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December 2008 Clinical Laboratory News: A New Role for Hemoglobin A1c

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A New Role for Hemoglobin A1c

Should It Be Used to Screen for Diabetes?

By Gina Rollins

Over the past two decades hemoglobin A1c has become an accepted and reliable measure of long-term glycemic control in diabetics. In fact, venerable organizations like the American Diabetes Association (ADA) recommend that diabetics have their HbA1c levels checked routinely as part of continuing care. Today, the growing epidemic of diabetes has focused attention on early identification of the disease before the multiple complications set in. Recent strides in standardizing the HbA1c test, along with the medical community's desire to identify and intervene earlier in the continuum between normal glycemic levels and frank diabetes, has focused attention on a broader role for HbA1c. Now an independent panel of diabetes experts has proposed using HbA1c as both a screening and diagnostic tool for diabetes, placing it alongside the two principal diagnostic measures, the oral glucose tolerance test (OGTT)—considered the gold standard—and fasting plasma glucose test (FPG).

While many clinicians welcome the use of HbA1c for this purpose, the idea is not without controversy, mainly due to ongoing concerns about the test's sensitivity and the lack of a definitive randomized controlled trial demonstrating that early intervention based on HbA1c levels improves long term outcomes for at-risk individuals. David Sacks, MD, associate professor of pathology at Harvard Medical School and one of the authors of the proposal published in the *Journal of Clinical Endocrinology Metabolism* (2008:2447–2453), said the group's intent was to "generate discussion in the community, get people to look objectively at the published data and see if there is a role for HbA1c."

Among the reasons the authors cite to consider HbA1c as a screening and diagnostic tool are the rising incidence and substantial disease burden of diabetes, the significant numbers of undiagnosed diabetics and people at risk for diabetes, and evidence that early intervention can slow or forestall diabetic complications. At the same time, both OGTT and FPG have limitations as tests, and both present practical challenges in performing the tests, primarily because patients must fast for at least 8 hours prior to the exam.

The Scope of the Problem

Diabetes is a gripping worldwide health problem. Fueled by a pandemic of obesity, the incidence of the disease is growing rapidly, as is its burden on society through increased healthcare costs

and decreased quality of life. CDC estimates that in the U.S. there are 24.1 million people with the disease, up by more than 3 million in just 2 years, with an associated $174 billion annual cost of care. On a global basis, WHO projects that by 2030 there will be at least 350 million people with diabetes, about double the current number.

The picture is even more serious in light of the number of people who have frank diabetes but have not been diagnosed, and the considerable number of so-called pre-diabetics. The latter includes people who have impaired fasting glucose (IFG) with fasting glucose levels between 100 and 125 mg/dL, impaired glucose tolerance (IGT) with a 2-hour post glucose load between 140 and 125 mg/dL, or both IFG and IGT. Approximately 25% of diabetics in the U.S.—about 6 million people—have not been diagnosed, and another estimated 57 million are considered pre-diabetics, according to CDC. Although the natural history of IFG and IGT varies, approximately one-third of people with either condition will go on to develop diabetes, one-third will remain pre-diabetics, and another third will return to normal glycemic levels. Since there is a long asymptomatic period during which many undiagnosed diabetics and pre-diabetics are likely to develop micro- and macrovascular complications, the concept of a screening and diagnostic program to identify those at risk is quite appealing.

Existing Guidelines

Longstanding guidelines of the ADA call for screening and diagnosing diabetes by one of three methods, including FPG, OGTT, or symptoms of hyperglycemia (See Box below) combined with a casual plasma glucose (CPG) test, with a repeat test on another day in the absence of unequivocal hyperglycemia. During the last major review of its screening and diagnostic criteria in 2003, ADA did not recommend using HbA1c for such purposes, citing a "lack of evidence on [its] prognostic significance and diagnostic thresholds."

