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Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus

Abbreviated Report of a WHO Consultation

World Health Organization

Executive Summary

This report is an addendum to the diagnostic criteria published in the 2006 WHO/IDF report "*Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia*" , and addresses the use of HbA1c in diagnosing diabetes mellitus. This report does not invalidate the 2006 recommendations on the use of plasma glucose measurements to diagnose diabetes.

A WHO expert consultation was held from 28 to 30 March 2009 . . A systematic review was conducted on the use of HbA1c as a diagnostic test for diabetes mellitus. The evidence was summarized and its quality evaluated using the GRADE methodology. The recommendation was formulated and its strength was rated on a two-point scale, based on the quality of evidence and the applicability and performance of the method in different settings.

The WHO Consultation concluded that HbA1c can be used as a diagnostic test for diabetes, provided that stringent quality assurance tests are in place and assays are standardised to criteria aligned to the international reference values, and there are no conditions present which preclude its accurate measurement.

An HbA1c of 6.5% is recommended as the cut point for diagnosing diabetes. A value less than 6.5% does not exclude diabetes diagnosed using glucose tests. The expert group concluded that there is currently insufficient evidence to make any formal recommendation on the interpretation of HbA1c levels below 6.5%.

GRADE quality of evidence: moderate
GRADE strength of recommendation: conditional

1. INTRODUCTION

The term diabetes mellitus describes a metabolic disorder with heterogenous aetiologies which is characterized by chronic hyperglycaemia and disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both (*1*). The long–term relatively specific effects of diabetes include development of retinopathy, nephropathy and neuropathy (*2*). People with diabetes are also at increased risk of cardiac, peripheral arterial and cerebrovascular disease (*3*).

Diabetes and lesser forms of glucose intolerance, impaired glucose tolerance (IGT) and impaired fasting glucose (IFG), can now be found in almost every population in the world and epidemiological evidence suggests that, without effective prevention and control programmes, the burden of diabetes is likely to continue to increase globally (*4;5*).

Because diabetes is now affecting many in the workforce, it has a major and deleterious impact on both individual and national productivity. The socio-economic consequences of diabetes and its complications could have a seriously negative impact on the economies of developed and developing nations (*6*).

It was against this background that on 20 December, 2006, the United Nations General Assembly unanimously passed Resolution 61/225 declaring diabetes an international public health issue and declaring World Diabetes Day as a United Nations Day.

1.1. Background to current report

WHO has published several guidelines for the diagnosis of diabetes since 1965 (*7-10*). Both diagnosis and classification were reviewed in 1999 and were published as the guidelines for the Definition, Diagnosis and Classification of Diabetes Mellitus(*1*).
The potential utility of HbA1c in diabetes care is first mentioned in the 1985 WHO report (*9*). As more information relevant to the diagnosis of diabetes became available, WHO, with the IDF, convened a joint expert meeting in 2005 to review and update the recommendations on diagnosis only(*10*). After consideration of the data available and the recommendations made at that time by other international and global organisations, the 2005 consultation made the following recommendations (*10*):

1. The previous (1999) WHO diagnostic criteria should not be changed.
2. The diagnostic cut-point for IFG (6.1 mmol/l; 110 mg/dl) should not be changed.
3. HbA1c should not be adopted as a diagnostic test, as the challenges of measurement accuracy outweighed the convenience of its use.

The full document can be downloaded from the WHO website:
http://www.who.int/diabetes/publications/Definition%20and%20diagnosis%20of%20diabetes_new.pdf

In March 2009, WHO convened the present consultation in order to update the 1999 and 2006 reports with the place of HbA1c in diagnosing diabetes, based on available evidence.

1.1.1. The update process

The members of the consultation included experts in diabetology, biochemistry, immunology, genetics, epidemiology and public health (Annex 4). The main question to be answered for the update was agreed upon by the expert group:

- How does HbA1c perform in the diagnosis of type 2 diabetes based on the detection and prediction of microvascular complications?

