The use of glucose measurements to improve screening for diabetes in clinical practice

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Abstract

Introduction: It is estimated that 4 million people will be living with diabetes in England by 2025. It is imperative that we can accurately identify people at risk of diabetes and target interventions to prevent its development.
Aim: To determine whether the addition of glucose measurements to the Leicester Risk Assessment Score (LRAS) improves the prediction of $HbA_{1c} \geq 42$mmol/mol (6.0%) compared with a risk score alone, and reduces the number requiring additional tests to determine their glycaemic status.
Method: LRAS and HbA_{1c} were assessed in 484 participants (aged 40–80 years). 184 participants recruited directly from primary care underwent a fasting glucose measurement while 300 participants recruited through advertisement to the general public attended for a random capillary glucose.
Results: A LRAS of ≥ 17 had a sensitivity of 79.6% and specificity of 60.1% to predict the HbA_{1c} value of ≥ 42 mmol/mol (6.0%). The addition of a fasting glucose to the LRAS improved the explained variation in HbA_{1c} from 20.8% with a risk score alone to 46.7%. In addition the number of people requiring further assessment of their glucose status was reduced from 43.8% to 33.2%. The addition of a random capillary glucose to the LRAS did not significantly improve the model.
Conclusions: The addition of a fasting blood glucose, but not a random capillary glucose, to the LRAS improves the prediction of $HbA_{1c} \geq 42$mmol/mol (6.0%) and reduced the number of people who would need further diagnostic testing for diabetes.

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Introduction

The past year has seen the launch of the National Diabetes Prevention Programme which aims to identify those at risk of diabetes early, and to undertake trials of preventative interventions. An efficient screening programme which will identify people at risk of diabetes who should be targeted for preventative intervention is needed. There are unresolved issues around the identification of those at future risk of diabetes, but one option recommended by the National Institute for Health and Care Excellence (NICE) is to use glycated haemoglobin (HbA_{1c}).[1] This approach is controversial, but it would avoid the issue of poor repeatability and inconvenience of the oral glucose tolerance test which has dogged the area for many years. There is a growing body of evidence around the use of HbA_{1c} in diagnosis and screening for diabetes.[2-5] The NICE guidance on diabetes risk identification and prevention and the Public Health England report on diabetes prevention recommend the use of an HbA_{1c} value of 42–47 mmol/mol (6.0–6.5%) to denote those at increased risk of future diabetes.[5,6] A recent health technology appraisal concluded it may also be the most cost-effective blood test.[7]

Despite the convenience of using HbA_{1c} as a screening tool, universal screening of the adult population by HbA_{1c} will be too expensive and will exceed capacity within the NHS, and so an inexpensive pre-screening test is needed.[7] Currently, screening is via a number of risk stratification scores which make use of simple non-invasive clinical data.[8-12] Nevertheless, despite pre-screening by these methods, a significant proportion (up to 50%) of the adult population would still need further blood testing.[9] Any further simple testing which could screen out larger numbers may represent a significant financial saving to the NHS. In this project, we explore the most efficient method of predicting an $HbA_{1c} \geq 42$ mmol/mol (6.0%) in order to minimise the numbers who need to proceed to further diabetes testing by HbA_{1c}.

Methods

Participants were recruited if they were aged 40–80 years and were not known to have diabetes. The results presented here were drawn from two separate study groups.

The first group was recruited directly from a GP list. The practice contacted registered patients who fulfilled the recruitment criteria listed above. With a single contact letter the positive response rate was 38%. Participants attended the Wellcome Clinical Research Facility at Southampton General Hospital. Information which allowed calculation of the Leicester Risk Assessment Score (LRAS) was collected: age, gender, ethnicity, family

Figure 1. Components of the Leicester Risk Assessment Score

Parameter		Score
Age	40-49	0
	50-59	5
	60-69	9
	70-75	13
Sex	Male	0
	Female	1
Ethnicity	White	0
	Other	6
First degree family history of type 2 DM	No	0
	Yes	5
Waist circumference	<90	0
	90-99	4
	100-109	6
	≥110 cm	9
Body Mass Index	<25	0
	25-29	3
	30-34	5
	≥35	8
Anti-hypertensive medication of high blood pressure	Yes	0
	No	5

Table 1 Clinical characteristics of participants

	Registered primary care patients	General population
Number (number female)	184 (102)	300 (218)
Median age (y) (range)	58.5 (41–80)	54.5 (40–79)
Ethnic groups		
White European	165	284
South Asian	11	8
African-Caribbean	2	4
Other	5	4
Body Mass Index (mean ± SD) kg/m²	28.2 ± 5.1	28.0 ± 6.2
HbA$_{1c}$ mmol/mol, mean ± SD (range)	39 ± 5 (23–62)	34 ± 5 (11–57)
DCCT %, mean ± SD (range)	5.7% ± 0.5 (4.3–7.8)	5.3% ± 0.4 (3.2–7.4)

history of diabetes, waist circumference, body mass index, and history of antihypertensive treatment. A copy of the score is shown in Figure 1. This group then underwent venous blood sampling for measurement of fasting blood glucose (FBG) by the Beckman Coulter Hexokinase method and HbA$_{1c}$ by Sebia capillary electrophoresis in the pathology department at University Hospital Southampton.

