Screening for NIDDM

Opportunities for detection, treatment, and prevention

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Although non-insulin-dependent diabetes mellitus (NIDDM) is a common and serious disease, in the U.S. about half of the people with this disease are unaware of it. Approximately four million Americans 20–74 years of age have undiagnosed NIDDM (1), making this disease a candidate for early detection and treatment (2). I will present my views on the principles of screening as applied to NIDDM and on the benefits, costs, methods, and unanswered questions regarding the screening and diagnosis of this disease.

In NIDDM, the affected person, whether diagnosed or not, does not require exogenous insulin to prevent ketoacidosis and death (3,4). NIDDM may be caused by the known, but relatively uncommon, genetic defects; but more commonly, the primary causes are still unknown. NIDDM also includes some cases of type 1 diabetes caused by autoimmune or infectious islet cell destruction that have not yet progressed to insulin-dependent diabetes mellitus (IDDM).

No universal agreement exists on diagnostic criteria for NIDDM in men and in nonpregnant women, and discrepancies between criteria are even greater in pregnancy. All criteria in common use are based on some measure of hyperglycemia, but the distribution of fasting or postload glucose concentrations in populations is continuous. Different groups of investigators have arbitrarily divided the continuum into several classes, which include normal glucose tolerance, nondiagnostic results (3), impaired glucose tolerance (IGT) (3,4), impaired fasting glucose (5), and diabetes (3,4). I point out these classification complexities to emphasize that hyperglycemia is a continuum and that the choice of cut-off points for defining diabetes is rather arbitrary.

Because of the serious consequences of diabetes in pregnancy to the mother and child, and evidence that treatment of diabetes in pregnancy improves the outcomes, all pregnant women should be tested for diabetes. This topic, including discussion of testing methods, is well discussed elsewhere (3,4,6–9) and will not be covered here.

Principles of screening

Screening is the use of a simple test to discriminate between people who are likely to have a disease and those who are likely not to have it. By implication, a different, definitive diagnostic procedure confirms the presence or absence of the disease. Screening can be conducted in different settings, including testing people seeking medical attention for other reasons, whether or not the disease is suspected. Screening also includes programs for testing people not seeking medical attention (e.g., the general population). A screening test suitable for widespread use should be simple, inexpensive, and cause little discomfort or harm, whereas a definitive test would be impractical for such use. For example, testing for occult fecal blood is a screening test for colon cancer, whereas the definitive tests might include much more invasive and expensive procedures such as X-ray contrast studies, colonoscopy, and biopsy.

Screening for NIDDM is different in that several tests can be considered either screening or diagnostic tests. The National Diabetes Data Group (NDDG) (3) and the World Health Organization (WHO) (4) published diagnostic criteria based on the oral glucose tolerance test (OGTT), but these criteria differ in some important respects (10). The WHO and NDDG criteria have been widely adopted in research, but they are not specific about diagnostic levels of hyperglycemia in the presence of symptoms or other clinical indications of diabetes and, appropriately, do not recommend an OGTT for the diagnosis of diabetes in these situations. For example, they recommend that in the presence of symptoms (which are impractical to define quantitatively) the diagnosis can be made from fasting or nonfasting blood or plasma glucose measurements. Because measurement of glucose is a simple, inexpensive, minimally invasive test that is applied widely in medical practice, it can also be considered a screening test.

There is little question that diagnosing the cause of a patient's complaints is beneficial, but it is uncertain whether screening people who do not seek medical attention and may have no symptoms from the disease is warranted. Extensive

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NIDDM, non-insulin-dependent diabetes mellitus; IDDM, insulin-dependent diabetes mellitus; IGT, imparied glucose tolerance; OGTT, oral glucose tolerance test; NDDG, National Diabetes Data Group; WHO, World Health Organization; ACE, angiotensin-converting enzyme; FPG, fasting plasma glucose.

literature describes the requirements for a worthwhile screening activity (11). I divide these requirements into three parts: the nature of the disease, the nature of the available screening and diagnostic methods, and organizational needs.

