

Diagnosing diabetes—time for a change?

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Abbreviations

ADA American Diabetes Association
IFCC International Federation of Clinical Chemistry

Recently an International Expert Committee including the authors of this paper proposed a revision of the diagnostic criteria for diabetes, recommending that HbA_{1c} may be a better means of diagnosing diabetes than measures of glucose (fasting and/or post-challenge) and that it be adopted as a diagnostic criterion for diabetes [1]. The international expert committee acknowledges that practical, medical, methodological and financial factors may prevent implementation of the recommendation, and in these cases recommends that current standard diagnostic methods are retained.

The recommendation is based on the association of microvascular complications with HbA_{1c} being at least as strong as those with fasting or post-challenge glucose, that

HbA_{1c} is subject to less day-to-day variability than fasting or post-challenge glucose, and can be measured at any time of the day without preparations such as fasting or a glucose challenge. So far, this is a proposal to be considered by organisations such as the EASD, American Diabetes Association (ADA), International Diabetes Federation (IDF) and the WHO, as well as by authorities in individual countries worldwide. This decision is not trivial. Redefining diagnostic criteria may re-define the severity of the disease [2], and if the same criteria are not used in all countries (as has been the case since 1997), a transatlantic trip may cure or cause diabetes simply as a result of small but important differences in diagnostic criteria [3, 4]. Redefining diagnostic criteria usually means that one set of criteria is replaced by another. Having different diagnostic procedures in place at the same time potentially creates confusion, not clarity. Consequently, now is the time for a careful evaluation of the existing evidence and the public health, economic and practical implications of redefining the diagnostic criteria for diabetes.

Identifying a diagnostic cut-off point

Although the clinical manifestations of diabetes were first described more than 2,000 years ago, the first common and internationally accepted criteria defining diabetes were agreed by a WHO expert committee less than 30 years ago [5]. Before that, different diagnostic thresholds, different glucose loads and time points during the OGTT had been used to classify an individual as having diabetes. This first set of diagnostic criteria was revised by new WHO expert committees in 1985, 1997, 2006 [3, 6, 7], and again this year a WHO expert committee has convened to

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review the diagnostic criteria for, and classification of, diabetes. These frequent revisions can only be partly explained by progression in our understanding of the underlying mechanisms leading to diabetes and significant new data related to the association between glucose and micro- or macrovascular complications.

Why is defining a diagnostic cut-off point for diabetes so difficult? The simplest answer (and perhaps also the correct answer) is that a cut-off point below which the risk of diabetes-related complications is zero, and beyond which it progressively increases may not exist. The risk of an event like a myocardial infarction increases progressively with increasing levels of the specific associated risk factor (e.g. blood pressure, cholesterol). Why should it be different for glucose? For macrovascular disease, glucose seems to be the same as other risk factors, with risk increasing continuously with increasing levels of 2 h plasma glucose after an OGTT [8] as well as with HbA_{1c} [9]. For stroke (fatal and non-fatal), a non-linear relationship with HbA_{1c} has been suggested, with those with an HbA_{1c} level of >7.0% showing an increased risk [10], but the number of events in each HbA_{1c} stratum is low, and each stratum is very wide. The two factors in combination may well produce artificial cut-off points, and, consequently, further studies would help identify whether thresholds really exist. The fact that macrovascular disease is not specific to diabetes may limit its usefulness in defining a diagnostic cut-off point, despite the fact that it represents by far the most frequent cause of death in patients with type 2 diabetes. The presence of microvascular complications seems to be more specifically related to the presence of diabetes according to the current diagnostic criteria [3, 11]. In a recent analysis of 48,418 people based on the database of the DETECT-2 collaboration [12], there was a glucose and HbA_{1c} range below which diabetes-specific moderate or advanced retinopathy was rare and above which it clearly increased with increasing levels of glycaemia. However, currently available statistical and mathematical models were not able to identify a clear cut-off point (K. Borch-Johnsen, S. Colagiuri, unpublished results). In the absence of a clear, objective cut-off point, all past and present cut-off points for diabetes represent a combination of the best available evidence and a round-table consensus among experts.

Do we need to define diabetes?

