Position statement on the use of HbA1C assays for the diagnosis of diabetes mellitus

The Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA)

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In July 2009, an International Expert Committee appointed by the American Diabetes Association (ADA), the European Association for the Study of Diabetes (EASD) and the International Diabetes Federation (IDF) published a report recommending that the glycated haemoglobin (HbA1C) assay be used for the diagnosis of diabetes in non-pregnant individuals. The report documents the shortcomings of plasma glucose measurements, the advantages and limitations of the HbA1C assay, and recommends threshold values for the diagnosis of diabetes and the identification of individuals at high risk for diabetes, i.e. those with impaired glucose tolerance (IGT) or impaired fasting glucose (IFG). These recommendations (summarised in Table I) were meant to stimulate debate and discussion. An important prerequisite is that the laboratory and HbA1C assay being considered for diagnostic use must be certified by the National Glycohemoglobin Standardization Program (NGSP).

The world view

In January 2010, the ADA published its Clinical Practice Recommendations and officially adopted the Expert Committee’s recommendation to use the standardised HbA1C assay for diabetes diagnosis (diagnostic cut point ≥ 6.5%), but modified the criterion for “categories of increased risk for diabetes” (previously IFG and IGT) to include individuals with an HbA1C ranging from 5.7 to 6.4%. The ADA acknowledges that the use of standardised HbA1C assays may not be practical or affordable globally, and has retained all traditional glucose-based diagnostic criteria, in addition to the HbA1C criteria. The EASD, Diabetes UK and IDF have not issued a position statement, and continue to use the 1999 World Health Organization (WHO) glucose-based diagnostic criteria for diabetes. The WHO has issued a statement that “evidence [for the use of HbA1C] is currently under review at WHO using the recently adopted GRADE system of grading evidence.”

Table I: Recommendations made by the International Expert Committee in 2009, for discussion

| For the diagnosis of diabetes: |
|--------------------------------|
| • The HbA1C assay is an accurate, precise measure of chronic glycaemic levels and correlates well with the risk of diabetes complications. |
| • The HbA1C assay has several advantages over laboratory measures of glucose. |
| • Diabetes should be diagnosed when HbA1C is ≥ 6.5%. Diagnosis should be confirmed with a repeat HbA1C test. Confirmation is not required in symptomatic subjects with plasma glucose levels ≥ 11.1 mmol/L. |
| • If HbA1C testing is not possible, previously recommended diagnostic methods (e.g. fasting plasma glucose (FPG) or 2-hour plasma glucose (2HPG), with confirmation) are acceptable. |
| • HbA1C testing is indicated in children in whom diabetes is suspected but the classic symptoms and a casual plasma glucose ≥ 11.1 mmol/L are not found. |

| For the identification of those at high risk for diabetes: |
|----------------------------------------------------------|
| • The risk for diabetes based on levels of glycaemia is a continuum; therefore, there is no lower glycaemic threshold at which risk clearly begins. |
| • The categorical clinical states of prediabetes, IFG and IGT fail to capture the continuum of risk and will be phased out of use as HbA1C measurements replace glucose measurements. |
| • As for the diagnosis of diabetes, the HbA1C assay has several advantages over laboratory measures of glucose in identifying individuals at high risk for developing diabetes. |
| • Those with HbA1C levels below the threshold for diabetes, but ≥ 6.0%, should receive demonstrably effective preventive interventions. Those with HbA1C below this range may still be at risk and, depending on the presence of other diabetes risk factors, may also benefit from prevention efforts. |
| • The HbA1C level at which population-based prevention services begin should be based on the nature of the intervention, the resources available, and the size of the affected population. |

*There was an error in glucose cut points quoted in the original publication*
evaluating the evidence, and recommendations appropriate for a global audience will be formulated and published in the spring."

Since the above recommendations were issued after publication of the current SEMDSA diabetes guideline,4 it was considered prudent to re-examine the document and provide a position statement on the use of the HbA1C.

**The South African (SEMDSA) view**

In reaching a consensus, SEMDSA has considered the following factors (summarised in Table II):

A. The pros and cons of adopting the Expert Committee’s recommendations to use the HbA1C assay for the diagnosis of diabetes have not been sufficiently studied and debated in the global context.

B. South Africa is a uniquely multiracial, multiethnic society with widely varying prevalences of diabetes and other confounding comorbidities. Access to healthcare services, including the availability of HbA1C assays, also varies widely.

C. There are a multitude of laboratories currently performing HbA1C testing in South Africa. Some laboratories use assays that are not Diabetes Control and Complications Trial- (DCCT-) standardised, and some even use point-of-care devices for testing. Neither of these can be certified by the NGSP. Those laboratories that perform HbA1C testing using the DCCT-standardised assays will still need to submit themselves for NGSP certification, at a cost of $3 500 per laboratory (central or satellite). Currently, only a few laboratories registered for clinical trials have obtained this certification. A register of NGSP-certified laboratories does not exist, meaning that medical practitioners cannot yet know whether measurements performed at a local laboratory are standardised.

D. HbA1C assays have varying abilities to detect haemoglobinopathies, and practitioners will need to be aware of local disease patterns and the ability of their local laboratories to detect these abnormalities.

