*Chapter 2*

# *Classification, Diagnostic Criteria, and Screening for Diabetes*

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SUMMARY

Diabetes mellitus comprises a heterogeneous group of disorders characterized by high blood glucose levels. Four major types of diabetes have been defined by the National Diabetes Data Group (NDDG) and the World Health Organization (WHO): insulin-dependent diabetes mellitus (IDDM), non-insulin-dependent diabetes mellitus (NIDDM), gestational diabetes mellitus (GDM), and diabetes secondary to other conditions. Diabetes can be diagnosed by the presence of the classic signs and symptoms of diabetes and unequivocally elevated blood glucose levels, by fasting plasma glucose (FPG) ≥140 mg/dl, or by venous plasma glucose ≥200 mg/dl at 2 hours after a 75-g oral glucose challenge.

In 1993, there were ~7.8 million diagnosed cases of diabetes in the United States, of whom ~43% were treated with insulin. IDDM with onset at age <30 years comprises ~7% of all diagnosed cases. Some studies indicate that ~7% of insulin-treated cases with onset at age ≥30 years may also be IDDM. If these data are correct, then insulin-treated NIDDM comprises ~30% of diagnosed diabetes and NIDDM not treated with insulin comprises ~55%. Diabetes associated with or secondary to other conditions may occur in ~1%-2% of all disorders comprising the syndrome of diabetes. In addition to these diagnosed cases, there are ~7 million undiagnosed cases of NIDDM in the United States. GDM occurs in ~3%-5% of all pregnancies.

Impaired glucose tolerance (IGT) is a class that encompasses persons whose glucose tolerance is intermediate between normal and diabetic. About 11% of adults have IGT when tested by oral glucose challenge.

About half of adults with diagnosed NIDDM indicate that they were symptomatic at diagnosis, but the other half report that their diabetes was diagnosed during a routine physical exam, through screening for diabetes, or while being treated for another condition. Virtually all people with NIDDM state that they had a blood test at diagnosis, with 38% indicating that an oral glucose tolerance test (OGTT) had been performed at diagnosis.

About 31% of adults without diagnosed diabetes in 1989 reported being screened for diabetes in the previous year. Blood glucose tests were ordered or performed in 23.5 million visits of patients without diabetes to office-based physicians in 1985, and urine glucose tests in 55.3 million visits. These tests were presumably used in screening for hyperglycemia and glycosuria. About 3.2 million OGTTs were performed annually during 1989-90 during patient visits to office-based physicians.

The onset of NIDDM, on average, is probably ~10 years before clinical diagnosis. A proportion of individuals with undiagnosed NIDDM develop microvascular disease of the eye and kidney and neuropathy during this preclinical period, and macrovascular disease and risk factors for vascular disease are very common in these persons. Consequently, screening for undiagnosed NIDDM appears warranted, particularly in persons at high risk for NIDDM, although controversy exists about screening. Detection of undiagnosed NIDDM can be conducted by an oral glucose challenge or FPG, although only ~25% of adults with undiagnosed NIDDM (2-hour post-challenge glycemia ≥200 mg/dl) have fasting hyperglycemia (≥140 mg/dl).

Screening is most appropriately carried out in groups at high risk for NIDDM. Major risk factors for NIDDM include older age; obesity; family history of diabetes; race/ethnicity of black, Hispanic, or American Indian; and presence of complications related to diabetes. As many as 78% of nondiabetic adults in the United States have at least one of these risk factors, and 23% have three or more. Rates of screening for diabetes are higher in people with these risk factors and with diabetes-related complications. In 1989, 39% of peo-

ple with three risk factors or complications, and 57% of people with four or more reported being screened for diabetes in the previous year. If the 75-g oral glucose challenge is used to screen for undiagnosed NIDDM in the U.S. population, the yield of positive screenees (2-hour glucose ≥200 mg/dl) would be 9% when people age ≥40 years who have a percent desirable weight (PDW) ≥120 are screened. This would capture 67% of all U.S. adults with undiagnosed NIDDM. The yield could be increased to 25% if people age ≥40 years with PDW ≥140 and a family history of diabetes were screened. This would capture only 25% of all cases of undiagnosed NIDDM, but only 6% of U.S. adults would have to be administered the oral glucose challenge. The cost-effectiveness and long-range benefit to the patient of such screening strategies remain to be defined.

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## CLASSIFICATION AND FREQUENCY OF THE TYPES OF DIABETES

Diabetes mellitus is a clinically and genetically heterogeneous group of disorders that have one common feature—abnormally high levels of glucose in the blood due either to insulin deficiency or to resistance of the body's cells to the action of insulin. It has been centuries since this syndrome was first recognized. However, over the past several decades, research has led to the recognition that the different types of diabetes have different causes although their pathologic courses after onset of diabetes may be similar. The classification of this heterogeneous group of disorders is summarized in Table 2.1. This classification is recommended by the NDDG of the National Institutes of Health[1] and by the WHO Expert Committee on Diabetes[2,3]. It includes the types of diabetes that occur in the United States but does not include diabetic syndromes common in some countries but rarely seen in the United States, such as malnutrition-related diabetes. The table highlights the different clinical presentations and genetic and environmental etiologic factors that permit discrimination among the types of diabetes.

In patients for whom inadequate information is obtained, it may be difficult to distinguish among IDDM, NIDDM, and diabetes secondary to other diseases. For

*Table 2.1*
Classification of the Types of Diabetes

| Class name | Characteristics |
|---|---|
| Insulin-dependent diabetes mellitus (IDDM) | Low or absent levels of circulating endogenous insulin and dependent on injected insulin to prevent ketosis and sustain life<br>Onset predominantly in youth but can occur at any age<br>Associated with certain HLA and GAD antigens<br>Abnormal immune response and islet cell antibodies are frequently present at diagnosis<br>Etiology probably only partially genetic, as only ~35% of monozygotic twins are concordant for IDDM |
| Non-insulin-dependent diabetes mellitus (NIDDM) | Insulin levels may be normal, elevated, or depressed; hyperinsulinemia and insulin resistance characterize most patients; insulinopenia may develop as the disease progresses<br>Not insulin-dependent or ketosis-prone under normal circumstances, but may use insulin for treatment of hyperglycemia<br>Onset predominantly after age 40 years but can occur at any age<br>Approximately 50% of men and 70% of women are obese<br>Etiology probably strongly genetic as 60%-90% of monozygotic twins are concordant for NIDDM |
| Gestational diabetes (GDM) | Glucose intolerance that has its onset or recognition during pregnancy<br>Associated with older age, obesity, family history of diabetes<br>Conveys increased risk for the woman for subsequent progression to NIDDM<br>Associated wlth increased risk of macrosomia |
| Other types of diabetes, including diabetes secondary to or associated with:<br>Pancreatic disease<br>Hormonal disease<br>Drug or chemical exposure<br>Insulin receptor abnormalities<br>Certain genetic syndromes | In addition to the presence of the specific condition, hyperglycemia at a level diagnostic of diabetes is also present<br>Causes of hyperglycemia are known for some conditions, e.g., pancreatic disease; in other cases an etiologic relationship between diabetes and the other condition is suspected |

*Source*: References 1-3

IDDM there may be evidence of insulinopenia by direct measurement of insulin or C-peptide levels, by inference through documentary episodes of ketosis, or by a history of insulin use equal to the duration of diabetes in thin patients. Diabetes secondary to another condition can only be established by clinical workup or medical history to determine the presence of the other condition (see Chapter 5). If IDDM and secondary diabetes can be excluded, patients who meet the diagnostic criteria for diabetes can be presumed to have NIDDM.

Table 2.2 shows the prevalence of diagnosed diabetes in the United States in 1992, by age and type of diabetes, based on self-reported data from the 1989 and 1992 National Health Interview Surveys (NHIS). Women in the survey who had diabetes diagnosed only during pregnancy have been excluded, and the small proportion of subjects with secondary diabetes (~1%-2%) could not be identified.

There are ~7.4 million diagnosed cases of diabetes in the United States, based on 1992 estimates of the population[4]. Of these, ~43% are treated with insulin[5]. IDDM with onset at age <30 years comprises ~7% of all diagnosed cases[5]. Some studies indicate that ~7% of insulin-treated cases with onset at age ≥30 years may also be IDDM[6-8]. If these data are correct, then insulin-treated NIDDM comprises ~30% of diagnosed diabetes and NIDDM not treated with insulin comprises ~55%. GDM occurs in ~3%-5% of all pregnancies (see Chapter 35). Diabetes associated with or secondary to other conditions may occur in ~1%-2% of all disorders comprising the syndrome of diabetes (Chapter 5). In addition to these diagnosed cases, there are ~7 million undiagnosed cases of NIDDM in the United States, based on the finding that there is about one undiagnosed case for every diagnosed case among adults[9,10].

