Screening for Type 2 Diabetes and Impaired Glucose Metabolism

The Australian experience

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OBJECTIVE — To assess the Australian protocol for identifying undiagnosed type 2 diabetes and impaired glucose metabolism.

RESEARCH DESIGN AND METHODS — The Australian screening protocol recommends a stepped approach to detecting undiagnosed type 2 diabetes based on assessment of risk status, measurement of fasting plasma glucose (FPG) in individuals at risk, and further testing according to FPG. The performance of and variations to this protocol were assessed in a population-based sample of 10,508 Australians.

RESULTS — The protocol had a sensitivity of 79.9%, specificity of 79.9%, and a positive predictive value (PPV) of 13.7% for detecting undiagnosed type 2 diabetes and sensitivity of 51.9% and specificity of 86.7% for detecting impaired glucose tolerance (IGT) or impaired fasting glucose (IFG). To achieve these diagnostic rates, 20.7% of the Australian adult population would require an oral glucose tolerance test (OGTT). Increasing the FPG cut point to 6.1 mmol/l (110 mg/dl) or using HbA_{1c} instead of FPG to determine the need for an OGTT in people with risk factors reduced sensitivity, increased specificity and PPV, and reduced the proportion requiring an OGTT. However, each of these protocol variations substantially reduced the detection of IGT or IFG.

CONCLUSIONS — The Australian screening protocol identified one new case of diabetes for every 32 people screened, with 4 of 10 people screened requiring FPG measurement and 1 in 5 requiring an OGTT. In addition, 1 in 11 people screened had IGT or IFG. Including HbA_{1c} measurement substantially reduced both the number requiring an OGTT and the detection of IGT or IFG.

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T ype 2 diabetes is a common and serious condition that is associated with reduced life expectancy and considerable morbidity. It may remain undetected for a number of years, and, consequently, a significant proportion of people with newly diagnosed type 2 diabetes has established complications at the time of diagnosis (1,2).

The role of early detection of undiagnosed type 2 diabetes in asymptomatic individuals as a strategy to reduce the personal, public, and economic cost of type 2 diabetes has been extensively reviewed (3). Although there is some circumstantial evidence that earlier detection is associated with improved outcomes (4), definitive evidence of benefit is lacking. Despite this, early detection of type 2 diabetes continues to be recommended by a number of organizations (5,6).

In Australia, the National Health and Medical Research Council has recently endorsed a national evidence-based guideline for case detection and diagnosis of type 2 diabetes (7). This guideline was developed through an extensive and systematic review of the literature. It recommends a stepped approach to the diagnosis of people with previously undiagnosed type 2 diabetes based on assessment of an individual's risk status, measurement of fasting plasma glucose (FPG) in individuals at risk, and further testing according to the FPG result (Fig. 1).

Since the release of the findings of the Finnish (8) and U.S. (9) diabetes prevention studies, there has been increased interest in identifying individuals with impaired glucose tolerance (IGT) to take advantage of the benefits of primary prevention in this high-risk group (10).

During 1999–2000, the Australian Diabetes, Obesity and Lifestyle (AusDiab) study was conducted and represents the first comprehensive national biomedical prevalence study for diabetes and cardiovascular risk factors in Australia (11). The study examined 11,247 people aged ≥25 years, each of whom completed a health questionnaire and had an oral glucose tolerance test (OGTT). The study found a diabetes prevalence of 7.4%, of which half were known to have diabetes and half had previously undiagnosed diabetes.

The AusDiab study population provides an opportunity to test the Australian screening protocol. Therefore, the aim of this study was to examine the performance of the Australian screening protocol and variations to this protocol for identifying people with previously undiagnosed type 2 diabetes and people with IGT or impaired fasting glucose (IFG).