The second group was recruited by advertisement to the general public and by the same inclusion criteria as the first group. This group had the same demographic and anthropometric measurements collected to allow calculation of the LRAS. HbA$_{1c}$ and random capillary blood glucose (CBG; Abbott Freestyle meter) were then measured. In this cohort, haemoglobin (Hb) was also measured to assess the relationship between Hb and HbA$_{1c}$ in a general cross section of the adult population.

Statistical analysis
The results from both groups were initially pooled to validate the performance of the LRAS in predicting an HbA$_{1c}$ of ≥42mmol/mol (6.0%). A sensitivity of 80% was taken as an acceptable benchmark in the context of diabetes screening, and the values closest to that target were assessed in terms of associated specificity and sensitivity. Subsequently, the impact of the FPG from the first group and the CBG from the second group were assessed in terms of change in numbers screening positive while maintaining a sensitivity as close as possible to 80%.

Diagnostic accuracy was measured by sensitivity (the detection of those participants who truly had a HbA$_{1c}$ ≥42 mmol/mol (6.0%)) and specificity (the detection of the participants with HbA$_{1c}$ <42 mmol/mol (6.0%)). Overall diagnostic accuracy was measured by the likelihood ratio positive (sensitivity divided by 1 minus specificity) and the Youden index (sensitivity + specificity - 100%).[13] Linear regression modelling y= a +b1 x1+ b2 x2 was used to determine the relationship of y= HbA$_{1c}$ to covariates x1=LRAS and x2=FBG (first group) or CBG (second group). The importance of the covariate x2 was determined with the increase of R2 when the covariate was added to the model. Here R2 stands for the percentage variance in HbA$_{1c}$ (y) explained by the model. The higher the increase, the more important is the covariate.

The area under the receiver operating curve (ROC) was used to compare models.

Results
Study subjects
A total of 184 individuals were studied in the practice based group and 300 in the general population group. The participant characteristics are shown in Table 1.

Performance of LRAS
In the pooled study group of 484 individuals, linear regression with HbA$_{1c}$ as the dependent variable and LRAS as the explanatory variable returned an R2 value of 20.3%. To examine the relationship in more detail, the sensitivity, specificity and numbers screening positive were calculated (Table 2). A LRAS value of ≥17 was associated with a sensitivity closest to 80% and was therefore adopted as the benchmark in subsequent comparisons.
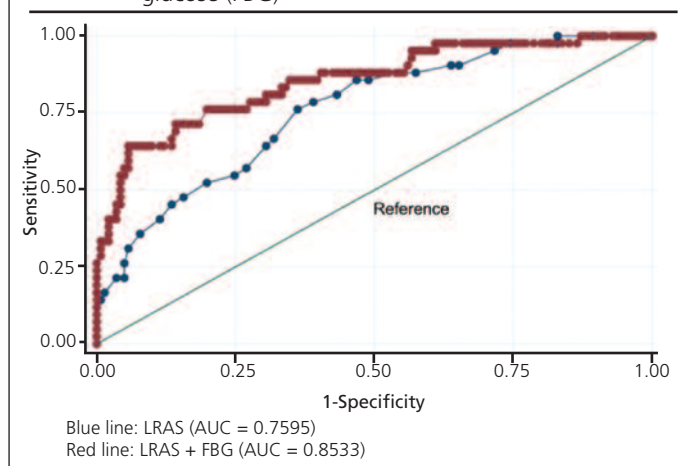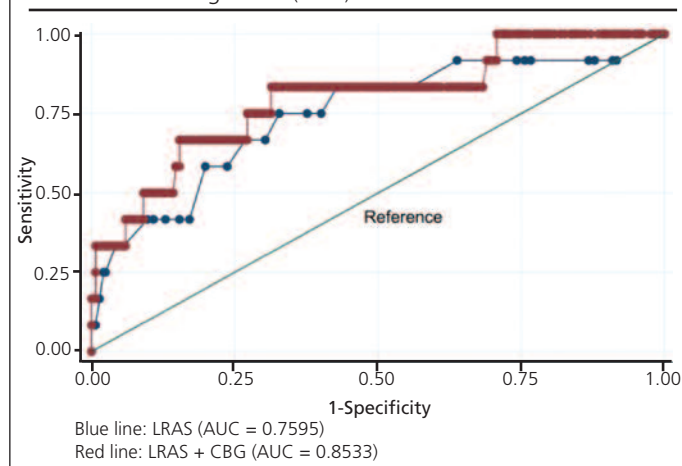
Performance of FBG and LRAS
In the practice based group, linear regression of HbA$_{1c}$ as dependent variable against the LRAS as predictor returned an R2 of 20.8%. The combination of the LRAS and FBG increased this value to 46.7%. Table 3 shows that the diagnostic accuracy as measured by the Youden Index and likelihood ratio positive is highest for LRAS ≥17 and FBG ≥ 5.3 mmol/L. Combining the result of LRAS ≥17 and FBG ≥ 5.3 mmol/L, the sensitivity to predict an HbA$_{1c}$ value of ≥ 42 mmol/mol (6%) was only marginally reduced at 76.2% but the numbers screening positive were reduced from 43.8% to 33.2% (Table 3). The area under the ROC curve was significantly increased from 0.76 to 0.85 by the addition of a FBG to the LRAS (p=0.0019) (Figure 2).

