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Use of haemoglobin A1c to detect impaired fasting glucose or Type 2 diabetes in a United Kingdom community based population☆

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ABSTRACT

Aims: To evaluate the diagnostic accuracy of haemoglobin A1c (HbA1c) in screening for impaired fasting glucose and Type 2 diabetes (T2DM).
Methods: We screened 3904 adults aged 45–70 (mean age 58.6 [standard deviation (SD) 6.9] years, mean body mass index (BMI) 29.9 [SD 4.7] kg/m^2), with fasting plasma glucose (FPG) and HbA1c as part of a large diabetes prevention programme. We assessed the diagnostic accuracy of HbA1c for predicting impaired fasting glucose (IFG), (defined either as FPG 5.6–6.9 mmol/l, or 6.1–6.9 mmol/l), and T2DM (FPG $\geq$ 7.0 mmol/l).
Results: The prevalences of IFG were 13.8% (FPG 5.6–6.9 mmol/l) and 4.5% (FPG 6.1–6.9 mmol/l) and of T2DM was 2.1%. Using FPG 5.6–6.9 mmol/l as the IFG reference standard, HbA1c of 39–47 mmol/mol (5.7–6.4%) was 63% sensitive and 81% specific, and HbA1c 43–47 mmol/mol (6.1–6.4%) was 21% sensitive and 98% specific, in diagnosing IFG. HbA1c $\geq$ 48 mmol/mol (6.5%) was 61% sensitive and 99% specific in diagnosing T2DM. Having HbA1c 39–47 mmol/mol (5.7–6.4%), male sex, and body mass index >29.5 together increased the odds of IFG 6.5-fold (95% confidence interval (CI) 5.5–7.8) compared to the pre-test odds.
Conclusion: Defining 'pre-diabetes' at a lower HbA1c threshold of 39 mmol/mol (5.7%) instead of 47 mmol/mol (6.1%) increases its sensitivity in diagnosing IFG, but current American Diabetes Association definitions of 'pre-diabetes' based on HbA1c would fail to detect almost 40% of people currently classified as IFG. This has implications for current and future diabetes prevention programmes, for vascular risk management, and for clinical advice given to people with 'pre-diabetes' based on fasting glucose data.

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1. Introduction

The detection of impaired glucose tolerance (IGT) or impaired fasting glucose (IFG) identifies people at highest risk of developing Type 2 diabetes (T2DM), and intervention at this stage with intensive diet and lifestyle changes have reduced the risk of developing T2DM in large clinical trials [1–4].

There has been intense debate recently about the revised criteria for the diagnosis of diabetes [5]. The American Diabetes Association (ADA) and others have proposed a diabetes diagnosis based on an HbA1c $\geq$ 6.5%, and 'pre-diabetes' (including IFG and IGT) as an HbA1c 39–47 mmol/mol (5.7–6.4%) [6] although others have suggested an HbA1c range of 43–47 mmol/mol (6.1–6.4%) as indicating increased risk of T2DM [7]. There are clear epidemiological benefits in this approach [6], and numerous methodological advantages of using HbA1c rather than a diagnosis based on a plasma glucose, which requires either fasting or glucose loading [5,8].

One of the major issues with this new approach is the new HbA1c definition of 'pre-diabetes', because it is unclear how this is related to glucose-based definitions of IFG or IGT, or the implications of these changes for existing and potential diabetes prevention studies, all of which are based on plasma glucose criteria. More recent studies have shown that HbA1c may be insensitive in diagnosing IFG and IGT, with sensitivities ranging from 27% to 47% in United States populations [9,10]. We also have no clear view on the rates of progression in HbA1c across these categories, and there remains the clinical issue that many people have been told they are at increased risk of vascular disease and T2DM, based on glucose criteria, but who may in fact appear not to have 'pre-diabetes'.

Test sensitivities and specificities depend not only on diagnostic thresholds, but also on the overall distributions of plasma glucose and HbA1c in the populations being tested [11]. In the United Kingdom (UK), it is rare for glucose tolerance tests to be undertaken in primary care for the diagnosis of diabetes, as they are time consuming, expensive and often undertaken inaccurately [12]. In recent years a national program of primary care vascular health checks has been developed for those at increased vascular and diabetes risk, which includes a fasting plasma glucose measurement [12]. In this study, we describe the screening data from the first part of a new diabetes prevention program which uses fasting plasma glucose as a screening tool, leading to a diabetes prevention intervention in IFG subjects delivered by lay trainers with existing T2DM. We report on the diagnostic accuracy of HbA1c and other risk factors in predicting IFG and T2DM.