FPG, OGTT, and CPG have screening and diagnostic cutoffs that are the same for each respective test. A diagnosis of diabetes requires an FPG level ≥126 mg/dL (7.0 mmol/L), 2-hour plasma glucose level of at least 200 mg/dL (11.1 mmol/L), or a casual plasma glucose level ≥200 mg/dl (11.1 mmol/L) and symptoms of hyperglycemia.

ADA recommends screening adults for diabetes starting at age 45, or at an earlier age if they are overweight or obese and have one or more additional risk factors, such as being physically inactive, having hypertension, or a first-degree relative with diabetes.

Current ADA Criteria for Testing for Diabetes and Pre-Diabetes in Asymptomatic Adults

1. Testing should be considered in all adults who are overweight (BMI ≥ 25 kg/m2) and have additional risk factors:

- physical inactivity
- 1st degree relative with diabetes
- being of high-risk ethnic populations
- women who delivered a baby weighing > 9 lb or were diagnosed with GDM
- hypertension
- HDL-C <35 mg/dL and/or triglyceride >250 mg/dL
- women with polycystic ovarian syndrome
- IGT or IFG on previous testing
- other clinical conditions associated with insulin resistance, such as severe obesity
- history of CVD

2. In the absence of the above criteria, age 45

3. If results are normal, testing should be repeated at least at 3-year intervals, with more frequent testing considered depending on initial test results and risk status.

Current ADA Criteria for the Diagnosis of Diabetes

1. FPG ≥ 126 mg/dL

2. Symptoms of hyperglycemia and a casual plasma glucose ≥ 200 mg/dL

3. 2-h plasma glucose by OGTT ≥ 200 mg/dL

Proposed Criteria for Screening and Diagnosis of Diabetes*

Screening

- FPG ≥ 100 mg/dL
- HbA1c > 6.0%
- RPG ≥ 130 mg/dL
- if result is negative, screen again in 3 years.
- if result is positive but below the diagnostic threshold, test again using a different method.
- if result is above the diagnostic threshold but a 2nd test doesn't reach the threshold, test again in 1 year.

Diagnosis

- FPG ≥ 126 mg/dL
- HbA1c ≥ 6.5%
- RPG ≥ 200 mg/dL
- diagnosis requires confirmation unless there are unequivocal symptoms of diabetes
- diagnosis through HbA1c requires confirmation using FPG or OGTT, or if 1st HbA1c is ≥ 7.0%, by a 2nd HbA1c ≥ 6.5%
- in asymptomatic individuals with HbA1c ≥ 6.5%, if FPG ≥ 126 mg/dL or RPG ≥ 200 mg/dL, diagnosis is confirmed
- if screening is positive but < diagnostic threshold, 2 tests must meet the diagnostic threshold

* proposed by an independent panel of diabetes experts
(J Clin Endocrinol Metab 2008; 93:2447–2453)

A Gold Standard?

FPG and OGTT have been used for decades to diagnose diabetes, and most studies have used OGTT levels to demonstrate the efficacy of primary prevention efforts. However, both tests have varying degrees of sensitivity, with OGTT considered the more sensitive, and both suffer from weak reproducibility. "OGTT is the Fool's Gold of a gold standard because the intra-subject variability is very high," said David McCulloch, MD, FRCP, clinical professor of medicine at the University of Washington and medical director for clinical improvement at Group Health Cooperative in Seattle. "It depends on how long the person has been fasting, if they exercised the day before, how stressed they are, and other factors."

Other drawbacks of the tests include the requirement for patients to fast at least 8 hours beforehand and the need for a confirmatory test on another day. "If a doctor sees a patient and tells them they need to come back for an OGTT or FPG, it's often inconvenient and many simply don't come back. The time to do a screening is when they're in the office for a routine physical," explained Sacks.

