Diagnosis of diabetes: HbA_{1c} versus WHO criteria

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The authors compared the diagnosis of type 2 diabetes using an HbA_{1c} cut-off point of ≥6.5% (≥48 mmol/mol) with current World Health Organization (WHO) criteria involving fasting plasma glucose and an oral glucose tolerance test. Diabetes was confirmed in 35% of Australian and 49% of UK participants using WHO criteria and a similar prevalence was obtained using HbA_{1c} – 31% and 46%, respectively. Using HbA_{1c} levels alone for diagnosis does not define the same people with diabetes as the WHO criteria. A considerable number of participants (38% of Australian and 49% of British) diagnosed with diabetes by WHO criteria would not have been diagnosed using a single HbA_{1c} test. More consideration of the use of HbA_{1c} as a screening test for diabetes is required.

The use of HbA_{1c} for the diagnosis of diabetes is appealing, as it is easier to organise than current World Health Organization (WHO) procedures since it does not involve fasting.

An International Expert Committee (2009) recommended diagnosing diabetes when HbA_{1c} is confirmed as ≥6.5% (≥48 mmol/mol) on repeat measurement. This proposal was based on established and emerging epidemiological evidence relating the risk of developing moderate retinopathy to HbA_{1c}. The HbA_{1c} cut-off point of ≥6.5% (≥48 mmol/mol) was selected on its specificity (the probability of excluding diabetes), rather than its sensitivity. More recently, in January 2010, the American Diabetes Association (ADA) revised their recommendation on diagnosis of diabetes to include HbA_{1c} levels of ≥6.5% (≥48 mmol/mol) along with their current criteria (ADA, 2010).

Background

WHO diagnostic criteria are mainly used in the UK and involve measuring fasting plasma glucose (FPG) supplemented by an oral glucose tolerance test (OGTT) if impaired fasting glucose (IFG) is present. These criteria have not yet been updated. Diagnoses using either

Article points

1. The World Health Organization (WHO) diagnostic criteria are mainly used in the UK and have not yet been updated. Diagnoses using either the WHO approach or HbA_{1c}, however, do not always identify the same individuals.
2. An HbA_{1c} value of <5.5% (<37 mmol/mol) would be appropriate to rule out diabetes. To rule in diabetes, an HbA_{1c} cut-off point of ≥7.5% (≥58 mmol/mol) would be appropriate.
3. WHO and other organisations will need to take into account the accruing evidence that different people are identified with diabetes using an HbA_{1c} level of ≥6.5% (≥48 mmol/mol) than those identified using glucose measurements.

Key words

- Diagnosis
- HbA_{1c}
- Sensitivity
- Specificity

Author details can be found at the end of this article.

Table 1. Details of participants.

	Melbourne, Australia	Birmingham, UK
Baseline characteristics		
n	1175	500
Median age (years) [interquartile range]	59 [49–68]	62 [53–72]
Male (%)	54	52
South Asian (%), otherwise Caucasian	2	10
At oral glucose tolerance test [interquartile range]		
Sampling method	Venous	Capillary
Median FPG (mmol/L)	6.0 [5.3–6.8]	6.7 [6.3–7.2]*
Median HbA_{1c} (%; *mmol/mol*)	6.0 [5.6–6.6] *42 [38–49]*	6.4 [5.9–6.7]* *46 [41–50]**
Median 2-hour PG (mmol/L)	8.3 [5.8–11.8]	9.6 [7.6–11.5]*§
Median HbA_{1c} by glycaemic status (%; *mmol/mol*) [interquartile range]		
Normoglycaemia	5.6 [5.3–5.9] *38 [34–41]*	5.9 [5.6–6.1] *41 [38–43]*
IFG	6.0 [5.7–6.2] *42 [39–44]*	6.0 [5.8–6.4] *42 [40–46]*
IGT	5.9 [5.6–6.2] *41 [38–44]*	6.3 [5.8–6.8] *45 [40–51]*
IFG plus IGT	6.2 [5.8–6.5] *44 [40–48]*	6.4 [5.9–6.7] *46 [41–50]*
Diabetes on FPG or OGTT	6.8 [6.3–7.5]** *51 [45–58]***	6.6 [6.2–7.0]** *49 [44–53]***
Diagnosed with diabetes (%) based on:		
FPG level	22	38
OGTT result	13	11
WHO criteria	35	49
If HbA_{1c} ≥6.5% (≥48 mmol/mol)	31	46
By algorithm	33	47
Sensitivity / specificity (%)		
HbA_{1c} ≥6.5% (≥48 mmol/mol)	69/90	61/69
Algorithm	93/100	97/100