2. Methods

2.1. Design and population

The reported data are derived from the feasibility elements of a large diabetes prevention programme (UEA-IFG study) undertaken in Norfolk, England [13]. This feasibility programme tested assumptions on recruitment, screening capacity, retention, and training of people with existing T2DM to deliver a diet and lifestyle intervention to those found to have impaired fasting glucose (IFG; FPG 6.1–6.9 mmol/l). In this feasibility programme, we screened 3921 adults aged between 45 and 70 years and registered with 69 primary care family practises, without previously diagnosed diabetes and with at least one of the following risk factors for glucose intolerance: (a) a first degree relative with T2DM, (b) body mass index (BMI) $>$ 25 kg/m^2, (c) waist circumference $>$ 94 cm in men and $>$80 cm in women, (d) personal history of coronary heart disease, (e) personal history of gestational diabetes or (f) reported to have IFG by their general practise or themselves. All participants underwent a single fasting plasma glucose and HbA1c measurement between December 2009 and April 2010. Virtually everyone resident in the UK is registered with a local family practise, therefore their patients are representative of local populations.

2.2. Data collection

Participants (n = 3921) completed a questionnaire on medical history and diabetes risk factors. Height, weight, blood pressure and waist circumference were measured by trained researchers and BMI calculated as kilograms/height^2. Blood was taken for FPG and HbA1c measurements after a standard overnight fast.

HbA1c was measured using dedicated high performance liquid chromatography (HA 8160: Menarini Diagnostics Ltd., Wokingham, RG41 5RA, UK). Plasma glucose was measured using a hexokinase/G-6-PDH method on an automated platform (Architect c8000: Abbott Diagnostics, Maidenhead, UK). We expressed HbA1c values both as percentages and as mmol/mol, as recommended by the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) [14,15].

IFG and pre-diabetes were defined using current ADA definitions [6]. For the present study the reference standard test was FPG, with IFG defined as FPG 5.6–6.9 mmol/l and with diabetes defined as FPG $\geq$ 7.0 mmol/l. HbA1c was the screening test of interest, with pre-diabetes defined as HbA1c 39–47 mmol/mol (5.7–6.4%) and with diabetes defined as HbA1c $\geq$ 48 mmol/mol (6.5%). For this study we repeated analyses after re-defining IFG as FPG 6.1–6.9 mmol/l, that is, the previous ADA definition until 2010 [16].

3. Statistical analysis

Prevalences of IFG and diabetes were estimated, with exact 95% confidence intervals. Characteristics of people with increasing FPG levels were compared using Cuzick's non-parametric test for trend. Correlation between HbA1c and FPG values was estimated using Pearson's correlation coefficient. We estimated the sensitivity, specificity and positive and negative likelihood ratios for each diagnosis, at different HbA1c thresholds. When analyzing diagnosis of IFG, individuals with diabetes (FPG $\geq$ 7.0 mmol/l) were excluded. We estimated the areas under receiver operating characteristic curves (AUCs) to compare the overall performance of HbA1c across its full range of values. Greater AUC indicates better diagnostic accuracy [17].

We carried out logistic regression analyses to assess the added value of other risk factors for IFG and diabetes, when combined with HbA1c. In these analyses IFG and diabetes were the outcome variables, and HbA1c, age, gender, BMI, waist circumference, family history of diabetes and personal history of coronary heart disease were potential explanatory variables. Age, BMI and waist circumference were converted to binary variables using their medians as cutpoints. Variables were removed from each model if they were not significant at the 5% level.

In logistic regression models, independent (mutually adjusted) associations between each predictor and outcome were expressed as positive and negative likelihood ratios as well as the more conventional odds ratios. Likelihood ratios have the advantage of combining information about sensitivity and specificity to quantify a test's value in making a diagnosis in different populations with different disease prevalences. The likelihood ratio for a positive test result is the post-test odds of having a condition if the test is positive, divided by the pre-test odds of having the condition; it typically has values greater than one. Similarly, the likelihood ratio for a negative test result is the post-test odds of having the condition if the test is negative, divided by the same pre-test odds of having the condition; it typically has values less than one. We adjusted the crude likelihood ratios for each test or risk factor with shrinkage factors obtained by multiple logistic regression, as described by Spiegelhalter and Knill-Jones [18]. The adjusted likelihood ratios of different predictors can be multiplied by each other because they are independent, that is, mutually adjusted [17]. Confidence intervals for adjusted likelihood ratios were estimated by non-parametric bootstrapping of logistic regression, with 1000 replications, using the bias-corrected percentile method [19]. All analyses were carried out with STATA version 11 (STATA Corp., TX, USA).