Nature of the disease. For people who are asymptomatic or not seeking medical attention to benefit from diagnosis, *1*) the disease should be serious enough to warrant medical attention; *2*) effective treatment should be available; and *3*) the prognosis should be better if the disease is diagnosed and treated early rather than late or never.

The availability of treatment encompasses not only the existence of therapeutic knowledge but also the socioeconomic resources needed to provide the treatment. Sometimes these are developed in conjunction with, or as a result of, screening programs. By prognosis, I include not only therapeutic benefits but also the costs and side effects of the treatments and of the diagnostic labeling itself.

NIDDM meets at least some of these criteria. The disease is unquestionably serious, and in developed countries treatments are generally available. Whether the prognosis is improved by early diagnosis is discussed below.

Nature of the screening and diagnostic methods. To justify use in people who are not seeking medical attention for a sign or symptom of the disease, the screening and diagnostic methods should have the following attributes: *1*) high accuracy (i.e., sensitivity, specificity, and predictive value); and *2*) low cost, inconvenience, and discomfort relative to the benefits of a diagnosis.

Ambiguity about accuracy of screening tests for NIDDM results from uncertainty in the diagnostic criteria themselves. There is disagreement about what tests (e.g., fasting glucose or OGTT) and diagnostic levels should be used. Because the screening and diagnostic methods for NIDDM are interchangeable, in my view, the question of accuracy of screening methods becomes primarily one of choosing the best diagnostic test (see *methods*). Costs of most tests for NIDDM are relatively low. The disease prevalence in the screened population is a determinant of the cost per diagnosis; the rarer the disease, the greater the cost.

Organizational requirements for screening. If screening for NIDDM occurs in the course of medical care, the provision of appropriate interpretation and follow-up of the screening test results should not be problematic. This issue must be dealt with, however, if screening is performed elsewhere (i.e., community screening). A system should be established for inviting, testing, and notifying subjects, and most importantly, for follow-up evaluation and treatment when indicated. Details of most of these points are discussed elsewhere (11) and, specifically regarding NIDDM, by the American Diabetes Association's position statement on screening for diabetes (12).

Indications for screening and diagnostic testing

According to these principles of screening, identifying previously undiagnosed people with NIDDM is worthwhile, at least in many settings. I will discuss these situations in decreasing order of my assessment of the potential benefit-to-cost ratio.

Symptoms or signs that suggest diabetes. There is little argument that people with signs or symptoms that suggest diabetes warrant a diagnostic workup.

Other conditions associated with diabetes. NIDDM is associated with many other diseases or conditions, including coronary artery disease, hypertension, renal disease (microalbuminuria, proteinuria, and renal insufficiency), eye diseases (retinopathy, cataract, and changing visual acuity), hyperlipidemia, peripheral vascular disease, neuropathy, medial arterial calcification, and periodontitis. A clinician caring for a patient with one of these conditions should consider diabetes and in many cases test for it.

Presence of indicators of high risk of NIDDM. People with first-degree relatives with NIDDM, members of ethnic groups with a high risk of NIDDM (e.g., American Indians, Pacific Islanders, Hispanic Americans), and obese and older people are more likely to have NIDDM. Thus, a screening program for such people will detect a higher proportion of cases of NIDDM. This is favorable in terms of the cost per diagnosis but does not necessarily imply that such people will derive more benefit from the diagnosis than those without such risk indicators.

General population. The least certain group for screening is the general population. Because many people with NIDDM detected through such screening have few signs or symptoms attributable to diabetes, they may receive little immediate benefit from a diagnosis and treatment. The possibility of other benefits is discussed in *benefits*. The degree of hyperglycemia is likely to affect the benefit-to-cost ratio. Those with a greater degree of hyperglycemia probably have a worse prognosis, which may be improved by early diagnosis and treatment, than those whose degree of hyperglycemia barely qualifies them for a diagnosis of NIDDM.

Benefits of screening and diagnosis

People with symptoms attributable to diabetes. Because symptoms attributable to hyperglycemia can usually be readily relieved by hypoglycemic therapy, people with symptomatic diabetes should benefit from a diagnosis followed by appropriate treatment. The diagnosis will often also lead to recognition of other associated conditions or chronic diseases for which treatment may also be beneficial.

