Glycosuric tests should not be employed in population screenings for NIDDM

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Summary

Background The aim was to evaluate self-testing for glycosuria in screening for diabetes mellitus (DM).

Methods All inhabitants aged 45–76 years in the investigation area were invited (3041 individuals). Participants received two foil-wrapped dipsticks and were asked to examine their postprandial urine. Results were marked on the reply card and returned. Test-positive screenees were offered a fasting blood glucose test at the laboratory, as were a random sample of 143 test-negative screenees.

Results The screening detected 15 cases of unrecognized DM. Among 106 test-negative screenees, 3 had DM and 4 had impaired glucose tolerance. Response rate was 76.9 per cent. Sensitivity was 20.80 per cent. Specificity was 99.14 per cent. Positive predictive value was 46.88 per cent. Negative predictive value was 97.17 per cent. Costs per new case of diabetes were 3155 DKK (approximately £332).

Conclusion The test has such a low sensitivity that it cannot be recommended as a screening test. If screening for DM is to be performed, it should not be on the basis of a glycosuric test. At least 11 of the 15 cases of screening-detected diabetes belonged to a risk group, and might have been detected by selective screening. We suggest that screening be carried out in general practice using blood sugar tests on risk groups.

Keywords: screening, diabetes mellitus, glycosuria, risk groups

Introduction

The total number of people with non-insulin-dependent diabetes mellitus (NIDDM) in Denmark (1990) is estimated to be 80 000–100 000, but 20 000–30 000 of these patients have disease which is unrecognized.1 The period of latency before diagnosis is at least 4–7 years,2 in which the individual is exposed to irreversible biochemical effects of hyperglycaemia, leading to the specific micro- and macro-vascular complications of diabetes.3

It has been convincingly demonstrated that people with poorly controlled insulin-dependent diabetes have an increased risk of diabetic complications.4 Such randomized controlled studies are still missing for NIDDM. However, data from several observational studies suggest that hyperglycaemia in NIDDM is associated with an increased risk of early retinopathy,5 nephropathy,6 neuropathy7 and arteriosclerosis.8

It seems likely, therefore, that earlier diagnosis and improved metabolic control are worth while in NIDDM as well as IDDM.

Screening for diabetes mellitus (DM) using glycosuria tests is controversial. The Bedford Population Study9 reported a high false-negative rate of 13.9 per cent, and at present WHO does not recommend urine screening for DM, because of the low sensitivity of the test.10 Other studies have suggested that testing for postprandial glycosuria may have better screening properties than fasting plasma glucose, regardless of the cut-off point for abnormal plasma glucose level,11 and that random urine glucose is fully comparable with random blood glucose12,13 and glycosylated haemoglobin, HbA1c.14,15 It appears that, although the glycosuria tests have a somewhat lower sensitivity than the blood tests, they exhibit a better specificity, thus reaching a higher positive predictive value. Furthermore, they are noninvasive and cheap, and, as shown in the Ipswich population study,16 they can be employed in a self-testing programme, thus perhaps reaching subjects who do not normally visit their family physician. Home has suggested that glycosuria dipsticks should be available free in pharmacies and community centres for people to use to detect unrecognized DM.17 Today the British Diabetic Association recommends testing for postprandial glycosuria as the method of choice for population screening.18

The Ipswich study16 was a population screening for NIDDM based on a postal request system for self-testing for postprandial glycosuria with the Clinistix R dipstick. Results were promising with respect to the test’s specificity and response rate. However, the sensitivity was either 90 per cent or 17 per cent depending on the calculation method, but in both cases the estimate was based on few individuals (namely three cases of impaired glucose tolerance out of a random sample of 50 test-negative screenees), and therefore very uncertain. Thus, the apparently low sensitivity did not seem discouraging in itself. Furthermore, it seemed possible to improve the sensitivity without any major
increase in expenses, partly by using a more sensitive dipstick, partly by testing twice instead of once.

The aim of the present study was to test this method on a Danish population.

Methods

Study population

The National Register provided address lists of all inhabitants aged 45–76 in four parishes in the Municipality of Ringkøbing (3183 persons). A pilot study was performed to test the suitability of the distributed material. This involved 142 persons, leaving 3041 for the main study.

Screening programme

Each person received written information and instructions, a reply card, a stamped addressed envelope, and two foil-wrapped dipsticks. The participants were asked to use the urine dipsticks 1–2 hours after a solid morning or evening meal on two separate days. They were also asked to avoid taking acetyl salicylic acid (ASA) products and vitamin C in the 24 hours before the tests, because these chemicals may cause false negative reactions on the dipstick. Participants were asked to fill in their age and sex, whether they were known to have diabetes mellitus, and whether the dipstick had changed colour when dipped into urine. Individuals who did not return the first reply card received a reminder after three months. The project was publicized in local newspapers, radio, and television. The screening programme was performed from January to May 1993. Permission for the study was obtained from the local ethics authorities.