4. Ethics

All participants provided written informed consent to take part in the study. Confidentiality of individual's identities was maintained. Ethical approval for the study was given by the Essex 1 Research Ethics Committee.

5. Results

5.1. Participants' characteristics

Of the 3906 screened participants, 539 (13.8%, 95% confidence interval (CI) 12.7–14.9%) had IFG according to the new ADA criteria (FPG 5.6–6.9 mmol/l), 176 (4.5%, 95% CI 3.9–5.2%) had IFG according to the pre-2010 ADA criteria (FPG 6.1–6.9 mmol/l) and 81 (2.1%, 95% CI 1.7–2.6%) had T2DM. Age, BMI, waist circumference and male sex were positively associated with increasing FPG (Table 1), and the correlation between HbA1c and FPG was $R = 0.72$ (95% CI 0.71–0.74).

5.2. Sensitivity and specificity of HbA1c

The sensitivity and specificity of HbA1c for detecting IFG (current and previous ADA definitions) and diabetes at different HbA1c thresholds are shown in Tables 2 and 3. With FPG 5.6–6.9 mmol/l as the reference standard, HbA1c 39–47 mmol/mol (5.7–6.4%) was 63% sensitive and 81% specific in diagnosing IFG and HbA1c 6.1–6.4% was 21% sensitive and 98% specific in diagnosing IFG. HbA1c $\geq$ 48 mmol/mol (6.5%) was 61% sensitive and 99% specific in diagnosing T2DM. The AUCs show that, when considering the full range of HbA1c values instead of using a single threshold, HbA1c was a better predictor of T2DM than of IFG, and a worse predictor of IFG according to the current ADA definition than according to the previous definition (Table 2).

5.3. HbA1c combined with risk factor information

Male gender and BMI were independently associated with IFG after adjustment for HbA1c in a logistic regression model (Table 4). Age, waist circumference, personal history of coronary heart disease and family history were not independently associated with IFG and were removed from the

Table 1 – Participants' characteristics in relation to fasting plasma glucose.

Patient characteristics	Normoglycaemia [6]; FPG < 5.6 mmol/l (N = 3286)	Impaired fasting glucose [8] (pre-diabetes); FPG 5.6–6.9 mmol/l (N = 539)	Diabetes [8]; FPG ≥ 7.0 mmol/l (N = 81)	P*
	Mean (SD)	Mean (SD)	Mean (SD)	
HbA1c (%) (mmol/mol)	5.4 (0.3) 35.5 (3.2)	5.8 (0.5) 39.9 (4.9)	7.2 (1.5) 55.2 (16.4)	<0.001
Age (years)	58.6 (6.9)	59.7 (6.7)	57.9 (7.3)	0.053
Body mass index (kg/m^2)	29.9 (4.7)	31.5 (4.6)	33.7 (6.6)	<0.001
Waist circumference (cm)	102.2 (20.0)	107.3 (12.9)	112.2 (14.2)	<0.001
	No. (%)	No. (%)	No. (%)	
Male	1391 (42.3)	304 (56.4)	44 (54.3)	<0.001
Family history of diabetes	1181 (35.9)	207 (38.4)	34 (42.0)	0.13
Personal history of coronary heart disease	465 (14.2)	70 (13.0)	16 (20.0)	0.74

FPG, fasting plasma glucose; HbA1c, haemoglobin A1c; and SD, standard deviation.
* Cuzick's non-parametric test for trend.

Table 2 – Accuracy of HbA1c in diagnosing impaired fasting glucose at different thresholds.