People with diabetes and no or minimal symptoms. The potential values of diagnosis and treatment to control hyperglycemia and other factors, such as hypertension and hyperlipidemia, are to prevent *1*) symptoms or acute complications; and *2*) the long-term vascular, renal, and neural complications. This discussion of prevention of long-term complications also applies to people with symptomatic diabetes.

The value of treatment to prevent

symptoms and acute complications is obvious, but the prevention of long-term complications is more controversial. Among those with diabetes, the degree of hyperglycemia, whether measured by glycated hemoglobin or fasting or postload plasma glucose (13), is associated with the risk of microvascular complications. Two randomized clinical trials have shown that in IDDM patients, intensive insulin treatment improves glycemic control and decreases the incidence rates and rates of progression of several complications (14,15). Although these studies were performed only in IDDM patients, I believe, as do others (16), that they confirm the hypothesis that hyperglycemia (or associated abnormalities that are influenced by insulin treatment) is causally related to these complications. If so, then lowering glycemia in NIDDM will also be beneficial. The challenge in extrapolating the results of studies in IDDM to NIDDM is in choosing the best way to lower glycemia because more treatment options are available, including sulfonylurea and biguanide drugs and nonpharmacological means. The optimal choice of hypoglycemic therapy in NIDDM is far from obvious because of a serious lack of relevant clinical trial data. In a pioneering study of this question, the University Group Diabetes Program did not provide strong evidence that any form of treatment for asymptomatic NIDDM prevented the long-term complications (17). The U.K. Prospective Study of Therapies of Maturity-Onset Diabetes (18), a multicentered clinical trial of treatment of NIDDM currently in progress, will provide additional data on this critical question.

High blood pressure predicts the development of diabetic nephropathy in NIDDM, and antihypertensive treatment decreases the rate of progression of renal disease in NIDDM (19,20). The effect of at least some antihypertensive drugs, such as angiotensin-converting enzyme (ACE) inhibitors, may be independent of their effect on lowering blood pressure (21,22) and may in fact benefit people with NIDDM and normal blood pressure. An important question, which affects assessment of the value of screening or early diagnosis, is whether people with NIDDM of short duration, regardless of blood pressure or albumin excretion rate, should be treated with ACE inhibitors to prevent or retard the development of nephropathy and possibly cardiovascular disease. I believe such a recommendation cannot be made from existing evidence, but clinical trials of this question are extremely important. Evidence favoring such treatment would be, in my opinion, the strongest argument yet for screening for NIDDM, especially in populations in which diabetic nephropathy is the most serious and life-threatening complication.

We need clinical trials not only of treatment effects in NIDDM, but also of screening itself, to determine whether treatments are more beneficial when started early, as a result of screening, than when initiated only after patients would otherwise receive medical attention.

People with genetic susceptibility factors. The possibility of screening for people with diabetes-susceptibility alleles at genetic loci known to influence the risk of NIDDM (23–27) is so new that little discussion has taken place about the therapeutic implications, let alone clinical trials. As the ability to identify diabetes-susceptibility genes increases, these questions will become more pressing. Some of the benefit-cost issues in detecting susceptibility alleles in people with or without NIDDM are similar to those of diagnosing NIDDM, but knowledge of a genetic mechanism may lead to better therapeutic or preventive methods, and the ability to screen early in life, at or before birth, might drastically alter the approach to prevention.

General health benefits and the prevention of NIDDM. A diagnosis of NIDDM will not provide optimal benefit unless it is accompanied by a health assessment during which other conditions that require treatment may also be detected. Many treatment approaches to NIDDM, especially those emphasizing dietary modification, exercise, and weight loss, can be expected to improve not only the hyperglycemia of NIDDM but also associated conditions such as hypertension, hyperlipidemia, and atherosclerotic vascular disease. The value of these interventions does not necessarily depend on the presence or diagnosis of NIDDM and hence may not depend on screening for NIDDM. Knowledge of the degree of hyperglycemia (assessed by measuring glucose or glycated hemoglobin) may, however, be helpful as part of an overall health assessment and influence the choice of therapy.