Choice of dipstick

The dipstick used was Glukotest R from Boeringer-Mannheim GmbH, Mannheim, Germany. The Glukotest R dipstick reaction is based on a glucose oxidase reaction, as is the Clinistix R reaction used in the Bedford study. The indicator in Glukotest R is tetramethylbenzidine, which changes colour from yellow to green when glucose is present. The Clinistix R uses theo-tolidine reaction, which changes from pink to blue in the presence of glucose. In a study that compared five methods of demonstrating glycosuria, including these two, Glukotest R showed the highest chemical sensitivity.

Test-positive participants

Participants who reported change of colour of the dipstick, and who did not have previously known DM, were contacted for a follow-up fasting blood glucose test (capillary ear blood) one week after the reply card was received by the investigators. A parallel study involving individual interviews was conducted to examine the psychosocial consequences of screening. These interviews were carried out after the report of a positive test result, but before the follow-up tests.

The test-positive participants were classified as having diabetes mellitus (DM), impaired glucose tolerance (IGT), or normal glucose metabolism. We employed the diagnostic criteria and procedure as proposed in the current Danish explanatory report and the Danish Medical Compendium. This is based on the 1985 WHO diagnostic criteria, but rounded to the nearest mmol/l. All measurements were based on capillary whole blood. Fasting blood glucose (f-BG) ≤5.0 mmol/l was considered normal. If f-BG was ≥7.0 mmol/l on two consecutive days, the subject was said to have diabetes mellitus. Subjects with f-BG between 5.0 and 7.0 mmol/l proceeded to glucose tolerance test (OGTT). If the 2 hour value was ≥11.0 mmol/l, the diagnosis was DM. If it was between 8.0 and 11.0 mmol/l, the diagnosis was IGT. Subjects with diabetes or IGT were contacted by telephone and letter. They were given general advice about diet, exercise and weight reduction, and were encouraged to contact their family physician for further treatment and follow-up.

Test evaluation

To evaluate the test, a random sample of 143 test-negative participants was selected. They were asked to undergo fasting blood glucose test and OGTT, and they were classified according to the same diagnostic criteria as the test-positive participants. Test-negative screenees with diabetes mellitus were classified as false negative, and those with normal f-BG or IGT were classified as true negative. Test-positive screenees with DM were classified as true positives, and test-positive screenees with normal f-BG or IGT as false positive.

Statistics

The National Register provided data on the age and sex distribution of the population, and the number of individuals who died or moved during the study. Response rates for age and sex were calculated from these numbers, using the x^2 test for trend and Mantel–Haenszel’s analysis of relative risk (RR). The sensitivity, specificity, and predictive value of positive and negative test results were calculated using maximum likelihood estimate, and 95 per cent confidence intervals were based on profile likelihood. This statistical method was chosen because it takes into consideration that the test evaluation was based on a minor proportion (namely 106) of the test-negative screenees.

The costs of the screening were calculated per newly diagnosed case of DM and per screened inhabitant.

Results

Response rates and responders

Of the 3041 inhabitants invited for the main study, 25 died and 21 moved out of the project area during the study period, and 78 reported having known DM. Of the remaining 2917
screenees, 2242 returned the reply card (response rate 76.9 per cent). Thirty-five people without previously known diabetes reported change of colour on one or both dipsticks, and were subsequently offered a follow-up blood test. The blood tests revealed 15 cases with previously unrecognized diabetes, none with impaired glucose tolerance, and 17 with normal fasting blood glucose. Three people did not attend follow-up.

The response rates are shown in Table 1. There was a tendency towards higher response rates with age. The tendency did not increase linearly, but it was statistically significant for men (trend: 6.44, \( p = 0.011 \)) but not for women (trend: 0.011, \( p = 0.917 \)). The rates were highest in the 65–69 (men) and 55–59 (women) year age groups.

Most age groups showed higher participation for women than for men. Stratification analysis shows higher participation rates for women, as the total relative risk (RR) of participating was 1.067 (1.025–1.110), \( p = 0.0015 \).

Test evaluation
Of the 143 dipstick negative responders who were asked to take part in a fasting blood glucose test, 106 (74.1 per cent) accepted: three had diabetes, four had IGT, and 99 had normal fasting blood glucose values. Thus, the test evaluation parameters can be estimated (Table 2).

