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Screening for Non-Insulin Dependent Diabetes

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SCREENING FOR NON-INSULIN DEPENDENT DIABETES MELLITUS (NIDDM)

This paper presents recommendations on screening activities to detect non-insulin dependent diabetes (type 2 diabetes) and impaired glucose tolerance. It provides guidance for health professionals who are considering activities aimed at identifying people with diabetes mellitus or its risk factors. It does not address the issue of community awareness of diabetes.

The document was initiated by a working group in 1993 comprising Professor Paul Zimmet (Convenor), Bernie Lowther, Dr Pat Phillips, Dr Gordon Senator and Dr Tim Welborn. The working group was subcommittee of the NHMRC Expert Panel on Diabetes. Their recommendations have been revised to encompass more recent views on screening and the prevention of diabetes and its complications. As a "position paper" it is necessarily provisional and will undoubtedly require upgrading when studies on the cost effectiveness of screening for type 2 diabetes become available. It is likely also that diagnostic criteria will change and will necessitate a major revision of the paper.

SUMMARY AND RECOMMENDATIONS
Effective screening should result in intervention that reduces morbidity and mortality from diabetes and its complications in persons in high risk categories.

Early intervention may reduce or prevent complications in NIDDM. It is recommended that screening for NIDDM, using blood glucose tests, be carried out selectively on individuals at high risk.

Screening programmes require the consent of participants and must include plans for diagnostic follow up and after-care. General practitioners in Australia are well positioned to encompass all aspects of a screening and follow up programme.

High risk individuals are those with diabetes symptoms that are unrecognised, or those with known risk factors for NIDDM.

RISK FACTORS

1.1 Ethnic groups with a high prevalence of NIDDM

1.2 Positive family history of NIDDM in direct relatives (parents, siblings, or children).

1.3 Overweight or obesity as defined by body mass index (BMI) >25 kg/m², or percentage ideal weight >115% or adverse waist hip ratio (>0.90 for males, >0.80 for females).

1.4 Age >50 years.

1.5 Previous abnormality of glucose tolerance, including gestational diabetes.
1.6 Pregnant women aged 30 years or more, or females with history of big babies (>4.5kg) or multiple miscarriages, or stillbirths.

1.7 Hypertension, dyslipidaemia, or clinical macrovascular disease.

1.8 Use of diabetogenic medications.

*Note:* Ethnic communities with very high prevalence of NIDDM justify total population screening, and/or screening of adults >30 years of age.

Screening for gestational diabetes mellitus, and insulin dependent diabetes mellitus (type 1 diabetes) are the subject of separate position papers.

The risk of developing NIDDM increases with increasing number of these risk factors.

1.9 Individuals who present with complications of unrecognised diabetes including retinopathy, nephropathy, and/or neuropathy.

**IMPAIRED GLUCOSE TOLERANCE (IGT)**

This diagnostic category is intermediate between normal and frank diabetes. Subjects with IGT require counselling because of their greater risk of progressing to diabetes. They are also likely to have coexisting vascular risk factors as part of the metabolic syndrome (Syndrome X) - see below.

**SCREENING FOR CARDIOVASCULAR RISK FACTORS IN INDIVIDUALS WITH NIDDM AND IGT.**

These individuals have multiple risk factors for cardiovascular disease, including abdominal obesity, hypertension, and dyslipidaemia. These and related risk factors including tobacco smoking should be assessed soon after diagnosis and at regular intervals thereafter.

**THE PANEL MAKES THE FOLLOWING RECOMMENDATIONS FOR ALTERNATIVE SCREENING METHODS:**

**Urine Glucose**

Testing the urine for glucose has very poor sensitivity and specificity for diabetes. Because of the variation in renal threshold, urine glucose tests yield high rates of false negative and false positive results. Where facilities exist for measurement of blood glucose levels, there is no place for urine glucose testing in screening for NIDDM.

**Oral Glucose Tolerance Test**

The oral glucose tolerance test is used to diagnose diabetes and also defines subjects with IGT. It is not a screening test and it is only necessary as a follow up diagnostic procedure in selected high risk subjects as described in this report.
SCREENING FOR NON-INSULIN DEPENDENT DIABETES MELLITUS (NIDDM) AND IMPAIRED GLUCOSE TOLERANCE (IGT).

