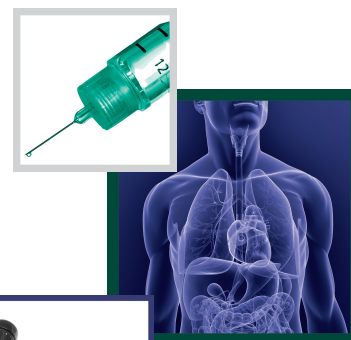


## REVIEW

# Detecting Type 2 diabetes and impaired glucose regulation using glycated hemoglobin in different populations

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### Practice Points

- HbA1c of 6.5% or more is recommended as a diagnostic tool for diabetes in some countries (e.g., the USA); however other countries are awaiting a WHO statement.
- There are some practical advantages to using HbA1c over traditional glucose testing as patients do not need to fast; therefore, screening appointments are not limited to morning sessions.
- HbA1c greater than or equal to 6.5% detects a different population from diabetes detected on glucose testing. Therefore, some people with diabetes who undergo glucose testing will not have 'diabetes' according to HbA1c.
- Certain medical conditions (e.g., hemoglobinopathies) can affect HbA1c values and may not reflect actual glycemic status.

**SUMMARY** Glycated hemoglobin, HbA1c, has recently been proposed as a diagnostic tool for detecting diabetes and impaired glucose regulation (IGR; also termed prediabetes). Many studies have reported the impact of using HbA1c to detect either glucose-defined diabetes or IGR. The aim of this article is to review recent studies from countries around the globe to assess these issues. Using HbA1c, greater than or equal to 6.5% to detect glucose-defined diabetes has a variable sensitivity of 17.0–78.2%, although specificity was generally stronger, at greater than 85%. Furthermore, most studies report that using the criteria HbA1c greater than or equal to 6.5% will decrease the prevalence of diabetes. Considering the development of glucose-defined diabetes in people without diabetes, HbA1c begins to show predictive values above 5.5–5.6%, although higher progression rates were reported at 5.9–6.1%. Most studies report the use of HbA1c as a poor tool to detect prevalent glucose-defined IGR, with a large degree of discordance between the results of people detected by different diagnostic tools.

Type 2 diabetes mellitus is considered by many people as underdiagnosed and this may partly explain why up to 50% of diabetes cases may remain undetected on a global scale [10]. This chronic condition also has an asymptomatic latent phase in early stages. The vascular

sequelae associated with diabetes can have devastating effects, with significant reductions on both life expectancy and quality of life [1]. This increased morbidity puts huge pressure on resources and financial budgets of health-care systems [2]. Therefore, there is a need to

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simplify the current screening and diagnostic tests for the diagnosis of diabetes itself in order to detect people earlier and more efficiently. This can help facilitate earlier implementation of appropriate lifestyle interventions aimed at preventing diabetes or its complications in those at risk.

Glycated hemoglobin (HbA1c) is the current tool for monitoring glycemic control once a diagnosis of diabetes is established. Its role in the diagnosis of diabetes has only recently come to attention. In the past, many international organizations have discussed the role of HbA1c in the diagnosis of diabetes and rejected this application as appropriately DCCT-aligned assays were not used or available globally [101]. However, a consensus statement in 2007 on assays used to report HbA1c has now further strengthened the case for a change in the diagnosis of diabetes [3]. Using HbA1c as a screening or diagnostic tool has some logistical advantages over traditional glucose testing (either an oral glucose tolerance test [OGTT] or fasting plasma glucose [FPG]). Patients can present for a relatively quick test in a nonfasted state at any point of the day, allowing more scope for opportunistic screening. HbA1c assay readings are less prone to recent influences of physical or emotional stress and provide an indication of longer term glycemic control spanning the last 2–3 months. Owing to such logistical advantages there are calls for HbA1c to become the preferred diagnostic tool over glucose tests [4].

#### **Diagnostic recommendations for HbA1c-based diabetes diagnosis**

In 2008, a US-based expert panel reviewed the available evidence and suggested HbA1c should indicate diagnosis of diabetes at levels greater than or equal to 6.5% [5]. This cut-off point is based upon three standard deviations above the mean HbA1c in the National Health and Nutrition Examination Survey (NHANES) III study (5.17%; standard deviation: 0.45). In some countries, HbA1c of 6.5% is now also reported alongside the International Federation of Clinical Chemistry units equivalent of 48 mmol/mol. The American Diabetes Association (ADA) has recommended reporting HbA1c together with an estimated average glucose.

A separate International Expert Committee (IEC) was formed in 2009 from several

international organizations, including representatives from the ADA and the European Association for the Study of Diabetes [6]. This expert panel reviewed current information on HbA1c for diagnosis and made a similar recommendation of using HbA1c of 6.5% or more to detect diabetes. This specific cut-off point was selected as it shares a value with the threshold above which prevalent retinopathy increases as with glucose diagnostic cut-off points, based on population data from the global DETECT-2 study [6], as moderate retinopathy is thought to be rare below an HbA1c of 6.5%.

In 2010, the ADA officially proposed using a HbA1c of 6.5% or more as a diagnostic criterion guideline in their 'Standards of Medical Care in Diabetes' position statement [7]. Furthermore, HbA1c recommendation was promoted above either FPG or 2 h plasma glucose, showing a degree of intent from the ADA. Finally, a brief joint position statement from the American Association of Clinical Endocrinology/American College of Endocrinology and a separate group, the Endocrine Organisation, recommended using a HbA1c value of 6.5% or more to detect diabetes [8].

Various committees and panels have stated that if asymptomatic people are found to have a HbA1c result in the 'diabetes range', a repeat confirmatory test should be performed, as with current glucose diagnostic criteria. However, some panels and committees have given specific points on the nature of this confirmatory test. The IEC suggest the follow-up test should be the same form as the initial test (i.e., two HbA1c tests or two glucose tests) [7]. By contrast, the ADA position statement suggests it is preferable to confirm diagnosis using the same initial test, as there is greater likelihood of concurrence of a positive test result; however, in the case of two different tests showing positive results, this should be diagnosed as diabetes [7]. Alternatively, in 2008, the US-based expert panel suggested random plasma glucose could form the second test and this may even be performed on the same day as the HbA1c, avoiding the requirement of a second day [5].

Furthermore, all committees agreed that using glucose for diagnostic testing is still valid; especially as many underserved or remote areas of the world may not have facilities to change to HbA1c. For this and other reasons, there is some debate about using HbA1c for diagnosis of diabetes [9]. The WHO has been more cautious

in promoting use of HbA1c, as they need to consider the global feasibility and availability of using HbA1c. However, the WHO has announced that their position statement would be released in 2010–2011. As many countries outside North America choose to follow WHO guidelines, their position statement will be seen as a key influence.

### How to appropriately interpret studies

In this article we wish to compare global studies regarding the impact of using HbA1c compared with traditional methods on the prevalence of diabetes or impaired glucose regulation (IGR), as well as how accurate HbA1c is at detecting glucose-defined diabetes and IGR.

Before analyzing the results from studies, it is important to interpret the findings appropriately. Each study is unique to some respect, especially with regard to the method employed and the population demographics. Therefore, comparison of studies against one another is not always straightforward. Furthermore, some studies report results as the impact on prevalence, while others choose to describe diagnostic indices, such as sensitivity and specificity. Comparing the prevalence of diabetes using HbA1c and glucose testing is similar to analyzing a ratio between the two. Therefore, factors explaining either side of the ratio must first be accounted for in-depth. Many of the points described in this section are more relevant to diagnosis of diabetes rather than IGR.

#### ■ Glucose testing

##### Has the study used FPG or OGTT as the glucose diagnostic tool?

Fasting plasma glucose is known to underdiagnose diabetes, as people with diabetic postprandial hyperglycemia will not be detected. This is more likely to be true of diabetes in its early disease stage. Therefore, FPG has a reported sensitivity of only 40–60% for detecting diabetes [10–12]. Thus, studies using FPG as the diagnostic tool would probably show a reduced prevalence of diabetes compared with using an OGTT. North American countries may argue that using this tool is appropriate in their region, as the ADA has previously recommended using FPG as the preferred glucose diagnostic tool over an OGTT [13]. Regarding prevalence of IGR, if FPG was used, then impaired glucose tolerance (IGT) would not be accounted for and thus prevalence of IGR would be lower.

##### Was diagnosis of diabetes based on one or two glucose tests?

Some epidemiological studies base their diabetes prevalence results on one glucose test, which is regarded as acceptable. However, due to the high variability of glucose, those with a test result within the diabetic range require a repeat confirmatory glucose test for diagnosis [101]. Thus, some people with an initial test result within the diabetic range may have a second repeat confirmatory test result in the nondiabetic range; the net effect is to reduce the prevalence of diabetes. Repeating the glucose test is more common in screening studies conducted in clinical practice. Therefore, this method point becomes important in the context of this article. By contrast, HbA1c readings have far less intrasubject variability when repeated and, therefore, diagnoses are less likely to change [14]; hence using one HbA1c test in a study is generally accepted, although repeating the test is preferred. Some studies adopt a policy of using HbA1c greater than or equal to 7.0% as an end point for diagnosing diabetes [15].