*Table 2.2*
Prevalence of Diagnosed Diabetes (Thousands) According to Type of Diabetes, U.S., 1992

| Type of diabetes and insulin use | Age group (years) | | | | |
|---|---|---|---|---|---|
| | All | <18 | 18-44 | 45-64 | ≥65 |
| All diabetes | 7,417 | 87 | 1,214 | 2,716 | 3,400 |
| IDDM, onset age <30 years | 528 | 87 | 375 | 57 | 9 |
| IDDM, onset age ≥30 years | 535 | 0 | 103 | 201 | 231 |
| NIDDM, using insulin | 2,183 | 0 | 285 | 913 | 985 |
| NIDDM, not using insulin | 4,171 | 0 | 451 | 1,545 | 2,175 |

The small proportion of persons with diagnosed diabetes who have secondary diabetes (~1%-2%) could not be identified. All subjects who do not have IDDM have been designated as NIDDM. All subjects age <18 years are assumed to have IDDM. For age ≥18 years, subjects with age at onset <30 years were defined as having IDDM if they had continuous insulin use since diagnosis and percent desirable weight (PDW) <120 (equivalent to BMI of <27 for males and <25 for females). For diabetic subjects with age at diagnosis ≥30 years, 8.5% with current age 30-49 years, 7.4% age 50-64 years, and 6.8% age ≥65 years appear to have IDDM, based on PDW <125 and continuous insulin use since diagnosis of diabetes (Reference 6). These data have been used to compute the prevalence of IDDM with onset at age ≥30 years and to decrease the prevalence of insulin-treated NIDDM by this amount.

*Source*: References 4-6

The heterogeneity within the syndrome of diabetes implied in Table 2.1 has important implications for research and for clinical management of patients. For example, different genetic, metabolic, environmental, and lifestyle factors result in similar diabetic phenotypes (hyperglycemia and microvascular complications), although the disorders in Table 2.1 differ markedly in pathogenesis, natural history, and responses to therapy and preventive measures. The exact causes of IDDM and NIDDM, the subject of intensive research over the past decades, remain unknown, although both can be accompanied by ketoacidosis, blindness, kidney failure, premature cardiovascular disease, stroke, amputations, and other complications. GDM may arise from the physiological stresses of pregnancy or it may be a degree of abnormal glucose tolerance that precedes pregnancy and is discovered during the routine metabolic testing that occurs during pregnancy (see Chapter 35). Diabetes associated with other conditions may be strictly secondary to the pathophysiology of these conditions (Chapter 5). Each class in Table 2.1 may be heterogeneous in etiology and pathogenesis, and further research is needed to define more precisely the different types of diabetes, determine their etiologies, and devise more appropriate preventive and therapeutic strategies.

## DIAGNOSTIC CRITERIA FOR DIABETES

### SCIENTIFIC BASIS FOR THE DIAGNOSTIC CRITERIA

Diagnosis of diabetes defines a group at high risk for micro- and macrovascular disease. The diagnostic criteria were established by the NDDG[1] and WHO[2] in 1979-80, and several criteria may be used (Table 2.3). For individuals with symptoms of diabetes, such as excessive thirst and urination or unexplained weight loss, only elevated FPG (≥140 mg/dl) or random plasma glucose ≥200 mg/dl is required to confirm the diagnosis. Many persons with symptomatic NIDDM who meet these criteria, however, have diabetes that has already progressed significantly in its severity before diagnosis. For example, diabetic retinopathy was present in 21% of patients with NIDDM at clinical diagnosis in southern Wisconsin[11,12] and in 16%-19% of Mexican Americans found to have NIDDM on

*Table 2.3*
Criteria for Diagnosis of Diabetes in Nonpregnant Adults

*I. In a clinical setting*

Any one of the following is considered diagnostic of diabetes. In each case, measurement of glucose concentration should be repeated on a second occasion to confirm the diagnosis.

A. Presence of the classic symptoms of diabetes, such as polyuria, polydipsia, ketonuria, and rapid weight loss, together with gross and unequivocal elevation of plasma glucose, e.g., postprandial or random plasma glucose concentration ≥200 mg/dl (11.1 mmol/L).

B. Elevated fasting glucose concentration on more than one occasion:
venous plasma ≥140 mg/dl (7.8 mmol/L)
venous whole blood ≥120 mg/dl (6.7 mmol/L)
capillary whole blood ≥120 mg/dl (6.7 mmol/L)

If the fasting glucose concentration meets these criteria, the OGTT is not required. Virtually all persons with FPG ≥140 mg/dl will exhibit an OGTT that meets or exceeds the criteria in I.C. below.

C. Fasting glucose concentration less than that which is diagnostic of diabetes (I.B., above), but sustained elevated glucose concentration during the OGTT. The NDDG requires that both the 2-hour sample and some other sample taken between administration of the 75-g glucose dose and 2 hours later meet the following criteria; the WHO requires only that the 2-hour sample meet these criteria:
venous plasma ≥200 mg/dl (11.1 mmol/L)
venous whole blood ≥180 mg/dl (10.0 mmol/L)
capillary whole blood ≥200 mg/dl (11.1 mmol/L)

*II. In an epidemiologic setting*

In epidemiologic research or during screening for diabetes, it will generally be impossible to conduct the careful plasma glucose measurements above. Any one of the following criteria, which are compromises, is considered sufficient to denote diabetes in these circumstances:

A. Medical history of diabetes diagnosed by a physician

B. A single fasting glucose concentration:
venous plasma ≥140 mg/dl (7.8 mmol/L)
venous whole blood ≥120 mg/dl (6.7 mmol/L)
capillary whole blood ≥120 mg/dl (6.7 mmol/L)

C. A single glucose concentration 2 hours after ingesting a 75-g glucose dose:
venous plasma ≥200mg/dl (11.1 mmol/L)
venous whole blood ≥180mg/dl (10.0 mmol/L)
capillary whole blood ≥200mg/dl (11.1 mmol/L)

FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; NDDG, National Diabetes Data Group; WHO, World Health Organization.

*Source*: References 1-3

screening[13,14]. Gross proteinuria was present in 11% of the Wisconsin cohort with <1 year duration of diabetes, in 37% of patients in France examined within 1 year after diagnosis, and in 10% of subjects detected to have NIDDM during a screening survey among Mexican Americans[15-17]. Among persons newly diagnosed with NIDDM in Finland, peripheral arterial disease was present in 20% and coronary heart disease in 59%, both of which were more frequent than in nondiabetic controls[18,19]. In addition, 40% of men with new NIDDM had calcifications of the abdominal aorta, and dilitation of the aortic arch was more prevalent than in controls[20]. Both of these indicate accelerated development of atherosclerotic lesions of the large arteries in the early, undiagnosed phase of NIDDM.

The NDDG and WHO recognized that complications of diabetes were developing in undiagnosed NIDDM. They examined data from long-term population-based studies in which individuals were administered a 2-hour oral glucose challenge at baseline and were followed prospectively for deterioration of glucose tolerance and development of diabetic complications[21-25]. A sentinel finding from these studies was that populations with high prevalence of NIDDM had a bimodal distribution of 2-hour post-challenge plasma glucose, with the antimode at ~200 mg/dl[26-29]. In addition, microvascular complications specific to diabetes did not develop or were rare in subjects with FPG <140 mg/dl or 2-hour post-challenge glucose <200 mg/dl. Subjects with fasting values ≥140 mg/dl or 2-hour post-challenge values ≥200 mg/dl were at high risk for diabetic retinopathy and nephropathy[30]. Consequently, the criteria for diagnosis of diabetes recommended by NDDG and WHO (Table 2.3) are based on plasma glucose levels that are predictive of the specific microvascular complications of diabetes.

The recommendations of the NDDG and WHO have been accepted and endorsed by the American Diabetes Association (ADA) and other national diabetes organizations representing the scientific bodies most concerned with diabetes. Earlier diagnostic criteria based on urine glucose or casual and postprandial glucose are no longer considered to be adequate for the diagnosis of diabetes.

## NDDG VERSUS WHO DIAGNOSTIC CRITERIA

The NDDG and WHO criteria for diabetes (Table 2.3) both permit a diagnosis based on the presence of the classic diabetic symptoms and random plasma glucose ≥200 mg/dl. Both also permit a diagnosis of diabetes based on FPG ≥140 mg/dl. In persons without unequivocal symptoms and in those with lower FPG, both require measurement of plasma glucose at 2 hours after a 75-g oral glucose challenge. For diagnosis of diabetes, this 2-hour value must be ≥200 mg/dl. The NDDG suggested that a midtest OGTT value ≥200 mg/dl is also required, but essentially all persons meeting the 2-hour criterion also meet this midtest

requirement. For example, 91% of persons in the Second National Health and Nutrition Examination Survey (NHANES II) of a representative sample of the U.S. population whose 2-hour value was ≥200 mg/dl also had 1-hour values ≥200 mg/dl[10]. This has been found in other populations as well[31,32]. Consequently, only the 2-hour post-challenge glucose value would appear to be required.

Both the NDDG and WHO criteria require a repeat determination of fasting or post-challenge plasma glucose for a definitive diagnosis of diabetes in an asymptomatic patient: that is, the diagnosis cannot be made with a single glucose result. For patients with symptoms of diabetes, a single elevated blood glucose value is considered sufficient for confirmation of the diagnosis.

