Diagnosing Diabetes

A Practitioner's Plea: Keep It Simple

In a technologically simpler but no less sophisticated time, Hippocrates, the "Father of Medicine," was the first to diagnose diabetes mellitus. Hippocrates' diagnostic tools were straightforward and accurate—a history of polyuria, polydipsia, and polyphagia coupled with a sweet taste to the patient's urine. This clinical approach sufficed for almost 2,500 years.

Fast-forward to the twentieth century. The detection of sugar in the urine and blood by simple chemical analysis has been followed by increasingly sophisticated tests to diagnose diabetes (for the purpose of this discussion, *diabetes* will refer only to type II diabetes) and assess its control—first the glucose tolerance test and then the glycated hemoglobin. While there is no doubt that these tests have greatly advanced medical science's understanding of the pathophysiology of diabetes and its complications, they create problems for the practicing physician: How do we explain the results to our patients, and what do they mean, in terms of patient management?

Call me from the "old school" if you want, but as a practicing clinician, my comfort level in diagnosing disease is highest when the diagnosis is linked to objective signs, symptoms, and pathology, and lowest when the diagnosis is defined solely by laboratory results that deviate one or two standard deviations from the statistical mean. In our diligence not to miss possible cases of diabetes we may order glucose tolerance tests to evaluate equivocal fasting sugar results. The glucose tolerance test has an aura of infallibility among clinicians as a defining test for diabetes. But by what "gold standard" do we interpret this test? That is, how do we know that diabetes is present, in the absence of signs and symptoms resulting from hyperglycemia and glycuria?

In an article in this issue of the Journal, Davidson and colleagues correlate 2-hr blood sugar values on standardized glucose tolerance tests with glycated hemoglobins.[1] They demonstrate that a majority of patients who meet current glucose tolerance test criteria for diabetes, as defined by 2-hr values, have normal glycated hemoglobins, and are therefore at low risk for diabetic complications. They therefore argue that these criteria should be raised to higher values. Before I outline why this study could prove to be a step in the right direction, three caveats:

- The authors used pooled data and acknowledged the difficulties in standardizing glucose tolerance tests and fractionations of glycated hemoglobin.
- The premise that glycated hemoglobin is central to the pathophysiology of diabetic complications, although supported by considerable circumstantial evidence in animal models, has not been proven in humans.[2]
- The authors acknowledged that 2-hr values are not recommended for routine diagnosis of diabetes, but only when there is ambiguity as to the interpretation of the fasting glucose.[3] This raises an important question: Why not simply correlate fasting glucose with glycated hemoglobin, and start using glycated hemoglobins as a defining test for diabetes?

In spite of these problems, practicing physicians will resonate with the authors' plea that the threshold for a valid diagnosis of diabetes must be a glycemic level that, if not lowered, would lead to microvascular complications. They also will understand immediately that the good intentions of a lower threshold for diagnosis, in terms of possible greater patient motivation, are more than negated by the unintended consequences created by carrying the diagnosis of diabetes on employability, insurability, patient psychology, and social relations.

In a quarter century of practice, I can count on one hand the number of times I have needed a glucose tolerance test to actually diagnose diabetes. In an overwhelming number of cases, the patient's history suggested the diagnosis and a urine sugar and a fasting blood sugar confirmed the diagnosis. What clinicians really need is a simple way to identify people at risk for diabetes, at a stage when diet and exercise may forestall the clinical onset of symptoms and the microvascular changes, unrelated to moment-to-moment changes in blood sugar. Toward this end, this practicing clinician looks forward to the day when glycated hemoglobin will be shown to assist us in assessing an imminent risk of diabetes. When studies confirming this utility are completed, glycated hemoglobin measurements may play a role in the diagnosis of diabetes comparable to the role they have already achieved in diabetic patient management: Given a patient with a history suggestive of diabetes, we will simply send a glycated hemoglobin and await the results.

But even this diagnostic advance does not go far enough. To expound further, we must return again to Hippocrates. Of Hippocrates' classic triad of diabetic symptoms—polyuria, polydipsia, and polyphagia—polyphagia is the most intriguing, for this symptom most likely reflects the intracellular (glucose deficiency) as opposed to extracellular (glucose excess) pathophysiology of diabetes.[4] In other words, perhaps hyperglycemia does not, by itself, entirely define the risk for diabetes or its complications. Perhaps our diagnostic zeal has been too narrowly focused on the blood sugar and its surrogate (glycated hemoglobin). Weight gain and insulin resistance, of which excessive calorie intake is the first clinical sign, are the keys to understanding not only type II diabetes, but also essential hypertension, dyslipidemia, and coronary artery disease. The pathophysiology of these conditions frequently antedates the onset of glucose intolerance and, for all we know, elevated glycated hemoglobins. To date, a straightforward, accurate, simple measure of insulin resistance is not available to clinicians; insulin levels are

only a surrogate marker for insulin resistance[5] and are rarely utilized in clinical practice, and "closed clamp" techniques are impractical outside of research settings. Such a tool would aid clinicians and their patients in identifying risk for all of the clinical consequences of insulin resistance at the earliest possible time, for the least expensive and most preventive of interventions—diet and exercise. It would also aid researchers in assessing the efficacy of new therapeutic agents. Let's hope we'll see the development of a simple measure of insulin resistance soon. However, based on what we now know, I wonder if I'll ever need to put another patient through a glucose tolerance test again.—**ARTHUR FOURNIER, MD,** *University of Miami School of Medicine, Miami, Fla.*

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