Australian Diabetes Screening Study: Impaired Glucose Tolerance and Non–Insulin-Dependent Diabetes Mellitus

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In preventing non–insulin-dependent diabetes mellitus (NIDDM) and its complications, screening high-risk individuals complements public health measures. Our screening instrument for patients of general practitioners was a questionnaire for self-determined high-risk groups plus a laboratory measurement of a random venous plasma glucose level. Collaborating practitioners evaluated 100 consecutive outpatients aged 40 years or older. The questionnaire identified patients with two or more diabetic symptoms or with two or more risk factors, and they were recommended to have their blood tested. For those with a random plasma glucose greater than 5.5 mmol/L, oral glucose tolerance tests (OGTTs) were advised. Of 50,859 subjects completing the study, there were 1,013 cases (2.0%) of new diabetes, 1,704 cases (3.4%) of impaired glucose tolerance (IGT), and 5,508 cases (10.8%) of previously diagnosed diabetes. Symptoms alone were a relatively poor discriminant. Almost all newly identified NIDDM and IGT patients had two or more risk factors for NIDDM. The risk ratios for abnormal glucose tolerance were as follows: high blood pressure, 2.4; overweight, 2.0; and positive family history, 1.7. Selection of cutoff points higher than 5.5 mmol/L would have substantially reduced the rate of newly discovered NIDDM and IGT. Screening for NIDDM and IGT in general practice is feasible and can be achieved with little disruption of office procedures. In preventive programs of this nature, the low screening threshold of 5.5 mmol/L for random venous plasma glucose maximizes the case-finding rate.

TYPE 2 DIABETES, or non–insulin-dependent diabetes mellitus (NIDDM), has a high mortality and morbidity and poses a huge healthcare burden because of its complications.[1-5] The microvascular complications are related to the duration and severity of hyperglycemia. At presentation, 10% to 12% of cases of NIDDM have retinopathy[6] and 5% have neuropathy, suggesting that diabetes has been present for years before diagnosis.[7] Accelerated atherosclerosis may precede the diagnosis of frank diabetes for many years.[8,9] There is evidence that the mortality for impaired glucose tolerance (IGT), a precursor of NIDDM, is almost the same as for frank diabetes.[10,11]

Such data emphasize the need for early case-finding of NIDDM and IGT, when treatment of the metabolic abnormalities could reduce the severity of complications or at least enable their prompt identification and management. Screening for unidentified NIDDM is a justifiable area for operational research.[12-14] In addition, finding subjects with IGT will define a group at much greater risk of progression to frank diabetes,[15] as well as having coexisting vascular risk factors.[16-18] In nondiabetic populations, there is compelling evidence that modifying the risk factors reduces cardiovascular events. Such principles should surely apply to populations with IGT and with diabetes.

The principle of screening high-risk groups for NIDDM is now generally recommended.[1-3,12,13] Those at high risk include persons with unrecognized symptoms and those with a positive family history of NIDDM, obesity, age greater than 50 years, previous abnormality of glucose tolerance, and ethnic predisposition (for example, the indigenous races of Australia and the Americas, Pacific Islanders, Asian Indians, Chinese, and Southern Europeans).[12,13]

General practices in Australia provide an ideal environment for such screening programs. Family doctors have good access to the community: 80% to 85% of the population will contact a general practitioner in 1 year.[19,20] General practitioners are able to identify individuals at risk, obtain informed consent for screening, and conduct the screening procedure. Importantly, they are available to supervise diagnostic follow-up evaluations and aftercare.

The aims of the project reported here were to assess the frequency of undiagnosed NIDDM and IGT in patients of general practitioners, using self-determined high-risk groups and measurement of random venous plasma glucose levels as the screening instrument.

SUBJECTS AND METHODS

General practitioners were surveyed to participate in the project. Respondents attended introductory workshops with an endocrinologist. After completion, a seminar was arranged to discuss outcomes. The project was endorsed by the Royal Australian College of General Practitioners and provided continuing medical education points. Of 650 practitioners who expressed initial interest, 535 completed the survey and returned data sheets.