## RESEARCH NEEDS FOR DIAGNOSTIC CRITERIA

The criteria for diagnosis of diabetes undoubtedly need further study and validation. For example, persons with diabetes who have high FPG levels may be at greater risk for developing complications than those who have FPG <140 mg/dl with post-challenge hyperglycemia ≥200 mg/dl. A Japanese study found the fasting value to be more predictive of mortality than the 2-hour value[33], while in Pima Indians both the fasting and the 2-hour value and glycosylated hemoglobin predict retinopathy and nephropathy[27,34,35]. Further research is needed to quantify these risks. In addition, further research is needed to determine whether blood glucose levels should continue to be the basis for diagnosing diabetes, or whether a simple measure such as glycosylated hemoglobin can accurately predict development of the complications of diabetes and hence be used for diagnosis of NIDDM.

## CRITERIA FOR GESTATIONAL DIABETES

Table 2.4 lists the criteria for GDM used most commonly in the United States. These criteria were promulgated in 1964[36,37] and were endorsed by the Second International Workshop on GDM[38]. GDM is considered in detail in Chapter 35.

## IMPAIRED GLUCOSE TOLERANCE

IGT was defined by the NDDG[1] and adopted by the WHO[2,3] to encompass persons whose FPG concentration is less than that required for a diagnosis of diabetes (<140 mg/dl) and whose plasma glucose value at 2 hours after a 75-g oral glucose challenge is intermediate between normal and diabetic (140-199 mg/dl). Thus the IGT class is defined not by clinical manifestations but by plasma glucose criteria, and a 75-g oral glucose challenge is required to place an individual in this class. "Impaired glucose tolerance" replaces the older terms "borderline diabetes" and "chemical diabetes," which are considered inappropriate because they invoke social, psychologic, and economic sanctions that are unjustified in light of the lack of severity of glucose intolerance in these persons.

*Table 2.4*
Criteria for Diagnosis of GDM

Two or more of the following glucose concentrations (fasting value and values at times after 100-g oral glucose) must be met or exceeded:

| | Venous plasma | Venous whole blood | Capillary whole blood |
|---|---|---|---|
| Fasting | 105 mg/dl (5.8 mmol/L) | 90 mg/dl (5.0 mmol/L) | 90 mg/dl (5.0 mmol/L) |
| 1 hour | 190 mg/dl (10.6 mmol/L) | 170 mg/dl (9.4 mmol/L) | 190 mg/dl (10.6 mmol/L) |
| 2 hour | 165 mg/dl (9.2 mmol/L) | 145 mg/dl (8.1 mmol/L) | 165 mg/dl (9.2 mmol/L) |
| 3 hour | 145 mg/dl (8.1 mmol/L) | 125 mg/dl (6.9 mmol/L) | 145 mg/dl (8.1 mmol/L) |

GDM, gestational diabetes mellitus. See Chapter 35 for a discussion of criteria for diagnosis of GDM.

*Source*: References 1, 36-38

There are some differences between the NDDG and WHO criteria for classifying persons as IGT. While both require the fasting and 2-hour values shown in Table 2.5, the NDDG suggests a midtest plasma glucose value ≥200 mg/dl. WHO criteria do not use this midtest value, and persons are categorized based only on their fasting and 2-hour values. The NDDG has modified its criteria to be concordant with the WHO for epidemiologic studies[10]. Use of the midtest value substantially changes the prevalence of IGT. Only about half of persons classed as IGT by WHO criteria are also classed as IGT by NDDG. The remainder are nondiagnostic, primarily because the midtest glucose value is <200 mg/dl[10].

Although persons with IGT have absent or minimal rates of retinopathy and nephropathy, they are at a higher risk of developing diabetes than persons with normal glucose tolerance. Prospective studies of the Pima Indians show that nondiabetic persons develop diabetes at a rate proportional to their 2-hour glucose value, with rates particularly high in those with

*Table 2.5*
Criteria for Impaired Glucose Tolerance

*I. NDDG and WHO criteria*

The NDDG requires that the three criteria A, B, and C must be met. The WHO requires that only criteria A and B be met.

A. Fasting glucose concentration:
- venous plasma <140 mg/dl (7.8 mmol/L)
- venous whole blood <120 mg/dl (6.7 mmol/L)
- capillary whole blood <120 mg/dl (6.7 mmol/L)

B. Glucose concentration at 2 hours after ingesting 75-g oral glucose:
- venous plasma ≥140 and <200 mg/dl (7.8 and 11.1 mmol/L)
- venous whole blood ≥120 and <180 mg/dl (6.7 and 10.0 mmol/L)
- capillary whole blood ≥140 and <200 mg/dl (7.8 and 11.1 mmol/L)

C. Glucose concentration at midtest (½ hour, 1 hour, or 1 ½ hours) after ingesting 75-g oral glucose:
- venous plasma ≥200 mg/dl (11.1 mmol/L)
- venous whole blood ≥180 mg/dl (10.0 mmol/L)
- capillary whole blood ≥200 mg/dl (11.1 mmol/L)

*II. In an epidemiologic setting or population screening*

In epidemiologic or population studies on diabetes, it may be impossible or impractical to meet the requirement of obtaining two or three blood samples. Consequently, a modification is recommended whereby a single blood sample should be drawn 2 hours after a 75-g oral glucose challenge. If the glucose concentration meets the criteria below, the individual may be assigned to the IGT class for epidemiologic purposes.

Glucose concentration at 2 hours after ingesting 75-g oral glucose:
- venous plasma ≥140 and <200 mg/dl (7.8 and 11.1 mmol/L)
- venous whole blood ≥120 and <180 mg/dl (6.7 and 10.0 mmol/L)
- capillary whole blood ≥140 and <200 mg/dl (7.8 and 11.1 mmol/L)

NDDG, National Diabetes Data Group; WHO, World Health Organization.

*Source*: References 1-3

IGT[27,39]. In studies of Caucasians, persons in the IGT class also have a higher risk of developing diabetes, with ~1%-5% becoming diabetic each year compared with <1% of persons classed as normal[23-25,40-49]. However, these studies also showed that, even after 10 years, the majority of persons remains in the IGT class and a substantial proportion retest as normal. Among Pima Indians, microvascular complications rarely occurred in persons with IGT[34] and, in a British study, persons with IGT also appeared to have little or no evidence of the microvascular disease found in persons with established diabetes[50]. However, mortality rates for IGT in the latter population were higher than those experienced by persons without diabetes, and much of the excess death was due to cardiovascular diseases[21,40,41,51]. The clinical significance of IGT and its prognostic significance for the development of complications thus remain to be fully investigated.

## THE ORAL GLUCOSE TOLERANCE TEST

In symptomatic individuals with random plasma glucose values >200 mg/dl, the OGTT is not required for a diagnosis of diabetes. However, in asymptomatic individuals and to establish a diagnosis of IGT, the OGTT is necessary[1-3]. The test should be performed in the morning on subjects who have had at least 3 days of unrestricted diet. The subject should have fasted overnight for 10-16 hours and remain seated and not smoke throughout the test. A fasting blood sample should be collected, after which the subject should drink 75 g of glucose in a concentration no greater than 25 g per 100 ml. Commercially prepared carbohydrate loads equivalent to this are available. The NDDG originally suggested that blood samples be taken at midtest (½ hour, 1 hour, or 1½ hours) and at 2 hours. However, in practice virtually all persons with 2-hour post-challenge values ≥200 mg/dl also have midtest values ≥200 mg/dl, and the midtest blood sample does not appear to be necessary. In addition, multiple blood samples are often not feasible in an epidemiologic or survey setting, and a single 2-hour blood sample can be considered adequate.

## DIAGNOSIS OF DIABETES IN THE U.S.: CIRCUMSTANCES AND METHODS

Figure 2.1 and Table 2.6 show the circumstances un-

*Figure 2.1*
Circumstances for Diagnosis of NIDDM in Adults, U.S., 1989

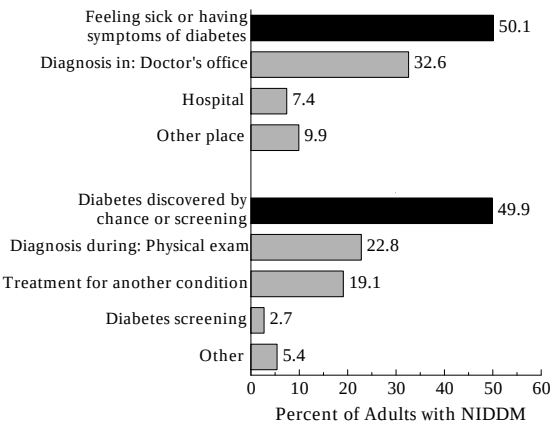



Figure shows the percent distribution of U.S. adults age ≥18 years with self-reported physician-diagnosed NIDDM, according to answers to questions about diagnosis of their diabetes. NIDDM was distinguished from IDDM by age at diagnosis, obesity, and hypoglycemic medication use.

