of data obtained using internationally harmonized assays that could contribute reliable answers to these questions of physiology. Certainly, we will need such clarity to unravel the intriguing new conundrum that despite $HbA_{1c}$ being consistently higher than predicted from glucose tolerance, there may be a lower $HbA_{1c}$ threshold for retinopathy in African Americans than in Caucasians (11). Perhaps improved knowledge of the pathways involved might not only resolve this seeming inconsistency but also identify mechanisms of injury amenable to intervention.

As we seek to prevent the complications of diabetes, the discordance between blood glucose and $HbA_{1c}$ also has implications for health care, health policy, and clinical trials. For example, if $HbA_{1c}$ is used as the primary measure of quality of diabetes care and provider performance, how is the apparent racial effect accounted for? If $HbA_{1c}$ is used as a primary diagnostic indicator for diabetes, is a binary threshold appropriate or should the probability of disease be determined based on a range? If $HbA_{1c}$ is used as the target outcome in clinical trials, how are interindividual differences in the glucose-$HbA_{1c}$ relationship to be accounted for? While the literature appears to show that $HbA_{1c}$—whatever its limitations—remains the strongest predictor we have of at least the microvascular outcomes of diabetes (35,36), ignoring the multiple sources of information contained within the $HbA_{1c}$ measurement will leave us with uncertainty as to what a particular $HbA_{1c}$ level truly means.

In essence, as clinicians and scientists we should not be concerned with choosing blood glucose or $HbA_{1c}$ as the most correct measurement. We do not need to succumb to the problem of a "man with two watches never knowing the time." Instead, we should consider the multiple measures as containing complementary information, with each telling us something about the patient. Moreover, let us consider agreement and conflict between measurements as an opportunity to better understand pathophysiology and raise the confidence we can have in individualizing treatment for all people with diabetes.

**Robert M. Cohen, MD[1,2]**
**Christopher J. Lindsell, PhD[3]**

From the [1]Department of Medicine, University of Cincinnati College of Medicine, Cincinnati, Ohio; the [2]Cincinnati VA Medical Center, Cincinnati, Ohio; and the [3]Department of Emergency Medicine, University of Cincinnati College of Medicine, Cincinnati, Ohio.

Corresponding author: Robert M. Cohen, robert.cohen@uc.edu.

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