The screening study kit included a descriptive outline of the study, instructions for the practice receptionist, a tally sheet to document 100 consecutive eligible patients and to record those refusing or unable to complete the questionnaire because of sickness or lack of comprehension, and posters and desktop notices. Survey questionnaire forms were provided together with blood collection guidelines, with instructions for dispatch of blood samples to participating laboratories.

The study commenced on December 1, 1994, and was completed by June 30, 1995. The protocol required 100 consecutive patients over 40 years of age in each practice to be given the survey questionnaire form plus a written invitation to participate and descriptive information about the pros and cons of early diagnosis of diabetes.

The questionnaire contained items for the self-recording of (1) previous diagnosis of diabetes or high blood glucose levels, the year of diagnosis, and current treatment; (2) current diabetic symptoms: excess thirst, frequent urination, unexplained weight loss, frequent skin infections, or frequent genital candidosis (thrush); and (3) presence of risk factors for NIDDM: age over 50 years, being overweight, having blood relatives with adult-onset diabetes, having checks on treatment for high blood pressure levels.

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Table 1. Final Diagnostic Category by Age and Sex

Diagnostic Category	40-49 yr		50-59 yr		60-69 yr		70+ yr		Males		Females		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Known diabetes	733	5.7	1,124	10.4	1,790	15.0	1,861	13.1	2,672	12.6	2,836	9.5	5,508	10.8
New diabetes	63	0.5	193	1.6	293	2.4	464	3.3	423	2.0	590	1.9	1,013	2.0
IGT	147	1.1	353	3.0	460	3.8	744	5.2	681	3.2	1,023	3.4	1,704	3.4
Total sample	12,890		11,750		11,961		14,258		21,161		29,698		50,859	
National prevalence of known diabetes[22]		1.6		3.7		6.1		7.8		4.5		4.5		4.3

Respondents with two or more symptoms or two or more risk factors as defined were offered a screening blood test. Venous blood was collected by the doctor or staff and dispatched to a collaborating pathology laboratory for measurement of plasma glucose using an enzymatic method.

Screening and Diagnostic Criteria

For subjects with positive symptoms or risk factors, we chose the low cutoff point for random venous plasma glucose of greater than 5.5 mmol/L. All such subjects were recommended to have an abbreviated oral glucose tolerance test (OGTT) at an accredited pathology center. This involved an overnight fast and collection of a fasting venous blood sample and a 2-hour venous blood sample after a standard 75-g oral glucose load with the subjects sitting quietly at rest. We used the following diagnostic criteria for the abbreviated OGTT[21]: (1) diabetes mellitus, fasting venous plasma glucose of at least 7.8 mmol/L and/or 2-hour venous plasma glucose of at least 11.1 mmol/L; and (2) IGT, fasting venous plasma glucose less than 7.8 mmol/L and 2-hour venous plasma glucose of 7.8 to 11.0 mmol/L. Not all positive screenees (random venous plasma glucose >5.5 mmol/L) underwent the OGTT, and we assigned the following categories to these subjects: (3) diabetes mellitus, two or more symptoms and random venous plasma glucose of at least 11.1 mmol/L or no symptoms but two or more risk factors and random venous plasma glucose of at least 15.0 mmol/L. The prevalence (risk) ratio for the screening categories was calculated as the rate for new diabetes (or IGT) with the category divided by the ratio for new diabetes (or IGT) without the category, using SPSS statistical software. (Baker Medical Research Institute, Prahran, Australia).

RESULTS

Fifty-four thousand seven hundred subjects were screened throughout Australia. There were 2,067 refusals (3.8%) from patients who were either unable or did not wish to participate. A further 1,774 subjects completed the initial questionnaire but were excluded from the analysis for protocol violations (eg, age <40 years, no. of patients exceeded 100, or incomplete information).