Table 2 Predictive performance of the Leicester Risk Assessment Score (LRAS) alone in screening for HbA$_{1c}$ of ≥42 mmol/mol (6.0%) in the combined groups

LRAS	Sensitivity (%)	Specificity (%)	% to screen	Likelihood ratio	Youden Index (%)
≥15	85.2	55.1	49.2	1.7	40.3
≥16	83.3	57.7	46.7	2.0	41.0
≥17	79.6	60.1	43.8	2.0	39.7
≥18	77.8	65.2	39.5	2.2	43.0
≥19	74.1	67.5	37.0	2.3	41.6

Table 3 Predictive performance of combined Leicester Risk Assessment Score (LRAS) at ≥17 with a fasting blood glucose (FBG) in screening for HbA$_{1c}$ of ≥42 mmol/mol (6.0%) in patients registered in primary care

	Sensitivity (%)	Specificity (%)	% to screen	Likelihood ratio	Youden Index (%)
LRAS ≥17 and FBG 5.2 mmol/L	81.0	55.4	40.2	1.8	36.4
LRAS ≥17 and FBG 5.3 mmol/L	76.2	79.6	33.2	3.7	55.8
LRAS ≥17 and FBG 5.4 mmol/L	69	80.1	30.6	3.5	49.1

Figure 2. Receiver operating characteristics curve predicting HbA$_{1c}$ >42 mmol/mol using Leicester Risk Assessment Score (LRAS), and LRAS + fasting blood glucose (FBG)

Blue line: LRAS (AUC = 0.7595)
Red line: LRAS + FBG (AUC = 0.8533)

Figure 3. Receiver operating characteristics curve predicting HbA$_{1c}$ >42 mmol/mol using Leicester Risk Assessment Score (LRAS) with and without capillary blood glucose (CBG)

Blue line: LRAS (AUC = 0.7595)
Red line: LRAS + CBG (AUC = 0.8533)

Performance of random CBG and LRAS

In the general population group, the utility of using a random finger prick CBG value to predict a HbA$_{1c}$ value of ≥42 mmol/mol (6%) was explored. Again, linear regression of HbA$_{1c}$ result against LRAS returned an R2 value of 16.0%. Addition of the CBG as predictor variable increased this value to 19.0%. There was a non-significant increase in the area under the ROC curve (Figure 3) from 0.75 to 0.80 (p=0.2286), showing no significant benefit by adding a random CBG to the LRAS.

Simple correlation of the HbA$_{1c}$ value against Hb demonstrated a weak positive correlation (r=0.16, p=0.005). However, inclusion of the Hb value in the regression equation with LRAS as a predictor of HbA$_{1c}$ did not significantly change the model statistics.