Do we need the condition ‘diabetes’, or is glucose just a continuous risk factor like all others? Clearly, glucose is a continuous risk factor, but it is also apparent that if an individual happens to fall in the diabetes category then the impact of other risk factors is greater, as demonstrated in

the Multiple Risk Factor Intervention Trial (MRFIT) [13]. This has therapeutic consequences. The absolute risk reduction associated with antihypertensive treatment is higher in people with diabetes than in non-diabetic individuals with the same blood pressure level [14], and lipid-lowering produces a greater reduction in the risk of macrovascular events in individuals with diabetes than in non-diabetic individuals [15]. Furthermore, the classical microvascular complications are specific consequences of prolonged hyperglycaemia, and therefore prevention of and screening for microvascular complications is relevant only in individuals with high glucose levels. Consequently, diabetes is a disease in its own right, not just a risk factor.

Diagnosing diabetes by HbA_{1c}—a possibility?

The idea of using HbA_{1c} to diagnose diabetes is not new. It has been discussed by previous WHO expert committees [7], but only now is it close to being adopted.

The first WHO expert committee report was published in 1980 [5]. At that time our understanding of the association between mean glucose levels and HbA_{1c} was still limited, and again in 1985 no data were available linking HbA_{1c} to the risk of complications in large cohorts including diabetic and non-diabetic individuals. The 1997 ADA expert committee [4] was the first to highlight that the association between an increase in HbA_{1c} from the normal to the diabetic range with retinopathy was similar to the relationships of fasting and 2 h plasma glucose with this diabetic complication. According to their data, the three different measures of glycaemia showed similar decile distribution relationships with retinopathy. In 1997, standardisation of the method used to determine HbA_{1c} was a major concern. This issue remained until the International Federation of Clinical Chemistry (IFCC) together with the EASD and ADA developed an anchor method and thereby provided the possibility for international standardisation of the HbA_{1c} measurement [16].

Diagnosing diabetes by HbA_{1c}—what are the pros?

Undiagnosed diabetes is a major problem in most countries. Epidemiological surveys have consistently demonstrated that 30–50% of all cases of diabetes are undiagnosed [17, 18], and this is a major reason why some countries and organisations recommend screening for diabetes. Diagnosing diabetes is, however, not simple at present. Fasting blood sampling interferes with daily activities such as work, increasing the likelihood that a person with few or no symptoms will remain undiagnosed. Furthermore, one in three cases of undiagnosed diabetes in Europe will have non-

diabetic fasting values [19], and therefore an OGTT will be required. This test is time-consuming, costly and inconvenient, and is therefore rarely used outside scientific studies and surveys. Measurement of HbA_{1c} would offer a convenient alternative, as the test can be taken at any time of the day. Once the blood has been drawn, it can be measured locally or sent for analysis further afield without altering the performance of the test. Therefore, shifting to HbA_{1c} could allow the earlier detection of diabetes, which could have a major public health impact.

Accuracy is another concern in relation to diagnosing diabetes based on plasma glucose. To provide a correct measure of plasma glucose, the sample should be placed on ice-water immediately and spun to isolate the plasma within 30–60 min [7]. This is not the standard procedure followed in routine clinical practice. If the sample is left unprocessed, the cells in the blood will continue to live on glucose, and consequently the glucose concentration falls by a median of at least 0.5 mmol/l. Furthermore the intra-individual biological variability in fasting plasma glucose is substantial at 12–15% [20, 21], and is even greater for 2 h plasma glucose, while it is only 2% for HbA_{1c} [22]. This is one reason why a diagnosis of diabetes requires two positive glucose-based tests.

Diagnosing diabetes by HbA_{1c}—what are the cons?

Testing for diabetes by measuring the HbA_{1c} level rather than by glucose testing is more expensive and therefore unaffordable in many, if not most, parts of the world. However, this consideration may not be as significant when viewed from a societal perspective. At present, the asymptomatic person undergoing diagnostic testing requires two morning fasting tests to confirm a diagnosis of diabetes. A substantial proportion will require an OGTT. For many, this results in losing one to three working hours twice before a diagnosis is made. For HbA_{1c}, the test can be performed outside normal working hours, and the increased costs of HbA_{1c} may be more than balanced by the decreased costs carried by the patient. Furthermore, if HbA_{1c} is introduced as a diagnostic test, market forces and competition should lead to a reduction in the costs of an HbA_{1c} test. Projected costs and effectiveness could easily be modelled to examine the economic impact under differing scenarios.