*P<0.001; §n=319 because OGTT is stopped if FPG is ≥7.0 mmol/L; **P<0.001 for glycaemic status.

FPG = Fasting plasma glucose; IFG = Impaired fasting glucose; IGT = Impaired glucose tolerance; OGTT = Oral glucose tolerance test; PG = Plasma glucose; WHO = World Health Organization.

the WHO approach or HbA_{1c}, however, do not always identify the same individuals (Botas et al, 2003; Manley et al, 2009a).

An HbA_{1c} level reflects the blood glucose over the preceding 3 months and is less expensive, as well as more reproducible, than performing an OGTT (Rohlfing et al, 2002). The distribution of HbA_{1c} values is such that there are no definitive ranges for the categories of glycaemia identified by FPG and OGTT (Manley et al, 2009a). The 2.5–97.5 percentile range for HbA_{1c} in normoglycaemic individuals (with an FPG of ≤6.0 mmol/L) age-matched to participants of the UK Prospective Diabetes Study (UKPDS; UKPDS Group, 1994) was 4.5–6.2% (26–44 mmol/mol) compared with 4.7–13.8% (28–127 mmol/mol) in UKPDS participants at diagnosis of diabetes when FPG was >6.0 mmol/L on two occasions.

There are, however, additional disadvantages of using surrogate markers of glycaemia alone for the diagnosis of diabetes, rather than glucose itself, as any factors that affect red blood cell turnover or haemoglobin may affect HbA_{1c}. HbA_{1c} results will be depressed if the half-life for red blood cells is reduced significantly and in some cases of renal disease and iron-deficient anaemia, HbA_{1c} results can be higher than expected (Gough et al, 2010).

The International Diabetes Federation (IDF) Clinical Guidelines Task Force (2005) recommended measurement of HbA_{1c} at diagnosis of diabetes. Since then, various studies have shown that a combination of FPG and HbA_{1c} may be a better predictor of diabetes than either marker alone (Ko et al, 1998, Inoue et al, 2008, Sato et al, 2009). An algorithm to reduce the requirement for OGTT when the HbA_{1c} level is <6.0% (<42 mmol/mol) and the FPG level is <7.0 mmol/L has been published (Manley et al, 2009a) and subsequently debated (Aldasouqi and Gossain 2009; Likhari and Gama, 2009; Manley et al 2009b). In this article, the authors have compared the recommendation to use an HbA_{1c} level of ≥6.5% (≥48 mmol/mol) with the current WHO criteria for the diagnosis of type 2 diabetes.

Methods

In 2009 the authors validated an algorithm combining FPG and HbA_{1c} for the diagnosis of

diabetes derived in people with IFG according to WHO criteria who were referred for OGTT by capillary sampling in south Birmingham. The methods are discussed in detail elsewhere (Manley et al, 2009a).

The validation cohorts for the algorithm were also used in the current study. In brief, 500 people from Birmingham and 1175 people from Australia participated in the study. The Australian cohort was selected because the procedures for OGTT involve venous rather than capillary sampling and the reasons for referral were not so narrow. In Australia, people attended for OGTT if their fasting or random glucose levels were elevated, if they had polyuria, polydipsia, metabolic syndrome, dyslipidaemia, polycystic ovary syndrome or gestational diabetes. An OGTT was not performed in the UK participants if FPG indicated diabetes or in Australia if more than a trace of glucose was detected in the urine (Manley et al, 2009a).