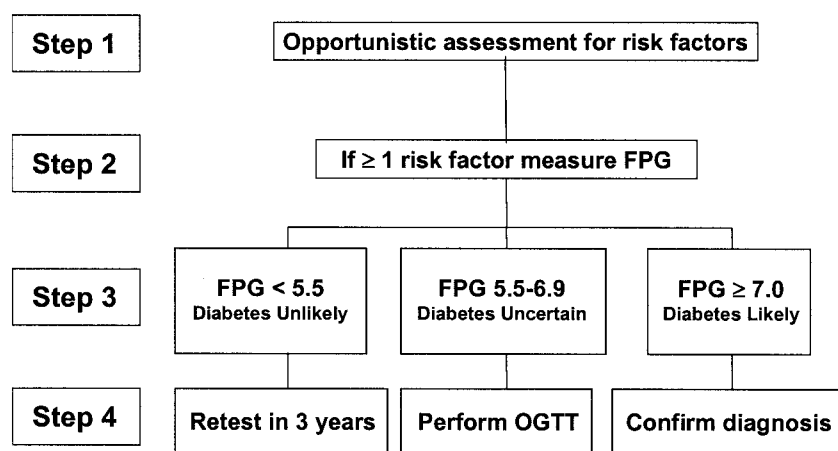●●●

Figure 1—*Australian protocol for screening for undiagnosed type 2 diabetes.*

RESEARCH DESIGN AND METHODS

Details of the AusDiab study have been published previously (11,12). A representative sample of the national population was drawn from 42 randomly selected urban and nonurban areas (census collector districts [CDs]) across Australia (six CDs in each of the six states and the Northern Territory). CDs containing <100 individuals aged ≥25 years, those classified as 100% rural, or those that contained more than a 10% Aboriginal or Torres Strait Islander population were excluded. Within each CD, all homes were approached, and adults aged ≥25 years who were usual residents were invited to attend the survey, which consisted of a short household interview followed by a biomedical examination. There were 11,247 people who took part in the biomedical examination (55.3% of those completing the household interview). Demographic details collected included date and country of birth, language spoken at home, ethnicity, personal and family history of diabetes, smoking habit, past health (including diagnosis and treatment for hypertension and dyslipidemia), cardiovascular disease (angina, heart attack, stroke) and, in women, past history of gestational diabetes. Each person underwent a physical examination including measurement of blood pressure, weight and height, and calculation of BMI, and blood was collected for measurement of lipids and HbA_{1c}. All people except those taking insulin or oral hypoglycemic agents had an OGTT that was performed and interpreted according to the 1999 World Health Organization criteria (6).

Table 1 lists the risk factors for undiagnosed diabetes specified in the Australian guidelines, which were derived from an extensive evidence-based review of the literature. Information collected as part of the AusDiab survey covered the majority of these risk factors except for knowledge of impaired glucose metabolism other than known diabetes and knowledge of a diagnosis of polycystic ovary syndrome. The sampling procedure for the AusDiab study was designed to reflect the Australian population and to avoid oversampling of high-risk groups. Consequently, this did not allow testing of the screening protocol criteria relating to high-risk minority groups because of small numbers. The AusDiab population included only 75 Aboriginal and Torres Strait Islanders aged ≥35 years, 8 of whom had newly diagnosed diabetes. Furthermore, information on ethnicity was collected through two questions: country of birth and language spoken at home. These questions were not sufficiently discriminating to provide information on the high-risk non–English-speaking group

criterion specified in the guideline. For example, a person from the Indian subcontinent born in the U.K. and speaking English at home could not be identified as coming from a designated high-risk group. Country of birth alone identified only 307 people in the high-risk ethnic groups aged ≥35 years, of whom only 19 had newly diagnosed diabetes. Only a parental history of diabetes was recorded, and this was used for the family history variable.

HbA_{1c} was measured using boronate affinity high-performance liquid chromatography (12), and data were available on 10,447 people without previously diagnosed diabetes, of whom 7,972 had normal glucose tolerance. The mean HbA_{1c} result in people with normal glucose tolerance was 5.06% (95% CI 5.05–5.06) with a range of 3.9–6.2%.

The performance of the guideline protocol and other screening strategies was assessed in relation to identifying new diabetes and lesser degrees of glucose intolerance (IGT and IFG). Performance criteria included sensitivity, specificity, positive predictive value (PPV), and the proportion of the population identified as requiring further testing.

The cost in Australian dollars ($A) to the health care system for the screening options for detecting each person with newly diagnosed diabetes or IGT/IFG was calculated using the following scenario. Risk factor assessment was done opportunistically at the time of a routine visit to the primary care physician without incurring an additional cost, the blood test was ordered as an additional test (cost $A 8.05 for FPG, $A 14.15 for HbA_{1c}), the person returned for a visit to the primary care physician specifically to obtain the result of the blood test (cost $A 25.05), and individuals with an equivocal FPG had an OGTT (cost $A 15.90) and then returned

Table 1—*Australian screening guideline risk factors for undiagnosed type 2 diabetes*