##### Was the study based on routine clinical data or as part of a research study?

Research studies are more likely to consist of robust methods that address recruitment issues in different age, gender and ethnic groups, with correct participant preparation prior to testing and appropriate handling of glucose samples after blood has been drawn [101]. The latter two points are key to producing an accurate glucose reading. However, research studies may also exclude people who suffer from significant morbidity or can not provide consent, in contrast to routine clinical data which screens the whole population.

##### Was study diagnosis of diabetes assessed by previous 'self-reported' diagnosis?

Some studies adopt a policy of using end points other than blood tests. The most common method is determining a diagnosis of diabetes through an interview. Participants are asked if they have previously been: first, informed they have a diagnosis of diabetes made by a doctor; or second, if they are taking oral hypoglycemic agents or administering insulin. The first point is generally accepted but simultaneously may not always produce accurate results. For instance, 'has a doctor ever told you that you have diabetes?' Answering this question

requires some degree of understanding and recall. Statements, such as ‘you may have diabetes and need a repeat test’ or ‘you have borderline diabetes/prediabetes’, could be confused with the actual conception that a patient has diabetes. However, it is necessary for cohorts to use this method. Such ‘self-report’ methods usually assess diabetes diagnosed in routine clinical practice, which itself introduces variation of screening practices for detecting diabetes and variable patient uptake of screening programs. A potential example comes from the Women’s Health Study (WHS), in which 20% of people with HbA1c of 7.0% or more without diabetes at baseline were subsequently still classified as not having diabetes (determined through self-report) after median follow-up of 10.1 years [15]. If formal glucose testing was performed at follow-up instead of self-report, it is possible the aforementioned group of 20% may have been lower.

**What is the mean age/age range of the cohort studied?**

Diabetes prevalence based on either glucose testing or HbA1c is known to increase with age [16,17]; therefore, IGR would be expected to show the same trend. Thus, a relatively older cohort may expect to have higher rates of diabetes, which is important to consider when comparing one study to another. Some studies have a specific age range as part of the inclusion criteria; therefore those within the age range of 25 to 75 years may observe different diabetes/IGR prevalence than those aged 45–75 years.

**Did the study focus on a previously undiagnosed population?**

Some studies focus exclusively on undiagnosed populations, while others report results of known diabetes and undiagnosed diabetes together. It is important to establish which the study chose to sample.

**■ HbA1c**

**Was HbA1c measured with a correctly aligned assay machine?**

This is important to ensure accurate HbA1c results are produced. Ion exchange high-performance liquid chromatography assays are currently considered the preferred assays for use. However, these instruments are expensive and may not be available in remote or underserved areas of the world. Point-of-care testing devices

(i.e., near-patient testing) are not considered appropriately aligned in general, currently preventing their use in diagnosis, however, even if appropriately aligned they may not be precise enough and are shown to have a lot of variability. It should be noted that different assay machines in different regions will have some degree of variability, even if correctly aligned, which potentially introduces some degree of variation between HbA1c values. Furthermore, studies with data older than 20–30 years may not have correctly aligned assays as less of these were available, or they may have measured levels of a previous less-specific marker, HbA1, rather than HbA1c.

In Japan, HbA1c is generally standardized to the Japanese Diabetes Society Committee for the Standardization of Glycohemoglobin [18]. An accepted simple and approximate conversion to National Glycohemoglobin Standardization Program consists of: JDS + 0.3% [18]. In this article, we report values in accordance with the National Glycohemoglobin Standardization Program.

**What was the ethnic prevalence of the cohort?**

It has been reported that nonwhite Europeans/nonwhite Caucasians have independently higher HbA1c values for equivalent levels of glycemic control [19]. Most ethnic groups (e.g., African–Caribbean, Asian/south Asian and Hispanic) have higher rates of glucose-defined diabetes compared with white Caucasian populations, but one could estimate that using HbA1c for diagnosis instead may further increase this gap. Furthermore, the effect of migration has now produced many multiethnic populations throughout Europe and North America; therefore it is important to consider what proportion of the population is of ethnic minority origin in such studies. However, one advantage multiethnic studies possess is the ability to compare different ethnic groups in the same cohort under the same standardized operating procedures.

Additionally, ethnic prevalence is also relevant in the setting of thalassemias, Hb variants and other genetic hemoglobinopathy disorders. Some hemoglobinopathies may not reflect actual glycemic control. Same thalassemias and Hb variants are more common in certain ethnic groups. For example, Hb S and C traits are common in African–Caribbeans; Hb S in Hispanic, Mediterranean and Middle Eastern populations; Hb D in Indians and Hb E in south east Asians and Indians [102]. Previously, HbA1c

assays were not able to adjust for all types of Hb variants; therefore specific assays were theoretically required in different areas where alternate Hb variants existed. At present, there are only a few assay methods where there is still interference from Hb S and C traits. Websites providing information on which assays receive interference from which Hb variants are available [103].

#### What is the prevalence of other medical conditions that affect HbA1c values?

Some medical conditions, such as iron deficiency anemia can inappropriately increase HbA1c levels [20]. Therefore, a study with a higher proportion of females, could observe an increase in mean cohort HbA1c.

In summary, comparing studies is not straightforward and requires thorough background knowledge of the methods employed and population demographics. It is also worth noting whether the study is population-based, high risk or somewhere between the two.

#### Studies comparing use of HbA1c & glucose testing for diagnosis of diabetes

For many years, researchers have been investigating the important topic of comparing glucose testing and HbA1c for diagnosis of diabetes. However, since 2008 there has been a flurry of studies. An augmented Medline search reviewed 18 studies from 1966 to 1994 on this specific topic [21]. Within this article we focus on the most recent studies reported from different countries that had a primary aim of addressing specific questions:

- Will use of HbA1c greater than or equal to 6.5% detect the same people as glucose-defined diabetes from use of: first, OGTT; or second, FPG? (i.e., how accurate is HbA1c at detecting glucose-defined diabetes on OGTT or FPG?)
- If different people are detected using HbA1c, will they be at the same risk of complications as those detected using glucose criteria?
- Will use of HbA1c greater than or equal to 6.5% detect more or less people as having diabetes compared with glucose testing?
- Is HbA1c greater than or equal to 6.5% the optimal cut-off point to detect undiagnosed diabetes?

This article has taken account of 23 recent studies, six were part of a multicenter study [22], which were published in diabetes and general

medicine journals (**Table 1**) [17,22–37]. The studies span five continents, although they had a strong bias for the USA [17,25,26,30,31,34,36,38,39] and Europe [22,29,35,37]. In addition, there were two studies from south Asia [23,24], although two multiethnic studies had information on migrant south Asians [22,29], three studies were conducted in the far-East [28,32,33], one was African [22] and one was Oceania [22]. Two studies focused exclusively on an elderly cohort [38,39], while a study of an African population had a mean age of only 37.6 years, suggesting a younger population [22]. Four studies sampled an age range starting from 20 years [23–26], while at least three studies focused on middle-aged people (40 to either 65 or 75 years) [26–29]. The total number of people within these 23 studies included over 76,000 people.

#### Impact of using HbA1c of 6.5% or more to detect diabetes

Using HbA1c greater than or equal to 6.5% to diagnose diabetes generally favored a trend of decreasing the prevalence of undiagnosed diabetes compared with glucose-defined diabetes (using either FPG or OGTT). This trend of HbA1c lowering the prevalence of diabetes was exemplified in ten of the studies reviewed in **Table 2**, with an absolute reduction of prevalence ranging from 1.3 to 3.5% [17,22–23,25–28,34,36,37]. This excludes the recent report from the Insulin Resistance Atherosclerosis Study (IRAS) [30], which over-sampled glucose intolerant categories and, therefore, can not be considered as population based. Other studies, such as NHANES, over-sampled African–Caribbean and Hispanic people specifically to match the distribution of the US population; therefore, these studies were considered population based. Only two studies compared the impact in men and women separately [28,38]; Chinese studies report no difference between genders [28]; however, a US cohort of elderly people had a higher proportion of women were detected with HbA1c criteria rather than FPG criteria [38]. When FPG was used as the glucose diagnostic tool, the differences in diabetes prevalence compared with HbA1c greater or equal to 6.5% were less pronounced than when using OGTT [25,30]. FPG is known to under-diagnose diabetes in comparison to OGTT [10–12]. For example, a sub-sample from NHANES (2003–2006) found a HbA1c greater than or equal to 6.5% detected 1.6% of this population, FPG 2.5% and OGTT 5.1% [25].

Table 1. Summary of recent studies comparing glucose testing and HbA1c for diagnosis of undiagnosed Type 2 diabetes.