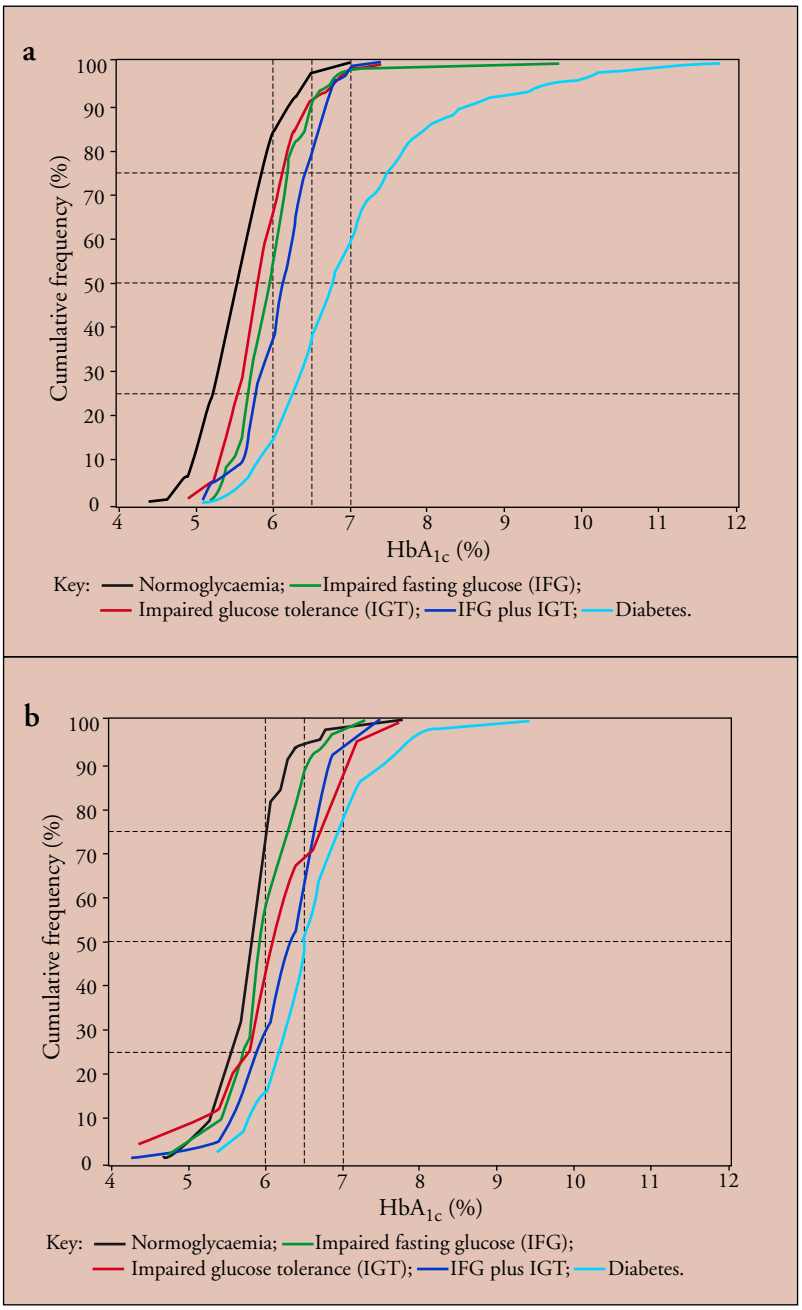
Glucose was measured using hexokinase in plasma from venous blood spun within 30 minutes of collection in Australia and in heparinised capillary plasma obtained from a finger-prick in the UK, with the capillary tubes spun immediately. Day-to-day variation in glucose measurement can be considered in terms of an error of ±6% based on internal laboratory rules for acceptability (inter-assay imprecision coefficient of variation [CV] was <3.0% in both centres), although this does not account for biological variation.