DEFINITIONS

Screening
Screening is the presumptive identification of unrecognised disease or defects by the application of tests, examinations, or other procedures which can be applied rapidly. Screening tests identify apparently well persons who probably have disease as compared to those who probably do not (1). Note that a screening test is not intended to be diagnostic.

Persons who have conditions detected by community based screening programmes must be referred to medical practitioners for definite diagnosis and appropriate management. Screening provides the opportunity to prevent the onset of symptomatic disease or to prevent or ameliorate the complications of that disease.

Diabetes Mellitus
Diabetes Mellitus is a heterogeneous group of disorders characterised by high blood glucose values that result from impaired insulin secretion and/or resistance to insulin action. Frank diabetes can be diagnosed by the presence of classical symptoms including excessive thirst, polyuria, weight loss, blurred vision, fatigue and recurrent infections. If these symptoms are present, the diagnosis is confirmed by unequivocal elevation of the blood glucose concentrations:

\[
\text{Fasting venous plasma glucose } \geq 7.8\text{mmol/l} \\
\text{OR} \\
\text{Casual (random) venous plasma glucose } \geq 11.1\text{mmol/l}
\]

These diagnostic levels also apply in asymptomatic subjects, although at least two confirmatory blood glucose readings should be obtained.

Fasting or casual venous plasma glucose levels >5.5mmol/l but less than the above levels lie in an uncertain range, and for diagnostic purposes a 75g oral glucose tolerance test should be performed according to WHO guidelines (2) and evaluated by established WHO criteria (3): See Table 1.
TABLE 1.
DIAGNOSTIC VALUES OF THE ORAL GLUCOSE TOLERANCE TEST

<table>
<thead>
<tr>
<th>Glucose concentration, mmol/litre</th>
<th>Venous plasma</th>
<th>Capillary plasma</th>
<th>Venous whole blood</th>
<th>Capillary whole blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting value</td>
<td>≥ 7.8</td>
<td>≥ 7.8</td>
<td>≥ 6.7</td>
<td>≥ 6.7</td>
</tr>
<tr>
<td>2 hr after glucose load</td>
<td>≥ 11.1</td>
<td>≥ 12.2</td>
<td>≥ 10.0</td>
<td>≥ 11.1</td>
</tr>
<tr>
<td>Impaired glucose tolerance</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting value</td>
<td>&lt; 7.8</td>
<td>&lt; 7.8</td>
<td>&lt; 6.7</td>
<td>&lt; 6.7</td>
</tr>
<tr>
<td>2 hr after glucose load</td>
<td>7.8-11.0</td>
<td>8.9-12.1</td>
<td>6.7-9.9</td>
<td>7.8-11.0</td>
</tr>
</tbody>
</table>

NON-INSULIN DEPENDENT DIABETES MELLITUS (NIDDM)
Globally, NIDDM outnumbers all other types of diabetes. In Western countries it constitutes approximately 80-85% of all cases of diabetes, as in Australia. There are ethnic groups including American Indians, South Pacific Islanders, Asian Indians, ethnic Chinese and Australian Aborigines where NIDDM is virtually the only form of diabetes. This class of diabetes occurs most commonly in adults and particularly with advancing age. The onset of symptoms may be insidious and unrecognised.

Patients with NIDDM will not be dependent on injected insulin to sustain life. However insulin may be required to control symptoms or to improve marked hyperglycaemia if this cannot be achieved by diet and oral agents. About one third of NIDDM patients in Australia are treated with insulin. In NIDDM patients, basal or fasting levels of insulin or C-peptide are normal or elevated indicating insulin resistance.

NIDDM can occur in young persons who do not require insulin and who are not ketotic.

IMPAIRED GLUCOSE TOLERANCE (IGT)
This category is intermediate between normality and diabetes and frank diabetes and has been described as a research category for the study of its natural history and complications (3). It is now known that there is a much greater risk of progression to frank diabetes (4) also subjects with IGT have an increased risk of cardiovascular disease and many show clustering of the features of the metabolic syndrome (Syndrome X) with abdominal obesity, hypertension, and dyslipidaemia. Subjects with IGT should always be assessed for the appropriate risk factors and counselled accordingly.