*Source*: Reference 52; 1989 National Health Interview Survey Diabetes Supplement

*Table 2.6*

Circumstances and Tests Used for Diagnosis of Diabetes in Adults with NIDDM, U.S., 1989

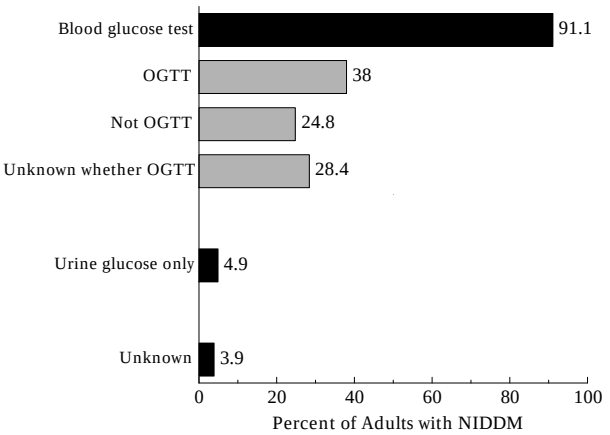
| Diagnostic situation or test | Age (years) ≥18 | 18-44 | 45-64 | ≥65 |
|---|---|---|---|---|
| Diabetes discovered when subject was sick or having symptoms of diabetes (%) | 50.1 | 64.4 | 53.0 | 43.9 |
| At his/her doctor's office | 32.6 | 37.5 | 34.8 | 29.6 |
| When hospitalized | 7.4 | 10.1 | 7.4 | 6.6 |
| Other | 9.9 | 16.8 | 10.6 | 7.5 |
| Unknown | 0.2 | 0.0 | 0.3 | 0.3 |
| Diabetes discovered by chance (%) | 49.9 | 35.6 | 47.0 | 56.1 |
| During routine physical exam | 22.8 | 15.1 | 20.3 | 26.9 |
| While being treated for some other condition | 19.1 | 15.3 | 19.2 | 19.9 |
| During screening test for diabetes | 2.7 | 2.1 | 3.0 | 2.6 |
| Other/unknown | 5.4 | 3.1 | 4.5 | 6.7 |
| Type of test used for diagnosis (%) | | | | |
| Blood test | 91.1 | 93.5 | 91.6 | 90.2 |
| Blood test only | 17.6 | 15.7 | 18.2 | 17.6 |
| Both blood and urine tests | 73.5 | 77.8 | 73.4 | 72.6 |
| Urine test only | 4.9 | 4.4 | 4.9 | 5.1 |
| Unknown | 3.9 | 2.0 | 3.6 | 4.7 |
| Oral glucose tolerance test (%)* | | | | |
| Yes | 38.0 | 42.8 | 41.5 | 33.7 |
| No | 24.8 | 29.1 | 24.0 | 24.4 |
| Unknown | 28.4 | 21.7 | 26.1 | 32.1 |

Table shows the percent distribution according to diagnostic situation of adults age ≥18 years with self-reported medical history of physician-diagnosed diabetes in a representative sample of the U.S. population. NIDDM was distinguished from IDDM by age at diagnosis, obesity, and hypoglycemic medication use. *Only individuals who indicated they were diagnosed by a blood test were asked whether an oral glucose tolerance test had been performed.

*Source:* Reference 52; 1989 National Health Interview Survey Diabetes Supplement

*Figure 2.2*

Type of Test Used for Diagnosis of NIDDM in Adults, U.S., 1989




OGTT, oral glucose tolerance test. A urine glucose test was reported to have been performed for 81% of diabetes cases diagnosed by a blood glucose test. Figure shows the percent distribution of U.S. adults age ≥18 years with physician-diagnosed NIDDM, according to answers to questions about diagnosis of their diabetes. NIDDM was distinguished from IDDM by age at diagnosis, obesity, and hypoglycemic medication use.

*Source*: Reference 52; 1989 National Health Interview Survey Diabetes Supplement

der which diabetes was diagnosed as reported by a representative sample of adults with NIDDM in the United States in the 1989 NHIS. About half (50.1%) of people with NIDDM reported that they were symptomatic (sick or feeling diabetic symptoms) at diagnosis of diabetes; the remaining half (49.9%) indicated that their diabetes was discovered "by chance." For symptomatic patients, most diagnoses occurred in a physician's office. This was also the case for asymptomatic patients; 22.8% of adults with NIDDM were diagnosed during a routine physical exam and 19.1% while being treated for another medical condition. The proportion who were symptomatic at diagnosis decreased with increasing age, and the proportion whose diabetes was discovered by chance increased with increasing age (Table 2.6).

Figure 2.2 and Table 2.6 show the type of test used for diagnosis of diabetes as reported by U.S. adults with NIDDM in 1989[52]. Almost all (91.1%) indicated that their diagnosis involved a blood test, 73.5% had both a blood and a urine test, and only 4.9% were diagnosed based on a urine test alone. Individuals who stated that they were diagnosed by a blood test were asked whether this test was an OGTT. About 38% of NIDDM adults indicated the OGTT was the method of diagnosis, but a large percentage (28.4%) did not know whether they had had an OGTT. The proportions diagnosed by blood, urine, and OGTT were similar across age groups (Table 2.6). These percentages are shown in Table 2.7 according to duration of diabetes. With more recent diagnoses, there appears to be a trend toward decrease in the use of urine glucose alone and use of the OGTT and an increase in use of blood tests that do not involve the OGTT.

## SCREENING FOR DIABETES IN THE U.S.: FREQUENCY AND METHODS

In the 1989 NHIS, a representative sample of U.S. adults with no medical history of diabetes were asked whether they had been screened for diabetes in the previous year. Figure 2.3 presents data on the proportion screened[53]. About 69% indicated they were not screened for diabetes. Of those who were screened, most were screened once (24.3%), and the remainder (6.7%) were screened more than once.

*Table 2.7*

Frequency of Tests Used in Diagnosis of Diabetes, by Duration of NIDDM, U.S., 1989

| Type of diagnostic test | Years since diagnosis of diabetes All | 0-4 | 5-9 | 10-14 | ≥15 |
|---|---|---|---|---|---|
| Proportion of NIDDMs (%) | 100.0 | 30.6 | 23.6 | 18.4 | 27.4 |
| Urine test only (%) | 4.9 | 3.2 | 4.7 | 6.1 | 7.0 |
| Blood test* | 91.2 | 95.4 | 90.9 | 91.9 | 88.1 |
| OGTT (%) | 38.0 | 36.4 | 35.6 | 40.3 | 42.1 |
| No OGTT (%) | 24.8 | 31.8 | 28.7 | 21.5 | 17.8 |
| Unknown whether OGTT (%) | 28.4 | 27.2 | 26.6 | 30.1 | 28.2 |
| Type of test unknown (%) | 3.9 | 1.5 | 4.4 | 2.1 | 5.0 |

OGTT, oral glucose tolerance test. Table shows the percent distribution according to type of diagnostic test of adults age ≥18 years with self-reported medical history of physician-diagnosed diabetes in a representative sample of the U.S. population. NIDDM was distinguished from IDDM by age at diagnosis, obesity, and hypoglycemic medication use. *82% of diagnoses involving a blood glucose test were stated to involve a urine test also.

*Source*: Reference 52; 1989 National Health Interview Survey Diabetes Supplement

The National Ambulatory Medical Care Survey (NAMCS) has provided data to examine several methods used in screening for diabetes, including blood glucose testing, urine glucose testing, and the OGTT. In the 1985 NAMCS, office-based physicians were asked to record, for a sample of their patient visits, whether they had ordered or performed a test for blood glucose or a test for urine glucose. These data were then extrapolated to all U.S. office-based physicians. For visits in which diabetes was recorded as a diagnosis in the patient, it was estimated that physicians conducted or ordered a blood glucose test in 13.3 million visits and a urine glucose test in 4.5 million visits in 1985[54]. Because the annual incidence of diabetes is only ~600,000 new cases each year[55], most of these tests were probably performed to measure glucose levels in patients with established diabetes and a minority were used to screen for and diagnose new cases of diabetes. For visits not involving diabetes, blood glucose tests were ordered in 23.5 million visits (3.8% of all visits to office-based physicians) and urine glucose tests in 55.3 million visits (9.0% of all visits)[54]. These tests were presumably used in screening for hyperglycemia and glycosuria.

*Figure 2.3*

Percent of Nondiabetic Adults Screened for Diabetes in the Past Year, U.S., 1989

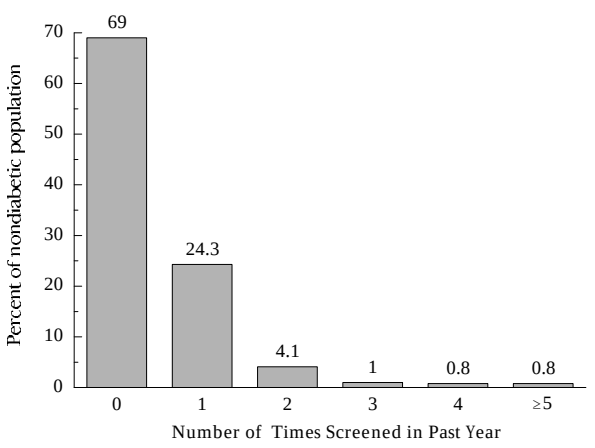



Figure shows the percent distribution of U.S. adults age ≥18 years who reported they had never been diagnosed with diabetes, according to self-reported frequency of being screened for diabetes in the previous year, based on the 1989 National Health Interview Survey Diabetes Risk Factor Supplement.