"DCCT aligned" HbA_{1c} was measured on ion-exchange high-performance liquid chromatography analysers that detect abnormal haemoglobins with an acceptability of ±6%, not including biological variation (inter-assay imprecision CV <3.0%). TOSOH G7 and G8 A1C Variant Mode analysers (TOSOH Europe, Tessenderlo, Belgium) were used to measure HbA_{1c} in the

Page points

1. In total, 500 people from Birmingham and 1175 people from Australia participated in the study.
2. In Australia, people attended for oral glucose tolerance test (OGTT) if their fasting or random glucose levels were elevated, if they had polyuria, polydipsia, metabolic syndrome, dyslipidaemia, polycystic ovary syndrome or gestational diabetes.
3. An OGTT was not performed in the UK participants if fasting plasma glucose indicated diabetes or in Australia if more than a trace of glucose was detected in the urine.

Figure 1(a). Australian cohort; (b) British cohort. Cumulative frequency plots for HbA_{1c} level by category of glycaemia.



UK and Bio-Rad Variant II Turbo IE HPLC analysers (Bio-Rad, California, USA) in Australia. HbA_{1c} levels were not reported in four UK participants because of the presence of variant haemoglobin.

Data were entered into Excel with subjects anonymised and SPSS 15.0 for Windows used with the exception of *Figure 1a* and *b* produced using SAS version 9.1.3 (SAS Institute Inc., Cary, North Carolina, USA). Ethnicity was ascertained from the name of the individual in the UK and deduced from prevalence data obtained for the Australian cohort. Glycaemic status was categorised by OGTT as follows:

- Capillary plasma: IGT defined as a 2-hour plasma glucose level within the range ≥8.9 to <12.2 mmol/L, diabetes as an FPG level ≥7.0 mmol/L or 2-hour plasma glucose level of ≥12.2 mmol/L.
- Venous plasma: IGT defined as a 2-hour plasma glucose level of ≥7.8 to <11.1 mmol/L and diabetes as an FPG level defined as ≥7.0 mmol/L or a 2-hour plasma glucose level of ≥11.1 mmol/L.

Groups were compared using unpaired Student's t-test, Chi-squared, Mann–Whitney U or Kruskal–Wallis tests.

Results

The age and gender of participants from both countries were similar with more people of south Asian origin referred in the UK (*Table 1*). FPG and HbA_{1c} levels were significantly higher in UK participants with 47% categorised with IFG at OGTT compared with 26% in the Australian cohort. In total, 35% of Australian and 49% of UK participants were diagnosed with diabetes by WHO criteria and 31% and 46% using an HbA_{1c} level of ≥6.5% (≥48 mmol/mol). There was a similar prevalence using the different procedures for diagnosis.

The sensitivity and specificity of possible cut-off points for HbA_{1c} (ranging from 5.0% [31 mmol/mol] to 7.5% [58 mmol/mol]) for diagnosis of diabetes versus current WHO criteria are shown in *Table 2*. An HbA_{1c} cut-off point of ≥6.5% (≥48 mmol/mol) gave a sensitivity of 69% in the Australian cohort and 61% in UK participants. The corresponding specificities were 90% and 69%. If HbA_{1c} cut-off points are selected to rule out diabetes or to rule it in based on the performance indicators being ≥97.5% in both cohorts, an HbA_{1c} value of <5.5% (<37 mmol/mol) would be appropriate for both populations to rule out diabetes. To rule in diabetes, an HbA_{1c} cut-off

point of ≥7.5% (≥58 mmol/mol) would be appropriate for both cohorts (the actual values for a specificity of ≥97.5% being 6.9% (52 mmol/mol) in the Australian cohort and 7.4% (57 mmol/mol) in the UK cohort. The data on "ruling diabetes in or out" are indicated in *Table 2* along with those related to the current HbA_{1c} cut-off point recommended by the expert committee and the ADA.

When the distribution of HbA_{1c} is plotted by the established categories of glycaemia (*Figure 1a* and *b*), it can be seen that a considerable number of participants (38% in Australia and 49% in the UK) diagnosed with diabetes by WHO criteria, would not be diagnosed using single test HbA_{1c} with a cut-off point of ≥6.5% (≥48 mmol/mol).