A search for existing systematic reviews in EMBASE and MEDLINE did not identify any relevant systematic review. Therefore, a systematic review to answer this question was conducted by the Boden Institute of Obesity, Nutrition and Exercise, The University of Sydney, Sydney, Australia.
The recommendation was drafted by the expert group following the GRADE methodology(*11*) and the process outlined in the WHO Handbook for Guideline Development . The decision process took into account the findings of the systematic review and the advantages and disadvantages of using HbA1c to diagnose diabetes (Annex 3). The recommendation, quality of evidence and strength of the recommendation were discussed and consensus was reached. All the experts agreed on the recommendation.

The systematic review with GRADE tables is available at http://www.who.int/topics/diabetes_mellitus/en/

The strength of the recommendation was based on the quality of evidence and feasibility and resource implications for low and middle-income countries. The strength of the recommendation is rated on a two-point scale:

- *Weak/conditional*: low/moderate/high quality of evidence and/or not applicable at population level in low-resource settings;
- *Strong*: high/moderate quality of evidence and applicable at population level in low-resource settings.

Diagnostic criteria based on plasma glucose values were reviewed in 2006 and were not revised in this update.

The main question, systematic review and draft recommendation were reviewed by WHO Regional Advisers for noncommunicable diseases and by additional three external experts. The peer reviewers had no disagreement with the recommendation.

2. GLYCATED HAEMOGLOBIN (HbA1c) FOR THE DIAGNOSIS OF DIABETES

Recommendation

HbA1c can be used as a diagnostic test for diabetes providing that stringent quality assurance tests are in place and assays are standardised to criteria aligned to the international reference values, and there are no conditions present which preclude its accurate measurement.

An HbA1c of 6.5% is recommended as the cut point for diagnosing diabetes. A value of less than 6.5% does not exclude diabetes diagnosed using glucose tests.

Quality of evidence assessed by GRADE: moderate

Strength of recommendation based on GRADE criteria: conditional

Glycated haemoglobin (HbA1c) was initially identified as an "unusual" haemoglobin in patients with diabetes over 40 years ago (*12*). After that discovery, numerous small studies were conducted correlating it to glucose measurements resulting in the idea that HbA1c could be used as an objective measure of glycaemic control. The A1C-Derived Average Glucose (ADAG) study included 643 participants representing a range of A1C levels. It established a validated relationship between A1C and average glucose across a range of diabetes types and patient populations (*13*). HbA1c was introduced into clinical use in the 1980s and subsequently has become a cornerstone of clinical practice (*14*).

HbA1c reflects average plasma glucose over the previous eight to 12 weeks (*15*). It can be performed at any time of the day and does not require any special preparation such as fasting. These properties have made it the preferred test for assessing glycaemic control in people with diabetes. More recently, there has been substantial interest in using it as a diagnostic test for diabetes and as a screening test for persons at high risk of diabetes (*16*).

Owing in large part to the inconvenience of measuring fasting plasma glucose levels or performing an OGTT, and day-to-day variability in glucose, an alternative to glucose measurements for the diagnosis of diabetes has long been sought. HbA1c has now been recommended by an International Committee and by the ADA as a means to diagnose diabetes (*16*). Although it gives equal or almost equal sensitivity and specificity to a fasting or post-load glucose measurement as a predictor of prevalent retinopathy (*17*), it is not available in many parts of the world. Also, many people identified as having diabetes based on HbA1c will not have diabetes by direct glucose measurement

and vice versa.

The relationship between HbA1c and prevalent retinopathy is similar to that of plasma glucose, whether glucose and HbA1c are plotted in deciles (*18*), in vigintiles (Figure 1) or as continuous variables (Figure 2). This relationship was originally reported in the Pima Indians (*19*) and has also been observed in several other populations including Egyptians (*20*), the NHANES study in the USA (*21*),, in Japanese (*22*) and more recently in the DETECT-2 analysis (Figures 1 and 2). Overall, the performance of HbA1c has been similar to that of fasting or 2-h plasma glucose. For all three measures of glycaemia, the value above which the prevalence of retinopathy begins to rise rapidly has differed to some extent between studies. Although HbA1c gives equal or almost equal sensitivity and specificity to glucose measurement as a predictor of prevalent retinopathy, it is not available in many parts of the world and in general, it is not known which is the better for predicting microvascular complications.