Treatment of people with IGT or other high-risk characteristics may prevent or delay NIDDM (28–30). Besides identifying people with undiagnosed NIDDM, screening programs uncover many with such high-risk characteristics, but no clear scientifically based treatment has been found to offer these people. The general health promotion measures discussed in the preceding paragraph should be beneficial but how to use the data on glycemia is unknown. My colleagues and I have strongly advocated diabetes prevention clinical trials in such people (29–32). Fortunately, answers to some of these basic clinical questions should be obtained from the planned U.S. randomized study Non-Insulin-Dependent Diabetes Primary Prevention Trial, in which treatment of people with high-risk characteristics such as IGT and those with newly discovered NIDDM, but without severe hyperglycemia, will be tested (33).

Adverse effects of screening and diagnosis

As do all medical procedures, screening and diagnostic tests for NIDDM have costs: economic, psycho-social, and medical. I will discuss the latter two.

Although offering the hope of improved prognosis through early treatment, a new diagnosis of NIDDM is very alarming and can transform an apparently healthy person into one who is aware of and frightened by having a serious illness. An NIDDM diagnosis may also affect

one's ability to obtain insurance and employment. From a medical standpoint, the diagnosis exposes a person to additional testing, follow-up, and treatment that may be bothersome, unpleasant, or even hazardous. The treatment may include diet and exercise programs and sometimes drugs with potentially serious or fatal side effects. Screening without adequate follow-up has additional dangers. Because of the high variability of the tests, a normal person may be found to be abnormal, a result that could lead to inappropriate diagnosis and treatment if not properly followed up. Conversely, a person with NIDDM or at high risk of developing it could be falsely reassured by a normal screening test and thus delay seeking needed care. These adverse effects are not sufficient reason to oppose screening for NIDDM, but they must be considered along with the potential benefits.

Methods of screening and diagnostic testing

Testing for NIDDM in nonpregnant people. The necessary test for NIDDM depends on the diagnostic goal. If a patient has severe hyperglycemia, a clinical suspicion of diabetes can be confirmed by any of a number of simple tests, including fasting plasma, serum, or blood glucose; glycated hemoglobin; or glycosuria by dipstick or quantitative glucose measurement. Each test is very sensitive in detecting NIDDM with severe hyperglycemia (34).

Diabetes with less severe hyperglycemia is more difficult to diagnose. The simplest tests, such as glycosuria or nonfasting blood glucose, are not well standardized because of variations in renal threshold and effects of time of day and last meal. To diagnose diabetes without severe hyperglycemia, more standardized tests, such as fasting plasma glucose (FPG) or OGTT, are needed. Even these tests, at the thresholds specified by the WHO criteria for diabetes, detect different conditions. The WHO FPG criterion for diabetes (≥7.8 mM or 140 mg/dl) reflects much greater hyperglycemia than the 2-h postload plasma glucose criterion for diabetes (≥11.1 mM or 200 mg/dl). In the U.S. National Health and Nutrition Examination Survey, 89% of those meeting the fasting glucose criterion also met the 2-h criterion, but only 26% of those with diabetes by WHO criteria had an FPG level ≥7.8 mM (10).

No simple answer can be found to the question of which test (fasting glucose or OGTT) should be used for either a screening or diagnostic test. Fasting glucose by WHO criteria will diagnose fewer people, but they will have more severe hyperglycemia (except for those who did not actually fast for the test). The difference, however, is not between a fasting or postload test, per se, but in the diagnostic levels chosen for each one. Thus, the decision rests on the balance between benefit and cost, which may depend on the degree of hyperglycemia to be detected.

