EASD/ADA Symposium: Provisional New WHO Diagnostic Criteria 2010

Written by Debra Gordon, MS

Recommendations for revised World Health Organization (WHO) diagnostic criteria for diabetes were submitted to the WHO in late 2009. These proposed criteria represent the first substantial changes to the criteria since those published in 1999 [World Health Organization. Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications 1999]. Although the criteria were evaluated in 2006, no changes were recommended at that time.

The current WHO guidelines for diagnosis, which recommend the use of fasting plasma glucose (FPG) or the 2-hour oral glucose tolerance test (OGTT) to diagnose the disease within certain thresholds, were based on cross-sectional studies— including one on the Pima Indians, and one from the third National Health and Nutrition Examination Survey, 1988-1994 [Knowler WC et al. *Diabetes Care* 1993; Harris MI et al. *Diabetes Care* 1998].

Although the WHO considered using HbA1C as a screening test during deliberations for the 1999 guidelines, the committee felt that it was too early in the history of the test to incorporate this strategy into the formal guidelines. When considered again in 2006, no changes were recommended.

However, it is clear that existing diagnostic testing recommendations that use the FPG and OGTT have significant disadvantages, including:

- No threshold for macrovascular complications
- Significant variability and cost of OGTT
- Need for fasting and the variability inherent with fasting instructions to patients
- Poor adherence to the need for dietary preparation on the evening before the OGTT
- Low specificity of the FPG, which gives false negatives in approximately 30% of individuals with diabetes [DECODE Study Group. *BMJ* 1998]
- Importance of appropriate handling of all blood samples for glucose measurement
- Value differences depending on sample (capillary, whole blood, venous)
- Use of cross-sectional data to determine cutoffs
- Lack of availability of OGTT in the community (used primarily as a research tool)
- Variability of diagnosis based on type of test used

The proposed updates to the guidelines were determined, based on the analysis of a large, 13-study database (including the 3 studies from the 1999 recommendation), involving 48,416 individuals (aged 20 to 79 years), with a focus on the cutoff point for the development of diabetic retinopathy (Table 1).

Highlights from the

46th Annual Meeting of the European Association for the Study of Diabetes

Table 1. Current versus Recommended WHO Criteria for Diabetes Diagnosis.

Current WHO Recommendations (1999)	Proposed WHO Recommendations (2009)
DM should be diagnosed based on current symptoms (ie, polyuria, polydipsia and unexplained weight loss) plus • A random venous plasma glucose concentration >11.1 mmol/L (>200 mg/dL), or • FPG concentration >7.0 mmol/L (126 mg/dL) (whole blood >6.1mmol/L, 110 mg/dL), or • A 2-hour plasma glucose concentration >11.1 mmol/L two hours after 75 g anhydrous glucose in an OGTT	• For practical reasons, glucose tests continue to be preferred to diagnose DM in many situations. No change from previously agreed cutpoints • Improvements in quality assurance and performance of assays are needed, as are better awareness of preanalytical errors • HbA1C can be used as a diagnostic test for DM providing that stringent quality assurance tests are in place and assays are standardized to criteria aligned to the international reference values, and that there are no conditions present that preclude its accurate measurement • An HbA1C of 6.5% is recommended as the cut point for diagnosing DM. A value <6.5% does not exclude DM that may be diagnosed using glucose tests. • Further investigation of HbA1C levels <6.5% is required to determine whether they can be used to identify people with intermediate hyperglycemia (currently comprising people with impaired fasting glucose and impaired glucose tolerance)
With no symptoms, diagnosis should not be based on a single glucose determination but requires confirmatory plasma venous determination. At least one additional glucose test result on another day with a value in the diabetic range is essential, either fasting, from a random sample, or from the two-hour post glucose load. If the fasting or random values are not diagnostic, the two-hour value should be used.	

DM=diabetes mellitus; FPG=fasting plasma glucose; OGTT=oral glucose tolerance test.

The proposed recommendations, shown in Table 1, suggest for the first time that HbA1C may be used as a diagnostic test, which the American Diabetes Association (ADA) recommended as a first-line diagnostic test in 2009 [Dietary Guidelines Advisory Committee. US Department of Health and Human Services 2010].

Of course, HbA1C, while having several positive benefits, is not ideal, either. Table 2 depicts the pros and cons of HbA1C as a diagnostic tool for diabetes.

Table 2. Pros and Cons of Current HbA1C Testing Options for Diabetes Diagnosis.

Pros	Cons
Stable measurement	Hematologic conditions, including anemia, may affect results
Assessment of glycemic status over time	Systemic conditions, including severe dyslipidemia or malignancy, cirrhosis, pregnancy or severe renal disease may affect results
Reproducible	Considered expensive
No preparation/fasting required	Ethnic variability *
Sample is stable for 7 days with no refrigeration required	Poor quality assurance in some countries
Daily intra-individual variation is low	Poor availability in some countries

* Herman WH et al. *Diabetes Care* 2007.

There is also concern that using the HbA1C for diagnosis with a 6.5% cutoff point will affect current estimates of the prevalence or incidence of individuals with diabetes. However, similar changes to diagnostic criteria have occurred over time for hypertension, dyslipidemia, and HIV/AIDS, with little negative effect. One concern that is often raised about HbA1C is cost, but once the "cost" of patient time is considered, HbA1C actually costs less than the OGTT (Table 3; example from Denmark, calculated as the mean costs from two different laboratories; costs may vary by country). Increased demand and usage are likely to drive costs down over time.

Table 3. Cost of Current Tests for the Diagnosis of Diabetes.

Test	Reagents, glass	+Labor	+Profit	+Lost productivity
FPG	€ 3.3	€ 5.1	€ 18.3	€ 51.3
HbA1C	€ 6.3	€ 8.1	€ 20.7	€ 20.7-37.2
OGTT	€ 16.0	€ 36.0	€ 47.3	€ 146.3

Assumptions: Costs = mean of SDC and commercial lab (+profit=commercial lab); Hours lost at work: FPG: 1 hr; HbA1C: 0–.5 hr; OGTT: 3 hr

While the WHO deliberates, individual countries are moving ahead with decisions on the most appropriate diagnostic strategy for diabetes. The United States and Germany, as well as numerous other countries, are following the ADA recommendation to use the HbA1C with a cutoff point of 6.5%.