Discussion

In individuals presenting for an OGTT, a similar incidence of diabetes, ranging from 30% to 50%, was observed when either the WHO criteria or an HbA_{1c} of ≥6.5% (≥48 mmol/mol) was used for diagnosis of type 2 diabetes. However, a substantial number of people diagnosed with diabetes by the current WHO criteria would not have been diagnosed using HbA_{1c} (*Figure 1a* and *b*). Similar discordance was found in a screening study in Australia (AusDiab) with a much lower incidence (4.6%) of diabetes (Lu et al, 2010).

The guidance from the ADA on diagnostic procedures following HbA_{1c} measurement is not clear. The authors of the present study have suggested a flowchart involving the use of HbA_{1c} to "rule in or rule out" diabetes followed by testing using FPG and 2-hour plasma glucose from OGTT based on current WHO criteria possibly incorporating an algorithm combining HbA_{1c} and FPG to further reduce the number of OGTTs required.

During assessment of glycaemia in a UK participant recently identified with diabetes on OGTT, the progression from IFG to diabetes was accompanied by a rise in HbA_{1c} level of <0.5% but his HbA_{1c} level was <6.5% (<48 mmol/mol) throughout. Using the ADA cut-off point for HbA_{1c}, he would not have been identified with diabetes, but using the flow-chart, diabetes would have been detected as per current criteria.

One advantage of this study is that there were no delays in measurement of glucose so the results reflect the plasma glucose concentration accurately. However, as different laboratory-based high-performance liquid chromatography analysers were used to measure HbA_{1c}, there could be small differences in the results reported by the analysers.

Despite advances in technology and calibration, differences in HbA_{1c} assay performance in laboratories or at point of care may affect its fitness for purpose when used in the diagnostic pathway (Manley et al, 2006). Repeat measurement of HbA_{1c} within about 40 days will only confirm that the sample came from the same person.

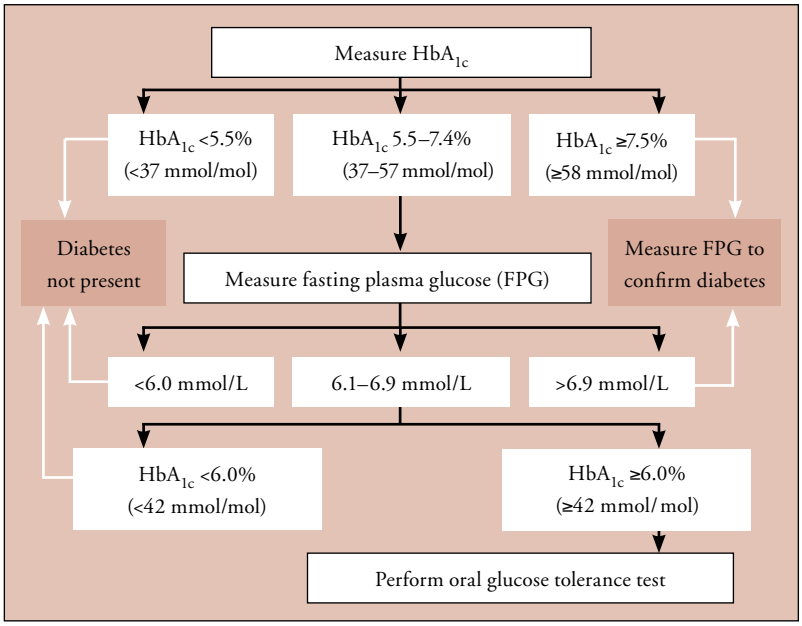
Recently, the New Hoorn study by van't Riet et al (2010), of 2753 people, concluded that the advantage of HbA_{1c} over an OGTT is limited as the highest combination of sensitivity (72%) and specificity (91%) for diagnosis was obtained in 12% of the population with an HbA_{1c} level of ≥5.8% (≥40 mmol/mol). Conversely, a study analysing the NHANES (National Health and Nutrition Examination Survey) cohort (n=6890) showed that an HbA_{1c} level of ≥6.5% (≥48 mmol/mol) was in reasonable agreement with FPG for diagnosing diabetes, but OGTT data was not available for the majority of the participants (Carson et al, 2010). Researchers from the Rancho Bernardo Study reported that the limited sensitivity of a single HbA_{1c} cut-off point of 6.5% (48 mmol/mol) may fail to identify a high proportion of people with diabetes and thus delay diagnosis (Kramer et al, 2010).