*Source*: Reference 53

In the 1989-90 NAMCS, office-based physicians recorded whether they had ordered or performed an OGTT during patient visits. An average of 3.2 million OGTTs were performed or ordered annually during visits to these physicians (Table 2.8)[52]. About 845,000

*Table 2.8*

Average Annual Frequency of OGTTs in Patient Visits to Office-Based Physicians, U.S., 1989-90

| Patient diagnosis | Average annual no. of OGTTs (thousands) | Proportion of total (%) |
|---|---|---|
| Pregnancy | 845.8 | 26.1 |
| Diabetes mellitus | 948.1 | 29.3 |
| Cardiovascular conditions and risk factors | 292.6 | 9.0 |
| Routine medical exams and laboratory determinations | 205.9 | 6.4 |
| Renal and urinary tract conditions | 156.7 | 4.8 |
| Infections | 124.5 | 3.8 |
| Arthritis and musculoskeletal conditions | 105.1 | 3.2 |
| Obesity and endocrine disorders | 93.9 | 2.9 |
| Gynecologic conditions | 93.9 | 2.9 |
| Gastrointestinal conditions | 84.9 | 2.6 |
| Neoplasms | 72.0 | 2.2 |
| Psychiatric diagnoses | 49.4 | 1.5 |
| Eye conditions | 13.8 | 0.4 |
| Neuropathy | 7.6 | 0.2 |
| Miscellaneous diagnoses | 144.1 | 4.4 |
| Total | 3,238.3 | 100.0 |

OGTT, oral glucose tolerance test. Data are derived from the 1989-90 National Ambulatory Medical Care Survey (NAMCS). The physician was asked to note, for a sample of patient visits, whether an OGTT had been performed or ordered, and these data were extrapolated to all U.S. office-based physicians. The NAMCS data form permits up to three diagnoses to be recorded by the physician. All visits in which pregnancy was one of these diagnoses are included as "pregnancy." All visits in which diabetes was listed (except those in which pregnancy was also listed) are included as "diabetes mellitus." For all other visits, the first-listed diagnosis is tabulated. The first-listed diagnosis is that condition considered by the physician to be most associated with the patient's primary reason for the office visit.

*Source*: Reference 52

OGTTs were recorded in pregnancy-related visits and were probably related to screening and diagnosis of gestational diabetes. This number can be compared with the average of 4.1 million births each year during 1989-90[56,57], suggesting that the majority of pregnancies go unscreened. About 29% of the OGTTs (948,100 per year) were associated with diabetes (without mention of pregnancy) and were presumably for the purposes of diagnosing new cases of diabetes or measuring post-challenge glucose in established diabetes, although these two circumstances cannot be distinguished. The remaining 1.4 million annual OGTTs occurred in visits for a variety of medical conditions. Diabetes was not listed on the patient record form for these visits, and thus the OGTT did not appear to result in a diagnosis of diabetes. Diabetes is associated with abnormalities in virtually every organ system, and Table 2.8 reflects the numerous conditions that may lead the physician to suspect diabetes.

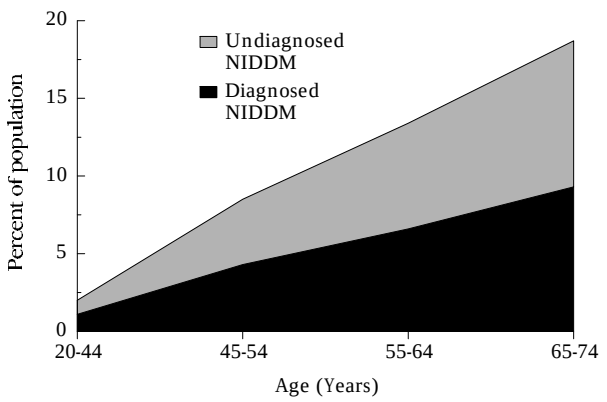
## PRINCIPLES OF SCREENING FOR UNDIAGNOSED NIDDM

The necessary requirements for screening for a disease have been summarized[58]. These principles include that the condition is an important health problem, an accepted treatment is available, the disease has an early asymptomatic stage, and a suitable screening test exists. Undiagnosed NIDDM meets all four requirements, as follows.

### PREVALENCE OF UNDIAGNOSED NIDDM

About 7 million adults in the United States meet diagnostic criteria for diabetes but are undiagnosed[59]. Figure 2.4, based on a representative sample of U.S. adults in 1976-80, shows the prevalence of diagnosed NIDDM determined by medical history and of undiagnosed NIDDM determined by OGTT. Total prevalence of NIDDM increases with age, from 2.0% at age 20-44 years to 18.7% at age 65-74 years[9]. About 50% of NIDDM is undiagnosed. This proportion is similar across all age groups, for both sexes, and for the three main racial/ethnic groups in the United States (Figures 2.4 and 2.5). The Pima Indians in Arizona have the highest prevalence of NIDDM of any population in the world[27,60]. However, undiagnosed NIDDM is virtually nonexistant among Pimas because of extensive screening for the disease in this population[61].

*Figure 2.4*
Prevalence of Diagnosed and Undiagnosed NIDDM in Adults, U.S., 1976-80



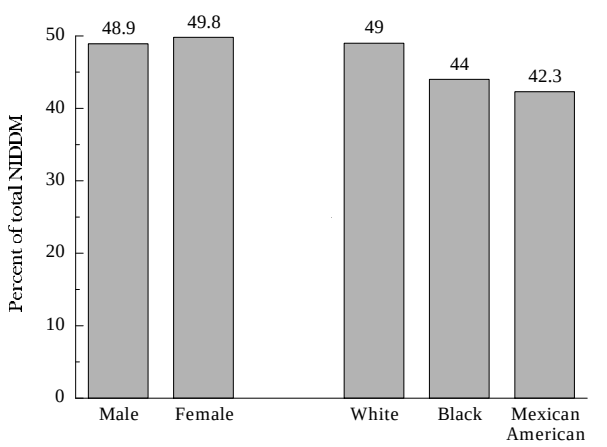

Diagnosed NIDDM was determined by medical history and undiagnosed NIDDM by oral glucose tolerance test using WHO criteria for a representative sample of U.S. adults age 20-74 years in the 1976-80 Second National Health and Nutrition Examination Survey.

*Source*: Reference 9

### THE PRECLINICAL PHASE OF NIDDM

The high prevalence of undiagnosed NIDDM indicates there must be a considerable preclinical phase for the disease, although this may not be an entirely asymptomatic period. Based on extrapolation of data on the prevalence of retinopathy, it has been estimated

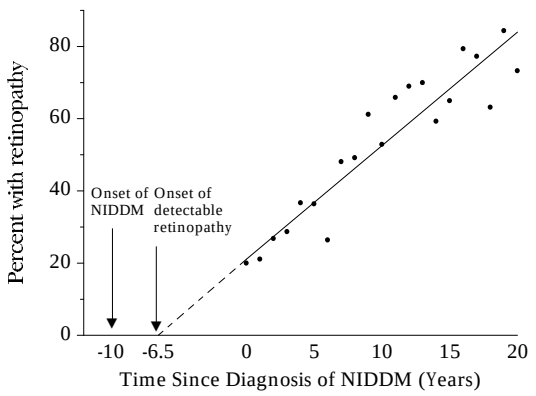
*Figure 2.5*
Percent of NIDDM That Is Undiagnosed in Adults, U.S., 1976-80




Total NIDDM determined by sum of diagnosed NIDDM (medical history of diabetes) and undiagnosed NIDDM (oral glucose tolerance test) in a representative sample of U.S. adults age 20-74 years in the 1976-80 Second National Health and Nutrition Examination Survey.

*Source*: References 9 and 59

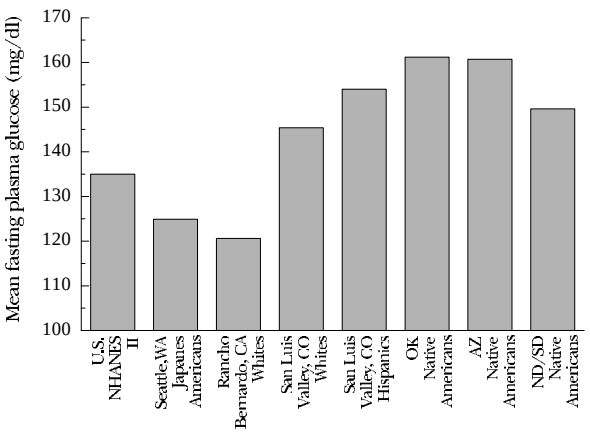
*Figure 2.6*
Estimated Time of Onset of Retinopathy and of NIDDM, Wisconsin, 1980-82




Data points are prevalence of any retinopathy in a representative sample of subjects with NIDDM according to time since diagnosis of diabetes. Line is linear regression of the data ($R^2$=0.89) to estimate time at which detectable retinopathy first began. Onset of NIDDM is believed to occur some years before evidence of detectable retinopathy.