Both fasting and postload plasma glucose measures are strongly related to the presence or future development of the microvascular complications of diabetes, and, in populations with high prevalence rates of NIDDM, both have bimodal frequency distributions, which suggests a natural division between diabetic and nondiabetic people. Consideration should not be restricted to these two measures, however, because these same properties are shared by glycated hemoglobin. Among Pima Indians, all three measures (fasting glucose, 2-h glucose, and glycated hemoglobin) are equivalent as predictors of diabetic retinopathy in those with diabetes diagnosed by WHO criteria (13) or in the entire population (35). We have thus suggested that no particular advantage lies in the conventional diagnostic methods based on fasting glucose or the OGTT, and when it is more convenient, diagnosis could also be made by glycated hemoglobin (35). This test has the advantage, both in large-scale screening programs and in routine clinical practice, of not requiring the subject to fast or to spend 2 hours being tested. The disadvantages of glycated hemoglobin as a diagnostic test are that the methods are poorly standardized and less outcome data are available than for the OGTT. In many settings, the laboratory, personnel, and logistic costs incurred in measuring glycated hemoglobin are less than those of obtaining fasting blood or performing an OGTT. In these settings, the glycated hemoglobin test is, in my opinion, the preferred screening and diagnostic test for NIDDM.

Testing for people with high-risk conditions such as IGT. Given the imprecision of the tests and the uncertainties about the appropriate diagnostic levels, a fuzzy boundary exists between diabetes and high-risk conditions such as IGT. During the process of screening and diagnosing NIDDM, regardless of the method and diagnostic levels used, many people will be found whose test results are just below the diagnostic level and who are at increased risk of developing diabetes in the future (or of being diagnosed if retested). In people without diabetes, many factors, such as IGT, obesity, fasting hyperinsulinemia, and others listed in *Indications*, predict its development or indicate a greater likelihood of undiagnosed diabetes. In addition, it has recently become possible to identify some people genetically at high risk of NIDDM by virtue of carrying abnormal alleles at the glucokinase, insulin, or other genetic loci (23–27). I predict that the ability to identify people with genetic susceptibility to NIDDM will increase greatly in the next few years. Certain HLA-DR and -DQ (human leukocyte antigen) types and antibodies to islet cells and GAD (glutamic acid decarboxylase) also indicate higher risk of diabetes that is primarily IDDM, but may include some people with or at high risk for developing NIDDM.

Conclusions and recommendations

NIDDM is a common disease that is often disabling or fatal, but approximately half of the adults with the disease are undiagnosed. NIDDM, which is easily detected in routine medical practice or population screening programs, is thus an obvious

candidate for increased efforts for screening and diagnosis.

The major controversy centers around which people will benefit from discovering the undiagnosed disease. A broad spectrum of people can be found, ranging from pregnant diabetic women and others with symptoms of diabetes, for whom diagnosis and treatment are clearly indicated, to asymptomatic people who have IGT or barely satisfy diagnostic criteria for diabetes, for whom the benefits of treatment or the optimal form of treatment are unknown. For these people, as well as those with other high-risk conditions (including genetic susceptibility), we need guidance from clinical trials. There is great hope that early interventions, such as treatment of IGT to prevent NIDDM or treatment of new-onset NIDDM with ACE inhibitors to prevent nephropathy, may be very beneficial in the long run, but we do not yet have sufficient evidence to recommend these measures except in the context of research studies.

I believe screening and diagnostic procedures are clearly indicated for pregnant women and people with symptoms or signs suspected of being caused by diabetes and for those with diseases often associated with diabetes for whom diagnosis and treatment of diabetes would help in their management. If screening is performed in other situations without a research component, relatively stringent diagnostic criteria should be employed to increase the probability that people detected will benefit from treatment.

There is insufficient evidence that widespread population screening for NIDDM is beneficial, but there seems to be a high probability that such benefit will be demonstrated by appropriate research studies, which need to be encouraged. Such research should also evaluate screening and diagnostic methods other than fasting glucose and the OGTT. Glycated hemoglobin appears to have the same desirable properties for a screening or diagnostic test plus many practical advantages.

Population screening programs for diabetes should usually be combined with screening for other treatable chronic diseases or risk factors. This is especially true in populations with a low prevalence of NIDDM, in which the value of screening for other conditions may be greater than for NIDDM. General recommendations regarding screening for diabetes-susceptibility genes are premature, but discussion of these topics will soon become much more important.

Screening and diagnosis are only the beginning of a process of helping people with undiagnosed NIDDM. Equally important are determining the optimal treatments for people with differing degrees of abnormality or with different causes of NIDDM and ensuring that when effective treatments are known, they are made available.

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