Study and/or region	Type	n	Age range/mean age (years)	Mean A1c (%)	DM prevalence (%; tool)	A1c $\geq 6.5\%$	Sensitivity/ specificity for DM with A1c $\geq 6.5\%$ (%)	$\kappa$ agreement measure	Optimal A1c cut-off point (%)	Ref.
NHANES 1999–2006 (USA)	Population <sup>†</sup>	6890	$\geq 20$	–	3.6 FPG	2.3	–	0.600	–	[26]
NHANES 1999–2004 (USA)	Population <sup>†</sup>	4935	–	–	–	–	45 <sup>‡</sup>	–	5.8	[31]
NHANES 2003–2006 (USA <sup>§</sup> )	Population <sup>†</sup>	1502	$\geq 20$	5.4	5.1 OGTT	1.6	–	–	–	[25]
NHANES 1988–1994 (USA)	Population <sup>†</sup>	2712	40–74	5.17	8 OGTT	5.4	–	–	–	[17]
Rancho Bernardo (USA)	Older cohort	2107	69.4	–	–	–	44	0.119	6.15	[39]
Health, Ageing study (USA)	Older cohort	1865	70–79	5.4	2.7 FPG	3.1	56.9	–	6.0	[38]
IRAS (USA)	Oversampled <sup>†</sup>	855	–	–	15.4 OGTT 7.1 FPG	5.2	30.3 OGTT 55.7 FPG	–	–	[30]
LEADER (UK)	Population <sup>†</sup>	8696	40–75	5.7	3.3 OGTT	5.2	–	0.477	–	[29]
Whitehall (UK) <sup>¶</sup>	Population	4563	60.5	5.2	3.7 OGTT	1.0	25.0	–	–	[22]
HOORN (Holland)	Population <sup>†</sup>	2753	40–65	5.5	4.0 OGTT	1.0	24	–	5.8	[27]
Telde (Spain)	Population	964	$>30$	–	6.4 OGTT	2.9	38.7	–	–	[37]
Inter99 (Denmark) <sup>¶</sup>	Population <sup>†</sup>	5932	46.2	5.8	4.2 OGTT	6.7	42.6	–	–	[22,35]
Greenland <sup>¶</sup>	Population <sup>†</sup>	2321	44.1	5.7	7.0 OGTT	3.9	29.6	–	–	[22,35]
Ausdiab (Australia) <sup>¶</sup>	Population	7800	50.9	5.1	4.0 OGTT	0.7	17.0	–	–	[22]
Hawaii, Philippines, Japan	Population <sup>†</sup>	933	54.2	–	15.5 OGTT 6.5 FPG	8.9	40.0 OGTT 68.9 FPG	–	5.8	[36]
CURES (India) <sup>¶</sup>	Population	2188	$\geq 20$	5.9	10.2 OGTT	12.9	78.2	–	6.1	[22,23]
Chandigarh (India)	Population	1972	$\geq 20$	5.6	–	–	65	–	6.1	[24]
China	Population	2332	34–75	–	13.4 m OGTT 10.8 f	11.8 m 10.2 f	28 m 21.9 f	0.2 m 0.14 f	5.6	[28]
China	Population	4886	$>20$	5.6 A	6.2 OGTT	–	50.5	–	6.3	[33]
Fungata (Japan) <sup>¶</sup>	Population	1799	35–89	–	–	–	16–20% <sup>†</sup>	–	5.6	[32]
Kenya <sup>¶</sup>	Population	296	37.6	5.0	7.0 OGTT	3.9	29.6	–	–	[22]

The IRAS study over-sampled certain numbers of people in different ethnic, age, sex and glucose tolerance groups (therefore likely to be high risk).

<sup>†</sup>Confirmed as a multiethnic population.

<sup>‡</sup>Estimated from graphical data, provided in article.

<sup>§</sup>Sub-sample only; note 7.8% in this population had previous self-reported diabetes as well. Optimal cut-off points are derived from ROC curve analysis.

<sup>¶</sup>Part of a multicenter report.

<sup>¶</sup>Japanese HbA1c values reported in equivalent of National Glycohemoglobin Standardization Program, not Japanese Diabetes Society.

A: Median HbA1c; A1c: HbA1c; DM: Diabetes mellitus; f: Female; FPG: Fasting plasma glucose; m: Male; OGTT: Oral glucose tolerance test.

**Table 2. Summary of recent studies comparing HbA1c accuracy for detecting impaired glucose regulation or impaired glucose tolerance.**

Study and/or region	Nature of cohort studied	n	Age range	Prevalence (%)	A1c Sensitivity (%)	A1c specificity	Optimal A1c cut-off point (%)	Ref.
Beijing (China)	Population	903	21–79	22.4	A1c ≥5.7: 59.4 <sup>†</sup> A1c ≥6.0: 25.2	A1c ≥5.7: 73.9 A1c ≥6.0: 94.8	5.7	[55]
Shanghai (China)	High risk	2298	–	29.3	A1c ≥5.6: 66.2 <sup>‡</sup>	A1c ≥5.6: 51.0 <sup>‡</sup>	5.6	[56]
Shanghai (China)	Population	4886	>20	17.1	–	–	5.9	[33]
NHANES 1988–1994 (USA)	Population, but BMI >24 only	2844	40–74	–	A1c ≥6.0: 16.7 <sup>§¶</sup>	A1c ≥6.0: 92.9 <sup>§¶</sup>	–	[59]
NHANES 1999–2006 (USA)	Population	7029	≥20	28.2	A1c ≥6.0: 9 <sup>†¶</sup> A1c ≥5.7: 27 A1c ≥5.4: 63	A1c ≥6.0: 99 <sup>†¶</sup> A1c ≥5.7: 93 A1c ≥5.4: 67	5.4	[62]
NHANES III + 2005–2006, SIGT (USA)	Population	4643	55, 46, 48	36.0	A1c ≥6.0: 13 A1c ≥5.7: 31	A1c ≥6.0: > 90	5.3–5.5	[34]
Health, Ageing study (USA)	Older cohort	1865	70–79	22.1	A1c ≥5.7: 47.0	A1c ≥5.7: 84.5	5.6	[38]
AusDiab (Australia)	At risk	5604	–	–	A1c ≥5.3: 42	A1c ≥5.3: 88.2	–	[57]
LEADER (UK)	Population <sup>†</sup>	9548	40–75	16.6	WE A1c >6.0: 47.4 SA A1c >6.0: 64.2	WE A1c >6.0: 52.5 SA A1c >6.0: 69.5	WE 5.8 SA 6.0	[53]
Florence (Italy)	Population	1215	30–70	10.8 m 4.8 f	A1c >5.5 or FPG >6.1: 59.0 M, 54.8 f <sup>‡</sup>	A1c >5.5 or FPG >6.1: 19.3 m, 9.3 f	–	[58]
CURES (India)	Population	2188	≥20	11.8	A1c ≥5.7: 65.3 A1c ≥6.0: 47.1 A1c ≥5.6: 65.6 <sup>‡</sup> , 60.0 <sup>§</sup>	A1c ≥5.6: 62.1 <sup>‡</sup> , 56.5 <sup>†</sup>	5.6	[23]

Data analyzed for IGR (i.e., using an OGTT) unless otherwise stated.  
 IFG refers to WHO 1999 definition unless indicated.  
<sup>†</sup>IFG only.  
<sup>‡</sup>IGT only analyzed.  
<sup>§</sup>Combined IGT and IFG together only.  
<sup>¶</sup>ADA-defined IFG.  
 A1c: HbA1c; E: Estimated from tabulated data; f: Female; IFG: Impaired fasting glucose; IGR: Impaired glucose regulation (defined as IGT and/or IFG); IGT: Impaired glucose tolerance; m: Male; OGTT: Oral glucose tolerance test; SA: South Asians; WE: White Europeans.

Overall, we found that only five studies observed an increase in prevalence of diabetes using HbA1c greater than or equal to 6.5% compared with glucose testing [22,23,29,35,38]; all three studies used an OGTT to define glucose-based diabetes. One cohort was multiethnic [29]; whilst another was in people from south Asia [22].

#### Ethnic groups & performance of HbA1c

Regarding ethnicity, studies were generally lacking on African–Caribbeans and Hispanic people; however, some US-based studies had some data for these groups. In NHANES (1999–2004) the optimal HbA1c cut-off point for detecting diabetes was 5.8% or more and produced a better sensitivity in African–Americans and Hispanic people compared with non-Hispanic whites (sensitivity and specificity: 93 and 86%, 95 and 91%,

84 and 93%, respectively) [31]. Furthermore, NHANES III 1988–1994 [17] extrapolated their results to the US population and predicted the percentage of people aged 40–74 years with HbA1c 6.5–6.9% as 0.98, 2.69 and 3.9% in non-Hispanic white, Mexican–Americans and non-Hispanic black people, respectively. The same study showed HbA1c levels increase with age and are higher for African–Americans and Hispanic people independent of glycaemia [17]. An elderly US-based cohort report using HbA1c criteria detected more African–Americans [38].

Regarding south Asians, both the Chennai Urban Rural Epidemiology Study (CURES) study (n = 2188) and south Asians within the Leicester Ethnic Atherosclerosis and Diabetes Risk (LEADER) study (n = 1940) showed an increase in diabetes prevalence using HbA1c

criteria [23,29]. The latter study found an increase in prevalence of 2.1- and 1.8-fold found in south Asians and white Europeans, respectively [29]. Interestingly, another UK-based study, Whitehall II, separately analyzed ethnic minority groups after the main analysis and reported south Asians (n = 204) had a decrease in diabetes prevalence using HbA1c greater than or equal to 6.5% [22]. The sensitivities of HbA1c greater than or equal to 6.5% for detecting glucose-defined diabetes in south Asians were reasonably high, 78.2 and 65% in the CURES and Chandigarh studies, respectively [23,24]. By contrast, Chinese and Japanese studies found that sensitivities of HbA1c for detecting diabetes were both less than 30% [28,32]. Hawaiian Japanese, Filipino and Native Hawaiians had a lower diagnosis of diabetes using HbA1c criteria compared with OGTT diabetes diagnosis [36].

