Screening for diabetes and hyperglycaemia: A retrospective study

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Article points

1. This study was undertaken to determine the most appropriate strategy for diabetes screening in North Cornwall.
2. The sensitivities and specificities of three methods (fasting plasma glucose [FPG], random plasma glucose and the 2-hour oral glucose tolerance test) were compared.
3. In this study population, the authors recommend use of the FPG test as an initial screening and diagnostic test.

Key words

- Impaired fasting glucose
- Impaired glucose tolerance
- Screening

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Random plasma glucose (RPG), fasting plasma glucose (FPG) and oral glucose tolerance tests (OGTTs) are three screening methods currently in use for the detection of type 2 diabetes and non-diabetic hyperglycaemic conditions such as impaired fasting glucose and impaired glucose tolerance. Despite increasing prevalence rates of type 2 diabetes, there is still no clearly defined screening method with which to detect those at high risk of this condition. This study aimed to compare the sensitivity and specificity of RPG, FPG and 2-hour post-glucose-load tests against the 'gold standard' OGTT, and to consider the relative practicalities of these procedures. Furthermore, it aimed to investigate patient characteristics that may improve the performance of these screening tests.

Type 2 diabetes mellitus (T2DM) is a common chronic disease leading to characteristic complications, and diabetes reduces life expectancy by 8 years when diagnosed in middle-aged adults (Roper et al, 1998). Currently in the UK about 1.8 million people are known to have diabetes, and the majority have T2DM. It has been estimated that the number of cases will rise to 3.0 million by the year 2010, as a result of increasing rates of prevalence and diagnosis (Diabetes UK, 2004). It is also recognised that T2DM is now occurring at a younger age, and this may be at least in part because of obesity in children and young adults becoming more commonplace.

It is now well established that both the microvascular and macrovascular complications of T2DM can be reduced considerably by effective treatment to reduce blood glucose levels and to control risk factors for macrovascular disease (UK Prospective Diabetes Study [UKPDS] Group, 1998a; UKPDS Group, 1998b; Adler et al, 2000; Stratton et al, 2000). These findings underline the need to detect T2DM as early as possible. The earlier that interventions are offered, the greater the potential to reduce the impact of complications such as blindness, end-stage renal failure and foot disease.

Historically, the majority of people with T2DM presented with typical symptoms of diabetes, such as weight loss, tiredness, excessive thirst, polydipsia and polyuria. However, in the authors' experience, in recent decades, with the more widespread availability of blood and urine tests, the introduction of routine health checks, and the rising awareness that T2DM is often asymptomatic, increasing numbers of asymptomatic patients are being identified.

Significantly, it has also been demonstrated that the development of T2DM can be reduced considerably by lifestyle interventions such as weight loss, improvements in diet and increases in physical exercise, either alone or in combination with drugs such as metformin and orlistat (Pan

et al, 1997; Tuomilehto et al, 2001; Knowler et al, 2002; Torgerson et al, 2004). These studies were performed in individuals at increased risk of T2DM due to impaired glucose tolerance (IGT), obesity or both. The potential implications of these studies are far-reaching and raise the question of whether the identification of categories of non-diabetic hyperglycaemia, such as IGT and impaired fasting glucose (IFG), should be considered for intervention as part of any population strategy to control the spread of T2DM.

Furthermore, it has been questioned whether it would be appropriate to screen routinely in order to detect T2DM earlier in its natural history, perhaps including the identification of IGT or IFG. This has been, and remains, a subject of controversy, since the resource implications of population screening are huge. In deciding the most appropriate course of action, it would be helpful to answer two key questions. Firstly, which test(s) are most appropriate in screening for T2DM, and, secondly, should screening be applied to the whole population or targeted at high-risk groups? This study was undertaken to determine the most appropriate strategy for diabetes screening in North Cornwall, by comparing the sensitivities and specificities of three methods in widespread use for screening for T2DM and non-diabetic hyperglycaemia – fasting plasma glucose (FPG), random plasma glucose (RPG) and the 2-hour oral glucose tolerance test (OGTT). It also investigated patient characteristics that may allow these tests to be better targeted at high-risk individuals. A national screening committee has also been assessing these questions, but has not yet reported.