*Source*: References 11 and 12

*Figure 2.7*
Mean Fasting Plasma Glucose in U.S. Adults with Undiagnosed NIDDM




NHANES II, 1976-80 Second National Health and Nutrition Examination Survey. Data are based on U.S. population and community-based surveys in which fasting plasma glucose and a 75-g oral glucose challenge were used to identify subjects with undiagnosed NIDDM.

*Source*: References 59, 62-65

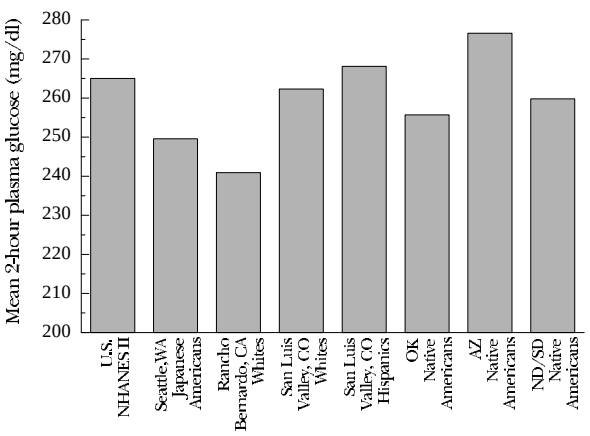
that onset of NIDDM may occur as long as 10-12 years before clinical diagnosis of NIDDM[11] (Figure 2.6). Microvascular complications of diabetes begin to develop during this period before clinical diagnosis.

## TREATABLE RISK FACTORS AND COMPLICATIONS IN UNDIAGNOSED NIDDM

Individuals with undiagnosed NIDDM have significant hyperglycemia, which is the primary risk factor for diabetic microvascular disease. Individuals age 40-69 years with undiagnosed NIDDM detected by OGTT in the 1976-80 NHANES II had mean FPG of 135 mg/dl and 2-hour post-challenge glucose of 265 mg/dl[59]. Similarly elevated values were found when undiagnosed NIDDM was detected by OGTT in Japanese Americans in Seattle, WA[62]; whites in Rancho Bernardo, CA[63]; Mexican Americans in the San Luis Valley, CO[64]; and Native Americans in Oklahoma, Arizona, North Dakota, and South Dakota[65] (Figures 2.7 and 2.8). Extremes of plasma glucose in the U.S. population age 40-69 years with undiagnosed NIDDM are shown in Figure 2.9. More than 30% have fasting hyperglycemia (≥140 mg/dl), and 25% have post-challenge glucose >300 mg/dl.

U.S. adults with undiagnosed NIDDM also have high levels of other risk factors for diabetes complications, including hypertension (67%, of which about half is uncontrolled), dyslipidemia (49% with total cholesterol ≥240 mg/dl; 62% with LDL-cholesterol ≥130 mg/dl; 28% with triglycerides ≥250 mg/dl), obesity (50% of men and 82% of women exceed 120% of desirable weight), and cigarette smoking (32%)[59]. Rates of microvascular and macrovascular disease and

*Figure 2.8*
Mean Two-Hour Post-Challenge Plasma Glucose in U.S. Adults with Undiagnosed NIDDM




NHANES II, 1976-80 Second National Health and Nutrition Examination Survey. Data are based on U.S. population and community-based surveys in which fasting plasma glucose and a 75-g oral glucose challenge were used to identify subjects with undiagnosed NIDDM.

*Source*: References 59, 62-65

*Figure 2.9*
Fasting and Post-Challenge Hyperglycemia in U.S. Adults with Undiagnosed NIDDM, 1976-80

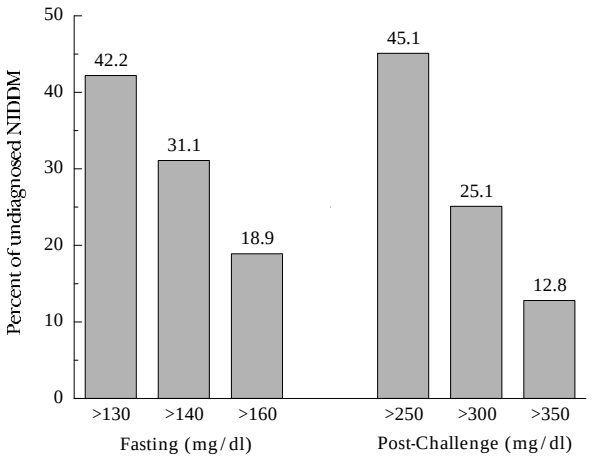



Figure shows percent with extremes of fasting and 2-hour post-75-g glucose challenge hyperglycemia in undiagnosed NIDDM (World Health Organization criteria) in a representative sample of the U.S. population age 40-69 years in the 1976-80 Second National Health and Nutrition Examination Survey.

*Source*: Reference 59

premature mortality are substantially higher than in the nondiabetic population[11,59,66,67]. For example, 21% of an NIDDM cohort in southern Wisconsin had retinopathy at diagnosis of diabetes (Figure 2.6)[11,12], and gross proteinuria was present in 11% when measured within 1 year of diagnosis[15].

## CONTROVERSIES IN SCREENING FOR NIDDM

Because of strong evidence that undiagnosed diabetes is highly prevalent, that it is associated with a high frequency of risk factors for complications, that there is a high prevalence of micro- and macrovascular complications, and that treatment for hyperglycemia and other risk factors is available, screening for undiagnosed NIDDM would appear to be appropriate, particularly in groups at high risk for NIDDM. Screening for the purpose of reducing morbidity and mortality has been advocated in reviews of undiagnosed NIDDM[59,68], and the ADA position statement on screening describes a major objective of a community screening program as being identification of individuals with one or more risk factors for diabetes[69].

However, controversy exists about screening for NIDDM[70-72]. Some of the controversy arises from the difficulty of conducting an OGTT and the low sensitivity of FPG in detecting NIDDM. Also, methods of treatment after diagnosis of diabetes are not wholly effective, as shown by the high rates of hyperglycemia, hypertension, and dyslipidemia in diagnosed NIDDM discussed in Chapter 7. In contrast, the Diabetes Control and Complications Trial (DCCT) showed that intensive treatment to reduce glycemia has a substantial effect on the incidence of microvascular complications, with decreases of 50%-75% in rates of retinopathy, neuropathy, and nephropathy[73]. It is likely that such intensive treatment would have similar benefits in NIDDM[74].

## SCREENING TESTS FOR UNDIAGNOSED NIDDM

Screening can be interpreted as public health screening in the community but also simply as testing for diabetes in patients in the clinician's office. It is unlikely that symptomatic NIDDM (criterion IA in Table 2.3) would be encountered in a screening situation, because severe symptoms characteristic of diabetes would likely have led such individuals to seek medical care and already be diagnosed as having diabetes. Several methods can be used for screening for asymptomatic undiagnosed NIDDM. For diagnosis of diabetes in an individual patient, a confirmatory test is required if the screening test is positive.

## EFFECTIVENESS OF SCREENING TESTS

Effectiveness of screening for diabetes can be evaluated by calculating four measures: a) Sensitivity—the percent with glucose levels ≥ the cutoff value among those meeting diagnostic criteria for diabetes; b) Specificity—the percent with glucose levels < the cutoff value among those not meeting diagnostic criteria for diabetes; c) Positive predictive value—the percent meeting diagnostic criteria for diabetes among all persons with glucose ≥ the cutoff value; and d) Percent requiring retesting—the percent with glucose ≥ the cutoff value among all persons screened (retesting is necessary because a repeat determination of fasting or post-challenge glucose is required to confirm a clinical diagnosis of diabetes).

## SCREENING BY ORAL GLUCOSE CHALLENGE

The OGTT is the internationally recognized standard for diagnosing asymptomatic NIDDM[1-3]. However, measuring post-challenge glucose can also be used to screen for NIDDM, and the data in Tables 2.6, 2.7, and 2.8 indicate that the OGTT is a common procedure

used to screen for and diagnose NIDDM. Measurement of plasma glucose at 2 hours after a 75-g oral glucose challenge has the characteristics of a satisfactory screening method (Table 2.9)[59,75]. Using a 2-hour value of ≥200 mg/dl, sensitivity is 97%; that is, only 3% of adults have 2-hour post-challenge glucose <200 mg/dl and are considered to have diabetes due to fasting values ≥140 mg/dl alone. Specificity is 100% because all nondiabetic subjects have 2-hour glucose values <200 mg/dl. Positive predictive value is also 100% because all persons with a 2-hour glucose value ≥200 mg/dl are considered to have diabetes. Thus a glucose challenge test has high specificity, high sensitivity, and high positive predictive value. The 2-hour oral glucose challenge has the drawback, however, that the subject must be fasting and must be at the screening site for at least 2 hours. The glucose challenge is thus a relatively complex procedure that requires considerable cooperation from the subject. Hence it is not ideal for use in screening for diabetes, either in asymptomatic patients considered to be at risk for diabetes or in the general population.