Inuit populations were described in two studies [22,35]. Use of HbA1c greater than or equal to 6.5% detected diabetes in 31.7% in Greenland and 21.3% in Inuit migrants, the highest prevalence of HbA1c diabetes of any population in this article, compared with 11.2 and 9.8%, respectively, with diabetes detected using an OGTT [35]. The same study found the Inuit population had higher HbA1c than a general Danish population at any given FPG and 2 h plasma glucose for normal glucose tolerance and IGR.

#### Sensitivity & specificity of HbA1c of 6.5% or more to detect glucose-defined diabetes

Overall, the sensitivity of HbA1c of 6.5% or more detecting diabetes from glucose testing was between 17.0–78.2%; only five studies produced sensitivity greater than 50% [22–24,33,36]. By contrast, HbA1c greater than or equal to 6.5% produced a high specificity, with seven out of eight studies reporting values greater than 98.0% [27,30–33,37,38].

#### Optimal HbA1c cut-off points from receiver operating characteristics curve analysis to detect glucose-defined diabetes

These were found to be lower than 6.5% and ranged from 5.6 to 6.3% [23,24,27,28,31–33,39]. Furthermore, five out of eight studies reviewed had an optimal HbA1c cut-off point of less than 5.9% [27,28,31,32,36]. The sensitivity produced from using optimal HbA1c cut-off points varied; the CURES study found their optimal cut-off point of HbA1c greater than or equal to 6.1% produced sensitivity and specificity of 88.0% and 87.9%

[23]. By contrast, Rancho Bernado study found their optimal HbA1c cut-off point of HbA1c greater than or equal to 6.15% produced both sensitivity and specificity below 65% [39]. The optimal cut-off points also varied when FPG and 2 h plasma glucose were considered separately, as demonstrated in the CURES study, with HbA1c greater than or equal to 6.4 and 6.1%, respectively [23]. A multiethnic Hawaiian population found an optimal receiver operating characteristics (ROC) cut-off point of HbA1c greater than or equal to 5.8%, giving sensitivity and specificity of 75.9 and 80.0%, respectively [36]. US-based study on elderly patients found an optimal ROC of HbA1c 6.0% giving sensitivity and specificity of 84.3 and 91.7%, respectively [38].

#### Area under the curve performance for HbA1c & fasting glucose to detect diabetes

Some studies compared the relative ability of HbA1c and FPG for detecting undiagnosed diabetes using analyzing area under the ROC curve (AUC). The HOORN study reported HbA1c had a lower AUC than FPG, 0.895 versus 0.937 [27]. Similarly, one Chinese study compared HbA1c to fasting capillary glucose (FCG); the AUC was significantly lower in HbA1c than FCG in both men and women [28]. This was the only study able to compare FCG and HbA1c. By contrast, a Japanese study found the AUC for undiagnosed diabetes was similar between HbA1c and FPG; 0.856 and 0.902, respectively [32]. A multiethnic Hawaiian population found HbA1c had an AUC of 0.68 [36], whilst an elderly US cohort had an AUC of 0.93 [38].

#### Discordance of diagnostic tests using $\kappa$ measurements

Using HbA1c seems to consistently detect a different population from use of FPG or OGTT, with variable degrees of overlap in people detected by using either test. The  $\kappa$  agreement measure was less than 0.5 in three out of four studies [28,29,39], with the remaining study reporting a  $\kappa$  of 0.6 [25].

#### Prevalence of people with diabetes on glucose testing but with a HbA1c less than 6.5% (false-negative diagnoses)

Regarding the percentage of people with false-negative diagnosis of diabetes from the use of OGTT, NHANES III 2005–2006/SIGT study reported 70% [34], while the Inter-99 found 58% for the same measure. When FPG was used in NHANES 1999–2006, 46.7% of people with diabetes had



HbA1c less than 6.5% [26]. The HOORN study reported that 44 and 22% of people with newly diagnosed diabetes had HbA1c less than 6.0% and 5.7%, respectively [27]; while the Rancho Bernardo study found a-third of people with diabetes on OGTT had HbA1c less than 6.0% [39]. By contrast, the CURES and LEADER studies reported only 7.6 and 10.3% of people with diabetes had HbA1c less than 6.0%, respectively [23,29].

#### Is there a change in phenotype & cardiovascular disease risk in people classified as having diabetes using HbA1c of 6.5% or more (false-positive diagnoses)?

The LEADER study demonstrated that people with diabetes, as determined by OGTT with HbA1c less than 6.5% (false negatives), had a more significantly adverse phenotype and cardiovascular risk factors compared with additional people detected (those with HbA1c greater than or equal to 6.5% but a nondiabetic OGTT) [29]. Furthermore, those with diabetes detected by OGTT but with a HbA1c less than 6.5% had significantly higher mean 10-year cardiovascular disease (CVD) risk compared with either additional people detected or those people with both HbA1c greater than or equal to 6.5% and diabetes according to OGTT [29], which is an important finding. By contrast, the Inter-99 study found the same general trends as the LEADER study, but these were not significant findings for change in phenotype and median 10-year ischemic heart disease risk (using PRECARD) between the same groups mentioned above [40]. However, the Inter-99 found that people with diabetes according to OGTT but with HbA1c less than 6.5% had significantly higher levels of hypertension and raised triglycerides than people with HbA1c greater than or equal to 6.5% and nondiabetic OGTTs. Both the LEADER and Inter-99 study showed trends of people with diabetes from both HbA1c and OGTT criteria as having the worst cardiovascular phenotype; however, the latter did not test for significance. Furthermore, a study of Inuit people in Greenland and Denmark found a similar trend [35].

The NHANES, from 1999 to 2006, and a Chinese study also measured many CVD risk factors and found no significant differences between additional people detected and those no longer classified as having diabetes using HbA1c [26,28]. However, the latter study may not have had sufficient numbers to detect a difference.

However, the additional people detected in NHANES 1999–2006 consisted of more African–Caribbeans who are generally reported to have higher rates of CVD [26]. NHANES III 2005–2006 SIGT found that additional people consisted of more African–Caribbeans, while false-negative diagnosis consisted of more non-Hispanic whites [34]. The LEADER study found similar results except with different ethnic groups: additional people consisted of significantly more south Asians and false negatives consisted of more white Europeans [29]. A small Spanish population reported people with diabetes detected by HbA1c criteria had less favorable cardiovascular risk profile than individuals with diabetes on OGTT – this appears to be the only study that reports this trend [37].

#### Long-term prediction of macrovascular events using HbA1c

There is little information on whether FPG, 2 h plasma glucose or HbA1c predicts macrovascular complications is better; the answer to this may determine which tool should be primarily used for diagnosis of diabetes. The Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study has reported that 2 h plasma glucose is more predictive for CVD than FPG [41], reflecting the continuous relationship between postprandial hyperglycemia and CVD.

The Atherosclerosis Risk in Communities (ARIC; n = 11,092, follow-up 14 years) found baseline HbA1c in people without diabetes to possess good prognostic value for future CVD; however FPG was a poor predictor in relative comparison [42]. A second ARIC study also found elevated HbA1c greater than or equal to 6.0% was associated with incident heart failure (multadjusted hazard ratio HbA1c 6.0–6.4%: 1.41 [1.10–11.80]); however, there was no association for FPG [43]. By contrast, the WHS (n = 26,563, follow-up 10.1 years) reported HbA1c was not associated with prognostic value for CVD [15]. A Finnish study (n = 593, follow-up 9.7 years) found that HbA1c predicted CVD only 6.5% or more and in women only, whereas 2 h plasma glucose predicted CVD in the IGT and diabetic range in women only; FPG did not predict CVD in either men or women [44]. The HOORN and AusDiab study reported 2 h plasma glucose had a stronger association with CVD or CV mortality compared with HbA1c [45,46]; a third study agreed with this for male mortality [47]. By contrast, the

US Rancho Bernado study reported that HbA1c had better predictive values for CVD in women only [48]. The cross-sectional Inter-99 study found HbA1c was a better predictor of 10-year ischemic heart disease risk of 30% or more and 40% compared with FPG or 2 h plasma glucose [40]. A recent systematic review analyzed 29 studies and found that HbA1c had a somewhat stronger association with coronary heart disease compared with FPG or 2 h plasma glucose [49]. The adjusted relative risks were 1.06 (1.00–1.12) for every 1 mmol/l increase in FPG; 1.05 (1.03–1.07) for every 1 mmol/l increase in 2 h plasma glucose (PG) and 1.20 (1.10–1.31) for every 1% increase in HbA1c. This suggested a 1% higher HbA1c was associated with 20% higher coronary risk; however, it was 6 and 5% for FPG and 2 h plasma glucose, respectively.