Methods

Design and participants

The research was approved by the local research ethics committee, and a retrospective, observational study was performed. The participants included were drawn from a 100% Caucasian population registered with a rural general practice in North Cornwall, England. The practice population was 4720 people and an audit in 2003 demonstrated a diabetes prevalence rate of 3.7% (n=176). Of these, 155/176 (88%) had T2DM and the remaining 21/176 (12%) had type 1 diabetes.

People considered to be at high risk of T2DM, but who were asymptomatic, were tested opportunistically with an initial RPG test to diagnose diabetes (based on the 2-hour plasma glucose cut-off of 11.1 mmol/l in an OGTT; World Health Organization [WHO], 1999) which was followed by an OGTT within the following 6 months. The OGTTs were carried out between May 2001 and August 2003.

Inclusion criteria were:

- body mass index (BMI) >27 kg/m^2
- family history of T2DM
- history of ischaemic heart disease (IHD), stroke, transient ischaemic attack or peripheral vascular disease
- dyslipidaemia
- hypertension
- medication including a statin or steroids.

The main exclusion criterion was the presence of osmotic symptoms (i.e. symptomatic diabetes). A retrospective computer search identified 97 patients who met the inclusion criteria and 64 patients were included in the study after the application of exclusion criteria. Characteristics of the study population can be seen in *Table 1.*

Clinical methods

Venous blood samples were collected and plasma glucose levels were measured routinely using the hexokinase enzymatic method (Neese, 1982). Lipid profiles performed at the time of the RPG measurement were also recorded. A follow-up OGTT was performed using WHO guidelines

Table 1. Participant characteristics (n=64).

Gender (% of participants)	Male 65.6, female 34.4
Current or ex-smoker (%)	47
Age (years)	64.4 ± 10.7
Weight (kg)	87.4 ± 19.1
Height (cm)	169.9 ± 9.6
Body mass index (kg/m^2)	30.3 ± 5.3
Family history of diabetes (%)	27.1
Treated hypertension (%)	59
Treated hypercholesterolaemia (%)	31

Data for continuous variables given as mean ± standard deviation

Table 2. Definitions (from Wikipedia, 2006a; 2006b).

Sensitivity
'The sensitivity of […] a test is the proportion of […] cases having a positive test result [out] of all positive cases […] A sensitivity of 100% means that all sick people […] are recognized as such.'

Specificity
'Specificity is the proportion of true negatives of all the negative samples tested […] For a test to determine who has a certain disease, a specificity of 100% means that all healthy people are labeled as healthy.'

Page points

1. On the basis of both time points of the oral glucose tolerance test (OGTT), 23/64 (35.9%) participants had type 2 diabetes.
2. Of these, ten exhibited diabetic levels on both the fasting plasma glucose test and the 2-hour value in the OGTT.
3. In addition to the 23 people with type 2 diabetes, a further 19/64 (29.7%) were found to have impaired fasting glucose or impaired glucose tolerance.

(WHO, 1999). The OGTT results provided information on FPG and 2-hour post-glucose-load levels (2-hour OGTT). WHO criteria for the OGTT specify an FPG level >7.0 mmol/l or a 2-hour post-glucose-load level of >11.1 mmol/l as indicative of diabetes (WHO, 1999). The majority (>60%; n=40/64) of participants had their OGTT within 4 weeks of the original RPG test. Risk factors for T2DM were identified from medical records, along with additional information on concurrent drug treatment.