Lower HbA1c threshold for diagnosis		Sensitivity (%)	Specificity (%)	Positive likelihood ratio	Negative likelihood ratio
(%)	(mmol/mol)				
Reference standard: (FPG 5.6–6.9 mmol/l)					
5.0	31	97.8	2.8	1.01	0.78
5.1	32	97.0	7.1	1.04	0.43
5.2	33	94.9	13.5	1.10	0.38
5.3	34	90.4	26.2	1.23	0.37
5.4	36	86.5	39.0	1.42	0.35
5.5	37	78.2	54.2	1.71	0.40
5.6	38	68.2	68.1	2.14	0.47
5.7	39	63.0	80.7	3.26	0.46
5.8	40	50.9	87.9	4.20	0.56
5.9	41	37.8	93.1	5.47	0.67
6.0	42	30.1	96.3	8.02	0.73
6.1	43	21.4	98.1	11.1	0.80
6.2	44	14.6	99.0	14.5	0.86
6.3	45	10.8	99.4	17.7	0.90
6.4	47	7.6	99.6	20.7	0.93
6.5	48	5.3	99.7	19.3	0.95
Reference standard: (FPG 6.1–6.9 mmol/l)					
5.0	31	99.5	2.8	1.02	0.18
5.1	32	99.5	6.7	1.07	0.08
5.2	33	98.5	12.6	1.13	0.12
5.3	34	97.0	24.3	1.28	0.12
5.4	36	96.0	36.1	1.50	0.11
5.5	37	92.4	50.5	1.87	0.15
5.6	38	87.9	64.2	2.46	0.19
5.7	39	80.3	77.4	3.6	0.25
5.8	40	71.2	85.3	4.8	0.34
5.9	41	59.1	91.2	6.7	0.45
6.0	42	53.0	94.9	10.5	0.49
6.1	43	40.4	97.2	14.2	0.61
6.2	44	29.8	98.4	19.0	0.71
6.3	45	23.7	99.0	24.6	0.77
6.4	47	17.7	99.4	29.1	0.83
6.5	48	13.6	99.6	35.3	0.87

FPG, fasting plasma glucose and HbA1c, haemoglobin A1c. Areas under receiver operating characteristic curves across all HbA1c thresholds: 0.77 (95% CI 0.75–0.79) for impaired fasting glucose (FPG 5.6–6.9 mmol/mol), and 0.86 (95% CI 0.83–0.89) for impaired fasting glucose (FPG 6.1–6.9 mmol/mol).

Table 3 – Accuracy of HbA1c in diagnosing diabetes (FPG ≥ 7.0 mmol/l) at different thresholds.

Lower HbA1c threshold for diagnosis		Sensitivity (%)	Specificity (%)	Positive likelihood ratio	Negative likelihood ratio
(%)	(mmol/mol)				
6.0	42	88.9	92.4	11.8	0.12
6.1	43	81.5	95.2	17.0	0.19
6.2	44	77.8	97.0	25.6	0.23
6.3	45	71.6	97.9	33.4	0.29
6.4	47	65.4	98.5	43.9	0.35
6.5	48	60.5	98.9	56.4	0.40
6.6	49	56.8	99.2	70.0	0.44
6.7	50	50.6	99.5	92.1	0.50
6.8	51	48.2	99.6	115	0.52
6.9	52	44.4	99.7	142	0.56
7.0	53	42.0	99.7	160	0.58

FPG, fasting plasma glucose and HbA1c, haemoglobin A1c. Area under receiver operating characteristic curve across all HbA1c thresholds: 0.98 (95% CI 0.97–0.99).

Table 4 – Multivariable prediction of impaired fasting glucose (fasting plasma glucose 5.6–6.9 mmol/l): logistic regression model.

Risk factor	Odds ratio[a]	95% CI	Likelihood ratio if positive[a]	95% CI	Likelihood ratio if negative[a]	95% CI
HbA1c 39–47 mmol/l (5.7–6.4%) vs. <39 mmol/mol (5.7%)	7.2	5.9–8.8	4.1	3.9–4.6	0.57	0.51–0.61
Male vs. female	1.8	1.5–2.2	1.2	1.1–1.3	0.83	0.72–0.93
BMI >29.5 vs. ≤29.5[b]	1.4	1.2–1.7	1.4	1.2–1.5	0.74	0.66–0.82
All 3 of above risk factors			6.5	5.5–7.8	0.35[c]	0.29–0.41

CI, confidence interval and BMI, body mass index.
[a] Mutually adjusted for all other predictors in the model.
[b] Median.
[c] All 3 risk factors negative.

models. The likelihood ratios show that, if HbA1c 5.7–6.4%, male sex and BMI > 29.5 were all present then the odds of IFG was 6.5 (95% CI 5.5–7.8) times as high as the pre-test odds. The negative likelihood ratios show that, if none of these three risk factors were present, then the odds of IFG was 0.35 (95% CI 0.29–0.41) times as high as the pre-test odds. Thus considering other risk factors as well as the HbA1c substantially improved the diagnostic accuracy of screening for IFG. After adjustment for HbA1c, no other risk factors were independently associated with T2DM.