The general trend on the impact of diabetes prevalence suggests using HbA1c of 6.5% or more will detect less people than current glucose testing, although a few studies report the opposite trend. However, it should be noted that as HbA1c testing can be performed in the nonfasting state in routine appointments, this may increase screening rates and could overall detect more people with diabetes in the long run. Diagnosis of diabetes requires a confirmatory test soon after the initial test; this is because glucose can have a large interindividual variability (i.e., some people may have diabetes on the initial test but not on the confirmatory test – in which case they do not have diabetes). Therefore, to get a true reflection of diabetes prevalence in a given population it is useful to know whether the study used a single diagnostic test only or confirmed diabetes diagnosis with a repeat test – the latter is more accurate. Most studies report prevalence using a single diagnostic test without using the confirmatory test when relevant; other studies do not report whether they used a single diagnostic test or two, therefore, it is assumed to be one test only [50,51].

It is known that higher mean cohort HbA1c values (e.g., >5.7%) favor an increase in prevalence using HbA1c compared with glucose testing and lower mean cohort HbA1c (i.e., <5.3–5.4%) favor a decrease in prevalence using HbA1c. This is because more of the population is effectively shifted above the HbA1c 6.5% cut-off point with a higher mean cohort HbA1c value and less shifted with a lower mean cohort HbA1c value. This proposed theory was correct in eight of the nine populations [22,23,25,29]; the only exception was a cohort from Greenland, which

had high mean HbA1c of 5.7% but still observed a decrease in prevalence using HbA1c compared with glucose testing [22]. This Greenland population had a relatively high prevalence of undiagnosed diabetes (7.0%) using glucose testing, especially given the mean age of 44.1 years. However, the study focused exclusively on Inuit people who are considered high risk. Therefore, it appears the prevalence of undiagnosed diabetes was so high that it masked over the effects of having a high mean cohort HbA1c.

The specificity of using HbA1c of 6.5% or more was relatively high, with a lower and more variable sensitivity. The optimal HbA1c cut-off point to detect glucose-defined diabetes was lower than 6.5%. This generally agrees with a systematic review which found that the most commonly reported HbA1c cut-off point was 6.1% [52], although some studies were common to the systematic review and our study. It should be noted that the differences between HbA1c optimal cut-off points may be due to different HbA1c assay methods, not necessarily population differences.

We also found HbA1c of 6.5% or more gave a higher prevalence of diabetes in nonwhite Caucasian people [26,29,34]. This could show the influence of nonwhite Caucasian people having higher HbA1c values independent of glycaemic control, which shifts a greater proportion of people above the HbA1c of 6.5% or more threshold; however this assumption is likely to be influenced by other factors, including assay method used.

The issue of false positives (additional people detected who did not have diabetes on glucose testing) and false negatives (people no longer classified as having diabetes) using HbA1c instead of glucose testing is a recurrent theme of studies. Within each glucose tolerance classification (i.e., normal glucose tolerance, IGR or diabetes), the HbA1c levels can generally vary from less than 5.7 to more than 6.5%. A concern for additional people detected is that within some countries (e.g., the USA) health insurance may be either denied or become more expensive. The concern is for false-negatives results, as these people may progress to developing complications without the opportunity for intervention, especially if classified into low-risk groups using HbA1c. However, it should be noted that people not diagnosed with diabetes from use of HbA1c will initially need to be rescreened at intervals, especially if within the IGR range or if other

risk factors are present. This would decrease the chances of false-negative results leading to development of complications without any intervention. In addition, these people can still have interventions initiated to decrease CVD risk if other risk factors are present (e.g., hypertension hypercholesterolemia).

Regarding discordance between diagnostic tests, we found  $\kappa$  values of less than 0.5 were common, suggesting weak agreement between HbA1c and glucose testing for diabetes. However, there are different ways of calculating a  $\kappa$  measurement and not all studies reported their chosen method. Some underserved countries and remote areas will not have access to HbA1c testing and therefore they will continue to use traditional glucose testing. This risks creating a global 'two-tier' system and may also cause different glycemic profiles to be interpreted as having 'diabetes' in different regions of the world.

### Studies comparing use of HbA1c & glucose testing for diagnosis of prevalent IGR (prediabetes)

#### ■ Introduction

The second part of this review investigates the use of HbA1c for identifying IGR (also termed prediabetes: impaired fasting glycemia [IFG]) and/or IGT. The IEC has suggested using HbA1c 6.0–6.4% but gave no real explanation for selecting these cut-off points [6]. By contrast, the ADA has recommended using a lower cut-off point from HbA1c 5.7–6.4%, based on a personal communication of ROC curve analysis of IFG from NHANES [7]. This could be seen as a similar move to the ADA reducing the diagnostic cut-off point of IFG from 6.1 to 5.6 mmol/l in 2003 [13]. The same cut-off points are endorsed by the Endocrine Society [104]. The American Association of Clinical Endocrinology/American College of Endocrinology has not recommended using HbA1c to detect IGR in an initial position statement. Instead, they have suggested that people with HbA1c 5.5–6.4% could undergo further glucose testing at this point [8]; however, populations with relatively high mean cohort HbA1c levels are likely to have a large proportion of people within these cut-off points [53].

The second issue, which adds more confusion, is the terminology used to describe this 'IGR' group. Most people now acknowledge that using dichotomous terms such as prediabetes is misleading as it incorrectly suggests all

people will eventually develop diabetes. Instead, phrases that reflect a spectrum of risk are preferable. For example, 'low risk for diabetes' rather than 'normal glucose tolerance' is a better way to confer to patients that everybody is at some risk of future diabetes, even if small. Therefore, a similar phrase for IGR group should be derived. The IEC have termed this 'higher risk for diabetes', whereas the ADA prefer regarding this as 'a category of increased risk for diabetes' [6,7]. Either is acceptable and conveys the correct message; however, global standardization is required.

The main questions to be addressed are:

- What is the impact of using either ADA or IEC recommended HbA1c cut-off points on prevalent IGR?
- What is the optimal cut-off point for detecting prevalent IGR?
- How accurate is HbA1c at detecting IGR, or IGT and IFG separately?
- Is combined HbA1c and FPG accurate at detecting IGR?

#### Impact on prevalence of IGR

The NHANES 2003–2006 sub-sample reported that using the recommended IEC criteria of HbA1c 6.0–6.4% decreased the prevalence of IGR to one-tenth of those diagnosed using an OGTT [25]. NHANES III + 2005–2006/SIGT study found 36% had IGR from use of OGTT, while 6.2 and 19.5% had HbA1c 6.0–6.4 and 5.7–6.4%, respectively [34]. A Finnish study reported by using HbA1c 5.7–6.4% detected 32.8% of their cohort compared with 51.6% with IGR using an OGTT [44]. By contrast, the LEADER cohort found an increase in prevalence of IGR by 1.1-fold and 2.8-fold from using HbA1c 6.0–6.4%, and 5.7–6.4% respectively [54]. Furthermore, use of ADA cut-off points detected 44.9% of the cohort. The mean HbA1c was relatively high in the LEADER cohort (mean 5.71%), increasing the proportion of the cohort above the HbA1c 5.7 or 6.0% cut-off point. By contrast, NHANES 2003–2006 had a mean HbA1c of 5.41% [COWIE CC, PERS. COMM.]. IRAS defined IGR as having an IGT, IFG or HbA1c of 5.7–6.4%; these detected 69.1, 59.2 and 23.6% cases of the IGR, respectively [55]. Furthermore, using the insulin sensitivity index and first phase insulin secretion, HbA1c was shown to less precisely correlate with insulin resistance and secretion than 2 h plasma glucose and FPG, respectively [55].

### Optimal cut-off point for IGR

Optimal cut-off point for IGR was found to vary between studies. Regarding population-based studies, the ADA stated that ROC curve analysis found that HbA1c greater than or equal to 5.7% was the optimal cut-off point for people from the USA with IFG [7], agreeing with a Chinese population-based study reporting the same value [56]. However, a separate Chinese population-based study reported HbA1c greater than or equal to 5.9%. Within south Asians, the optimal cut-off points for IGR were reported as HbA1c greater than or equal to 5.6 and 6.0% from the CURES and the LEADER study, respectively; the latter also showed that white Europeans had an optimal cut-off point of HbA1c greater than or equal to 5.8% [23,54]. NHANES III + 2005–2006/ SIGT study combined three cohorts and reported the optimal cut-off point was between 5.4 and 5.6% [34].

