HbA1c for diabetes diagnosis: is it all it seems?

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The findings of the International Expert Committee on the role of HbA1c in diabetes diagnosis was presented to the ADA conference in June 2009 and their Report was published in Diabetes Care the following month.[1] The Committee (comprising members appointed by the ADA, EASD and the IDF) recommended that diagnosis in type 2 diabetes should now usually be made solely on the basis of an HbA1c confirmed to be ≥6.5%, without the need to measure a plasma glucose concentration in the subject. It now falls on national and international diabetes organisations to decide whether this is the most appropriate means of establishing the presence, or otherwise, of the disease. This article summarises the advantages of using HbA1c but also focuses on the problems that such a move could present.

Advantages to using HbA1c to diagnose diabetes

The Expert Committee document highlights many of the advantages to using HbA1c. These include the undoubted benefit of being able to test in the non-fasting state. Also, the biological variability of HbA1c within an individual is somewhat smaller than that of fasting glucose and considerably less that of 2 hour glucose (CV 3.6% vs. 5.7% vs. 16.6% in one study[2]), so it should be possible for repeated measurements to be more consistent using HbA1c. There is also the argument that, by giving an estimate of glycaemia over the preceding few weeks or months, HbA1c could provide a more complete view of glycaemia than a one-off fasting glucose or the artificial conditions of an OGTT. HbA1c measurement is also the most common means of guiding management and adjusting therapy, so its use for diagnosis would simply be an extension of this role.

One of the main hurdles previously to even considering using HbA1c for diagnosis has been the lack of standardisation in the assay, meaning that results could vary depending on the particular laboratory method used. Now that this is being addressed through IFCC standardisation this particular reservation should now be less of an issue.[3]

Disadvantages to using HbA1c to diagnose diabetes

Given these advantages, it would appear that the case to move to HbA1c for this purpose is a compelling one. However, there are also some real problems which could be encountered in any wholesale move to this means of diagnosis. Indeed, the Expert Committee authors accept many of the inherent problems there can be in using HbA1c for diagnosis but do not discuss the practicalities that the limitations are likely to cause. For example, we know that while one HbA1c instrument might be able to identify and account for certain haemoglobinopathies but not others, a different analyzer could pick up (or miss) a completely different spectrum of abnormal haemoglobins. Just how, therefore, are we going to be sure that someone does not have a haemoglobinopathy which is causing them to be diagnosed (or not) inappropriately? In patients already known to have diabetes, the NIH recommend being mindful of this possibility in people of African, Mediterranean or Southeast Asian heritage, citing that this should be considered when glucose measurements are discrepant to that of HbA1c, when the HbA1c result is unexpected, when the result is greater than 15% (sic) or when a value changes drastically following a change in laboratory method. But if HbA1c is the sole means of diagnosis and there is encouragement not to self-monitor glucose until insulin treated how, without concurrent haemoglobinopathy screening, will we identify many of these patients? Do we also need to exclude the common condition of iron deficiency anaemia, where the HbA1c can be 1-1.5% higher than usual,[4 5] coming down after iron treatment? Should we actively be eliminating the possibility of haemolytic anaemia in anyone we want to test? What about patients with renal failure, which can cause a variable effect (through haemolytic and iron deficient processes as well as the formation of carbamylated haemoglobin) on HbA1c, as well as conditions such as HIV where HbA1c appears 1% lower in patients on treatment? The Committee authors breeze over the effect of ageing (0.4% higher in 70 rather than 40 year olds apparently despite the same glucose tolerance)[6] and ethnicity (0.5% higher in afro-caribbeans than caucasians)[7] because their 'etiology and significance are unclear'. So in the meantime we do not know if we will wrongly singling out the elderly and non-caucasians subjects to be diagnosed with the condition.

Even the move to IFCC standardisation and numbers, although necessary for a number of reasons, will not instantly bring with it an improvement in assay performance either. Instead, if an analogy is made between lab HbA1c analysers and

wristwatches, then IFCC standardisation is the equivalent to setting our watches to an atomic clock rather than the Big Ben of DCCT/NGSP harmonisation. However this, in itself, does not make our watches immediately more accurate. And so, as a recently as June 2009, UKNEQAS found that the spread (±2SD) of HbA1c values around 6.5% (48mmol/mol) amongst 251 UK labs was anywhere between 5.8 and 7.2% (40 and 55mmol/mol). Not to mention, from a global perspective, that this performance is what is able to be achieved in a developed country with the both the resource to measure HbA1c and over a decade of method harmonisation.

Suddenly these issues, and the potential list of tests required in addition to the 'simple' HbA1c, seems to make the idea of just fasting overnight for a glucose test much more appealing.

There also remains the concern of how well HbA1c compares with glucose in predicting microvascular risk, even after excluding subjects where HbA1c measurement is likely to pose a problem. The main figure in the Report shows 3 studies (Pima Indians, Egyptian and NHANES populations) demonstrating that the risk of retinopathy increases with rising FPG, 2hr glucose and HbA1c levels at roughly the same decile, inferring that the tests are interchangable. However, this would be expected within a population no matter how poorly one of the tests predicts risk compared to another. What is not mentioned is that in all 3 studies ROC curves show fasting and/or 2hr glucose measurement (with all its inherent biological variability and poor GTT reproducibility) to be superior to that of HbA1c. Before considering any change, we also need to know how the current WHO recommendation of measuring 2hr glucose in IFG patients (as practiced in many countries) compares to that of solely measuring FPG or HbA1c.

Lastly, there is the cut off of 6.5% itself. A prelude publication to the Expert Committee Report looked towards HbA1c to help reduce the time between diabetes onset and diagnosis and to pick up the third of patients who have diabetes but do not know it.[8] According to NHANES data, 50-60% of patients with a FPG≥7mmol/L will have an HbA1c <6.5%, which actually adds patients to this missing third as well as delaying the time to diagnosis for most when compared to current criteria.[8] What this also means is that for subjects where it is already known that HbA1c measurement

will be unreliable, the use of glucose criteria will presumably make them 2-3 times as likely to be diagnosed as having diabetes as someone where HbA1c can be used. And what of a person with a fasting glucose of 10mmol/L and an HbA1c of 6.4% (47mmol/mol). Will they have diabetes or not?

Measuring fasting and 2hr glucose values to diagnose diabetes has its own- well documented- limitations but, for reasons including those described here, there may be less risk that these measurements could lead to an individual subject being completely misdiagnosed in the way that HbA1c potentially can. The hope is that there is much further discussion before decisions are made by the ADA, EASD, IDF and WHO about the merits of an 'HbA1c-only' approach.

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