It is unclear whether HbA1c or blood glucose is better for predicting the development of retinopathy, but a recent report from Australia has shown that a model including HbA1c for predicting incident retinopathy is as good as or possibly better than one including fasting plasma glucose (*23*).

The use of HbA1c can avoid the problem of day-to-day variability of glucose values, and importantly it avoids the need for the person to fast and to have preceding dietary preparations. These advantages have implications for early identification and treatment which have been strongly advocated in recent years.

However, HbA1c may be affected by a variety of genetic, haematologic and illness-related factors (Annex 1) (*24*). The most common important factors worldwide affecting HbA1c levels are haemoglobinopathies (depending on the assay employed), certain anaemias, and disorders associated with accelerated red cell turnover such as malaria (*16;25*).

The utility and convenience of HbA1c compared with measures of plasma glucose for the diagnosis of diabetes needs to be balanced against the fact that it is unavailable in many countries, despite being a recognized valuable tool in diabetes management. In addition the HbA1c assay is not currently well enough standardized in many countries for its use to be recommended universally at this time. However, there will be countries where optimal circumstances already exist for its use. Factors influencing HbA1c assays are presented in Annex 2 and 3.

There are aspects of the measurement of HbA1c that are problematic. Although in some laboratories the precision of HbA1c measurement is similar to that of plasma glucose, global consistency with both assays remains a problem (*16*). Whether it is the glucose or HbA1c assay that is used, consistent and comparable data that meet international standards are required. This is starting to happen in many countries but obviously is still not standard across the world. Within any country, it is axiomatic that results for glucose and HbA1c should be consistent between laboratories.

The National Glycohemoglobin Standardization Program (NGSP) (*26*) was established following the completion of the Diabetes Complications and Control Trial (DCCT). For many years it was the sole basis for improved harmonization of HbA1c assays. More recently the International Federation of Clinical Chemists (IFCC) established a working group on HbA1c in an attempt to introduce an international standardization program (*27*). An important part of this effort was establishment of reference method procedures for HbA1c. Currently, both the NGSP and the IFCC base their evaluations on reference method procedures that have further enhanced the harmonization of HbA1c assays across manufacturers. Finally in the USA, the College of American Pathologists (CAP) has mandated more stringent criteria for individual assays to match assigned values for materials provided in the CAP proficiency programme (*28*).

A further major factor concerns costs and availability of HbA1c assays in many countries. Also, the situation in several of these countries will be exacerbated by high prevalences of conditions such as haemoglobinopathies, which affect HbA1c measurement, as discussed earlier.

A report published in 2009 by an International Expert Committee on the role of HbA1c in the diagnosis of diabetes recommended that HbA1c can be used to diagnose diabetes and that the diagnosis can be made if the HbA1c level is ≥6.5%(*16*). Diagnosis should be confirmed with a repeat HbA1c test, unless clinical symptoms and plasma glucose levels >11.1mmol/l (200 mg/dl) are present in which case further testing is not required. Levels of HbA1c just below 6.5% may indicate the presence of intermediate hyperglycaemia. The precise lower cut-off point for this has yet to be defined, although the ADA has suggested 5.7 – 6.4% as the high risk range (*29*). While recognizing the continuum of risk that may be captured by the HbA1c assay, the International Expert Committee recommended that persons with a HbA1c level between 6.0 and 6.5% were at particularly high risk and might be considered for diabetes prevention interventions.

The WHO consultation reviewed the evidence on the relationship between HbA1c and prevalent and incident microvascular complications presented in the systematic review. Tables 1 and 2 show HbA1c and glucose cut-off points associated with prevalent and incident microvascular complications in available