Improving the Diagnostic Accuracy of HbA_{1c}

BY MIRIAM E. TUCKER

FROM THE ANNUAL MEETING OF THE EUROPEAN ASSOCIATION FOR THE STUDY OF DIABETES

STOCKHOLM – Use of a "rule-in" hemoglobin A_{1c} cut point of 6.8% and a "rule-out" value of 5.8%, with glucose testing for individuals who fall in the middle of the diagnostic cutoff, was more accurate in diagnosing type 2 diabetes than was a single cutoff value of 6.5%.

The finding from a multiethnic cohort study of 8,696 previously undiagnosed primary care patients addresses some of the concerns about false-positive and false-negative diagnoses associated with using a single measure of HbA_{1c}. Multiple studies have shown that the 6.5% cutoff can conflict with the results of an oral glucose tolerance test (OGTT), said Dr. Samiul A. Mostafa, a clinical research fellow in the diabetes research unit of the University of Leicester (England).

Despite the slight reductions in positive predictive values, 'overall, we feel using the [hemoglobin A_{1c}] cut points of 5.8% and 6.8% is still diagnostically accurate.'

Last year, an international expert committee recommended the use of HbA_{1c} for diagnosing diabetes, with a cutoff of 6.5% or above following a repeat confirmatory HbA_{1c} test. In January, the American Diabetes Association endorsed that recommendation. The EASD and the World Health Organization are expected to issue similar statements soon.

The study participants were identified from two systematic screening programs during 2002-2008. Three-quarters (75%) were white Europeans and 23% were South Asians. The mean HbA_{1c} for the entire cohort was 5.7%. All underwent an OGTT and also had their HbA_{1c} levels measured. With the WHO criteria (a 2-hour plasma glucose level of 200 mg/dL or above, following a 75-g glucose load), the OGTT detected 291 persons (3.3% of 8,696 study participants) with type 2 diabetes.

Among the white Europeans, use of the 6.5% HbA_{1c} cutoff had a sensitivity of 62% and a positive predictive value of 45%. The investigators compared those values with a rule-out cutoff of 5.5% and a rule-in cutoff of 7.0%, with a confirmatory OGTT used for those falling in between (Diabetes Care 2010;33:817-9).

That method gave an improved sensitivity of 98% and positive predictive value of 76% in the white European group. With either method, specificity and negative predictive values were close to 100%. For the South Asians, the 6.5% cutoff gave a sensitivity of 79% and positive predictive value of 36%, both of which improved to 99% and 68%, respectively, with the two–cut-point criteria. Again, specificity and negative predictive values were strong with either method, Dr. Mostafa reported.

"Impaired HbA_{1c}," the term used for the values between the two cutoffs (5.6%-6.9%), was found in 59% of the total cohort, who thus required confirmatory tests. Noting that those in the impaired HbA_{1c} group (55% of the total cohort) had A_{1c} values between 5.6% and 6.4%, they tried various cut points and arrived at a rule-out value of 5.8% or below and a rule-in value of 6.8% or above. That left 28% of the total cohort in the "impaired HbA_{1c}" category when defined as an A_{1c} of 5.9%-6.7%.

"We believe [a rule-out value of 5.8% and a rule-in value of 6.8%] would be a more feasible strategy to implement in clinical practice," Dr. Mostafa said.

These cutoffs gave sensitivities of 92% for white Europeans and 98% for South Asians, and positive predictive values of 70% and 54%, respectively, while maintaining the nearly 100% specificity and negative predictive values for both groups. Despite the slight reductions in positive predictive values, "overall, we feel using the cut points of 5.8% and 6.8% is still diagnostically accurate, with the major advantage that only a quarter of the population would have to return for a subsequent test," he said.

In a final analysis, the investigators looked at mean HbA_{1c} values in various undiagnosed populations. Compared with the U.K. cohort's mean of 5.7%, the Australian cohort had a mean of 5.1%, which resulted in 24% falling into their 5.6%-6.9% "impaired HbA_{1c}" category. That led to the hypothesis that broader cut points are acceptable when mean HbA_{1c} is relatively low, but a tighter range is required when mean HbA_{1c} is higher. ■

VITALS

Major Finding: A rule-out value of 5.8% or below and a rule-in value of 6.8% or above reduced the size of the "impaired HbA_{1c}" category from 55% to 28% of the cohort.

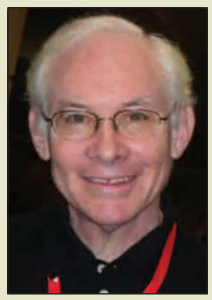
Data Source: A study of 8,696 adults identified from two systematic screening programs during 2002-2008.

Disclosures: Dr. Mostafa stated that he had no relevant financial disclosures.

VIEW ON THE NEWS

Glucose Testing Should Continue to Play a Role in Diagnosing Diabetes

This study assesses a strategy that I think is quite reasonable, and was suggested in the American Association of Clinical Endocrinologists' position statement a number of months ago.



One must recognize that a "negative" hemoglobin A_{1c} level (below 6.5%) misses from one-third to one-half of those with diabetes by glucose tolerance test criteria, whereas a "positive" value (6.5% or greater) may not be the result of diabetes in persons who have greater degrees of hemoglobin glycation. Because high glycation is present in blacks, older populations, and people with iron deficiency, and also is a common variant in the overall population, I would even suggest that blood glucose confirmation – although not necessarily with glucose tolerance testing – should be done in all persons with high HbA_{1c}, regardless of the level.

Similarly, there are people whose degree of hemoglobin glycation is lower than average. Thus, if there is clinical reason to look for diabetes, it is reasonable to perform glucose tolerance testing even with rather low A_{1c} levels.

Given this inherent variability in glycation, just as the 6.5% diagnostic cutoff is incorrect for many persons whose diabetes status is being ascertained, the use of a specific HbA_{1c} goal of, say, 6.5% or 7.0%, may not be appropriate for all patients with known diabetes.

Again, assessment of actual blood glucose levels is crucial in the management of diabetes.

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TNF Inhibitors Reduced Diabetes Risk in Rheumatoid Arthritis

FROM THE ANNUAL SCIENTIFIC MEETING OF THE AMERICAN ACADEMY OF RHEUMATOLOGY

ATLANTA – Use of tumor necrosis factor inhibitors reduced the risk of developing type 2 diabetes by 60% in a single-center study.

Dr. Jana Antohe of Geisinger Health System in Danville, Penn., and her colleagues followed 1,287 nondiabetic incident rheumatoid arthritis patients identified during January 2001–March 2008 at a rural tertiary health center.

The researchers compared the 884 patients who had never used TNF inhibitors with the 403 patients who had ever used them. Patients in the ever-use group had a higher median body mass index and C-reactive protein (CRP) level than did the never-use group, but these differences were not significant.

After a median follow-up time of 35 months for the ever users and 23 months for the never users, the researchers identified 13 new cases of diabetes in the ever-use group and 43 in the never-use group, for incidence rates of 11/1,000 and 22/1,000 person-years, respectively.

The median age of the patients was 61 years, the median BMI was 28.6 kg/m^2, 63% were women, and 97% were white. The findings were adjusted for gender, age, race, hypertension, BMI, positive rheumatoid factor and anti–cyclic citrullinated peptide (anti-CCP) levels, and other variables.

Dr. Antohe had no financial conflicts to disclose. Several of her co-investigators have received research grants from pharmaceutical companies including Wyeth, Amgen, and Centocor.

–Heidi Splete