COMMENTS AND RESPONSES

International Expert Committee Report on the Role of the A1C Assay in the Diagnosis of Diabetes

Response to the International Expert Committee

Members of the International Expert Committee have recommended that diabetes should be diagnosed if A1C is ≤6.5%, without need to measure the plasma glucose concentration (1). We are concerned that practical limitations will lead to false positives and negatives with this approach.

A given A1C instrument may identify some but not other abnormal hemoglobins (http://www.ngsp.org/prog/index2.html). How, therefore, can we be sure whether a hemoglobinopathy is causing (or preventing) diagnosis? Before diagnosis, should we not also exclude iron deficiency anemia, which may increase A1C by 1–1.5%, as well as hemolytic anemia and renal failure or chronic infections, which also lower A1C (2)? The International Expert Committee breezes over the effect of aging (0.4% higher in 70-year-old subjects than in 40-year-old subjects, apparently, despite the same glucose tolerance) and ethnicity (0.5% higher in Afro-Caribbeans than Europids) because their "etiology and significance are unclear." Before this matter is settled, surely potential overdiagnosis of the elderly and non-Europids is inappropriate? These issues, and the possible list of tests required in addition to the simple A1C, still make the idea of fasting overnight for a glucose test an attractive option.

How well does A1C compare with glucose in predicting microvascular risk? The International Expert Committee mentions three studies (on Egyptian population and Pima Indians and the National Health and Nutrition Examination Survey) that demonstrate risk of retinopathy increasing with rising fasting plasma glucose, 2-h glucose, and A1C levels in a similar fashion; this is expected within a population no matter how poorly one of the tests predicts risk compared with another. In all three studies, however, receiver operating characteristic analysis shows fasting and/or 2-h glucose measurement to be superior to A1C. One study cited to justify the 6.5% A1C cutoff even found that random glucose provided "similar results" (3). It is, of course, not possible to comment on the report's unpublished personal communication.

What about the recommended cutoff of 6.5%? The National Health and Nutrition Examination Survey data show over half of subjects with fasting plasma glucose ≥126 mg/dl have an A1C <6.5% (4). If fasting glucose is measured in any of this majority, will they or will they not have diabetes? In individuals who need to have glucose measured because their A1C is known to be unreliable, is it discriminatory for them to have a two to three times greater chance of diagnosis than subjects without hemoglobinopathy, anemia, renal failure, etc.?

On the basis of current evidence, there is far less risk of an individual subject being completely misdiagnosed with fasting and 2-h glucose than with A1C. There is a clear case for further discussion and evidence before decisions are made by the American Diabetes Association, the European Association for the Study of Diabetes, the International Diabetes Federation, and the World Health Organization on the merits of an A1C-only approach and the specific cutoff point for diagnosis of diabetes to identify subjects at increased microvascular risk.

ERIC S. KILPATRICK, MD[1]
ZACHARY T. BLOOMGARDEN, MD[2]
PAUL Z. ZIMMET, MD[3]

From the [1]Department of Clinical Biochemistry, Hull Royal Infirmary, and Hull York Medical School, Hull, U.K.; the [2]Department of Medicine, Mount Sinai School of Medicine, New York, New York; and the [3]International Diabetes Institute, Melbourne, Australia.

Corresponding author: Eric S. Kilpatrick, eric.kilpatrick@hey.nhs.uk.

DOI: 10.2337/dc09-1231

Acknowledgments— No potential conflicts of interest relevant to this article were reported.

References

1. International Expert Committee. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. Diabetes Care 2009;32:1327–1334
2. Gallagher EJ, Le Roith D, Bloomgarden ZT. Review of hemoglobin A_{1C} in the management of diabetes. Diabetes 2009;1:9–17
3. Sabanayagam C, Liew G, Tai ES, Shankar A, Lim SC, Subramaniam T, Wong TY. Relationship between glycated haemoglobin and microvascular complications: is there a natural cut-off point for the diagnosis of diabetes? Diabetologia 2009;52:1279–1289
4. Saudek C, Herman W, Sacks D, Bergenstal R, Edelman D, Davidson M. A new look at screening and diagnosing diabetes mellitus. Clin Endocrinol Metab 2008;93:2447–2453