The total number of records analyzed from 535 general practitioners was 50,859. This number is the denominator for the subsequent rates for diagnostic categories. The patients were screened in New South Wales (45.3%), Victoria (27.3%), Queensland (9.0%), South Australia (7.6%), Western Australia (7.5%), and Tasmania (3.2%). Results between States showed negligible geographic variation. There were equivalent numbers in the age groups 40 to 49, 50 to 59, 60 to 69, and 70 years or older (Table 1). Patients who stated that they had previously diagnosed diabetes (n = 5,508) were excluded from the subsequent screening by the general practitioner. Of the remaining subjects, 4,009 (7.8%) had two or more symptoms, 22,947 (45.1%) had two or more risk factors, and 24,305 (47.8%) had one or both of these categories. Twenty-three thousand two hundred subjects (45.6%) were referred for random plasma glucose measurements identifying 8,648 subjects (37.3% of those tested) with a value exceeding 5.5 mmol/L, and 6,550 subjects (28.2%) were further referred for an abbreviated OGTT.

Final diagnostic categories (Table 1) included 1,013 cases of new diabetes representing 2.0% of the analyzed records. There were 1,704 cases of IGT, or 3.4% of the screened population. Thus 5.4%, altogether, of new cases of abnormal glucose tolerance were discovered. Rates of new diabetes and IGT increased with age. Within age groups, the frequency of discovered diabetes in the sample was 30% to 45% of the estimated national prevalence for self-reported diabetes.[22] The frequency of IGT in the sample was about 75% of the estimated national prevalence of self-reported diabetes.

There was a high rate of previously diagnosed diabetes in the sample (Table 1). Fifty-five hundred eight subjects (10.8%) reported positive histories for diabetes/high blood glucose, a rate more than twice the estimated national prevalence rate.[22] The median duration of diabetes/high blood glucose was 6 years. Twelve percent were on insulin injections, 50% on tablets, and 26% on diet alone, and 12% stated that they were on no treatment.

The frequency of positive symptoms and positive risk factors for NIDDM in the diagnostic categories (Table 2) shows anticipated trends. Subjects with known and previously diagnosed diabetes had symptoms more often than the nondiabetics, but screening for two or more symptoms alone would have identified only 15% of all newly diagnosed subjects. In contrast, almost all of the new diabetic and IGT subjects had two or more

Table 2. Frequency (% of sample) of Positive Symptoms and/or Positive Risk Factors by Final Diagnostic Category

Diagnostic Category	Two or More Symptoms	Two or More Risk Factors	Overweight	Age >50 yr	Positive Family History	High Blood Pressure
Known diabetes	19	52	34	54	27	38
New diabetes	15	97	66	92	34	67
IGT	12	98	65	91	34	66
Nondiabetic	8	45	34	66	21	28

Table 3. Prevalence Ratios for Symptoms and Risk Factors (age-standardized) in Newly Diagnosed Diabetes and IGT

Category	New Diabetes		IGT	
	Ratio	95% CI	Ratio	95% CI
Two or more symptoms	2.6	2.2-3.3	1.7	1.3-2.2
Overweight	2.2	2.0-2.4	2.1	2.0-2.4
Positive family history	2.1	1.9-2.5	2.1	1.8-2.4
High blood pressure	2.2	1.9-2.4	2.2	2.0-2.5
Any 2 risk factors	2.1	2.0-2.3	1.9	1.7-2.0
Any 3 risk factors	2.6	2.2-3.1	2.6	2.2-3.1
Any 4 risk factors	2.9	1.9-4.3	2.4	1.6-3.7

Abbreviation: CI, confidence interval.

risk factors. Two thirds had self-reported overweight, and two thirds had self-reported high blood pressure. Prevalence (risk) ratios for new diabetes and IGT, respectively, by the various screening categories were as follows: high blood pressure, 2.4, 2.4; two or more risk factors, 2.2, 2.2; overweight, 1.9, 2.0; positive family history, 1.7, 1.7; age greater than 50 years, 1.4, 1.4; and two or more symptoms, 1.8, 1.5. The age-standardized results are shown in Table 3. The prevalence ratios were very similar in new diabetes and IGT groups, and most were significant as reflected by the 95% confidence limits.