E. Comorbidities which may interfere with the interpretation of HbA1C measurements are not uncommon, although the exact prevalence and distribution of these disorders are not well characterised locally. These disorders limit the usefulness of HbA1C as a diagnostic test.

a. Haemoglobinopathies, such as sickle cell trait (HbS), haemoglobin C (HbC) trait and thalassaemia, increase red cell turnover and may result in falsely low HbA1C values with approximately one-third of the assays currently in use. In the absence of accurate local prevalence data, it is noteworthy that 10% of African Americans carry HbS or HbC traits,5,6 and our experience is that thalassaemia traits are common in the South African Indian community.

b. Iron deficiency (with or without anaemia), which is highly prevalent in the female Asian population (it affects > 11% of premenopausal US women), can elevate HbA1C by 1-1.5%, and may result in overdiagnosis of all categories of dysglycaemia.7,8

c. Antiretroviral drugs (ARVs) can lower HbA1C by about 1%.9 The direct effect of HIV on red cell turnover and HbA1C has not been systematically investigated. The impact of HIV and ARVs on HbA1C in South Africa is, as yet, unknown.

d. Renal impairment can have varying effects on HbA1C.

F. Ageing and ethnicity can affect HbA1C values; HbA1C is ± 0.4% higher in a 70-year-old compared to a 40-year-old with the same level of glucose tolerance, and is higher by a similar margin in Afro-Caribbeans than in Europids.10,11 The implications of this for the South African population remain to be determined.

G. FPG, 2HPG and HbA1C are continuous variables for diabetes and cardiovascular risk, and any cut-off value, whether it be FPG, 2HPG or HbA1C, is likely to be arbitrary. Moreover, these tests are known to be discordant, in that they do not identify the same “at-risk” population, e.g. using an FPG > 7.0 mmol/l alone fails to detect about 30% of individuals who will have

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**Table II: Limitations of the 2009 International Expert Committee recommendations for the use of the HbA1C assay for diabetes diagnosis**

- The proposed HbA1C diagnostic threshold does not always identify the same individuals with diabetes that are diabetic based on glucose measurements, i.e. the tests are discordant.
- Using the proposed diagnostic threshold is a less sensitive diagnostic test for diabetes, and may artificially reduce the prevalence of diabetes (denies treatment to many individuals).
- HbA1C assays are more expensive than glucose assays.
- The NGSP-standardised HbA1C assay is not available nationally.
- HbA1C assays cannot be used for the diagnosis of diabetes in pregnancy.
- HbA1C assays may not be useful, or more specific assays may be necessary, in a variety of circumstances:
  - Haemoglobinopathies (HbS, HbC, HbF, HbE, thalassaemia traits)
  - States of increased or reduced red cell turnover (haemolytic anaemia, chronic malaria, blood loss, blood transfusions).
  - Age ( Elevates HbA1C)
  - Different race/ethnic groups
  - Rapid onset type 1 diabetes

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diabetes by the 2HPG value. Similarly, in the National Health and Nutrition Examination Survey (NHANES), more than 50% of individuals with an FPG > 7 mmol/l (and, therefore, diabetic by definition) had a non-diagnostic HbA1C value < 6.5%. This discordance between three diagnostic tests is likely to cause more uncertainty for physicians, patients and healthcare funders.

H. The natural history of IFG and IGT have been well characterised and multiple intervention studies for the prevention of progression from IGT to diabetes exist. The natural history of subjects with raised HbA1C in the absence of raised plasma glucose is less well defined, and no intervention studies exist for the prevention of diabetes based on HbA1C alone.

In light of the foregoing observations, SEMDSA has adopted the position that the HbA1C assay should NOT be used currently for the diagnosis of diabetes mellitus, and recommends that:

A. Studies examining the prevalence and effect of haemoglobinopathies, malaria, iron deficiency anaemia, HIV infection and antiretroviral therapy on HbA1C within the various ethnic groups in South Africa should be encouraged.

B. A register of all NGSP-certified laboratories should be established and made accessible to all practitioners. All major laboratories should submit themselves for NGSP certification as a matter of urgency.

C. Cross-sectional and longitudinal epidemiological data examining the diagnostic relationship between FPG, 2HPG and HbA1C must be analysed for diabetes, IFG and IGT, within and among multiple ethnic groups in South Africa.

D. The 2009 SEMDSA guidelines for diabetes diagnosis (based on plasma glucose measurements) should remain unchanged. The HbA1C assay and finger stick (capillary) glucose should NOT be used alone for the diagnosis of diabetes or prediabetes. However, when feasible and affordable, the FPG and/or 2HPG should be analysed together with an HbA1C measurement. Laboratories are encouraged to collaborate in collecting and analysing these data in order to determine local concordance/discordance rates between the three measurements.

Footnote: The initial draft of this position statement was prepared by Aslam Amod (Chairperson, SEMDSA), and circulated to the SEMDSA Executive Committee, all academic heads of endocrinology and the Centre for Diabetes and Endocrinology (CDE) for comment.

The paper was peer-reviewed, modified, and approved by the Executive Committee (Aslam Amod, Ayesha Motala, Fraser Pirie, Joel Dave, Jacobus van Dyk, Naomi Levitt, Nigel Crowther and William Ferris) in August 2010.

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