### Combined use of HbA1c & fasting plasma glucose for detecting IGR

Regarding high-risk populations, a Chinese cohort found the optimal cut-off point for IGT was HbA1c greater than or equal to 5.6% giving a sensitivity and specificity of 66.2 and 51.0%, respectively; these increased to 87.9 and 33.4% with combined use of HbA1c of 5.6% or more or FPG greater than or equal to 5.6 mmol/l [57]. The AusDiab study investigated a sub-sample of people with at least one risk factor for diabetes [58]. Using HbA1c greater than or equal to 5.3% (an optimal ROC cut-off point for diabetes and IGR together) produced a low sensitivity but good specificity of 42.0 and 88.2%, respectively; these increased to 60.3 and 80.8% with combined use of HbA1c greater than or equal to 5.3% or FPG greater than or equal to 5.5 mmol/l. The last two studies again show that combined use of HbA1c and FPG increases absolute sensitivity, in a trade-off for decreasing specificity for detecting IGR. An Italian study of 1215 people found HbA1c greater than or equal to 5.3% combined with FPG of 6.1 mmol/l or more had sensitivity of 59 and 54.8% in men and women, respectively, and specificity of 19.3 and 9.3% in men and women, respectively [59].

### Discordance between diagnostic tests

Most studies report that HbA1c was generally a poor tool for detecting IGR [23,27,54–56,58], IGT [21,59–61] or IFG [62]. Regarding discordance between glucose testing and HbA1c, a

Chinese population-based study suggested 74.8 and 40.6% of people with glucose-defined IGR had an HbA1c less than 6.0% and less than 5.7%, respectively, even with an HbA1c AUC of 0.73 [56]. NHANES III + 2005–2006/SIGT study found that 89 and 70% of people with IGR had HbA1c less than 6.0 and 5.7%, respectively [34]. NHANES 1999–2006 proposed that their results would reclassify 37.6 million US adults with IFG to be at low risk with HbA1c criteria and 8.9 million without IFG to have IGR [63]. Only two studies directly compared IEC and ADA criteria for IGR, they found using the latter criteria produced less false-positive IGR diagnoses but more false-positive IGR diagnoses [34,54].

### Is there a change in phenotype & cardiovascular risk in people classified as having IGR using HbA1c criteria?

Using IEC criteria, the LEADER cohort found people who received false-positive diagnosis for IGR (i.e., additional people) were more likely to be south Asian than white European, slimmer (using waist circumference, waist, circumference, hip ratio and BMI) and have lower levels of hypertension compared with false-negative diagnosis [54]. Using ADA criteria, false positives were less likely to be obese (waist circumference and BMI), had higher levels of hypertension and microalbuminuria, but lower levels of low-density lipoprotein-cholesterol compared with false negatives [54]. However, there was no significant difference in 10-year Framingham CVD risk with either criteria. By contrast, using ADA criteria only NHANES 1999–2006 reported false-positives were more likely to be women, non-Hispanic black, hypertensive, have hypercholesterolemia, chronic kidney disease, microalbuminuria and elevated C-reactive protein compared with false-negatives [63]. No differences were found in BMI or waist circumference. Despite the contrasting profiles, both studies found people with IGR, as determined by both glucose and HbA1c criteria, had the worst cardiovascular phenotype/profile [54,63]. NHANES III + 2005–2006/SIGT and IRAS studies reported that false-positives/HbA1c 5.7–6.4% were more likely to consist of non-Hispanic black and less non-Hispanic white people [34,55]. A US-based cohort of elderly patients reported that African-Americans were more likely to be detected with HbA1c 5.7–6.4%, but non-Hispanic white people were more likely to be detected using ADA glucose criteria [38].

### ■ Discussion

The main limitation was lack of available data/amount of data in this area; most studies have reported this information through a subanalysis, which primarily focuses on the impact of using HbA1c for prevalent diabetes prevalence. Four studies reported a decrease in prevalence of IGR using HbA1c criteria [25,54,63], whilst only the LEADER reported an increased prevalence [54]. The optimal HbA1c cut-off points for IGR from ROC curve analysis were lower than IEC recommended levels, generally ranging from 5.6 to 5.8%, with reported sensitivities and specificities often both below 60%. Therefore, this could suggest that using ADA cut-off points is more appropriate than those recommended by the IEC. Furthermore, populations with a lower mean cohort HbA1c could benefit from using the ADA recommendations, as fewer people would be classified in their range. However, using ADA criteria detected just below 50% of one cohort as having IGR [54]. Clearly more data needs to be assessed. It should be noted that the differences between HbA1c optimal cut-off points over space and time may be due to different HbA1c assay methods employed, not necessarily population differences.

Furthermore, the degree of discordance between diagnostic tests is potentially larger for IGR compared with diabetes, suggesting the number of false-positive and false-negative diagnoses will be relatively high. The use of FPG and HbA1c together appears to increase sensitivity for detecting IGR; however, this strategy has not been proven to be cost effective.

Regarding changes in phenotype, studies reporting false positives would consist of non-Hispanic black or south Asian and less non-Hispanic white people. However, false positives were reported to have worse cardiovascular phenotype in NHANES but a better profile in the LEADER study compared with false negatives. Hypertension and obesity are two strong predictors of the development of diabetes.

### Studies analyzing progression of baseline HbA1c values to developing incident diabetes

#### ■ Introduction

The prognostic role of a baseline HbA1c to predict incident diabetes in those who do not have diabetes at baseline, should be considered important if HbA1c becomes the preferred diagnostic tool. In contrast to studies investigating glucose

testing and HbA1c for diagnosis of diabetes, there are fewer studies for incidence of diabetes using baseline HbA1c values. Therefore, formulating conclusions may not be so easy.

#### ■ Aims

The questions to be assessed are:

- Is there evidence that baseline HbA1c can predict future diabetes?
- At what point does a baseline HbA1c begin to predict diabetes?
- What is the optimal baseline HbA1c cut-off point to best predict progression to diabetes? Is one HbA1c cut-off point universal for all populations?
- How often should we rescreen people for incident diabetes using baseline HbA1c in the general public and in people with IGR?
- Is there a role for combined use of HbA1c and FPG in predicting progression to diabetes?
- Is the optimal HbA1c cut-off point for incident diabetes in people without diabetes similar to the optimal HbA1c cut-off point for prevalent IGR?

We focused on 18 studies from diabetes and general medicine journals, although not every study had a primary aim of investigating baseline HbA1c progression to diabetes (Table 3). Furthermore, some studies focused more on the combined use of HbA1c and FPG, without providing data on HbA1c progression alone. Results from various studies were expressed in a variety of methods, including percentage progression to diabetes, ratios (odds, hazard or likelihood) or relative risk. Furthermore, the ratios were created from models that adjusted for different dependent variables, once again making comparison of studies invariably difficult.

Six studies were based in Japan [64–69], five within the USA (although one study focused on Pima Indians) [15,42,70–72], five from Europe [44,73–76] and two studies were conducted in China [77,78]. Data were lacking in Hispanic, African and south Asian populations. Regarding the latter population, we were not able to find data from the control arm of Indian Diabetes Prevention Program. The age ranges/means in various studies were approximately similar and appeared appropriate for people at risk of diabetes. The Kansai Health

**Table 3. Demographics of selected studies with data available on baseline HbA1c progression to developing diabetes.**

Study and/or region	Cohort	n	Age (range/mean)	Follow-up (years)	DM diagnosis	Incident DM (%)	Progression of HbA1c (reported in various forms)	Ref.
ARIC (USA)	Non-DM	11,092	-	14 <sup>†</sup>	FPG, OHA, SR	20.3	For HbA1c categories: <5.0, 5.0–5.4, 5.5–5.9, 6.0–6.4 and ≥6.5%: - % progression: 6, 12, 21, 44 and 79% - Multiadjusted HR: 0.52 (0.4–0.69), 1.00 (comparator category), 1.86 (1.67–2.08), 4.48 (3.92–5.13) and 16.47 (14.22–19.08) Cumulative incidence of diabetes at 10 years was highest with combined HbA1c 5.7–6.4% and FPG ≥5.6–6.9 mmol/l (48.8%) compared with 9.69 and 7.19% for HbA1c 5.7–6.4 and FPG ≥5.6–6.9%, respectively	[42,71]
WHS (USA)	Non-DM, f only	26,563	>45	10.1 <sup>†</sup>	SR	4.7	For HbA1c categories: <5.0, 5.0–5.4, 5.5–5.9, 6.0–6.4, 6.5–6.9 and ≥7.0%: - Multivariable adjusted RR: 1.0 (comparator category), 2.9, 12.1, 29.3, 28.2 and 81.2	[15]
VAMC (USA)	Non-DM	1197	45–64	3	FPG, SR, HbA1c >7.0%	6.1	For HbA1c categories: ≥5.5, 5.6–6.0 and 6.1–6.9%: - Annual incidence: 0.8; 2.5 and 7.8% - Obese people with HbA1c 5.6–6.0%: 4.1%	[69]
Pima Indians (USA)	Non-DM	257	46.7 <sup>‡</sup>	3.3 <sup>‡</sup>	OGTT <sup>§</sup>	44	For HbA1c categories <6.03 and ≥6.03%: - % progression: 12.1 and 50% - If IGT only: % progression: 27.7 and 68.4% - For a 1% increase in HbA1c in people with IGT: OR: 6.76 (1.77–25.8)	[70]
Kansai (Japan)	Non-DM m only	6804	40–55	4	FPG OHA	9.7	For HbA1c categories: <5.3, 5.4–5.7, 5.8–6.2, 6.3–6.7 and ≥6.8%: - % progression: 3; 6.5, 20.6, 41.9 and 69.1%	[64]
Japan	Non-DM	449	23–65	7	FPG	3.8	For HbA1c categories: <6.1 and ≥6.1% - % progression: 2.0 and 18.8% - HbA1c ≥6.1% combined with IFG: progression 66.7%, adjusted OR HbA1c: 3.03 (1.73–5.32)	[66]
Japan	Non-DM	10,042	-	5.5 <sup>‡</sup>	FPG CD	3.7	HR: HbA1c <5.5% + ADA IFG: 14.4 (11.9–27.8); HbA1c 5.6–6.4% + FPG <5.6: 7.43 (4.70–11.7) HbA1c 5.6–6.4% + ADA IFG: 38.4 (24.6–59.9)	[65]
Fungata (Japan)	Non-DM	1189	35–89	5	OGTT	4.8	For HbA1c categories: <5.3, 5.3–5.5 and ≥5.6%: - % progression: 1.4; 3.7, 18.7% - OR: 1.0, 2.14 (0.91–5.05), 10.06 (4.44–22.79) - IGT only % progression: 0.4, 1.5 and 15.3%	[63]
Kobe (Japan)	Non-DM	2659	42.2	4.1 <sup>‡</sup>	OGTT or FPG	1.4	HbA1c predicted diabetes: OR: 176.8 (62.2–502.6). Optimal HbA1c cut-off point: ≥5.6%, HbA1c AUC 0.933 (0.885, 0.981)	[67]