- People aged ≥55 years
- People aged ≥45 years who have one or more of the following risk factors:
  - Obesity (BMI ≥30 kg/m²)
  - First-degree relative with type 2 diabetes
  - Hypertension (taking antihypertensive medications or blood pressure ≥140/90 mmHg)
- Aboriginal and Torres Strait Islanders aged ≥35 years
- People from high-risk non–English-speaking background groups aged ≥35 years
- People with IGT or IFG
- All people with clinical cardiovascular disease (myocardial infarction, angina, or stroke)
- Women with previous gestational diabetes
- Women with polycystic ovary syndrome who are obese

Table 2—*Performance of various screening strategies for the detection of type 2 diabetes and impaired glucose metabolism*

	Newly diagnosed diabetes			IGT or IFG			% Population requiring test		
	Sensitivity (%)	Specificity (%)	PPV (%)	Sensitivity (%)	Specificity (%)	PPV (%)	FPG	HbA$_{1c}$	OGTT
RF and FPG ≥5.5 (current guideline)	79.9	79.9	13.7	51.9	86.7	45.5	43.4	—	20.7
RF and FPG ≥6.1	63.6	93.9	29.4	34.6	100.0	100.0	43.4	—	6.6
RF and FPG ≥5.5 then HbA$_{1c}$ ≥5.3%	73.7	89.2	21.4	33.5	94.1	54.8	43.4	20.7	11.6
RF and FPG ≥5.5 or HbA$_{1c}$ ≥5.3%	84.9	73.5	11.4	60.3	80.8	40.2	43.4	43.4	27.1
RF and HbA$_{1c}$ ≥5.3%	78.7	82.8	15.5	42.0	88.2	43.2	—	43.4	19.5

All data were weighted to the Australian adult population. RF, risk factor.

for a final visit to the primary care physician for the result (cost $A 25.05). These costs are based on the published national fees specified by the Health Insurance Commission of Australia.

Statistical analysis

Statistical analysis was performed using the SPSS statistical software release 11.0 (SPSS, Chicago). All data were weighted to the Australian population, using Stata Statistical Software Release 6.0 (Stata Corporation, College Station, TX). Sensitivity (percentage of people with undiagnosed diabetes, IGT, or IFG who had a positive screening test), specificity (percentage of people without undiagnosed diabetes, IGT, or IFG who had a negative screening test), and PPV were calculated for various screening protocols for the prediction of undiagnosed diabetes, IGT, and IFG. PPV depends on the prevalence of diabetes and was calculated using the prevalence of newly diagnosed diabetes from the AusDiab study. For calculations of sensitivity, specificity, and PPV for IGT/IFG, individuals with undiagnosed diabetes were excluded. The best predictive cutoff values for HbA$_{1c}$ for detecting people with new diabetes and impaired glucose metabolism were identified using the optimal sensitivity and specificity values by the receiver operating characteristic (ROC) curve. In the ROC curve, sensitivity value is plotted against the 1-specificity value for each cutoff value. The nearest value to the intersection of the ROC curve and the 100%-to-100% diagonal line was considered the best predictive value for identifying diabetes and IGT/IFG. Estimates of the percentage identified as being at high risk and requiring further testing were weighted to represent the Australian population.

RESULTS — Of the 11,247 participants in the AusDiab study, 475 had known diabetes and data were missing in another 264, leaving 10,508 people who could be included in the analyses. Of these, 5,604 had at least one identifiable risk factor for undiagnosed diabetes specified in the Australian protocol and would be recommended to have an FPG measured. When weighted to the Australian population, 43.4% of adults aged ≥25 years would require screening with an FPG.

Of the 5,604 with risk factors, 2,723 (48.6%) had an FPG <5.5 mmol/l (99 mg/dl), 210 (3.7%) had an FPG ≥7.0 mmol/l (126 mg/dl), and the remaining 2,671 (47.7%) had an FPG between 5.5 and 6.9 mmol/l and would have been recommended to have an OGTT.

The single risk factor that identified most people (71.5%) as being at high risk for undiagnosed diabetes was age ≥55 years, and another 24.2% were identified because they were age 45–54 years with one of the following: BMI ≥30 kg/m^2, hypertension, or family history of diabetes. Together these two risk factors identified 86.9% of people with newly diagnosed diabetes. Inclusion of past history of a cardiovascular event or gestational diabetes identified only seven more people with previously undiagnosed diabetes.