In the initial screening process, random venous plasma glucose levels were measured in 23,200 subjects. The distribution of these levels by final diagnostic category shows substantial overlap between groups (Fig 1). There are peak modal ranges for nondiabetic subjects (4.6 to 5.5 mmol/L) and IGT subjects (5.6 to 7.5 mmol/L), but for subjects with new diabetes there is a broad modal range of 5.6 to greater than 8.5 mmol/L.The effect of varying the cutoff point for random venous plasma glucose on the number of subjects identified in final diagnostic categories is shown in Table 4. If the cutoff point had been set at greater than 6.5 mmol/L, 29% of new diabetics and 58% of IGT subjects would not have been identified. At a cutoff point of greater than 7.5 mmol/L, 51% of new diabetics and 81% of IGT patients would not have been identified.

Table 4. Final Diagnostic Category by Selected Cut-off Points for Random Venous Plasma Glucose Levels

Random Venous Plasma Glucose	New Diabetes	IGT
>5.5 mmol/L	1,013	1,704
>6.5 mmol/L	721	728
>7.5 mmol/L	502	323

DISCUSSION

This study reports operational research into screening for NIDDM and IGT in general practice using the principle of self-determined high-risk groups and measurement of random venous plasma glucose levels. The use of a simple questionnaire avoided disruption of office procedures in general practice. Our study confirms the feasibility of this approach. We excluded questions on ethnic origin and on abnormal blood lipid fractions and more precise assessment of obesity, since all of these procedures were likely to jeopardize the efficacy of screening and response rates.

While there are no data to support screening for NIDDM and IGT in terms of the long-term prevention of symptomatic diabetes or its complications, we have outlined evidence

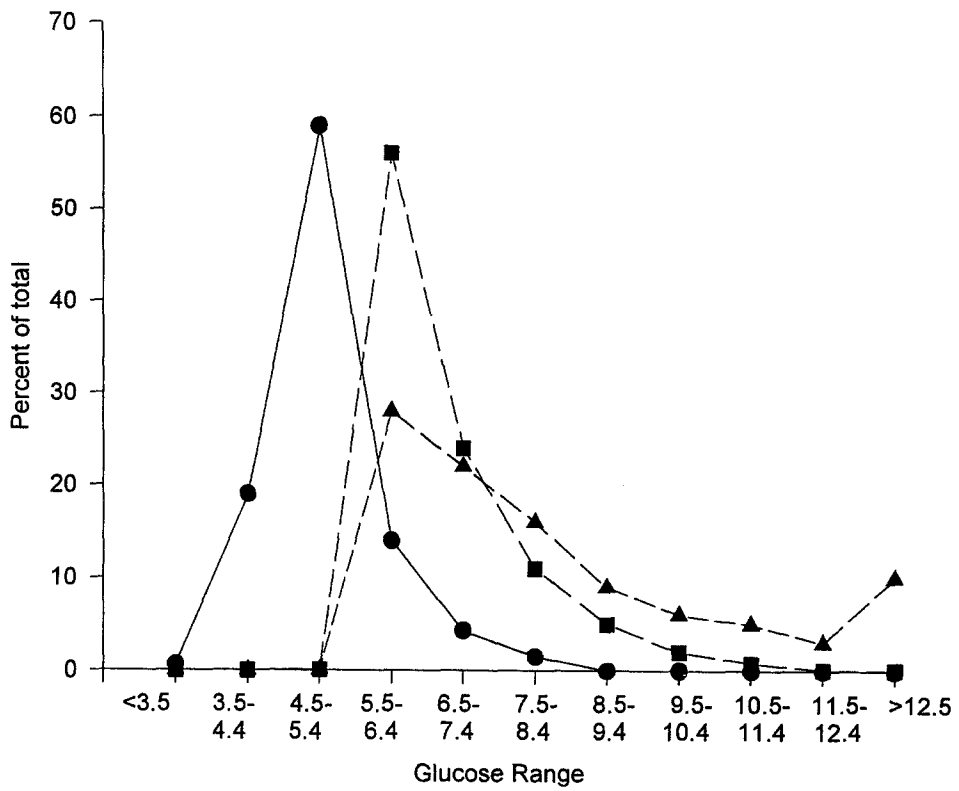

Fig 1. Distribution of random venous plasma glucose levels by final diagnostic category. (●) Nondiabetic, (■) IGT, (▲) new diabetic.

suggesting the potential benefits and the need for further studies.