Screening by glucose challenge has the virtue that most individuals with 2-hour values ≥200 mg/dl will be confirmed to have NIDDM on a repeat OGTT, and they are at high risk for already having or for developing the complications of diabetes. Conversely, subjects with lower 2-hour glucose values do not appear to be at risk for complications. For example, persons with IGT (2-hour glucose 140-199 mg/dl) in a 10-year study did not develop diabetic retinopathy as long as they remained as IGT, although retinopathy began to develop within 5 years in those who progressed to overt diabetes[50].

*Table 2.9*

Factors in Screening for NIDDM by Glucose Challenge and Fasting Plasma Glucose, U.S., Age 40-69 Years

| Screening test (mg/dl) | Sensitivity % | Specificity % | PPV % | PRR % |
|---|---|---|---|---|
| Post-challenge plasma glucose | | | | |
| 2-hour ≥200 | 97 | 100 | 100 | 5.5 |
| Fasting plasma glucose | | | | |
| ≥80 | 98 | 4 | 6 | 96.3 |
| ≥90 | 93 | 32 | 8 | 69.8 |
| ≥100 | 83 | 76 | 17 | 27.4 |
| ≥110 | 65 | 93 | 37 | 10.1 |
| ≥120 | 54 | 98 | 65 | 4.7 |
| ≥130 | 42 | 100 | 91 | 2.6 |
| ≥140 | 31 | 100 | 100 | 1.8 |

PPV, positive predictive value; PRR, percent of screenees requiring retesting by oral glucose tolerance test. Data are based on a representative sample of adults age 40-69 years in the 1976-80 Second National Health and Nutrition Examination Survey. NIDDM was defined by fasting plasma glucose ≥140 mg/dl and/or 2-hour OGTT glucose ≥200 mg/dl. Subjects with a medical history of diabetes were excluded. See text for definitions of screening parameters.

*Source*: References 59 and 75

## SCREENING BY FASTING PLASMA GLUCOSE

In the U.S. population, there is a broad distribution of FPG among adults with undiagnosed NIDDM (Figure 2.10), and only ~26% of people age 20-74 years with undiagnosed NIDDM have fasting hyperglycemia (≥140 mg/dl)[10]. Other studies have also found that as many as 80% of diabetes cases discovered in population screening by OGTT have FPG <140 mg/dl[32,75-81]. Thus, FPG appears to be an insensitive test in population screening for undiagnosed NIDDM. Appendices 2.1 and 2.2 show the prevalence of IGT and undiagnosed NIDDM, and their percent distributions, according to fasting plasma glucose.

Table 2.9 presents information on screening by FPG in the U.S. population age 40-69 years[75]. The data indicate that no FPG cutoff point provides an adequate screening method in the general population. For example, at FPG ≥100 mg/dl, sensitivity and specificity are moderate (83% and 76%, respectively) and the percent requiring retesting for confirmation of the diagnosis of diabetes is relatively low (27%). How-

*Figure 2.10*

Percent Distribution of Fasting Plasma Glucose in U.S. Adults, 1976-80

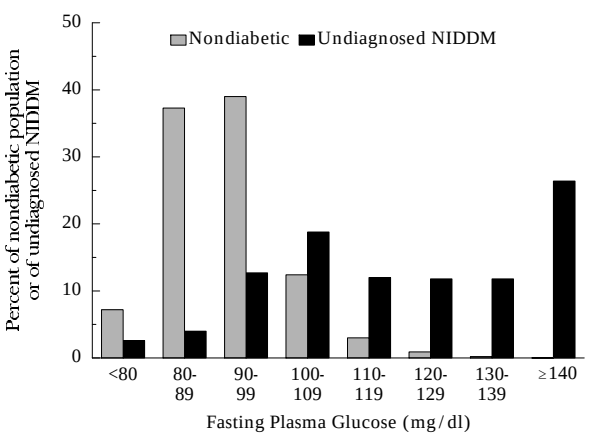



Figure shows the distribution of nondiabetics (2-hour OGTT glucose <200 mg/dl) and those with undiagnosed NIDDM (2-hour OGTT glucose ≥200 mg/dl), according to plasma glucose after an overnight 10-16 hour fast. Data are based on a representative sample of people age 20-74 years in the 1976-80 Second National Health and Nutrition Examination Survey.

*Source*: References 59 and 75

ever, positive predictive value is low: Only 17% of persons with FPG ≥100 mg/dl meet diagnostic criteria for diabetes. Thus, for every six subjects identified by such screening, only one might actually have diabetes.

Table 2.10 presents the sensitivity and percent requiring retesting by confirmatory OGTT when FPG ≥100 mg/dl is used as a screening criterion in various high-risk groups in the United States[75]. Sensitivity is somewhat lower in women compared with men, but there is little effect of age or ethnicity. Body mass index (BMI) <23 is associated with considerably lower sensitivity, with no difference between the two higher BMI categories (23-26.9 and ≥27). However, individuals with BMI <23 constitute only ~10% of all NIDDM cases. Hypertension, treated or untreated, has no consistent effect on sensitivity. In summary, variations in sensitivity by age, sex, ethnic group, BMI, or blood pressure status appear to be too small to have practical implications regarding the effectiveness of screening by FPG. Thus, while FPG ≥100 mg/dl is relatively more effective than other FPG cutoff points (Table 2.9), it is inadequate for screening in the total U.S. population or in high-risk groups (Table 2.10). Other studies on screening for undiagnosed NIDDM are shown in Table 2.11.

*Table 2.10*
Sensitivity and Percent Requiring Retesting (PRR) for FPG ≥100 mg/dl in High-Risk Groups, U.S., Age 40-69 Years

| | Sensitivity % | PRR % |
|---|---|---|
| Total | 83.1 | 27.4 |
| Sex | | |
| Men | 88.8 | 32.4 |
| Women | 79.6 | 23.1 |
| Age (years) | | |
| 40-49 | 82.6 | 22.7 |
| 50-59 | 81.9 | 27.7 |
| 60-69 | 84.2 | 33.6 |
| Race | | |
| White | 83.5 | 27.4 |
| Black | 79.2 | 30.1 |
| BMI | | |
| <23 | 43.3 | 14.1 |
| 23-26.9 | 84.0 | 26.2 |
| ≥27 | 89.4 | 39.0 |
| Blood pressure | | |
| Normotensive | 82.0 | 20.7 |
| Hypertensive | | |
| Untreated | 82.7 | 36.0 |
| On AHM | 84.5 | 39.9 |

FPG, fasting plasma glucose; BMI, body mass index. Hypertension defined by systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg or use of antihypertensive medications (AHM) including diuretics. Data are based on a representative sample of adults age 40-69 years in the 1976-80 Second National Health and Nutrition Examination Survey. NIDDM was defined by FPG ≥140 mg/dl and/or 2-hour oral glucose tolerance test glucose ≥200 mg/dl. Subjects with a medical history of diabetes were excluded.

*Source*: Reference 75

It is likely that screening by FPG ≥140 mg/dl identifies a group at greater risk for developing complications than those who have FPG <140 mg/dl with post-challenge hyperglycemia ≥200 mg/dl. A Japanese study found the fasting value to be more predictive of mortality than the 2-hour value[33], while in Pima Indians both the fasting and the 2-hour value and glycosylated hemoglobin predict retinopathy and nephropathy[27,34,35].

## SCREENING BY OTHER METHODS

Other methods of screening for undiagnosed NIDDM have been evaluated and found to be inadequate[68]. Glycosylated hemoglobin has the same advantages as FPG, requiring only one blood sample and minimal patient cooperation, and in addition is not affected by time of day or recent food intake. However, in populations such as in the United States, with prevalence of undiagnosed diabetes of ~5%-10% among adults and a minority of undiagnosed NIDDM having fasting hyperglycemia, there is considerable overlap between the glycohemoglobin distribution of nondiabetic and diabetic groups[32,82-86]. If the screening value is set high enough, specificity is high but sensitivity is low[32] (Table 2.11). In populations such as the Pima Indians that have a high prevalence of fasting hyperglycemia, diabetes, and microvascular complications, glycosylated hemoglobin is as effective as FPG or 2-hour post-challenge glucose in detecting NIDDM (Table 2.11) and predicting the development of retinopathy and nephropathy[35,87]. Measurements of casual or random blood glucose or urine glucose are not acceptable screening methods because these cannot be standardized with regard to risk of having diabetes or developing its complications, due to the considerable fluctuations of blood and urine glucose levels according to the interval since the preceding meal, the unstandardized content of the meal, and the often-unknown renal threshold for glycosuria.