Because of the effect of coexisting haematological illnesses or other conditions on HbA_{1c} levels, it is important to carry out careful assessment of a person's suitability for use of HbA_{1c} as a surrogate marker of glycaemia (Manley et al, 2009c). The A1c-Derived Average Glucose study (Nathan et al, 2008), involving 24-hour continuous blood glucose monitoring and regular HbA_{1c} measurement, showed that the concentration of glucose and length of exposure of red blood cells to glucose were associated with HbA_{1c}, but some haematological parameters such as reticulocytes were not measured in the study.

Cohen et al (2008) suggested that differences in the turnover of red blood cells in haematologically normal people could have clinically significant effects on HbA_{1c} values. In addition, detailed investigation of a person with diabetes and polycythaemia rubra vera revealed an elevated reticulocyte count, indicative of increased red cell turnover and markedly depressed HbA_{1c}, by approximately 4–5 percentage points relative to corresponding glucose and fructosamine measurements (Manley et al, 2008).

The current study cannot provide information on how HbA_{1c} relates to complications of diabetes (Stratton et al, 2000), but there is well established evidence that people newly diagnosed with type 2 diabetes may have had the condition for several years, possibly up to 15, as some people present with retinopathy and microalbuminuria (UKPDS Group, 1990; Manley, 2003).

Figure 2. Possible role for HbA_{1c} in diagnostic pathway for type 2 diabetes.



Conclusion

The WHO and other organisations will need to take into account the accruing evidence that different people are identified with diabetes using an HbA_{1c} level of ≥6.5% (≥48 mmol/mol) than those identified using glucose measurements. There may also be problems related to the availability and cost of HbA_{1c} assays in different parts of the world. These constraints will need to be balanced with the epidemiological evidence linking HbA_{1c} to the development of diabetes complications. More consideration of the performance of HbA_{1c} as a screening test for diabetes is now required in other populations. ■

Table 2. Performance of different cut-off points of HbA_{1c} for the diagnosis of diabetes versus World Health Organization criteria.

	Australian cohort		UK cohort	
HbA_{1c} cut-off point* (%) (mmol/mol)	Sensitivity (%) *n*=1175	Specificity (%) *n*=1175	Sensitivity (%) *n*=495	Specificity (%) *n*=495
5.0 (31)	100.0	3.7	100.0	2.0
5.5 (37)**	98.5**	25.6	97.5**	8.3
6.0 (42)	88.3	63.8	86.3	37.4
6.5 (48)§	68.9§	89.8§	61.4§	68.9§
7.0 (53)	44.7	98.6	28.2	93.7
7.5 (58)**	27.4	99.9**	11.6	98.8**

*Classification of diabetes if HbA_{1c} ≥ the cut-off point. §Performance of HbA_{1c} cut-off point recommended by expert committee in 2009 and ADA in 2010. **Possible HbA_{1c} cut-off points "to rule in" and "rule out" diabetes (performance ≥97.5% in both cohorts).

Competing interests

Susan Manley: has been recompensed for lecturing for TOSOH and GlaxoSmithKline, and provided with research funds by Novo Nordisk. She has also received support for a research study from Bio-Rad, Menarini, Metrika, Roche Diagnostics, Siemens and TOSOH. She also received expenses for attending conferences from Bio-Rad, Menarini, GlaxoSmithKline, Novo Nordisk and TOSOH; **Peter Nightingale**: none; **Irene Stratton**: none; **Kenneth Sikaris**: none; **Janet Smith** and **Stephen Gough:** have received support for an ongoing research study in people with diabetes and variant haemoglobin from Bio-Rad, Menarini, Metrika, Novo Nordisk, Roche Diagnostics, Siemens and TOSOH. Janet Smith also received travelling expenses and consultation fees from Menarini; **Robert Cramb**: none.

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