Statistical methods

Data were analysed using the software Statistical Package for Social Sciences (SPSS; SPSS UK, Woking) version 11.5. Continuous variables that were normally distributed were described with means and standard deviations. Continuous data were compared, between groups, using the non-paired *t*-test. Categorical data were compared using the Chi-square test or Fisher's exact test, as appropriate. Statistical significance was defined as $P<0.05$ (two-tailed). Receiver operating characteristic ('ROC') curves were generated, and sensitivities and specificities of RPG, FPG and 2-hour values on OGTT were determined, with reference to OGTT as the 'gold standard'.

Results

Detection of diabetes and non-diabetic hyperglycaemia

On the basis of both time points of the OGTT, 23/64 (35.9%) participants had T2DM. Of these, ten exhibited diabetic levels on both the FPG test and the 2-hour value in the OGTT. Fourteen people exhibited diabetic levels on the FPG test and another nine on the 2-hour value alone. Only seven (30.4%) of these 23 were found to have diabetic glucose levels with the RPG test alone. Moreover, the RPG test failed to detect 10/14 (71.4%) of people found to have diabetes with the FPG test. The very poor performance of the RPG test in detecting diabetes is illustrated in *Figure 1*, which shows how this test missed most people with 2-hour plasma glucose >11.1 mmol/l on OGTT.

In contrast, the FPG test detected more patients with T2DM than RPG, so that it detected 14 out of 23 (60.9%) patients correctly. The good performance of the FPG method in detecting diabetes is shown in *Figure 2*.

In addition to the 23 people with T2DM, a further 19/64 (29.7%) were found to have IFG or IGT. Of these, 3/64 (4.7%) had IFG, 9/64 (14.0%) had IGT and 7/64 (10.9%) were identified as having a combination of both IFG and IGT. Obviously, the RPG test was not able to classify non-diabetic hyperglycaemic states.

Sensitivity and specificity of RPG and FPG

Sensitivity and specificity (see *Table 2* for definitions) in detecting T2DM were determined for RPG, FPG and 2-hour post-glucose-load tests across a range of cut-off values (data not shown). The values for an RPG of >11.1 mmol/l show a high specificity of 95.0% but a very low sensitivity of 17.4%. At a lower RPG value, the sensitivity increases but the specificity falls; for example, with a T2DM cut-off at 7.8 mmol/l the specificity was 41.5% and the sensitivity 69.6%.

In contrast, an FPG cut-off at >5.5 mmol/l showed a specificity of 58.5% and a sensitivity of 91.3%. Using a T2DM detection cut-off at >6.0 mmol/l the FPG test had a specificity of 75.6% and a sensitivity of 87.0%, while an FPG cut-off at >6.65 mmol/l had a specificity of 97.6% and sensitivity 69.6%. This demonstrates that even with a high detection rate, the FPG is less likely than the RPG to give false negatives or positives and therefore performs better as a screening tool. A comparison of the specificity and sensitivity of the RPG,

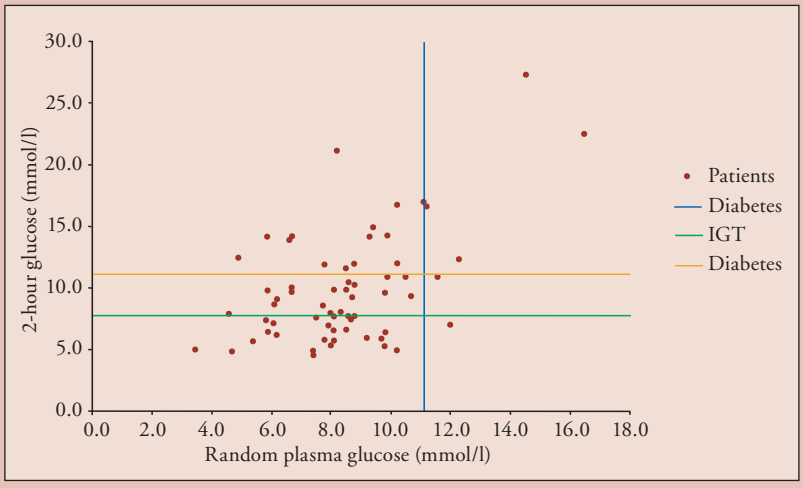


Figure 1. Scatterplot of RPG versus 2-hour glucose on OGTT. Categories of glucose tolerance are shown by the coloured lines. The majority of people with type 2 diabetes are missed by the RPG test. (IGT = impaired glucose tolerance; OGTT = oral glucose tolerance test; RPG = random plasma glucose.)