Discussion

The consensus in diabetes screening is that there is value in screening the adult population for diabetes although clear evidence for long term benefit is presently lacking.[14] Although NICE published guidance on prevention of diabetes, it stopped short of advocating a universal screening programme.[5] Nevertheless, the recent proposal from NHS England to fund diabetes prevention opens the topic for review once again as it will be important to detect those at risk for targeted preventative strategies.[15]

For the purposes of this study we have used the absolute value of HbA$_{1c}$ recommended by NICE and NHS England as the marker of glucose dysregulation. Traditionally, diabetes or prediabetes have been defined by glucose measurements based on a substantial body of evidence.[1,16] However, there is also consid-

erable support for the use of HbA$_{1c}$ as a predictor of both microvascular and macrovascular disease.[17-19] Measurement of HbA$_{1c}$ has practical advantages over the use of glucose measurements. It need not be taken on a fasting sample, is stable during transport to the laboratory and measurement is now subject to a recognised standard. For these reasons, we have opted to use HbA$_{1c}$ for screening in this report. At a cut-off point of 42 mmol/mol (6.0%), the relative risk of vascular disease is approximately 1.5 and retinopathy becomes apparent. The Epic-Norfolk trial demonstrates that 36% of cases of incident diabetes are detected in the 6% of the population with an HbA$_{1c}$ in the range 42–47 mmol/mol (6.0–6.5%) over a 3-year period.[3] It is also important to note that the screening uptake is likely to be significantly higher with the use of HbA$_{1c}$ rather than alternative testing such as an oral glucose tolerance test.[7]

The accepted method for pre-screening for diabetes is by the use of simple risk scores. This is supported by a recent health technology appraisal as universal screening is likely to exceed capacity and not be cost effective unless the prevalence of diabetes in the population is particularly high.[7] For the purposes of this work, we have used the LRAS as it is published and validated in the UK, returns a numerical score which can be handled statistically and is commonly in use, forming the basis of the diabetes risk score on the Diabetes UK website. We have validated the use of the LRAS to detect the target HbA$_{1c}$ value in our combined study population, finding a value of ≥17 to be optimal with a sensitivity closest to the target value of 80%. In the original work from Leicester, UK, a cut-off point of 16 was found to be the best fit to detect any glucose dysregulation.[8] Their study population was considerably larger and ethnically more diverse, and these factors may account for the small difference. The optimal LRAS cut-off point of >13 quoted in the Public Health England report is markedly different from those reported here. The reasons for this relate to the fact that their data were taken from the Health Survey for England, and therefore included all individuals over the age of 16 years.[6] Furthermore, data on family history of diabetes were not available as part of that survey and were set to null. As the purpose of that report was to compare different risk scores, the setting of family history to null for all scores did not affect the comparison between them. However, both of these factors skewed the distribution for the results of the LRAS markedly to the left. For the purposes of this study we have used the cut-off point of 17 as the reference.[6]

The use of the LRAS at a cut-off point of 17 will screen out approximately 57% of the population from further investigation. Nevertheless, the measurement of HbA$_{1c}$ for 43% of the adult population at a unit cost to the NHS of approximately £4.04,[20] together with clinical and administrative staff time, would be expensive. We therefore examined whether any other measurements could reduce the numbers needed to screen. Unsurprisingly, measurement of a laboratory FBG performed well as a predictor of HbA$_{1c}$ and, in combination with the LRAS, screened out a further 10% of the population from further testing. We found a FBG level of 5.3 mmol/L to be the best fit with a sensitivity closest to 80%. This figure is lower than the figure

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Key messages

- The addition of a fasting blood glucose to a Leicester Risk Assessment Score improves the prediction of HbA$_{1c}$ compared with a risk score alone
- This has the potential to reduce numbers requiring further tests to determine glycaemic status
- A random capillary glucose was not found to be valuable when used in conjunction with a diabetes risk assessment score

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of 5.6 mmol/L derived in a study designed to detect impaired glucose tolerance using an oral glucose tolerance test.[21] This discrepancy underscores the problems encountered when trying to find equivalence between the various categorical definitions of diabetes and glucose regulation. Despite these findings, use of FBG is not practical as a screening tool as it is less convenient for patients and requires a high volume of early morning appointments in primary care. However, it provides proof of concept that glucose measurements can screen out significant numbers from further testing. As a lower cost option, a random CBG was modelled. Unfortunately this did not improve the model in terms of screening out individuals from further testing. This would agree with the work of others who looked at this previously, albeit with a view to predict diabetes diagnosed by glucose testing.[22,23]

In this study we have confirmed that there is a weak association between HbA$_{1c}$ and Hb. This has been a subject of discussion in the debate over the validity of HbA$_{1c}$ measurement in the diagnosis of diabetes, particularly as it is known that various anaemias can affect the HbA$_{1c}$ result.[24,25] In this study, the association was weak and was not found to be a significant factor in prediction of HbA$_{1c}$ when included with the various other factors included in diabetes risk scoring.

In conclusion, we have confirmed that current risk factor based screening for diabetes and prediabetes can be useful in screening out over 50% of the population from the need for further testing. At present, use of risk scoring using simple clinical data remains the gold standard. However, we have demonstrated that glucose measurements have the potential to screen out further significant numbers, but random glucose measurement has little value.

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