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.[1,2] 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.[2-4] Until now, the diagnosis of diabetes has rested upon demonstrating an elevated plasma glucose level (Table I).[2-5] 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.[6] Notably, this year the American Diabetes Association (ADA) has, for the first time, added an HbA_{1c} assay to its recommended methods for the diagnosis of diabetes.[2] 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).[3] 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 degree of hyperglycaemia as an FPG ≥7 mmol/l and a similar risk for retinopathy. In 1997 (and again in 2003) an Expert Committee on the Diagnosis and Classification of Diabetes Mellitus recommended that these cut-points be accepted for the diagnosis of diabetes and both the WHO and ADA adopted these values.[2,4,5] Furthermore, this committee also recognised two further groups of patients whose glucose levels were not high enough for them to be classified as diabetic but were, nevertheless, high enough to increase their risk of progression to diabetes, diabetic microvascular complications and cardiovascular disease. They were labelled as pre-diabetic and classified as having impaired fasting glucose (FPG 6.1 - 6.9 mmol/l, re-defined by the ADA in 2003 as 5.6 - 6.9 mmol/l, but this latter definition has not been universally accepted) and impaired glucose tolerance (2hPG after a 75 g OGTT 7.8 - 11.0 mmol/l).[2-5]

Investigators and clinicians have debated the comparability of these glucose cut-points as a person may be diagnosed with diabetes or pre-diabetes with the one test but not with the other. Furthermore, studies have shown the poor reproducibility of the classification of pre-diabetes.[7] Wong *et al.*[6] have also challenged the validity of these cut-points by stating that a major limitation of the three studies on which these cut-points were based is the inaccurate assessment of retinopathy because direct clinical ophthalmoscopy or a single retinal photograph was used. In their opinion these methods underestimate the prevalence of retinopathy as they visualise only a small area of the retina. Therefore, they designed a study to determine the relationship between FPG and retinopathy using multiple field retinal photographs – the 'gold standard'. Using cross-sectional data from three large population-based cohorts they were unable to find a glycaemic threshold for retinopathy. Furthermore, in their populations they showed that 7.4 - 13.4% of people with an FPG <7 mmol/l had retinopathy. Similarly, the Diabetes Prevention Program showed that 7.9% of patients with pre-diabetes (impaired fasting glucose and impaired glucose tolerance) had retinopathy, again suggesting that retinopathy may occur below a glucose threshold of 7 mmol/l.[8]

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.[5] 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 HbA_{1c} assay to diagnose diabetes

In 2009 an International Expert Committee report on the role of the HbA_{1c} assay in the diagnosis of diabetes suggested that an HbA_{1c} ≥6.5% could be used to diagnose diabetes as this assay has become

Table I. WHO and ADA criteria for the diagnosis of diabetes and pre-diabetes (adapted from references 2 and 5)

	WHO	ADA
Diabetes	FPG ≥7.0 mmol/l or 2hPG* ≥11.1 mmol/l	HbA_{1c} ≥6.5% or FPG ≥7.0 mmol/l or 2hPG* ≥11.1 mmol/l or Symptoms plus a random plasma glucose ≥11.1 mmol/l
Pre-diabetes		
Impaired fasting glucose	FPG 6.1 - 6.9 mmol/l	FPG 5.6 - 6.9 mmol/l
Impaired glucose tolerance	2hPG 7.8 - 11.0 mmol/l	2hPG 7.8 11.0 mmol/l

*2 hours after a 75 g oral glucose load.

Table II. Advantages and disadvantages of using an HbA_{1c} assay for the diagnosis of diabetes

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

an accurate measure of chronic glycaemia and correlates well with the risk of diabetes complications.[9] If the HbA_{1c} is ≥6.5%, it should be confirmed with a second HbA_{1c} test unless the patient is symptomatic and has a random plasma glucose ≥11.1 mmol/l. The Committee further suggested that the HbA_{1c} should be added to previously recommended methods for the diagnosis of diabetes (i.e. FPG and 2hPG). The rationale for their suggestion was based on data from observational studies showing a more consistent relationship between the HbA_{1c} and diabetic complications than between plasma glucose and diabetic complications. The HbA_{1c} cut-off of ≥6.5% was derived from an analysis of 28 000 subjects from nine countries where it was shown that retinopathy began to increase when the HbA_{1c} was ≥6.5%, but that it was virtually non-existent below this level.[9] The ADA officially adopted these recommendations in its 2010 guidance on the diagnosis of diabetes.[2] They also suggested that an HbA_{1c} of 5.7 - 6.4% can be used to identify persons with pre-diabetes. Both the International Expert Committee and the ADA emphasise that the HbA_{1c} assay must be standardised to the Diabetes Control and Complications Trial (DCCT) method and certified by the National Glycohemoglobin Standardisation Programme (NGSP). Point-of-care HbA_{1c} instruments have not yet been proven to be accurate enough for the diagnosis of diabetes. The WHO and other international and national diabetes regulatory bodies have not yet adopted this recommendation.

The advantages and disadvantages of using an HbA_{1c} to diagnose diabetes are listed in Table II. Notably, there are numerous factors, other than glycaemia, that influence the HbA_{1c} value:

In 2009 an International Expert Committee report on the role of the HbA_{1c} assay in the diagnosis of diabetes suggested that an HbA_{1c} ≥6.5% could be used to diagnose diabetes as the HbA_{1c} assay has become an accurate measure of chronic glycaemia and correlates well with the risk of diabetes complications.

- Co-morbid disease
  Various diseases affecting turnover of red blood cells can give falsely elevated (iron deficiency anaemia, polycythaemia) or falsely decreased values (haemolytic anaemia, haemoglobinopathies, malaria, blood loss, blood transfusion, HIV infection, use of antiretroviral drugs, renal impairment).

- Age
  In the Framingham Offspring Study (FOS) and the National Health and Nutrition Examination Survey (NHANES) 2001-2004, Pani *et al.* found HbA_{1c} levels to be positively associated with age in non-diabetic populations.[10] The HbA_{1c} 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 HbA_{1c} 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).[11]

- Ethnicity
  In the Diabetes Prevention Program, after adjusting for independent predictors of HbA_{1c}, the mean HbA_{1c} 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 ($p<0.001$).[12] Also, analysis of the NHANES III data by Davidson and Schriger showed an effect of ethnicity on HbA_{1c} levels independent of glucose concentrations.[11]

The Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA) has issued a statement *not* to support the use of the HbA_{1c} 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 HbA_{1c} within the various ethnic groups in South Africa need to be collected. In addition, they suggest that all laboratories offering the HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} assay would certainly offer clinicians and patients a more efficient and speedier method for the diagnosis of diabetes. However, since the HbA_{1c} 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 HbA_{1c} 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 has recommended the use of the HbA_{1c} 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 HbA_{1c} is ≥6.5% and pre-diabetes be diagnosed if the HbA_{1c} is 5.7- 6.4%.
- The HbA_{1c} must be done according to the DCCT method and in a laboratory accredited by the NGSP.