FPG and 2-hour post-glucose-load tests can be seen in the ROC curve in *Figure 3*.

Patient characteristics that can improve performance of screening tests

BMI was higher in the people with diabetes (P=0.02). Additionally, of borderline significance, HDL-cholesterol was lower (P=0.05) and age was higher (P=0.06) in those with diabetes compared to those without. Although not found to be statistically significant in this study, almost twice as many people with diabetes (41.7%) had a family history of T2DM compared to those without diabetes (22.2%) and current or former smoking was more common in the group with diabetes (61.1%) compared to those without (41.5%).

Characteristics were also compared in those found to have diabetes and those with non-diabetic hyperglycaemia. Although none of the characteristics were significantly different, BMI approached significance (P=0.07): the people with diabetes had a higher mean BMI of 32.6kg/m^2 compared to a mean of 29.7kg/m^2 in the IGT/IFG group. In those with diabetes the mean HDL-cholesterol level was lower, age was higher and family history of diabetes was more common than in the IGT/IFG group. These findings were not statistically significant, perhaps on account of small sample size. In addition, almost twice as many people with diabetes were current or former smokers compared to the IFG/IGT group.

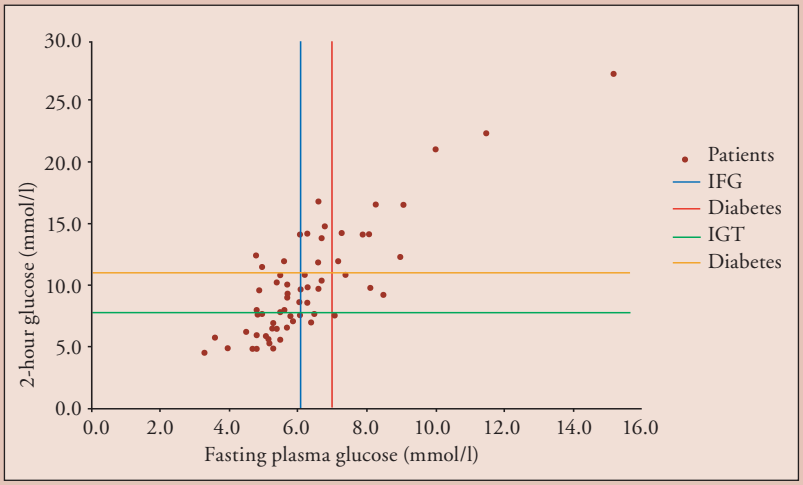
Discussion

This study has demonstrated major differences in the sensitivity, specificity and acceptability of RPG, FPG and 2-hour OGTT tests when screening for diabetes and non-diabetic hyperglycaemia. FPG testing compared favourably with 2-hour OGTT as a screening tool for T2DM, whereas the RPG test was unacceptable. Although RPG is cheap and easy to perform opportunistically, it only performs satisfactorily at much higher levels of blood glucose and so would be more appropriately used as a diagnostic tool for symptomatic patients; in our opinion it should not be used as a screening tool for asymptomatic patients. With the RPG, 2/7 (28.6%) results >11.1mmol/l were false positives who subsequently were not found to have diabetes, further emphasising the inadequacy of RPG in screening for T2DM in asymptomatic people.

Thus, although very convenient, the major disadvantage of the RPG is that it has unacceptably poor specificity and sensitivity. This study suggests that RPG should not be used as a screening tool in asymptomatic individuals.

