THE EFFECTIVE PHYSICIAN

HbA_{1c} for Diabetes Diagnosis

BY WILLIAM E. GOLDEN, M.D., AND ROBERT H. HOPKINS, M.D.

Background

Glucose tolerance tests and fasting glucose measures have long been the standard tests for screening and diagnosis of diabetes mellitus. In July 2009, the American Diabetes Association, the European Association for the Study of Diabetes, and the International Diabetes Federation Expert Committee published a consensus report recommending that hemoglobin A_{1c} be used for the diagnosis of type 2 diabetes in nonpregnant individuals.

Conclusions

Patients with unequivocal symptomatic hyperglycemia or type 1 diabetes do not commonly pose a diagnostic challenge. The early diagnosis of type 2 diabetes is a significantly greater clinical problem.

The fasting plasma glucose and oral glucose tolerance measurements on which the diagnosis of type 2 diabetes has relied for decades are values along a continuum of blood glucose readings; the values selected as diagnostic of diabetes are somewhat arbitrary. Since 1997, the values used to diagnose diabetes have been based on the level of glycemia that is associated with an increased risk of diabetic retinopathy.

Recent studies have shown closer correlation between long-term measures of glycemia such as HbA_{1c} and the development of retinopathy than exist with single or repeated fasting glucose levels.

The 1997 guidelines on the diagnosis of diabetes recommended against the use of HbA_{1c} for the diagnosis of diabetes because HbA_{1c} assays were not standardized, and the 2003 guidelines reaffirmed this recommendation. More recent analyses have shown that the accuracy and precision of HbA_{1c} is equal, if not superior, to the accuracy of glucose testing.

HbA_{1c} values are more stable than glucose measurements. Glucose values have been demonstrated to fall as much as 10 mg/dL when whole blood is stored at room temperature for 1-4 hours. HbA_{1c} values also vary less from day to day than do fasting glucose levels (an average of less than 2% for HbA_{1c} vs. 12%-15% for fasting glucose).

Diabetes-specific retinopathy has been found to be very rare in patients with HbA_{1c} levels under 6.5%. An HbA_{1c} of 6.5% is at least as predictive of diabetes as are current fasting glucose (126 mg/dL or higher) and glucose-tolerance test results (2-hour glucose level of 200 mg/dL or higher) in most nonpregnant individuals.

Additional advantages of HbA_{1c} are the lack of need for fasting prior to measurement, and the current clinical use of HbA_{1c} results in daily management of patients with diabetes.

Implementation

HbA_{1c} measurement in the clinical laboratory is the preferred test for diagnosis of diabetes in nonpregnant adults. Point-of-care HbA_{1c} tests are not recommended, as sufficient precision and accuracy have not yet been shown.

The expert committee supports fasting glucose or glucose tolerance testing as alternative tests when HbA_{1c} cannot be measured. No one testing method shows sufficient superiority to be considered the "gold standard" test for the diagnosis of diabetes.

Whichever testing method is used, confirmatory testing is usually warranted; the test initially used should be repeated for confirmation. Confirmatory testing is not required in persons with diabetes symptoms and glucose levels over 200 mg/dL, nor is it necessary in those at the highest risk for diabetes and HbA_{1c} of 6%-6.5%.

HbA_{1c} testing is recommended when diabetes is suspected in children and adolescents who do not have classic diabetes symptoms and/or have a plasma glucose level over 200 mg/dL. Glucose measurement remains the preferred method of testing for diabetes in pregnant women.

Diabetes should be diagnosed in persons with confirmed HbA_{1c} of 6.5% and higher.

Persons with HbA_{1c} over 6% but under 6.5% and those with lower HbA_{1c} plus risk factors for diabetes should receive interventions to reduce their risk for ultimate development of diabetes. The risk for development of diabetes is a continuum; there is no threshold value that, alone, predicts risk. The terms impaired fasting glucose and impaired glucose tolerance fail to capture this continuum of risk and should be phased out as the use of HbA_{1c} for diagnosis becomes more routine.

Abnormal hemoglobin traits, such as hemoglobin S or C, interfere with some HbA_{1c} test methods, so testing methods that correct for these must be used in certain patients. Conditions that alter the erythrocyte turnover rate and recent packed red blood cell transfusion may lead to spurious HbA_{1c} results. Unusual clinical settings, such as rapidly evolving diabetes, may be missed with the use of HbA_{1c} for the diagnosis of diabetes, but symptoms and/or glucose measurement should make these cases evident. Physicians need to be aware of these potential limitations in HbA_{1c} testing for diabetes.

