Diagnosis of diabetes in 2010

Diabetes continues to be an important disease and the incidence is rising.

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The number of people with diabetes is expected to increase from 171 million in 2000 to 366 million in 2030. However, although almost 5% of the world's population is expected to have this disease, the methods used for its diagnosis are still being debated. Over the years the various blood glucose cut-points for the diagnosis of diabetes have been altered, with the current cut-points having been defined in 1997 and endorsed in 2003. Until now, the diagnosis of diabetes has rested upon demonstrating an elevated plasma glucose level (Table I). As this is the major problem in diabetes, a 'glucocentric' approach to its diagnosis has made sense pathophysiologically. However, many suggest that there is no threshold above which diabetes complications occur and that it is rather a continuous relationship. Notably, this year the American Diabetes Association (ADA) has, for the first time, added an HbA1c assay to its recommended methods for the diagnosis of diabetes. This has not yet been accepted by the World Health Organization (WHO) and other international diabetes regulatory bodies.

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Using a 'glucocentric' approach to diagnose diabetes

The current blood glucose cut-points for the diagnosis of diabetes were based on data derived from three large epidemiological studies of different populations (Egyptians, Pima Indians and Americans). In these studies the choice of a fasting plasma glucose (FPG) value ≥7 mmol/l for the diagnosis of diabetes largely rested on the demonstration that above this value there was a marked increase in the prevalence of retinopathy, but below this value retinopathy was rare. Furthermore, this cut-point was similar in all three populations. In the same studies, a 2-hour plasma glucose (2hPG) value ≥11.1 mmol/l after a 75 g oral glucose tolerance test (OGTT) was shown to represent a similar plasma glucose threshold of 7 mmol/l.

Despite these limitations both the WHO and ADA maintain glucose cut-points for the diagnosis of diabetes and pre-diabetes. Although recognising the continuum of risk of glucose values, the WHO has stated that these cut-points represent threshold values above which individuals are definitely at risk of both microvascular and macrovascular complications. They further maintain that individuals with glucose values below those required to diagnose pre-diabetes have the lowest risk of microvascular or macrovascular complications.

Using an HbA1c assay to diagnose diabetes

In 2009 an International Expert Committee report on the role of the HbA1c assay in the diagnosis of diabetes suggested that an HbA1c ≥6.5% could be used to diagnose diabetes as this assay has become

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<table>
<thead>
<tr>
<th>Table I. WHO and ADA criteria for the diagnosis of diabetes and pre-diabetes (adapted from references 2 and 5)</th>
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<tbody>
<tr>
<td><strong>Diabetes</strong></td>
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<tr>
<td><strong>Pre-diabetes</strong></td>
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<td>Impaired fasting glucose</td>
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<td>Impaired glucose tolerance</td>
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</table>

*2 hours after a 75 g oral glucose load.
The advantages and disadvantages of using an HbA1c assay for the diagnosis of diabetes

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
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<tr>
<td>Not affected by short-term lifestyle changes</td>
<td>Expensive</td>
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<td>Good marker of chronic glycaemia</td>
<td>Not widely available</td>
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<tr>
<td>Correlates well with diabetic microvascular complications</td>
<td>Can be influenced by various non-glycaemic factors such as co-morbidities, age and ethnicity</td>
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<td>Stable after collection</td>
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<td>Less variability than a plasma glucose value</td>
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<td>Convenient for the patient as no fasting is required and can be taken at any time of the day</td>
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In a nutshell

In 2009 an International Expert Committee report on the role of the HbA1c assay in the diagnosis of diabetes suggested that an HbA1c ≥6.5% could be used to diagnose diabetes as the HbA1c assay has become an accurate measure of chronic glycaemia and correlates well with the risk of diabetes complications.

- **Age**
  - In the Framingham Offspring Study (FOS) and the National Health and Nutrition Examination Survey (NHANES) 2001-2004, Pani et al. found HbA1c levels to be positively associated with age in non-diabetic populations. The HbA1c could vary by up to 0.6% in persons ≥70 years old compared with those <40 years old. Davidson and Schriger also describe an increase in HbA1c with advancing age (in persons aged 40 - 74 years there was a 0.10% increase per decade in those with normoglycaemia and a 0.07% increase per decade in those with pre-diabetes).

- **Ethnicity**
  - In the Diabetes Prevention Program, after adjusting for independent predictors of HbA1c, the mean HbA1c levels were found to be 5.78% for whites, 5.93% for Hispanics, 6.00% for Asians, 6.12% for American Indians, and 6.18% for blacks (p<0.001).
  - Also, analysis of the NHANES III data by Davidson and Schriger showed an effect of ethnicity on HbA1c levels independent of glucose concentrations.
  - The Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA) has issued a statement not to support the use of the HbA1c assay for the diagnosis of diabetes at this time (JEMDSA, in press). They state that before this test can be endorsed for the diagnosis of diabetes in South Africans local data on 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 need to be collected. In addition, they suggest that all laboratories offering the HbA1c assay should ensure that they become certified with the NGSP and that a list of certified laboratories be made readily available to all doctors. Finally, SEMDSA states that the diagnosis of diabetes should not be made using an HbA1c assay and fingerstick (capillary) glucose alone but should rather be made using plasma glucose measurements in line with the 2009 SEMDSA Guideline for the Diagnosis of Diabetes.

Conclusions

For the moment, the diagnosis of diabetes and pre-diabetes should be made using plasma glucose values as proposed by the WHO and endorsed by SEMDSA. Using the HbA1c assay would certainly offer clinicians and patients a more efficient and speedier method for the diagnosis of diabetes. However, since the HbA1c value is influenced by a number of factors other than glycaemia, it seems prudent to delay its use until the full effect of these factors on HbA1c values in South Africans is known.

References available at www.cmej.org.za

IN A NUTSHELL

- The WHO recommends that diabetes be diagnosed if the fasting plasma glucose is ≥7 mmol/l or the 2-hour plasma glucose value following a 75 g oral glucose tolerance test is ≥11.1 mmol/l. This is endorsed by SEMDSA.
- Pre-diabetes can be diagnosed if the fasting plasma glucose is 6.1 - 6.9 mmol/l (impaired fasting glucose) or the 2-hour plasma glucose value following a 75 g oral glucose tolerance test is 7.8 - 11.0 mmol/l (impaired glucose tolerance).
- The ADA defines impaired fasting glucose as a fasting plasma glucose of 5.6 - 6.9 mmol/l. This has not yet been widely accepted.
- For the first time the ADA recommends the use of the HbA1c assay for the diagnosis of diabetes. This has not yet been accepted by the WHO or any other international diabetes regulatory body, including SEMDSA.
- The ADA recommends that diabetes be diagnosed if the HbA1c is ≥6.5% and pre-diabetes be diagnosed if the HbA1c is 5.7-6.4%.
- The HbA1c must be done according to the DCCT method and in a laboratory accredited by the NGSP.