DIABETES PREVALENCE AND RISK FACTORS
The prevalence of diagnosed diabetes mellitus in the Australian population aged 25 years and over is estimated to be 3.0%. The prevalence rises to at least 8.0% over the age of 75 years. An estimated 335,000 persons in Australia have diabetes (5). 80-85% of known diabetic subjects have NIDDM. The rate of undiagnosed NIDDM in Australia is probably equal to the rate of known cases (6).

The risk factors for NIDDM are as follows:-

1. Ethnic groups with high prevalence including Aborigines and Torres Strait Islanders, Polynesians, Mauritians, Maltese, Chinese, and Asian Indians.

2. Positive family history of NIDDM in direct relatives (parents, siblings or children).

3. Overweight or obesity as indicated by body mass index (BMI) >25kg/m\(^2\) or percentage ideal weight >115% or increased abdominal obesity (waist hip ratio >0.90 for males, >0.80 for females).

4. Age >50 years, where there is marked increase in prevalence with increasing age. Note that with high prevalence ethnic groups a lower cut point for age for example >30 years may be selected.

5. Previous abnormality of glucose tolerance including gestational diabetes.

6. Pregnant women aged 30 years or more, or females with a history of birth of big babies >4.5kg, multiple miscarriages, or unexplained stillbirths.

7. Hypertension, dyslipidaemia, or clinical macrovascular disease. Note that treated hypertension is a risk factor, and some treatments including thiazides and beta blocking drugs may exacerbate the risk of diabetes. The dyslipidaemia associated with NIDDM is usually manifest by high triglyceride (>2.2mmol/l), low HDL-cholesterol (<1.0mmol/l).

8. Use of medications including glucocorticoids, oestrogens, thiazide diuretics, beta blockers and nicotinic acid.

The greater the number of risk factors present in an individual, the greater is the chance of developing NIDDM. Finding NIDDM in an individual with no risk factors is considered uncommon.

SCREENING FOR NON-INSULIN DEPENDENT DIABETES MELLITUS (NIDDM)
OBJECTIVES AND RATIONALE
The question of screening for NIDDM has caused controversy over several decades. The underlying philosophy is that detection of diabetes in asymptomatic individuals, or those with unrecognised symptoms, will result in effective treatment. Treatment early in the course of the disease is considered likely to diminish the severity of complications or at least to identify complications that can be treated, thus reducing premature morbidity and mortality.

Patients with NIDDM, like all types of diabetes, have the risk of developing chronic microvascular complications. These include retinopathy, nephropathy and neuropathy, all of which are related to the duration and degree of hyperglycaemia. There is good evidence that control of hyperglycaemia reduces the frequency and severity of these complications (7).

In addition subjects with NIDDM have accelerated atherosclerotic disease with an increased rate of coronary heart disease, stroke and peripheral vascular disease. In non-diabetic populations there is compelling evidence that modifying risk factors reduces cardiovascular events: this should also apply to subjects with NIDDM (and IGT) although no preventive trial data is available.

Well designed screening programmes can provide valuable information about the prevalence of diabetes and of IGT and the natural history of these conditions in different populations. Inevitably such screening programmes also enhance community awareness.

The first diabetes screening workshop in 1978 concluded that only screening for diabetes in pregnancy should be encouraged (8). Evidence for the benefits of screening for other forms of diabetes did not outweigh the evidence of potential deleterious effects and the cost was not considered to be justified.

More recently positive recommendations in favour of screening for NIDDM have been made by authoritative bodies (9-12), even though the performance and cost effectiveness of the proposed strategies have not yet been evaluated. The approach recommended here of selective screening of subjects with high risk factors for NIDDM has been promulgated by the American Diabetes Association (9), the British Diabetic Association (13), the Canadian Taskforce on Periodic Health Examinations (14), and the World Health Organisation (10).

