

"Another Problem": Chem-Case for GH2-B (Educational Exercise)

In the GH2-B mailing, we presented the following scenario:

The patient is an obese 70 year-old man with a long history of coronary artery disease and hypertension.

He required coronary artery bypass surgery 20 years ago and a stent to one of the grafts 10 years ago. His last cardiovascular exam was three years ago at which time he exhibited exercise-induced ischemia; catheterization did not reveal significant change from baseline. He has stable angina, treated with sublingual nitroglycerin, aspirin and clopidogrel. His hypertension is well-controlled using multiple drugs, but he is hyperlipidemic with an LDL cholesterol level of 139 mg/dl (reference range: < 130). Triglycerides are elevated at 198 mg/dl (< 150) and HDL cholesterol is low at 20 mg/dl (> 40). He refuses to use statins because of severe myositis associated with their use in the distant past.

He has noticed increased lower extremity edema for the past few months. This morning, he noted chest pain more severe than his baseline stable angina and he called for an ambulance to take him to the local hospital. His troponin level was 1.1 ng/ml (< 0.3) and he was admitted for treatment of acute myocardial infarction. He is mildly anemic with a hemoglobin level of 12.3 g/dl (13.5-17.7). His fasting plasma glucose was elevated at 122 mg/dl (70-100). Hemoglobin A1c was ordered as follow-up testing.

We should have noted that the target for this patient's LDL cholesterol is < 100 mg/dl (or even lower) because he has known coronary artery disease. Also, we should have specified that the cardiac troponin result was for troponin I.

We asked you to choose the most appropriate conclusion regarding this patient's glycemic state from the following statements, assuming that the result your laboratory obtained for specimen GH2-04 was the hemoglobin A1c result reported:

The patient is euglycemic.

The patient has pre-diabetes.

The patient has diabetes mellitus.

The patient has hyperglycemia associated with critical illness.

The hemoglobin A1c result is suspect because the patient is anemic.

The target value for GH2-04, as determined by the NGSP Secondary Reference Laboratories, was 6.6%. This is just above the new recommended cut-off for hemoglobin A1c when the test is used for the diagnosis of diabetes.

The diagnosis of diabetes mellitus has previously depended on the detection of elevated plasma glucose levels but accurate measurement of plasma glucose is not as easy as many people think. Instrument bias, diurnal variation, the effect of eating, and pre-analytic factors (especially in vitro glycolysis by red blood

cells) complicate its use for diabetes screening and diagnosis. For some time, people have questioned whether glycated hemoglobin, the target for many years for managing glycemic control in known diabetic patients, could also be used to diagnose diabetes.

The diagnostic cut-offs for glucose are based on a review by an international panel of experts of epidemiological studies linking the risk of significant microvascular complications to glucose levels. This panel actually considered recommending the use of hemoglobin A1c for screening when they revised glucose cut-offs years ago. The same threshold effect that showed increased risk of microvascular disease above a fasting glucose of 126 mg/dl (or post-challenge glucose of 200 mg/dl during a glucose tolerance test) is seen with hemoglobin A1c greater than 6.5%. However, the panel did not believe that the assay for hemoglobin A1c was sufficiently standardized at that time.

Now, however, different commercial assays for hemoglobin A1c, whether they use chromatography or immunoassay approaches, are harmonized to the procedure used in the original Diabetes Control and Complications Trial (DCCT), thanks to the National Glycohemoglobin Standardization Program. Also, an international working group has developed primary reference materials and a new reference method, using HPLC and either tandem mass spectrometry or capillary electrophoresis.

Consequently, the panel recently proposed that screening for and diagnosis of diabetes no longer be performed using plasma glucose but that hemoglobin A1c be used instead. Major advantages of this paradigm shift include the fact that the patient no longer needs to be fasting, and the inconvenience of glucose tolerance testing becomes a thing of the past. Hemoglobin A1c should not be used for gestational diabetes; the traditional approach should continue to be used in pregnant patients. Also, patients in whom altered red blood cell turnover may be present (e.g. hemolysis, major bleeding or recent transfusion) should be stabilized before using hemoglobin A1c as a screen for diabetes.

The results of Chem-Case question were mixed. Some (29%) appeared to be aware of the new recommendation and concluded that the result indicated that the patient had diabetes. Others (39%), who may have obtained a result between 6-6.5%, concluded that the patient had "pre-diabetes". The new recommendation does, in fact, suggest that individuals being screened for diabetes using hemoglobin A1c with results in this range be identified as at increased risk.

A significant number (26%) attributed the elevated plasma glucose to critical illness and a small number (4%) believed that the patient's mild anemia precluded using the hemoglobin A1c result to make the diagnosis of diabetes.

These are both reasonable concerns. It may be worthwhile suggesting that screening for diabetes using hemoglobin A1c be performed only when critically

ill patients are stabilized. Very few respondents (2%) believed that the patient was euglycemic.

Patients with diabetes are at increased risk of cardiovascular disease. The new diagnosis of diabetes is unlikely to have a significant impact on this patient's acute course, as his cardiovascular disease is well-recognized. But it may have some relevance to his care in the future.

Read more about it: Sacks DB: The diagnosis of diabetes is changing: How implementation of hemoglobin A1c will impact clinical laboratories. Clin Chem 2009; 55:1612-1614.

NOTE: Chem-Cases are educational exercises using CAP proficiency testing specimens to mimic real-life laboratory situations. Participation is optional. Responses will not be graded and will not be included in the individual laboratory reports.

James D. Faix, MD
Chemistry Resource Committee