A clinical approach for the diagnosis of diabetes mellitus: an analysis using glycosylated hemoglobin levels

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Authors' objectives
To determine whether a glycosylated haemoglobin (HbA1c) level can be used instead of an oral glucose tolerance test (OGTT) to diagnose diabetes mellitus.

Searching
MEDLINE was searched from 1966 to 1994 for articles in any language with English abstracts. No search strategy was reported. The references of retrieved articles and the files of one reviewer were checked for further studies.

Study selection
Study designs of evaluations included in the review
No inclusion criteria relating to study design were specified.

Specific interventions included in the review
Studies in which HbA1c levels were measured concurrently with the performance of OGTT in the same person were eligible for inclusion. Only data from patients who had HbA1c levels measured were used in the analysis. Definitions of a positive index test were not reported for the individual included studies.

Reference standard test against which the new test was compared
Studies using OGTT, performed concurrently with the index test, as the reference standard were eligible for inclusion. A normal OGTT was defined as a fasting plasma glucose of less than 6.4 mmol/L and a 2-hour post-dextrose value of less than 7.8 mmol/L. Diabetes was defined as a fasting plasma glucose of at least 7.8 mmol/L and a 2-hour post-dextrose value of at least 11.1 mmol/L. Impaired glucose tolerance (IGT) was defined as any condition that was not diabetes or normal.

Participants included in the review
Studies of individuals who did not have conditions that would alter glucose tolerance (e.g. pregnancy, cystic fibrosis) were eligible for inclusion. The included studies were of patients with a prior positive screening test result; individuals self-referred from the general population; individuals referred from high-risk populations; and populations purposely enriched with patients known to have diabetes.

Outcomes assessed in the review
No a priori inclusion criteria relating to the outcome measures were specified. The review reported the mean HbA1c levels in populations with normal, IGT and diabetic OGTT results. Some estimates of sensitivity, specificity and positive predictive values (assuming a 6% prevalence of diabetes) were reported for a number of HbA1c cutpoints.

How were decisions on the relevance of primary studies made?
The principal investigators of potentially relevant studies were contacted.

Assessment of study quality
The principal investigators of the included studies were contacted for data for the analysis. All available data, published and unpublished, were provided on studies included in the analysis. No process of data checking was described. Three studies for which there was no response from the principal investigator, and 13 for which data could not be obtained, were excluded from the analysis.

Data extraction
Data from the original studies were transferred to a new database by one reviewer and checked against the original data by a second. Patient characteristics, sample size, prevalence of diabetes, details and results of the OGTT, and HbA1c levels were recorded.

**Methods of synthesis**

How were the studies combined?
Comparison of OGTT results and HbA1c levels.

Sensitivity, specificity and positive predictive values for HbA1c levels in individuals whose OGTT results met the World Health Organization (WHO) criteria for diabetes were calculated. The positive predictive value was calculated for a hypothetical diabetes prevalence of 6%.

Analysis of distribution of HbA1c levels.

Bimodal and trimodal models were estimated using pooled data from all 10 studies. The trimodal model was found to be significantly better. Assuming that the first sub-population represents normal, the second undetermined, and the third diabetes, the ability of various HbA1c cutpoints to distinguish between these theoretical sub-populations was investigated. Sensitivity, specificity, and the fraction of the second sub-population defined as having diabetes were calculated. Sensitivity was defined as the probability that someone from the third sub-population has a HbA1c value greater than the cutpoint, while specificity was defined as the probability that someone from the first sub-population has a HbA1c value below the cutpoint.

How were differences between studies investigated?
The authors did not report a method for investigating between-study heterogeneity.

**Results of the review**

Of the 34 studies eligible for inclusion, 31 authors responded when contacted and 18 of these provided relevant information. Therefore, 18 studies (11,276 patients) were initially included. However, because HbA1c showed the least variance in normal individuals, only data from the 8,984 participants (in 10 studies) who had HbA1c levels measured were included.

In those patients whose OGTT result met the criteria for diabetes, the sensitivity, specificity and positive predictive values (assuming a diabetes prevalence of 6%) were: for an HbA1c level of mean HbA1c plus 2 standard deviations (SDs), 66, 98 and 63%, respectively;

for an HbA1c level of mean HbA1c plus 3 SDs, 48, 100 and 90%, respectively; and

for an HbA1c level of mean HbA1c plus 4 SDs, 36, 100 and 97%, respectively.

The diagnoses of diabetes by HbA1c level and the results of the OGTT were not equivalent.

A proposed HbA1c cutpoint of 7% was derived from the trimodal model. Of those patients with an HbA1c level of at least 7%, 89.1% had diabetes, 7.1% had IGT and 3.8% were normal.

**Authors' conclusions**

An HbA1c level of 7.0% or higher often requires pharmaceutical intervention and is most often associated with the diagnosis of diabetes by WHO standards. An HbA1c level below 7.0% would usually be treated with diet and exercise, regardless of the diagnosis of IGT or diabetes by OGTT. Therefore, the measurement of HbA1c levels may represent a reasonable approach to identifying treatment-requiring diabetes.

**CRD commentary**

The review addressed a clear and relevant question and limited inclusion criteria were defined. The search strategy was
limited and it is therefore possible that relevant studies may have been overlooked. In addition, no attempt to identify data from unpublished studies was reported. The principal investigators of all 34 potentially relevant studies were contacted. However, the process of selecting relevant studies and obtaining and checking the data was unclear. From a total of 13,628 participants in the original 34 studies, only 8,984 participants from 10 studies were included in the analysis. This means that approximately one third of the potentially relevant data were not included in the analysis; such a loss of data could potentially have a substantial effect on the findings of the review. The authors’ conclusions, whilst probably valid, make substantial reference to the clinical application of HbA1c levels in practice, an area not addressed by the review.

**Implications of the review for practice and research**
Practice: The authors stated that to confirm the diagnosis of diabetes, a positive test should be repeated.
Research: The authors did state any implications for further research.

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