Accuracy in measurement and standardisation of assays remains a concern with regard to HbA_{1c} measurement. Although the IFCC together with EASD and ADA have developed a ‘reference anchor’ and thereby provided the possibility for international standardisation of the HbA_{1c} measurement [16], this has not been fully implemented at present, but an updated examination of the laboratory

measurements of glucose and HbA_{1c} by the current International Expert Committee indicates that with advances in instrumentation and standardisation, the accuracy and precision of HbA_{1c} assays at least match those of glucose assays.

The HbA_{1c} test is not available in many parts of the world. This is primarily a problem in low- and middle-income countries, and is definitely a major concern. Introduction of HbA_{1c} as *the* diagnostic test in this situation is not possible. These countries must have the option (as recommended in the report of the International Expert Committee [1]) of continuing with the current diagnostic criteria until the alternative becomes accessible and affordable.

Testing for diabetes by measuring HbA_{1c} is not possible in all patients with abnormal haemoglobin traits, such as HbS, HbC, HbF and HbE, as they interfere with some HbA_{1c} assay methods [24]. Many assay methods can correct for the presence of the most common haemoglobin traits (see www.NGSP.org, accessed 8 August 2009). Alternatively, affinity assays that are unaffected by haemoglobin traits may be used [23]. However, where HbA_{1c} testing is limited or not currently available, the use of different routine methodologies to deal with these situations will not be practical in the short term.

Conditions that change erythrocyte turnover, such as haemolytic anaemia, chronic malaria, major blood loss or blood transfusions will lead to spurious HbA_{1c} results. As for settings where HbA_{1c} assays are unavailable, the traditional glucose-based diagnostic tests must be used in individuals for whom interpreting the HbA_{1c} level is problematic.

How to reach a conclusion

The basis for the current diagnostic criteria for diabetes, namely the relationship between glucose and retinopathy, is as strong for HbA_{1c} as other measures of glycaemia. Therefore, the adoption of HbA_{1c} as a method for diagnosing diabetes becomes a discussion not about science but about practical considerations. In this regard, HbA_{1c} has some clear advantages but also a number of significant disadvantages, especially in less developed countries.

The ultimate goal would be to have a single universal diagnostic test for diabetes. Unfortunately, given the clinical situations that interfere with its accurate measurement, HbA_{1c} is unlikely to be that test in the near future without significant technological advances. Consequently, a recommendation to use HbA_{1c} as the only diagnostic criterion for diabetes on a global scale is not possible at present. For the foreseeable future, glucose measurement will continue to have an important role in the diagnosis of diabetes. This means that on the global scale we will see different diagnostic tests being used in different countries.

However, within an individual country there should be a nationally endorsed protocol for diagnosing diabetes to avoid confusion among patients and health professionals. When making the decision of whether to adopt HbA_{1c} as a diagnostic test, the country will need to consider the availability, cost and performance of local HbA_{1c} assays and the prevalence of clinical situations that interfere with its measurement.

While the world continues to struggle with the dilemma of how best to diagnose diabetes, the introduction of an additional diagnostic criterion will add to the current problem: that whether or not an individual has diabetes will vary by country and the test used to diagnose it. Nevertheless, a move to include HbA_{1c} as a diagnostic criterion is likely to be a positive step in the journey towards the ultimate goal of having a single universal diagnostic test for diabetes, and to have a test that can reduce the number of people with undiagnosed diabetes worldwide. Making progress will be challenging, but persevering with old habits will not take us forward. As Nirmal in *The Hungry Tide* finds himself torn ‘between the quiet persistence of everyday change and the heady excitement of revolution—between prose and poetry’ [24] we are also torn between established criteria and convenience against potential—but somewhat uncertain—advantages.

Duality of interest K. Borch-Johnsen is head of the Steno Diabetes Center, a hospital integrated in the Danish National Health Care Service, but owned by Novo Nordisk. K. Borch-Johnsen holds shares in Novo Nordisk. S. Colagiuri has no duality of interest relevant to this paper.

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