Although the complete OGTT (i.e. both the fasting and 2-hour tests) remains widely used, its poor reproducibility is a well-recognised limitation (Ko et al, 1998). Nevertheless, it can also be used to identify patients with IFG and IGT. The state of IGT now has assumed increased significance for the identification of individuals who will benefit from interventions for diabetes prevention (Tuomilehto et al, 2001; Knowler et al, 2002).

Lastly, it might be asked whether a 2-hour OGTT time point could be used in isolation



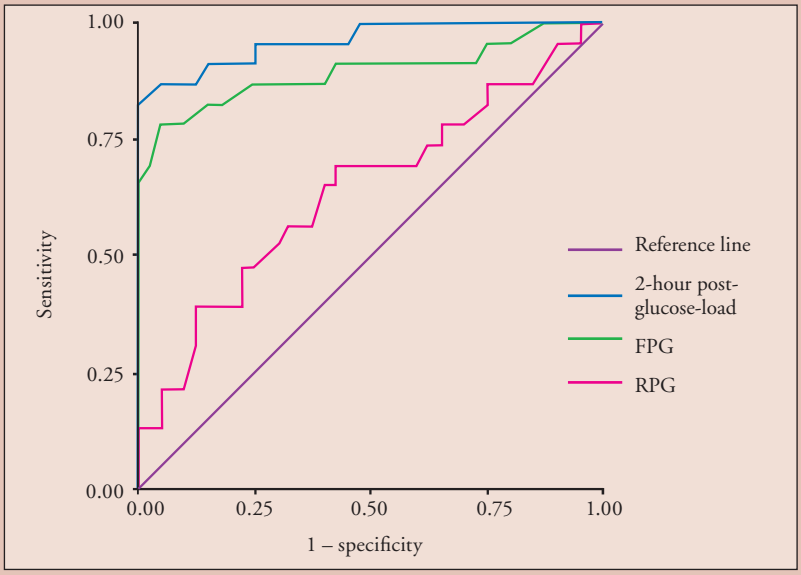


Figure 2 (top). Scatterplot of FPG versus 2-hour glucose on OGTT. The various categories of glucose tolerance are shown by the coloured lines. The majority of people with type 2 diabetes are detected by the FPG test.
Figure 3 (above). Receiver operating characteristic curve demonstrating the sensitivity and specificity of RPG, FPG and 2-hour OGTT tests. The total area under each line denotes how well each test performs. The reference line represents 'chance'. (Abbreviations: FPG = fasting plasma glucose; IFG: impaired fasting glucose; RPG: random plasma glucose; OGTT = oral glucose tolerance test.)

Page points

1. An alternative to a single-testing strategy is a stratified policy whereby an initial test is performed, followed by a second if appropriate.
2. It may be possible to improve the performance of screening tests, such as fasting plasma glucose and the oral glucose tolerance test, by targeting them preferentially at higher-risk individuals.
3. The use of a risk score prior to screening, whether by questionnaire or use of data held on computer systems in general practice, would therefore further increase the sensitivity and specificity of the testing.

for the diagnosis of both diabetes and IGT – for example, providing a patient with the 75g glucose load to take home with instructions for the test, and then to attend the surgery only for a 2-hour blood sample. A potential problem with this strategy is unsupervised OGTTs yielding inaccurate results. In Cornwall, a recent audit of 2045 OGTTs identified poor supervision of the test as a problem leading to under- and over-estimation of blood glucose levels at 2 hours, and therefore misclassification, because of patients' unsupervised activities during the test (i.e. eating and physical activity; personal communication, Dr R Fisher, 2006).

An alternative to a single-testing strategy is a stratified policy whereby an initial test is performed, followed by a second if appropriate. Thus, an OGTT might only be performed if the initial investigation was below the diagnostic threshold for diabetes (i.e. <7.0 mmol/l for FPG and <11.1 mmol/l for RPG) but was sufficiently raised to merit further investigation. An appropriate cut-off point for an OGTT may be determined by analysing the sensitivities and specificities of each test and determining both the acceptability of the testing methods and whether the clinician is seeking purely a diagnosis of T2DM or T2DM plus non-diabetic hyperglycaemia.