Costs
The total costs for the screening were 47 330 DKK [stamps 18 844 DKK, urine dipsticks 16 800 DKK, paper and copying 1404 DKK, secretarial expenses 7740 DKK (90 working hours), lists of addresses and labels 596 DKK]. The cost per screenee was 20 DKK (approximately £2.10) and per screening-detected case 3155 DKK (approximately £332).

Discussion
Many false negatives
Of the 106 test-negative individuals, 3 had diabetes and 4 had IGT. This suggests that many cases of diabetes are overlooked by this screening method, and we certainly presume that there were far more than 15 subjects with undiagnosed diabetes among the 2325 responders.

Knowledge about the prevalence of undiagnosed DM is limited, but the Glostrup population study\(^2\) supplies us with prevalence rates of undiagnosed DM among certain age groups from a geographically defined area in Denmark (1088 men and 1059 women). Those without known DM were offered an OGTT, and the prevalence of undiagnosed DM was calculated as 1.5 per cent, 8.0 per cent and 9.0 per cent for men aged 40, 60 and 70 years, respectively, and 0.5 per cent, 6.0 per cent, and 11.0 per cent for women aged 40, 60 and 70 years. Applying these rates to our population gives an estimated number of 147 persons with undiagnosed diabetes among the responders. In other words, about ten times as many as the recognized cases. This is in accordance with the estimated low sensitivity of the present study.

Many false negatives were also found in the Bedford study.\(^9\) A random sample of 543 subjects without glycosuria were asked to give an OGTT: 76 had DM, giving a false negative rate of 13.9 per cent. It should, however, be noted that the OGTT procedure and the diagnostic criteria for diabetes using OGTT have changed since 1962.\(^10\)

Calculation of the sensitivity
In the Ipswich study,\(^16\) a sensitivity of approximately 90 per cent was reported. In that study, a follow-up examination was done for all test-positive individuals and a small sample of

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### Table 1 Screening results

<table>
<thead>
<tr>
<th></th>
<th>Invited</th>
<th>Responders</th>
<th>Response rates (%)</th>
<th>Screening detected DM</th>
<th>False positive test result</th>
</tr>
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<tbody>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45–49</td>
<td>383</td>
<td>270</td>
<td>70.5</td>
<td>0</td>
<td>3</td>
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<td>50–54</td>
<td>278</td>
<td>205</td>
<td>73.7</td>
<td>2</td>
<td>1</td>
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<tr>
<td>55–59</td>
<td>228</td>
<td>159</td>
<td>69.7</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>60–64</td>
<td>169</td>
<td>131</td>
<td>77.5</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>65–69</td>
<td>151</td>
<td>132</td>
<td>87.4</td>
<td>0</td>
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<tr>
<td>70–75</td>
<td>178</td>
<td>131</td>
<td>73.6</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td><strong>Sum</strong></td>
<td>1387</td>
<td>1028</td>
<td>74.1</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45–49</td>
<td>379</td>
<td>294</td>
<td>77.6</td>
<td>0</td>
<td>2</td>
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<tr>
<td>50–54</td>
<td>249</td>
<td>198</td>
<td>79.5</td>
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<td>2</td>
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<td>193</td>
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<td>2</td>
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<td>79.2</td>
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<td>216</td>
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<td>80.1</td>
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<td>2</td>
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<tr>
<td>70–75</td>
<td>231</td>
<td>177</td>
<td>76.6</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td><strong>Sum</strong></td>
<td>1530</td>
<td>1214</td>
<td>79.3</td>
<td>7</td>
<td>10</td>
</tr>
</tbody>
</table>
Table 2 Test evaluation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Maximum likelihood estimate (%)</th>
<th>95% confidence interval, based on profile likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lower limit (%)</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>20.80</td>
<td>8.14</td>
</tr>
<tr>
<td>Specificity</td>
<td>99.14</td>
<td>98.54</td>
</tr>
<tr>
<td>Predictive value of positive test</td>
<td>46.88</td>
<td>24.29</td>
</tr>
<tr>
<td>Predictive value of negative test</td>
<td>97.17</td>
<td>90.32</td>
</tr>
</tbody>
</table>

test-negative subjects, as in the present study. However, in the calculation of the sensitivity, this unbalanced design was not taken into account. The sample consisted of 50 test-negative screenees, and among these, 3 were found to be false negative. Among test-positive screenees, 28 were found to be true positive. The sensitivity was then calculated as number of true positives, divided by number of sick persons found, i.e. 28 / (3 + 28) = 90 per cent. However, the random sample was only a small proportion of those with negative test result. Thus, the false-negative rate should have been extrapolated to the whole population of test-negative screenees, namely 2290 subjects. A better estimation of the sensitivity would therefore have been 28 / [(2290 x 3/50) + 28] = 17 per cent.