Perhaps the greatest arguments in favor of HbA1c as a screening and diagnostic test are that it can be performed at any time, involves a simple blood draw, and is highly reproducible. The test also reflects long-term glycemic levels and is not as subject to short-term lifestyle changes as OGTT or FPG. Since the average erythrocyte lifespan is about 120 days, the HbA1c value represents a weighted average of ambient glucose levels and will not be affected by what the patient has eaten the day of or days before the test.

Anecdotal information and some published data indicates that clinicians already are using HbA1c as a defacto screening and diagnostic test, according to Sacks. McCulloch, for one, uses it as an unofficial screening test in his practice. "If a patient comes in and I have a high suspicion that he might have diabetes, I will run a HbA1c. If it's above 7 percent, it's virtually certain that he has diabetes. But because of insurance requirements and medical-legal issues, I still will verify it with two FBGs," he explained. A survey cited by the authors of the recommendation found that 93% of physician respondents reported routinely screening for diabetes, with 49% using HbA1c for screening and 58% for diagnosis.

The Variability Factor

If HbA1c has the advantage of ease-of-use and little intra-subject variability, it is not without limitations. Most notably, HbA1c varies considerably between individuals. For instance, one study found that inter-individual variance accounted for 85% of the index of individuality, versus only 6% for intra-individual variability (Diabetes Care 1998; 21: 261–4).

HbA1c also does not produce valid results for all populations. "If a patient has any condition involving altered red blood cell turnover, it can't be used for monitoring or screening for glycemic levels," said Sacks. Examples include hemolytic anemia, aplastic anemia, and lack of a spleen, which slows red cell clearance. In addition, HbA1c is higher for African Americans and certain other ethnic groups. Other hemoglobin proteins, including HbS, HbC, and possibly HbE

may interfere with certain assays. However, as of mid-2008 only about 5% of labs use assay methods with clinically significant HbS and HbC interference, according to the authors of the new recommendation.

While standardization of HbA1c was a significant problem at the time the landmark Diabetes Control and Complications Trial (DCCT) was published in 1993, the National Glycohemoglobin Standardization Program (NGSP) has been instrumental in standardizing and establishing a true reference method for HbA1c. Today, more than 99% of labs that measure HbA1c in the U.S. use NGSP-certified methods. In addition, CAP proficiency testing criteria will be steadily tightened over the next 4 years with a reduction from the current +/- 12% to +/– 6%. Further, based on results of the A1c-Derived Average Glucose (ADAG) study, which demonstrated a linear relationship between estimated average daily glucose (eAG) and HbA1c, ADA now recommends that laboratories provide physicians with both eAG and HbA1c (CLN, October 2008).

One of the most controversial aspects of using HbA1c as a screening and diagnostic tool, however, is the body of evidence surrounding its utility for those purposes. The DCCT demonstrated that tight glycemic control, measured by decreases in HbA1c levels, lowered the risk of microvascular disease in type 1 diabetics, and the United Kingdom Prospective Diabetes Study (UKPDS) found a similar relationship in type 2 diabetes. These seminal studies imply that lowering HbA1c levels would yield similar results for prediabetics, but a definitive randomized controlled trial demonstrating it unequivocally has not been conducted. "The reasoning is not flawed and one would intuitively find it acceptable, but there is not that much data around interventions in the IGT or IFG population," noted Gojka Roglic, MD, medical officer for the WHO diabetes program.

Published research presents a complicated picture of the efficacy of HbA1c in at-risk populations. For instance, one recent analysis found that addition of HbA1c to the Framingham Risk Score in the EPIC-Norfolk Study cohort made a small but statistically significant improvement to discrimination of coronary heart disease events in men but not in women (Arch Intern Med 2008;168:1209–1216). Another involving the same population found that in both men and women, the relationship between HbA1c and both cardiovascular disease and all-cause mortality was continuous and significant throughout the whole distribution. The relationship was apparent in persons without known diabetes (Ann Intern Med 2004; 141:413–20).