The overall performance of the guideline protocol is shown in Table 2. The protocol has a sensitivity of 79.9%, specificity of 79.9%, and PPV of 13.7% for detecting previously undiagnosed type 2 diabetes. Of the 20.1% of people in whom the diagnosis of diabetes was missed, 62.7% did not have one of the identifiable risk factors, and the remaining 37.3% had an FPG <5.5 mmol/l. To achieve this diagnostic rate, 20.7% of the Australian

adult population would require an OGTT. The risk factor assessment alone has a satisfactory sensitivity of 87.4% but a low specificity of 58.4%.

The effect of various modifications to the current guideline was also assessed (Table 2). Changing the FPG below which undiagnosed diabetes is considered unlikely, from 5.5 to 6.0 mmol/l (108 mg/dl) (at Step 3 in Fig. 1), resulted in a fall in sensitivity to 63.6%. But specificity increased to 93.9% and PPV to 29.4%, and the proportion of the population that would require an OGTT was reduced to 6.6%.

Screening strategies that include measurement of HbA$_{1c}$ were assessed in the 10,447 people without previously diagnosed diabetes who had HbA$_{1c}$ measured. ROC curve analysis indicated that the optimal HbA$_{1c}$ cut point for detecting previously undiagnosed diabetes and IGT/IFG was 5.3%. If HbA$_{1c}$ measurement is performed in the group with a risk factor and an equivocal FPG result between 5.5 and 6.9 mmol/l, and those with an HbA$_{1c}$ ≥5.3% have further testing with an OGTT (an additional step between Step 3 and 4, Fig. 1), then the sensitivity falls to 73.7% for detecting new diabetes, but the specificity increases to 89.2% and the PPV to 21.4%, and the proportion of the Australian adult population that would require an OGTT is reduced to 11.6%. If FPG and HbA$_{1c}$ are measured in all people with a risk factor (at Step 2, Fig. 1) and further testing is performed if either FPG is between 5.5 and 6.9 mmol/l or HbA$_{1c}$ is ≥5.3%, then the sensitivity is 84.9%, specificity is 73.5%, PPV is 11.4%, and the proportion of the Australian adult population that would require an OGTT is 27.1%. Measurement of HbA$_{1c}$ in all people who have a risk factor (at Step 2,

Fig. 1) followed by an OGTT in those with a result ≥5.3% has a sensitivity of 78.7%, specificity of 82.8%, and a PPV of 15.5%, and 19.5% of Australian adults would require an OGTT.

The performance of the screening options in detecting IGT and IFG was also evaluated. Of the 10,508 people included in this study, 1,372 (11.0%) had IGT (FPG <7.0 [126 mg/dl] and 2-h plasma glucose ≥7.8 [140 mg/dl] and <11.1 mmol/l [200 mg/dl]) and 642 (5.9%) had IFG (FPG 6.1–6.9 and 2-h plasma glucose <7.8). The Australian protocol had a sensitivity of 51.9% and specificity of 86.7% for detecting IGT or IFG (Table 2). Increasing the FPG cutoff to ≥6.1 mmol/l (110 mg/dl) decreased sensitivity to 34.6%. Similarly strategies for detecting IGT/IFG that relied on HbA_{1c} measurement alone to determine the need for further testing with an OGTT were associated with lower sensitivities compared with protocols that based further testing on FPG measurement (Table 2).

The overall performance of the Australian guideline for the detection of dysglycemia (new diabetes or IGT or IFG) showed a sensitivity of 57.1%, specificity of 86.7%, and PPV of 52.9%.

The cost for detecting each person with newly diagnosed diabetes using the current Australian protocol is $A 746, and $A 260 for each person with IGT or IFG. Increasing the FPG cut point to ≥6.1 mmol/l alters costs to $A 700 for diabetes and $A 292 for IGT or IFG, whereas the corresponding costs for a protocol based on risk factor assessment followed by measurement of HbA_{1c} are $A 828 and $A 352, respectively. It should be noted that the cost of making a clinical diagnosis of diabetes will be slightly higher because of the repeat testing required to confirm the diagnosis.

CONCLUSIONS — Despite continuing controversy surrounding the benefit of early detection of type 2 diabetes, the high prevalence of undiagnosed diabetes has led to a number of organizations advocating opportunistic screening of people presenting to the health system as part of an overall strategy to reduce the burden of diabetes. This strategy has recently been ratified in Australia with the endorsement by the National Health and Medical Research Council of national ev-

idence-based guidelines for case detection and diagnosis of type 2 diabetes (7).