This sensitivity is more in accordance with the study presented here, as well as the Bedford study. From the published figures of the Bedford study the sensitivity can be calculated as approximately 12 per cent. The calculation in the Ipswich study is unfortunate because it leads to the conclusion that self-testing for glycosuria is a successful method that should be encouraged. Employing a screening method with a low sensitivity will cause a false sense of safety among users, and might lead to a delayed diagnosis of DM.

Reasons for a low sensitivity

The most probable reason for the low sensitivity in our and in the two UK studies is an inter-individual variation in the renal threshold for glucose. The threshold ranges at least from 8.3 to 13.3 mmol/l blood glucose for persons 45–75 years of age, and it increases with age.23 The dipstick used in this investigation had a lower limit of glucose detection at 2.2 mmol/l, and was the most sensitive of those initially considered.13 Thus, the sensitivity cannot be increased by using another dipstick. Another source of error giving a false negative result may appear if screenees test their urine pre- instead of postprandially. In the random sample study, all seven test-negative screenees with DM or IGT were asked about this, and all had used the test correctly. Also, all 26 persons participating in the interview study declared that the instructions were easily understood. From this we conclude that erroneous use of the test had little or no influence.

Specificity

The screening method showed an acceptable specificity. This has also been found in other screening studies employing dipsticks.9,11–13,15

Non-responders

The dropout of 675 non-responders presents a problem: do they have a different prevalence of unrecognized DM from the responders? Unfortunately, we have little information about the non-responders. Only 10 people gave a reason for not wanting to participate: four people did not want to stop their vitamin C or ASA intake. Four mentioned that they had just been checked elsewhere, and two expressed a fundamental resistance against screening in general.

Unlike other screening programmes, this screening test did not require a visit to a medical centre, and was carried out in the homes of the participants. Therefore people suffering from immobility owing to illnesses associated with DM, such as obesity or arteriosclerosis, were not precluded from participation.

The diagnostic criteria

There is a slight difference between the current WHO diagnostic criteria10 and the current Danish criteria.1,20 The WHO diagnostic level for DM is f-BG ≥6.7 mmol/l [Denmark (DK): 7.0 mmol/l] or 2 hour OGTT ≥11.1 mmol/l (DK: 11.0 mmol/l). For impaired glucose tolerance, the 2 hour OGTT blood-glucose value is in the range 7.8–11.1 mmol/l (DK: 8.0–11.0 mmol/l). All measures are based on capillary whole blood. However, reviewing the blood-sugar laboratory results, one finds that none of the subjects would have been classified differently with the WHO criteria.

Screening-detected cases

Eleven of the 15 new cases of DM detected by the screening participated in individual interviews. All 11 belonged to risk groups for NIDDM, e.g. possession of a family history of diabetes with at least one first-degree relative (6 persons), severe obesity with body mass index >40 (5 persons), and/or other diseases associated with diabetes (diagnosis or treatment by the family physician): hypertension, dyslipoproteinaemia,
coronary heart disease (8 persons). This suggests that a policy of screening those at high risk might be beneficial.

Costs
Expenses in the present study were about four times those in the Ipswich study. There are three main reasons for this: (1) the Glukostest R was more expensive than the less sensitive Clinistix R; (2) it was necessary to send written reminders to reach an acceptable reply rate; (3) we included more secretarial hours (90), than in the Ipswich study, in which only 10 working hours were included for the whole screening. Still, it is a relatively inexpensive screening method.

Conclusion
Although the chemical sensitivity of the employed dipstick was higher than that of other available dipsticks, the statistical sensitivity of the screening method was low. The procedure of self-testing did not seem to cause difficulties for the participants. We conclude that the low sensitivity of the screening method is connected to the use of a glycosuric test, rather than to a certain dipstick or to self-testing as a method. Because many elderly people have a high renal threshold for glycosuria, screening for NIDDM by testing for glycosuria will give many false negative results. On the other hand, screening on the basis of blood tests, whether fasting or random blood glucose, OGTT or HbA1C, is expensive and inconvenient when applied to large unselected populations.

In the present study, at least 11 of 15 newly diagnosed subjects belonged to a risk group, having a diabetes-related disease, a family history of diabetes, or obesity. The present study suggests that screening of risk groups by means of blood tests might be more fruitful. Further investigations of such a combined procedure are recommended.

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