95% confidence intervals are provided for ratios if provided in the study. Japanese and Swedish HbA1c values converted to NGSP values for this table.  
<sup>†</sup>Median.  
<sup>‡</sup>Mean.  
<sup>§</sup>DM diagnosis WHO 1985 with FPG >7.8 mmol/l or 2 h plasma glucose 11.1 mmol/l.  
<sup>\*</sup>Retrospective study that investigated referred cases of diabetes.  
 ADA: American Diabetes Association; CD: Clinical diagnosis; DM: Diabetes mellitus; f: Female; FPG: Fasting plasma glucose; HR: Hazard ratio; IGT: Impaired glucose tolerance (WHO criteria 1999 unless stated); Insulin: Insulin therapy use; IQR: Interquartile range; LR: Likelihood ratio; m: Male; NFG: Normal fasting glucose (WHO 1999 criteria unless stated); OGTT: Oral glucose tolerance test; OHA: Oral hypoglycemic agent; OR: Odds ratio; RR: Relative risk; SR: Self-report.

**Table 3. Demographics of selected studies with data available on baseline HbA1c progression to developing diabetes.**

Study and/or region	Cohort	n	Age (range/mean)	Follow-up (years)	DM diagnosis	Incident DM (%)	Progression of HbA1c (reported in various forms)	Ref.
Toyko (Japan)	Non-DM	16,313	49.7	3.0	A1C ≥6.5% OHA	3.2	Cumulative incidence for diabetes for HbA1c categories: <5.5, 5.0–5.4, 5.5–5.9 and 6.0–6.4% were 0.05, 0.05, 1.2 and 20%, respectively	[68]
China	Non-DM, high risk	208	35.0 <sup>†</sup>	1.6 <sup>‡</sup>	OGTT	21.2	– HbA1c ≥6.1% + IFG and NFG: LR: 9.32 and 0.90 Crude progression rate: 44.1 and 8.7%/year – HbA1c <6.1% + IFG and NFG: LR: 1.06 and 0.58 Crude progression rate: 17.4 and 8.1%/year	[77]
China	IGT only	123	22–66	1.7 <sup>‡</sup>	OGTT	23.6	2 h plasma glucose predicted progression to diabetes: RR: 2.31 (1.22–4.37) HbA1c not an independent predictor	[76]
DESIR (France)	Non-DM	1323 m 1407 f	30–65	6	FPG, OHA/insulin	2.1 f 4.3 m	– For HbA1c categories: 4.5–5.0, 4.5–5.5, 4.5–6.0 and 4.5–6.5%: OR: 0.90 (0.5–1.5), 1.5 (0.7–3.4), 5.0 (2.0–12.8), 32.7 (11.5–92.6) – For a 1% increase in HbA1c combined with FPG categories: <5.6, 5.6–6.9 and ≥6.10: OR: 0.78 (0.2–3.07), 1.47 (0.36–5.8), 7.20 (3.0–17.0)	[72]
Sweden	Non-DM	‡	–	5.4 <sup>‡</sup>	164	–	OR: HbA1c ≥5.7%: men 16.0 (2.23–115.3), women 19.6 (2.52–152.4)	[73]
Inter99 (Denmark)	Non-DM	6600	≥39	5	160	2.42	People who developed diabetes: median (IQR): HbA1c 6.1% (5.8–6.4%)	[74]
EPIC (Norfolk)	Non-DM HbA1c <6.4%	5735	40–74	3 <sup>‡</sup>	HbA1c ≥6.5% SR	1.3	For categories HbA1c: <5.0, 5.0–5.4, 5.5–5.9 and 6.0–6.4%; multiaadjusted OR: 1.0, 1.6 (0.7–3.6), 3.3 (1.5–7.4), 15.6 (6.9–35.7); 3-year cumulative incidence (%): 0.5 (0.3–0.9), 0.8 (0.5–1.2), 1.5 (1.0–2.3), 7.0 (4.8–10.1)	[75]
Finland	Non-DM	593	–	9.7 <sup>‡</sup>	OGTT	17.1	HbA1c 5.7–6.4%: 32.8% of people developed diabetes Crude RR ratio: unadjusted 2.78 (1.80–4.31); multiaadjusted 2.42 (1.50–3.91)	[44]

95% confidence intervals are provided for ratios if provided in the study. Japanese and Swedish HbA1c values converted to NGSP values for this table.

<sup>†</sup>Median.

<sup>‡</sup>Mean.

<sup>§</sup>DM diagnosis WHO, 1985 with FPG >7.8 mmol/l or 2 h plasma glucose 11.1 mmol/l.

<sup>\*</sup>Retrospective study that investigated referred cases of diabetes.

ADA: American Diabetes Association; CD: Clinical diagnosis; DM: Diabetes mellitus; f: Female; FPG: Fasting plasma glucose; HR: Hazard ratio; IGT: Impaired glucose tolerance (WHO criteria 1999 unless stated); Insulin therapy use; IQR: Interquartile range; LR: Likelihood ratio; m: Male; NFG: Normal fasting glucose (WHO 1999 criteria unless stated); OGTT: Oral glucose tolerance test; OHA: Oral hypoglycemic agent; OR: Odds ratio; RR: Relative risk; SR: Self-report.

study focused on men only [65], while the WHS provided data on females [15]; by contrast, the Epidemiological Study on the Insulin Resistance Syndrome (DESIR) study compared progression rates for both males and females directly in the same cohort [73]. The length of follow-up also varied between studies; the ARIC, WHS and a Finnish study provided long-term follow-up data of approximately 10 years or more [15,42,44], while most others (n = 13) focused on 3–7 years.

## ■ Results

### HbA1c to predict incident diabetes

Two long-term studies of more than 10 years showed that baseline HbA1c predicted diabetes beyond HbA1c greater than or equal to 5.5% (Table 3). In the ARIC study, the multiaadjusted hazard ratio of HbA1c 5.0–5.5% was 1.86 (95% CI: 1.67–62.08); with 21% of people in this range progressing to diabetes [42]. The WHS study found the relative risk of developing diabetes increased from 2.9 to 12.1 with HbA1c 5.0–5.4% and 5.5–6.0%, respectively [15]. However, both studies found higher progression above this range. The ARIC study reported that HbA1c 6.0–6.4% produced a hazard ratio of 4.48 (CI: 3.92–95.13), with 44% progressing to diabetes; the WHS reported those with HbA1c 6.0–6.4% had a higher relative risk of 29.3. A third long-term study found that 32.8% of Finnish people with HbA1c 5.7–6.4% developed diabetes after 9.7 years (multiaadjusted crude risk ratio: 2.42 [1.50–53.91]) [44].

In shorter studies, a population-based Veterans Administrative Medical Centre (VAMC) study (n = 1197 people without diabetes, follow-up 3 years) found people with HbA1c 6.1–6.9% had the highest annual incidence of incident diabetes, at 7.8% (CI: 5.2–10.4%) [70] compared with those with HbA1c less than or equal to 5.5% and HbA1c 5.6–6.0%, which were 0.8% (CI: 0.4–1.2) and 2.5% (CI: 1.6–3.5), respectively. However, people who were obese and had 5.6–6.0% HbA1c had an annual incidence of 4.1%. The authors made two important conclusions in their report; people with HbA1c of less than 5.5% may not require screening until after 3 years, whereas those with higher HbA1c values will require earlier rescreening, especially if greater than 6.0% or obese. To complement this, a large Japanese study found that cumulative diabetes incidence rates at 3 years were very low (<1%) below HbA1c less than 6.0%; however, for those with HbA1c greater than or equal to 6.0% rescreening at 1-year intervals would

be a reasonable strategy [69]. The ARIC study reported that diabetes incidence at 10 years was approximately 15% with ADA-IFG compared with 22% with HbA1c 5.7–6.4%. The European Prospective Investigation into Cancer (EPIC)-Norfolk study (n = 5735) performed serial HbA1c measurements at baseline and 3 years on people without self-reported diabetes and HbA1c less than 6.5% [76]. Only 35 (0.6%) people had HbA1c of 6.5% or more at the end of 3 years; by contrast, 37 (cumulative incidence 0.6%: 0.4–0.9) people self-reported glucose-defined diabetes. A third of incident diabetes cases were equally divided between HbA1c 6.0–6.4, 5.5–5.9 and less than 5.5% groups. However, a 0.5% increase in baseline HbA1c led to a twofold risk increase in glucose-defined diabetes and/or HbA1c of 6.5% or more.