Risk factors associated with T2DM were increased in people with diabetes compared to those without diabetes. This finding suggests that it may be possible to improve the performance of screening tests, such as FPG and OGTT, by targeting them preferentially at higher-risk individuals who have these risk factors. The use of a risk score prior to screening, whether by questionnaire or use of data held on computer systems in general practice, would therefore further increase the sensitivity and specificity of the testing (Baan et al, 1999; Park et al, 2002; Spijkerman et al, 2002; Smith et al, 2003).

Study limitations

The patients at this rural North Cornwall practice tended to be elderly and were all Caucasian. Clearly, this would mean that the findings may not be directly applicable to areas with different social and ethnic mixes. In multiethnic urban populations in the UK, including Caucasian people, the prevalence of diabetes and hyperglycaemic disorders would be considerably higher (Riste et al, 2001). The sample size in this study was also relatively small at 64 patients. In a larger study, one would expect to see risk factors such as family history of diabetes emerging as significant predictors of T2DM.

The study population was also enriched with people at increased diabetes risk prior to screening – i.e. healthcare professionals had known them to be obese or have dyslipidaemia or IHD. If the study had been performed on unselected patients who simply had an elevated RPG (with or without other risk factors), the sensitivity and specificity of these tests would probably have been lower.

If the clinician wishes to adopt a strategy for IGT detection, so that preventative strategies for diabetes and cardiovascular disease may be adopted, and also has the resources to do this, then more OGTT testing would be required as a FPG alone can not detect IGT. Clearly, whether or not OGTT is to be used will depend on whether a diagnosis of IGT is sought.

Concluding remarks

In conclusion, for the identification of T2DM alone, these results support the use of the FPG method as the initial screening and diagnostic test in this particular population. In individuals who fall short of the criteria for diabetes on the basis of FPG alone, OGTTs could be used selectively. Appropriate FPG cut-off values to trigger an OGTT are debatable; although >6.0 mmol/l is widely used, a level of 5.5 mmol/l is also justifiable. This would provide a more rational approach to screening and a more effective use of limited resources than global use of the OGTT.

In contrast, our results suggest that an RPG test can neither rule in nor rule out a diagnosis of diabetes in asymptomatic individuals and should not be used for this purpose. These data also support the view that individuals' characteristics provide additional predictive information, and therefore that the presence of risk factors may be a useful way to identify high-risk people for FPG screening. While a comprehensive review of the many factors that identify individuals

at increased risk of T2DM, and the optimum interval for screening tests, are subjects beyond the scope of this discussion, based on the findings both of this study and of others, these factors include family history of diabetes in a first-degree relative, membership of a high-risk ethnic group, history of clinical cardiovascular disease (e.g. IHD, stroke or peripheral vascular disease), dyslipidaemia, hypertension, cigarette smoking, and a previous history of gestational diabetes or of polycystic ovary syndrome, particularly in the presence of excessive body weight or obesity. Thus, Diabetes UK has previously suggested a BMI threshold of 25 kg/m^2 in individuals with other risk factors for consideration for screening for diabetes (Diabetes UK, 2002).

More recently, in recognition of the importance of central obesity as a risk factor for diabetes and cardiovascular disease, the International Diabetes Federation has based its definition of the metabolic syndrome on waist circumference >94 cm or >80 cm for men and women of European origin respectively, with lower cut-offs for other ethnic groups (Alberti et al, 2005). It remains to be determined how waist circumference measures will perform as criteria for diabetes screening in the UK. ■

Page points

1. Factors that could help with identifying high-risk people for fasting plasma glucose screening include family history of diabetes in a first-degree relative, membership of a high-risk ethnic group, history of clinical cardiovascular disease, obesity, high waist circumference, dyslipidaemia, hypertension, cigarette smoking and a previous history of gestational diabetes or of polycystic ovary syndrome.
2. It remains to be determined how waist circumference measures will perform as criteria for diabetes screening in the UK.

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