In Australia, any recommendation for screening is based on the knowledge that diabetes is quite common and rising in frequency here, but there are approximately as many undiagnosed as diagnosed cases of NIDDM, and that at presentation a significant proportion of patients will show manifest complications of diabetes indicating that an unrecognised preclinical stage of the condition has been present for four to seven years (15). Early identification should lead to correction of the metabolic abnormalities, and to the prevention or the treatment of complications.
While screening for IGT has not been recommended, the discovery of cases of IGT is an inevitable outcome of screening for NIDDM if glucose tolerance tests are used as the diagnostic procedure. Cases with IGT require counselling to prevent progression to diabetes and to control concurrent risk factors for cardiovascular disease.

It is important to remember that a positive screening test does not confirm NIDDM but confers a higher probability than normal of the individual having the disease. The provision of effective follow up for diagnostic testing, and after-care for those individuals found to have NIDDM or IGT is essential.

Other important considerations in the design of a screening programme include:-

- An estimate of the sensitivity and specificity of the screening test
- Cost effectiveness that includes cost of the screening methodology and of any necessary follow up.
- The definition of the target population to be screened.

There are potential adverse effects of screening. Thus it is important that appropriate explanations are given in advance of the screening tests, and that individuals participating have consented and are aware of these:-

- Diagnosis of diabetes can influence insurance and sometimes employability.
- A false negative screening test can provide false reassurance.
- Medical complications of the screening test include venipuncture and the need for follow up of positive screenees.
- A false positive screening test will result in psychological stress, and additional costs.

SCREENING RECOMMENDATIONS FOR NIDDM
The Position Statement of the American Diabetes Association (9) is endorsed by the ADS Council. They are reproduced here with modifications for Australian conditions.

The criteria for the diagnosis of diabetes and the guidelines for screening are made mindful of the following principles:-

- The risk of diabetes is graded with respect to blood glucose levels especially where there are only minor or borderline elevations (16).
- Availability of blood glucose measurement techniques is variable. For standardisation in Australia, use of venous plasma glucose via measurements via an accredited laboratory is recommended.
• Use of blood glucose meters is not recommended for screening programmes. There are major limitations in the use of random fingerprick blood determinations by reflectance meter (16) as well as issues of infection control.

• An individual has variability of blood glucose measures including responses to an oral glucose load. Borderline positive tests for NIDDM or IGT are quite likely to become negative on re-testing. For such individuals, repeat screening at annual intervals at the discretion of the medical practitioner is recommended. The social implications of the diagnosis of diabetes, particularly in borderline cases, need to be balanced against the potential for neglect of undiagnosed individuals.

General guidelines for conducting diabetes screening in medical practitioners’ consulting rooms, and in community health centres, and in population screening programmes are described below:-

1. Screening programmes should identify individuals with two or more diabetes risk factors as described above. A written or verbal questionnaire will identify the categories. Those individuals with symptoms, or with two or more risk factors, should be advised to have a screening blood glucose test.

2. Screening by blood glucose measurements should be performed on:-

   2.1 individuals with symptoms of diabetes that are unrecognised
   2.2 individuals at increased risk of diabetes on the basis of known risk factors
   2.3 individuals with possible complications of diabetes (clinical features of retinopathy, neuropathy, or nephropathy).

3. Screening criteria for blood glucose levels (18) are as follows:-

   3.1 Fasting venous plasma glucose (mmol/l)
       < 5.5 probably excludes diabetes
       5.5-7.7 indication for diagnostic testing if symptoms or risk factors are present
       ≥ 7.8 probable diabetes

   3.2 Random venous plasma glucose (mmol/l)
       <5.5 probably excludes diabetes
       5.5-11.0 indication for diagnostic testing where symptoms or risk factors are present
       ≥11.1 indicates probable diabetes but further confirmation required.
Note: These screening criteria apply to high risk subjects for whom further diagnostic tests will identify NIDDM or its precursor IGT or their absence. The blood glucose values selected for screening are much lower than diagnostic criteria for clinical diabetes.

These screening levels should not be applied indiscriminately to low risk subjects (those without symptoms or with less than two risk factors) for the yield of new NIDDM or IGT will be very low.

4. Screening programmes must have an established mechanism for follow up of persons who have a positive screening test. It is important that all such subjects pursue medical attention. A written record of the screening information must be kept, with due care about confidentiality, and a copy given to all individuals tested. The record should contain:-

- Name, address, and phone number
- Identified risk factors for diabetes
- Test results including date, type of test (fasting or casual blood glucose levels) whether venous or capillary blood, techniques of measurement including whole blood or plasma .
- Instructions about the further medical potention required including evaluation for possible NIDDM or IGT.