The Australian screening protocol was formulated on the basis of an extensive and systematic review of the literature from which a stepped protocol was derived. The initial step identified at-risk individuals based on a set of risk factors that could each identify an individual with a 1 in 20 (5%) chance of having undiagnosed diabetes. Individuals with risk factors would have an FPG measurement and proceed to have an OGTT depending on the result (Fig. 1). The recently completed AusDiab prevalence survey provided the opportunity to test the performance of this and modifications to this protocol.

The combined risk factor assessment and measurement of FPG had an overall sensitivity of 80%, specificity of 80%, and a PPV of 14% for identifying people with previously undiagnosed type 2 diabetes who participated in the AusDiab study. Of importance in judging the performance of a screening protocol is the proportion of the population who would need to undergo testing to achieve a diagnosis of diabetes. This protocol would require 43.4% of Australian adults to have measurement of FPG and 20.7% (with an equivocal result between 5.5 and 6.9 mmol/l) to have an OGTT.

The favorable outcomes of the Finnish and U.S. prevention studies have stimulated great interest in the detection of people with IGT (8–10). A byproduct of any screening protocol for type 2 diabetes that includes blood glucose measurement is the detection of people with lesser degrees of glucose intolerance. The Australian screening protocol, which was not designed to detect impaired glucose metabolism, had a sensitivity of 52%, a specificity of 87%, and a PPV of 46% for detecting IGT or IFG.

This study also investigated variations to the current protocol. Increasing the FPG cut point to determine the need for an OGTT to 6.1 mmol/l decreased sensitivity, increased specificity, and substantially reduced the proportion of people requiring an OGTT from 21 to 7% (Table 2). The effect of using measurement of HbA_{1c} to determine the need for an OGTT generally gave similar results to the protocols that used FPG alone, and 12–27% of people required an OGTT. The optimal cut point for HbA_{1c} was 5.3%, which is similar to the 5.5% value reported by Ko

et al. (13). However, the protocols that used an increased FPG cut point or an HbA_{1c} measurement to determine the need for an OGTT substantially reduced the detection rate of IGT. Therefore, although increasing the FPG cut point or including HbA_{1c} measurement offers some advantages in screening protocols for detecting undiagnosed diabetes, especially by reducing the numbers requiring an OGTT with only a small reduction in sensitivity, this is at the expense of not detecting people with IGT and IFG who could be the focus of efforts to prevent or delay the future development of diabetes.

Although varying in detail, most studies that have addressed the issue of screening for diabetes in asymptomatic individuals have attempted to identify people at increased risk by questionnaires (14–18). These risk factor assessment protocols have been developed from population prevalence studies, and some have been tested in populations other than those used to develop the risk assessment. In general, these questionnaires perform poorly as stand-alone tests (3). The finding of this study was similar, with risk factor assessment alone having a sensitivity of 87% but a low specificity of 58%. However, it should be noted that the Aus-Diab study questionnaire did not include all risk factors specified in the Australian screening protocol; therefore, the current assessment of the performance of the protocol is limited to only some of the risk factors. Within this limitation, age alone or combined with obesity, hypertension, or parental history of diabetes accounted for 87% of people with previously undiagnosed diabetes, and the inclusion of a history of previous cardiovascular disease or gestational diabetes had little additional effect.

In summary, the Australian screening protocol performed well in identifying and detecting people with undiagnosed diabetes when applied to a representative sample of the Australian population. Overall, the protocol identified ~8 of 10 people who had previously undiagnosed diabetes, 5 of 10 who had IGT, and 7 of 10 who had IFG. The number needed to screen to identify one new case of diabetes is 32, with 4 of 10 people screened requiring measurement of FPG and 1 in 5 requiring an OGTT. The number requiring an OGTT for detecting new diabetes could be reduced to 1 in 15 by increasing the plasma glucose cut point, but this

would also reduce the number detected with new diabetes to 1 in 41 people screened and halve the detection rate of IGT or IFG.

The costs of screening associated with protocols that used HbA$_{1c}$ were predictably higher than those that relied on FPG, but, overall, the costs were not particularly high and generally could be considered affordable in the context of opportunistic screening programs. However, screening for type 2 diabetes has major resource implications not only for the screening itself, but also the additional resources required to care for the increased numbers of people with newly diagnosed diabetes. Because there are no definitive data, as yet, on the effectiveness of screening in improving diabetes outcomes, the capacity of the health system to implement a screening program requires individual assessment, taking into account locally available resources.

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