Another controversy surrounding HbA1c is establishing screening and diagnostic cutoffs with adequate sensitivity and specificity. Sacks and his coauthors saw their proposal as a two-step process, first with agreement in the medical community that HbA1c is an appropriate screening and diagnostic test, followed by further analysis of cutpoints. However, they did put forth suggested cutpoints, based on "available literature, but it wasn't an independent analysis of all papers on HbA1c," noted Sacks. For screening, the panel recommended a cutpoint of 6.0%, which is 2 standard deviations above the population mean, as described in the National Health and Nutrition Examination Survey (NHANES) II and III. Based on the NHANES data, that cutpoint would yield a 63% to 67% sensitivity and 97% to 98% specificity, which "would avoid an undue burden of false-positive tests," according to the authors.

Also based on NHANES II and III data, the authors recommended HbA1c of 6.5% as a baseline diagnostic threshold, which would yield a sensitivity of 43% to 44% and a specificity of 99.6%. They suggested that at levels between 6.5% and 6.9%, the diagnosis should be confirmed with either FPG or OGTT. However, if the initial test is 7.0% or higher, a confirmatory test could be done with HbA1c because interference with the assay would be unlikely.

Other analyses have found HbA1c not to be as robust a diagnostic measure. One review of primary cross-sectional studies found a cutpoint of 6.1% with a sensitivity ranging from 78% to 81% and specificity from 79% to 84%, and that HbA1c and FPG both had low sensitivity for the detection of IGT (Diabet Med 2007 24:333–43).

Given the mixed picture of HbA1c, some professional organizations believe it is premature to endorse the test as a screening and diagnostic tool. One such group is the American College of Endocrinology (ACE). The ACE task force on pre-diabetes consensus statement on the diagnosis and management of pre-diabetes pointedly did not address the possibility of adopting HbA1c for such a purpose, and indeed, did not include further evaluation of HbA1c in its recommendations for further research needed. "There are no data to judge HbA1c as a predictor of diabetes risk and no known utility of the measure for prediabetes assessment," noted Alan Garber, MD, PhD, chair of the ACE task force and professor of medicine, biochemistry and molecular biology at Baylor College of Medicine in Houston.

WHO also has no immediate plan to reassess its HbA1c-related recommendations, according to Roglic. During the last revision of its diagnostic guidelines in 2006, HbA1c "was not even discussed," she said. Aside from a concern about insufficient data in support of HbA1c's predictive value, WHO faces practical considerations in making any HbA1c-related

recommendations. "The consensus paper was written from the position of the U.S., which has resources, populations, and needs that are not quite the same as the WHO clientele," Roglic explained. "Many countries in sub-Saharan Africa don't have a lab infrastructure even to measure blood glucose, so practices there won't change as a result of any updated screening or diagnosis guidelines." Nonetheless, WHO does intend to revisit diagnostic or screening criteria or possibly both, perhaps in late 2009.

Meanwhile, ADA, the International Diabetes Foundation, and the European Association for the Study of Diabetes are towards the end of a major review of available data, including an extensive meta-analysis, according to Richard Kahn, PhD, chief scientific and medical officer of ADA. "My guess is that we will recommend that HbA1c is an appropriate diagnostic tool for some patients," he said. "We've tentatively said it's a pretty good test, sensitive, precise, and reproducible." He indicated that an announcement should be forthcoming early next year.

With data and opinions falling on both sides of the utility of HbA1c as a screening and diagnostic tool, the debate will no doubt continue. At its core is the importance of chronic hyperglycemia and HbA1c as an effective bellwether of the condition, said William Winter, MD, professor of pathology and laboratory medicine at the University of Florida in Gainesville. "The issue is, is an elevated HbA1c a suitable marker of chronic hyperglycemia that should either supplement or even replace blood glucose testing as a diagnostic criteria for diabetes? One can argue that diabetes is a disease of chronic hyperglycemia and an elevated A1c-emia alone is a laboratory finding and not a disease unto itself."

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