Individuals with two or more risk factors for NIDDM and a positive screening test should see their usual family doctor and a diagnostic oral glucose tolerance test should be performed at the discretion of the medical attendant.

The written record should include information that the screening test is not necessarily diagnostic and may be subject to other factors which might influence the result. It should be stated that further laboratory tests may be considered necessary by the individual’s medical practitioner.

ORAL GLUCOSE TOLERANCE TESTING

The oral glucose tolerance test (OGTT) is the current diagnostic standard for the diagnosis of diabetes and IGT. It is not a screening test (unless the 2 hour abbreviated OGTT is used in high prevalence population studies. Staff conducting OGTTs should ensure that subjects conform to correct procedures as outlined in the WHO recommendations (2) (including adequate carbohydrate intake for three days before the test, adequate fasting interval before the glucose load, detection of intercurrent stresses or infections which may invalidate the tests, and the correct administration of the specified 75
gram oral glucose (dextrose monohydrate) load in the morning.

**SCREENING FOR DIABETES USING URINE GLUCOSE REAGENT STRIPS**

There is no place for urinary glucose testing in screening for NIDDM where facilities exist for measurement of blood glucose. Urinary glucose testing has poor sensitivity and specificity associated with marked variations in renal threshold, and resulting in unacceptably high false positive and false negative rates.

**SCREENING FOR RISK FACTORS FOR CARDIOVASCULAR DISEASE IN NIDDM AND IGT**

NIDDM is a major risk factor for morbidity and mortality from coronary heart disease, cerebrovascular and peripheral vascular disease. The prevalence of macrovascular disease in the diabetic population is two to four times higher and is often associated with major cardiovascular disease risk factors. Thus the diagnosis of diabetes should lead to early detection and treatment of such risk factors. IGT as part of the metabolic syndrome (Syndrome X) also implies increased risk of cardiovascular disease (4).

The consensus statement of the American Diabetes Association on the role of cardiovascular risk factors in the prevention and treatment of macrovascular disease in diabetes (19) makes the following conclusions:-

1. The commonly identified risk factors for macrovascular disease, including hypertension, dyslipidaemia and smoking, do operate in diabetic subjects and appear to be additive to diabetes in their adverse impact on atherosclerosis (Note - diabetes itself confers substantially increased risk whether IDDM or NIDDM).

2. Additional risk factors for macrovascular disease have been identified in studies of diabetic subjects including proteinuria, specific disturbances in the pattern of lipoproteins, and possible elevation of fibrinogen levels.

3. There is good evidence in the general population that modifying body weight, hypertension, dyslipidaemia and smoking habits is of value in preventing coronary heart disease. There are no randomised clinical trials of intervention in these areas in diabetic subjects.

4. General principles of intervention or treatment for vascular risk factors in diabetic subjects parallel those applied to the population at large, in terms of modifying lifestyle factors such as diet, exercise and smoking. Where drug therapy is used for hypertension and/or dyslipidaemia, separate guidelines for diabetic subjects may be necessary, as some therapeutic agents used in the management of these diseases may prejudice diabetes control.

5. Much additional research is needed in the area of risk factors for, and treatment of, diabetic macrovascular disease and the impact of interventions on outcome.
Because diabetes and IGT pose a high risk for accelerated atherogenesis, screening for cardiovascular risk factors should occur soon after the diagnosis of IGT or diabetes, and appropriate counselling and treatment should be available. Patients with cardiovascular disease risk factors should be scheduled for regular surveillance. Personnel who conduct community screening programmes must be adequately trained and demonstrate competence in the testing procedures used. They must be well informed of the principles of screening. Topics that should be included in the training programme include:-

- Ethical issues and informed consent.
- How to screen for diabetes risk factors (risk assessment questionnaire)
- Planning blood glucose testing (sample collection, labelling, storage, and transit)
- Data processing (collection, attention, analysis of the screening test information)
- Distribution of results to participants, and with permission to their doctors
- Infection control and waste disposal procedures
- Diagnostic follow up and structured after-care and/or referral procedures
- Any legislative requirements

REFERENCES