6. Discussion

The biochemical definitions of 'pre-diabetes' and T2DM are important both for screening policies and in the detection of 'at risk' groups for diabetes prevention. In keeping with other recent studies [9,10], we found that HbA1c was generally insensitive in diagnosing IFG and T2DM, based on previous fasting glucose criteria [5], with a false negative rate ranging from 37% (lower limit HbA1c threshold: 39 mmol/mol (5.7%)) to 78.6% (lower limit HbA1c threshold: 43 mmol/mol (6.1%)) for IFG, and of 39.5% for T2DM.

The United Kingdom's National Health Service recently introduced a primary care-based Vascular Health Check [19], a population-based diagnostic screening programme for vascular risk factors targeted at all adults aged 40–74 years with a BMI > 30 kg/m^2, or with other risk factors including a high fasting plasma glucose. Those with FPG 6.0–6.9 mmol/l or HbA1c 42–47 mmol/mol (6.0–6.4%) are classified as having ''non-diabetic hyperglycaemia'', and those with FPG ≥ 7.0 mmol/l or HbA1c ≥ 48 mmol/mol (6.5%) are classified as having ''probable diabetes''. Our data suggest that screening with HbA1c, using UK Vascular Health Check criteria, would fail to detect 70% of people with IFG as currently defined by ADA (that is, sensitivity = 30%, Table 2), indicating that the Vascular Health Check HbA1c threshold for ''non-diabetic hyperglycaemia'' should be reduced, if this programme continues. One of the issues raised by these data is the clinical issue of diabetes and vascular risk estimates already given to people with IFG based on existing fasting glucose data. These subjects may not fall into one of the newer HbA1c based criteria for 'pre-diabetes'. It is possible that the shift to categorization of glycaemic thresholds by HbA1c will shift patients from a pre-diabetes diagnosis based on glucose to a lower risk category, which may be a complex process to explain clinically. In addition, people with IFG and IGT can be given relatively accurate estimates of annual risk of transition to T2DM based on existing glucose data, but at the moment transition rates across the HbA1c diagnostic categories are unknown.

Using both HbA1c and IFG for screening together could increase diagnostic accuracy [20,21], but would be more costly. Combining HbA1c data with other risk factor data increases the positive likelihood ratios (Table 4), compared to the corresponding likelihood ratios for HbA1c considered alone (Table 2).

The likelihood ratios from this study can be used to estimate the probability, after testing, that an individual has IFG or diabetes [17]. There was inevitably a trade-off between sensitivity and specificity as the HbA1c threshold was varied. The main problem with low sensitivity is that people who would benefit from intervention would be missed and may be falsely reassured. On the other hand, the main drawback of a screening test with low specificity is that more people without the condition need to have a second, confirmatory, test which increases the cost of screening, and may unnecessarily create anxiety in people who turn out not to have the condition.

It was beyond the scope of this study to assess whether HbA1c or FPG are better predictors of impaired glucose tolerance or complications of diabetes. In epidemiologic studies in which FPG and A1c were both evaluated, FPG is a poor predictor of microvascular and macrovascular complications compared to HbA1c [22,23], and these findings further demonstrates the lack of concordance between HbA1c and some glucose based criteria for impaired glycaemia.

These data add to the literature on HbA1c in screening for diabetes and 'pre-diabetes', in a largely white European population at modestly increased risk of Type 2 diabetes. It provides original evidence about the accuracy of HbA1c in screening for IFG. A strength is that the study population was a community-based population. A limitation is that the study was carried out in one county in England, amongst individuals at moderate risk of T2DM who responded to an invitation to screening, and so may not be generalisable to other populations. Previous studies have shown how different prevalence estimates amongst different ethnic groups can dramatically affect sensitivity and specificity, for example [24,25]. However, it is precisely individuals such as our study population who would be expected to take part in a UK screening programme.

Also, these findings could be applied to other populations by modelling, using alternative prevalence estimates [17].

Conflict of interest

There are no conflicts of interest.

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