Similarly, while there are no data on preventing macrovascular disease or its progression in subjects with NIDDM and IGT, there is an enormous literature on abnormal glucose tolerance as a component of the syndrome of insulin resistance.[16-18] Comprising this syndrome are modifiable vascular risk factors including obesity, hypertension, glucose intolerance, and dyslipidemia.

Our screening procedure provided a moderate yield of cases of abnormal glucose tolerance. The data suggest that it is useful for general practitioners to screen the elderly and those with acknowledged risk factors for NIDDM, particularly hypertension and obesity. We found an extremely high rate of diagnosed diabetes in persons attending general practitioners as compared with national prevalence figures, and this was uniform throughout the practices and the States. A partial explanation is that persons with diabetes attend doctors more frequently than nondiabetic persons. It is also possible that the national prevalence figures[22] are an underestimate.

The project was educational for participating general practitioners, who reported favorably in their evaluations. They developed a better appreciation of the diagnostic criteria for the diagnosis of diabetes. In addition, the study provided continuing education on the syndrome of insulin resistance as an important risk factor for abnormal glucose tolerance, as well as for cardiovascular disease.

The issue of diagnostic criteria was the major focus for interactive discussions between the general practitioners and the endocrinologists. A project of this nature highlights the gulf between the diagnostic criteria recommended in the clinical setting and the criteria used for epidemiological or population screening purposes as recommended by the World Health Organization.[1,21] In the clinical setting, the diagnosis of diabetes can be made if a patient has typical symptoms and unequivocal elevation of plasma glucose. Alternatively, in the absence of symptoms, two or more abnormal blood glucose values are needed for diagnosis, either a fasting level greater than 7.8 mmol/L or an OGTT with abnormal values greater than 11.1 mmol/L at 2 hours after the oral glucose load and at one intervening time.

For epidemiological or population screening purposes, the 2-hour value after 75 g oral glucose may be used alone or with the fasting value.[1,21] Indeed, a single 2-hour reading greater than 11.1 mmol/L is sufficient to diagnose diabetes. It is on the basis of glucose tolerance tests in population samples without regard to the presence of symptoms that current criteria were shown to discriminate those at risk of subsequent microvascular complications of diabetes.[15]

The criteria for blood glucose levels in screening programs require clarification. The tests have to be simple and acceptable, and the results must be easy to interpret. While selective screening of high-risk subjects is generally approved,[12,14] there are varied recommendations regarding the blood glucose levels that necessitate follow-up evaluation (fasting venous plasma glucose values of 6.5 to 6.7 mmol/L and random venous plasma glucose of 7.0 to 8.9 mmol/L are cited.[12-14] The World Health Organization states that in patients without symptoms of diabetes, random venous plasma glucose levels of 5.5 to 11.0 mmol/L are in an uncertain range and further follow-up evaluation may be required.[21] Our selection of the cutoff point of 5.5 mmol/L for random venous plasma glucose as a basis for follow-up study enabled the identification of many more cases of newly diagnosed diabetes at risk of microvascular disease, and many more cases of abnormal glucose tolerance (NIDDM plus IGT) at increased risk of macrovascular disease. There is obviously the need to continue research into the complex issue of screening high-risk groups for NIDDM. Alternative diagnostic criteria for diabetes have been suggested, including glycated hemoglobin or fasting venous plasma glucose measurements.[23] We suggest that a simple questionnaire to identify risk and a random venous plasma glucose measurement is a feasible screening method.