HbA_{1c} levels appear to increase with age, and racial differences in the relationship between glucose levels and HbA_{1c} may exist; however, these limitations are not thought to pose clinically relevant limitations to the use of HbA_{1c} in the diagnosis of diabetes.

Reference

Nathan D.M., et al. International Expert Committee report on the role of the A_{1c} assay in the diagnosis of diabetes. Diabetes Care 2009;32:1327-34.

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Basal Plus Prandial Insulin Gets Results

BY KATE JOHNSON

MONTREAL — Insulin added to oral therapy in patients with long-standing type 2 diabetes is best initiated as a basal formulation and then intensified with prandial doses, according to the 3-year results of the Treat to Target in Type 2 Diabetes (4-T) trial.

"The results of our trial support current guidelines, which suggest that basal and prandial insulin regimens should be considered if adequate glycemic control is not achieved with initial regimens," reported lead author Dr. Rury Holman of the diabetes trials unit at Oxford (England) University.

The findings were announced at the World Diabetes Congress, with simultaneous publication in the New England Journal of Medicine (2009;361:1736-47).

"We now have very clear evidence that the sequence of basal with added prandial gives you less weight gain and less hypoglycemia," Dr. Holman said in an interview immediately following his presentation.

"The 4-T study supports the initiation of treatment with basal insulin, which is consistent with the concept that fasting hyperglycemia contributes more than postprandial hyperglycemia to glycated hemoglobin levels during periods of poor glycemic control," Dr. Michael Roden of the German Diabetes Center and the Heinrich Heine University of Düsseldorf, Germany, said in an editorial in the same issue.

However, "it seems premature to recommend specific insulin regimens for patients with newly diagnosed disease," he said.

The 4-T multicenter, open-label trial included 708 patients who had inadequate glycemic control on dual oral metformin and sulfonylurea therapy. Mean patient age was 61.7 years, and mean disease duration was 9 years.

They were randomized to one of three regimens in the first year: prandial insulin aspart (NovoRapid) three times daily, biphasic insulin aspart (NovoMix 30) twice daily, or basal detemir (Levemir) once or twice daily.

In the second year, sulfonylureas were replaced by a second insulin if hyperglycemia became unacceptable, which was the case in almost 90% of the patient population, Dr. Holman said.

For patients who had started on biphasic insulin, a midday prandial dose was added. Treatments converged for those who had started on either basal or prandial regimens, so that the basal group added prandial doses (10% of the daily basal dose with a minimum and maximum limit) and the prandial group added a basal dose (10 units at bedtime).

"The importance here is the temporal sequence—they are not identical," Dr. Holman said. "So basal plus prandial was not the same as prandial plus basal. … Those who started with prandial had substantially more prandial than basal at the end, and those who started with the basal and then added prandial ended up with about 50/50."

Preliminary results published after the first year of the study did not favor the basal insulin regimen, which was the least successful at bringing hemoglobin A_{1c} levels to 6.5% or less (N. Engl. J. Med. 2007;357:1716-30).

However, "the difference in outcomes from the first to the third year is startling," Dr. Roden said in his editorial.

Final results showed that fewer than 45% of all patients achieved the HbA_{1c} target of 6.5% or less. In addition, significantly fewer patients on the biphasic regimen (31.9%), compared with the prandial (44.7%) and basal (43.2%) groups, reached the target.

The basal group gained significantly less weight (3.6 kg) than did the biphasic and prandial groups (5.7 and 6.4 kg, respectively), and the median number of hypoglycemic events per patient per year was lowest in the basal group (1.7), compared with the biphasic (3.0) and prandial groups (5.5).

"Median glycated hemoglobin levels converged after 1 year and remained stable in all groups, for an overall value at 3 years of 6.9%," wrote the authors (7.1% for biphasic, 6.8% for prandial, and 6.9% for basal, with no significant differences).

The final mean reduction from baseline was 1.3% in the biphasic group, 1.4% in the prandial group, and 1.2% in the basal group.

"The overall message of the [final 4-T results] is that you need complex insulin regimens to obtain adequate glycemic control," Dr. Roden said in an interview.

The 4-T study was supported by Novo Nordisk A/S and Diabetes UK. Dr. Holman reported receiving grants, consulting fees, and lecture fees from pharmaceutical companies, including Novartis and Novo Nordisk, and royalties from sale of the Unistik single-use safety lancet. Dr. Roden reported receiving consulting and lecture fees from several drug makers, including Novo Nordisk. ■