Another Japanese study showed HbA1c greater than or equal to 5.6% can predict diabetes in shorter term studies, similar to results from the ARIC and WHS [64,66,67], whilst a French cohort suggests HbA1c greater than or equal to 5.7–5.8% [47]. The Inter-99 study found 160 people who developed diabetes within 5 years had a median baseline HbA1c of 6.1% (interquartile range: 5.8–6.4%) [75]. Using graphical information provided, HbA1c had an AUC for detecting diabetes of 0.650.

### Combined use of HbA1c & FPG

The ARIC study reported the cumulative incidence of diabetes at 10 years was highest with combined HbA1c 5.7–6.4% and FPG greater than or equal to 5.6–6.9 mmol/l (48.8%) compared to either test alone (9.69 and 7.19% for HbA1c 5.7–6.4 and FPG greater than or equal to 5.6–6.9%, respectively) [72]. A Chinese high-risk population (n = 208, mean follow-up 1.6 years) found people with HbA1c greater than or equal to 6.1% and normal fasting glucose had a likelihood ratio of 0.90 of developing diabetes and a 8.7% crude progression to diabetes per year [78]. When people with HbA1c greater than or equal to 6.1% and WHO-defined IFG were assessed the likelihood ratio increased sharply to 9.32, with 44.1% crude progression per year.

A Japan-based cohort (follow-up 7 years; 449 people) found those individuals with HbA1c less than 6.1% and greater than or equal to 6.1% had progression to diabetes of 2 and 18.8%, respectively [67]. When assessing people with HbA1c greater than or equal to 6.1% and



WHO-defined IFG, the percentage progressing was higher at 66.7%. A second Japanese study (follow-up 5.5 years; n = 10,042) reported people with 5.6–6.4% HbA1c and normal fasting glucose had a lower hazard ratio of 7.43 (95% CI: 4.70–11.7) than those with HbA1c 5.6–6.4% and WHO-defined IFG; 38.4 (95% CI: 24.6–59.9) [66].

The Japanese Kansai health population study (follow-up 4 years; n = 6736 men aged 40–55 years) found the progression rates to incident diabetes increased from 6.5 to 20.6% in people with HbA1c 5.4–5.7% and HbA1c 5.8–6.2%, respectively [65]. FPG and HbA1c were both independently associated with developing diabetes; however, the combined use of both FPG and HbA1c had a significantly high AUC. The DESIR study (follow-up 6 years; white Europeans) found HbA1c independently predicted future diabetes, especially beyond HbA1c greater than or equal to 5.7–5.8%, with over 10% of both men and women developing diabetes at HbA1c of 5.9% or more [73]. Furthermore, if people with HbA1c greater than or equal to 5.9% were combined with those who had FPG of 6.1–6.9 mmol/l or more, the risk of progression was 50% (odds ratio [OR]: 7.20).

#### HbA1c progression in people with IGT

The value of HbA1c progression in people with IGT has also been reported. A study of 257 predominantly Pima Indians without diabetes investigated progression over 3.3 years; 50% of people with HbA1c greater than or equal to 6.03% progressed to diabetes, in contrast to 12.1% of those with HbA1c less than 6.03% [71]. If people with IGT were analyzed using the same two categories, the progression values were 68.4 and 27.7%, respectively. Furthermore, a 1% increase in HbA1c in people with IGT led to an increased OR of 6.76 for developing diabetes.

The Japanese Fungata study followed 1189 people without diabetes for 5 years [64]. Baseline HbA1c values began to predict future glucose-defined diabetes beyond greater than or equal to 5.6% (OR: 10.06; 95% CI: 4.44–22.79) with 18.7% of people with HbA1c greater than or equal to 5.6% developing diabetes after 5 years; however, the majority of these people (15.3%) had IGT at baseline. By contrast, a China-based study of people with IGT only found 2 h plasma glucose, and not HbA1c, was an independent predictor of future diabetes after 1.71 years [77].

#### The HbA1c optimal cut-off point for detecting incident diabetes

The optimal cut-point for incident diabetes was reported in three studies, as HbA1c of 5.4% or more in the Fungata study (sensitivity: 86.0%; specificity: 61%), of 6.1% or more in DESIR (sensitivity: 64%; specificity: 77%) and of 5.6% or more in the Kobe study (sensitivity: 84.2%; specificity: 92.1%) [64,68,73]. Interestingly, the DESIR study also found that optimal cut-off point for FPG still had higher sensitivity, specificity and AUC for predicting diabetes compared with HbA1c [73].

#### ■ Discussion

HbA1c is able to predict glucose-defined diabetes in nearly all studies where this was reported, with only one letter finding it could not [77]. Data has shown that diabetes can be predicted starting from approximately HbA1c 5.5–5.6% in both long-term [15,44,64,66,67] and short-term studies [65,67,70,71,73,78]. This would accommodate the ADA HbA1c criteria of 5.7% or more for IGR. However, shorter term studies also show stronger progression rates to developing diabetes starting from HbA1c 5.9–6.1% [65,67,70,71,73,78]. This would match results from the Diabetes Prevention Program, which stated that those with HbA1c greater than or equal to 6.0% were more likely to progress to diabetes [56] [UNPUBLISHED DATA]. A recent systematic review found similar results [79], although it was not able to include the most recent studies [44,76]. They found HbA1c values from 5.5 to 6.5% were associated with an increased risk for developing glucose-defined diabetes. Furthermore, for HbA1c categories 5.0–5.5, 5.5–6.0 and 6.0–6.5% the 5-year incidence of diabetes was less than 5–9, 9–25 and 25–50%, respectively [79].

We found that the best cut-off points for incident diabetes are HbA1c 5.9–6.1%; therefore, this may suggest a threshold for the IGR group as these people can be rescreened more regularly and given intensive lifestyle advice. However, more data is required; furthermore, the optimal cut-off points derived from ROC curve analysis based on prevalent IGR were generally lower at HbA1c 5.6–5.8%. Considering the information available, how often people should be rescreened, based on incidence rates to developing diabetes, is still debatable. Data suggest that those with risk factors for diabetes, especially previous IGT, IFG or obesity, should be rescreened sooner; by contrast, those at low risk and with lower HbA1c values could be rescreened

less often. Current recommendations from some countries suggest that people 40–75 years of age should have a test for diabetes every 3 years (using traditional glucose tests), while specific high-risk groups (e.g., IGT and/or IFG) could be rescreened every 2 years [105]. Whether these principles could be transferred to HbA1c groups is not yet proven as an effective strategy.

A question we were not able to answer is whether HbA1c or FPG is actually a better tool to predict progression to developing glucose-defined diabetes. Studies showed that HbA1c generally predicts diabetes much stronger if FPG is raised into the WHO-defined IFG range. While screening with both HbA1c and FPG remains an option, this strategy has never been proven as cost effective.

### Overall conclusion

While diagnosis of diabetes and IGR may shift from traditional glucose testing to being based around HbA1c, there will be a variable impact on prevalence in different populations, which has been reported in a previous multicenter study [22]. HbA1c greater than or equal to 6.5% has a good specificity but weaker sensitivity for diabetes; however, the optimal cut-off point from ROC curve analysis was lower than 6.5%. HbA1c performed better in screening for glucose-based diabetes than glucose-based IGR. Within either glycemic category, there is a degree of discordance between people detected from use of glucose testing and HbA1c; however, this discordance is larger with IGR. The change in a person being detected as having diabetes using HbA1c criteria may lead to a change in phenotype and CVD risk.

While the diagnostic HbA1c cut-off points for diabetes is agreed between many international organizations ( $\geq 6.5\%$ ), the lower cut-off point for IGR needs further review. The ADA

recommendations using a lower cut-off point of HbA1c 5.7%, which generally seems to match ROC curve analysis of prevalent IGR cut-off points (most commonly reported at HbA1c 5.6–5.8%). By contrast, IEC recommendations of 6.0% HbA1c generally seem to match the best cut-off points for progression of baseline HbA1c to incident diabetes in the general population (5.9–6.1% most commonly reported). More research is required before HbA1c becomes the official diagnostic tool and cut-off points for IGR are determined.

### Future perspective

The prevalence of Type 2 diabetes is expected to rise. Therefore, it is important to simplify screening tests for diabetes so that more people can be screened and the undiagnosed population with diabetes is minimized. Using HbA1c for diagnosis represents a potential method of achieving this. This could lead to many changes in the way diabetes is screened over the next 5–10 years.

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