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REFERENCES

1. World Health Organization: Prevention of diabetes mellitus. Report of a WHO Study Group. World Health Organ Tech Rep Ser 844:3-10 1994

2. King H, Dowd JE: Primary prevention of type 2 (non–insulin dependent) diabetes mellitus. Diabetologia 33:3-8, 1990

3. Knowler WC, Narayan KMV, Hanson RL, et al: Preventing non–insulin dependent diabetes. Diabetes 44:483-488, 1995

4. American Diabetes Association: Direct and Indirect Costs of Diabetes in the United States in 1992. Alexandria, VA, American Diabetes Association, 1993

5. Rubin RJ, Altman WM, Mendelson DN: Health care expenses for people with diabetes mellitus. J Clin Endocrinol Metab 78:809A-809F, 1994 (suppl)

6. Harris MI, Klein R, Welborn TA, et al: Onset of NIDDM occurs at least 4-7 years before clinical diagnosis. Diabetes Care 15:815-819, 1992

7. Lehtinen JM: Prevalence of neuropathy in newly diagnosed NIDDM and non-diabetic control subjects. Diabetes 38:1307-1313, 1989

8. Haffner SM, Stern MP, Hazuda HP, et al: Cardiovascular risk factors in confirmed pre-diabetic individuals. JAMA 263:2893-2898, 1990

9. McPhillips JB, Barrett-Connor E, Wingard DL: Cardiovascular disease risk factors prior to the diagnosis of impaired glucose tolerance and non–insulin dependent diabetes mellitus in a community of older adults. Am J Epidemiol 131:443-451, 1990

10. Jarrett RJ, McCartney P, Keen H: The Bedford Survey: 10 year mortality rates in newly diagnosed diabetics, borderline diabetes, and normoglycaemic controls, and risk indices for coronary heart disease in borderline diabetes. Diabetologia 22:79-84, 1982

11. Fuller JH, Shipley MJ, Rose G, et al: Mortality from coronary heart disease in relation to degree of glycaemia: The Whitehall Study. Br Med J 287:867-870, 1983

12. American Diabetes Association: Screening for diabetes (position statement). Diabetes Care 18:5-7, 1995 (suppl 1)

13. Engelgau MM, Thompson TJ, Aubert RE, et al: Screening for NIDDM in non-pregnant adults. Diabetes Care 18:1606-1618, 1995

14. Engelgau MM, Thompson TJ, Smith PJ, et al: Screening for diabetes mellitus in adults: The utility of random capillary blood glucose measurements. Diabetes Care 18:463-466, 1995

15. Harris MI, Zimmet P: Classification of diabetes mellitus and other categories of glucose intolerance, in Alberti KGMM, Defronzo RA, Keen H, et al (eds): International Textbook of Diabetes Mellitus. London, UK, Wiley, 1992, pp 3-18

16. Reaven GM: Role of insulin resistance in human disease. Diabetes 37:1595-1607, 1988

17. DeFronzo RA, Ferrannini E: Insulin resistance: A multi-faceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidaemia, and atherosclerotic cardiovascular disease. Diabetes Care 14:173-194, 1991

18. Eschwege E, Balkau B, Fontbonne EA: Dyslipoproteinaemia, regional obesity and diabetes mellitus as coronary risks, in Ditschuneit H, Gries FA, Hauner H, et al (eds): Obesity in Europe 93. London, UK, Libbey, 1994, pp 501-507

19. Australian Bureau of Statistics 1989-90: National Health Survey: Summary of Results. Canberra, Australian, Australian Government Printing Service, 1991 (catalog no. 4364.0)

20. Driver B, Brit H, O'Toole B, et al: How representative are patients in general practice morbidity surveys? Fam Pract 8:261-269, 1991

21. World Health Organization: Diabetes mellitus: Report of a WHO Study Group. World Health Organ Tech Rep Ser 727:10-12, 1985

22. Welborn TA, Knuiman MW, Bartholomew HC, et al: 1989-90 National Health Survey: Prevalence of self-reported diabetes in Australia. Med J Aust 163:129-132, 1995

23. McCance DR, Hanson RL, Charles M-A, et al: Comparison of tests for glycated haemoglobin and fasting and two-hour plasma glucose concentrations as diagnostic methods for diabetes. Br Med J 308:1323-1328, 1994