### SCREENING IN HIGH-RISK POPULATIONS

The major risk factors for NIDDM include older age; obesity; a family history of diabetes; race/ethnicity of black, American Indian, or Hispanic; and presence of complications related to diabetes. These data are readily obtainable through interview and the simple meas-

*Table 2.11*
Sensitivity and Specificity of Some Tests Used in Screening for Undiagnosed NIDDM

| Ref. | Population | Screening test | Sensitivity (%) | Specificity (%) |
|---|---|---|---|---|
| 76 | Rancho Bernardo, CA, whites age 50-64 years | FPG ≥110 mg/dl | 88 | 87 |
| | | FPG ≥140 mg/dl | 31 | 99 |
| 76 | Rancho Bernardo, CA, whites age 65-79 years | FPG ≥110 mg/dl | 60 | 80 |
| | | FPG ≥140 mg/dl | 21 | 100 |
| 77 | San Antonio, TX, age 25-64 years | | | |
| | Mexican American | FPG ≥140 mg/dl | 55 | 100 |
| | Non-Hispanic white | FPG ≥140 mg/dl | 32 | 100 |
| 78 | Wadena, MN, sample of primarily white adults | FPG ≥115 mg/dl | 68 | 97 |
| | | FPG ≥140 mg/dl | 40 | 100 |
| 32, 75 | Israel, sample of Jewish population age 40-70 years | FPG ≥100 mg/dl | 92 | 45 |
| | | FPG ≥140 mg/dl | 38 | 100 |
| | | HbA1 ≥6.0 (mean of normal population=6.8) | 92 | 21 |
| 79 | Arizona, Pima and Tohono O'odham Indians, age >15 years | FPG ≥110 mg/dl | 95 | 90 |
| | | FPG ≥123 mg/dl | 88 | 98 |
| | | FPG ≥140 mg/dl | 75 | 100 |
| | | HbA1c ≥5.8 | 92 | 89 |
| | | HbA1c ≥6.3 | 80 | 98 |
| | | Quantitative nonfasting glycosuria ≥1.94 mmol/L | 81 | 98 |
| 81 | Nauru, South Pacific, age ≥20 years | FPG ≥126 mg/dl | 78 | 98 |
| | | FPG ≥140 mg/dl | 60 | 99 |
| 82 | Paris, France, selected group of outpatients at a diabetes screening center | FPG ≥140 mg/dl | 52 | 99 |
| | | HbA1c >6 (mean of normal population=5.0) | 60 | 91 |

All studies used either World Health Organization or National Diabetes Data Group criteria for diabetes; FPG, fasting plasma glucose.

*Source*: References are listed within the table

urement of height and weight. Hence these are excellent candidates for use in screening for undiagnosed NIDDM.

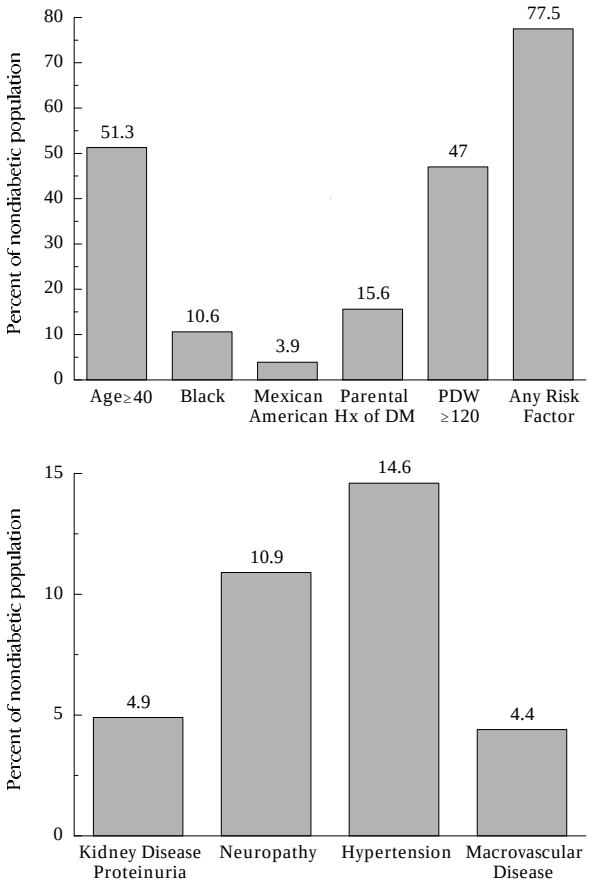
## PREVALENCE OF RISK FACTORS FOR NIDDM

The frequency of risk factors for NIDDM and of complications related to NIDDM in a representative sample of the U.S. population age ≥18 years without diagnosed diabetes is shown in Figure 2.11 and Table 2.12[53]. About 51% of U.S. adults are age ≥40 years, and 47.0% are 20% or more above ideal weight (based on self-reported height and weight). Blacks and Mexican Americans comprise 10.6% and 3.9% of adults, respectively, and 15.6% of all adults have a parental history of diabetes. About 78% have at least one risk factor for NIDDM. A small proportion of adults report conditions that are complications related to NIDDM, with hypertension being reported most frequently (14.6%). Figure 2.12 shows the percent distribution of adults and number of people (in millions), according to number of risk factors for NIDDM or diabetes-related complications[53]. A large proportion of U.S. adults (22.9%, 38 million people) have three or more risk factors or diabetes-related complications.

## PREVALENCE OF UNDIAGNOSED NIDDM IN HIGH-RISK GROUPS

Figure 2.13 shows the prevalence of undiagnosed NIDDM determined by OGTT in a representative sample of U.S. adults according to the presence or absence of risk factors for diabetes[53]. Undiagnosed NIDDM is significantly more prevalent in those age ≥40 years, those with a family history of diabetes, and those with PDW ≥120. Prevalence among individuals with all three of these risk factors for NIDDM was 11.7%, whereas prevalence among individuals with none of these risk factors was only 0.4%. Prevalence of NIDDM in those age 20-74 years was also somewhat higher among blacks and Mexican Americans, compared with non-Hispanic whites.

*Figure 2.11*
Frequency of Risk Factors for and Complications of NIDDM in Nondiabetic Adults, U.S., 1989




PDW, percent desirable weight; hx, history; DM, diabetes. Figure shows prevalence of risk factors for NIDDM (top panel) and complications related to NIDDM (bottom panel) reported by a representative sample of U.S. adults age ≥18 years with no medical history of diabetes, based on the 1989 National Health Interview Survey Diabetes Risk Factor Supplement.

*Source*: Reference 53

## NIDDM SCREENING RATES IN HIGH-RISK GROUPS

The proportion of nondiabetic adults who reported being screened for diabetes in the previous year is shown in Figure 2.14 and Table 2.12 according to risk factors and complications related to NIDDM[53]. The percent screened increased with age. Screening rates were higher for women (34.2%) compared with men (27.6%) and for blacks compared with other racial/ethnic groups. The percent screened was higher in those with a family history of diabetes compared with those without, and the percent increased with increasing level of PDW. Screening rates were consistently higher in persons with complications related to NIDDM compared with those without, particularly in those with hypertension and macrovascular disease.

*Table 2.12*
Distribution of Nondiabetic Adults and Percent Screened for Diabetes in the Past Year, U.S., 1989

| | Percent distribution | Percent screened for diabetes | Age-standardized percent screened for diabetes |
|---|---|---|---|
| All persons | 100.0 | 31.0 | |
| Age (years) | | | |
| 18-39 | 48.7 | 23.1 | |
| 40-64 | 35.7 | 35.6 | |
| ≥65 | 15.6 | 46.0 | |
| Sex | | | |
| Men | 48.7 | 27.6 | 28.2 |
| Women | 51.3 | 34.2 | 33.6 |
| Race | | | |
| Non-Hispanic white | 79.5 | 31.2 | 30.6 |
| Non-Hispanic black | 10.6 | 36.0 | 37.4 |
| Mexican American | 3.9 | 27.9 | 32.1 |
| Other Hispanic | 3.1 | 24.9 | 27.0 |
| Asian/Pacific Islander | 2.2 | 16.0 | 18.8 |
| American Indian | 0.7 | 21.8 | 23.1 |
| Parental history of diabetes | | | |
| Yes | 15.6 | 38.4 | 38.3 |
| No | 84.4 | 29.5 | 29.7 |
| Current PDW | | | |
| <100 | 11.7 | 24.0 | 25.7 |
| 100-119 | 41.3 | 29.5 | 30.3 |
| 120-139 | 28.5 | 32.7 | 31.5 |
| ≥140 | 18.5 | 36.4 | 34.6 |
| Kidney disease or proteinuria | | | |
| Yes | 4.9 | 39.4 | 38.2 |
| No | 95.1 | 30.5 | 30.6 |
| Sensory neuropathy | | | |
| Yes | 10.9 | 40.1 | 37.1 |
| No | 89.1 | 29.9 | 30.2 |
| Hypertension | | | |
| Yes | 14.6 | 47.6 | 38.8 |
| No | 85.4 | 26.5 | 27.7 |
| Macrovascular disease | | | |
| Yes | 4.4 | 50.0 | 41.4 |
| No | 95.6 | 28.7 | 29.4 |
| Marital status | | | |
| Married | 64.2 | 32.4 | 31.5 |
| Widowed | 6.9 | 42.9 | 26.4 |
| Divorced/separated | 9.8 | 29.8 | 29.6 |
| Never married | 19.2 | 22.9 | 29.2 |
| Urban/rural | | | |
| Central city | 30.4 | 32.4 | 32.7 |
| Not central city | 46.9 | 31.2 | 31.4 |
| Nonfarm | 21.3 | 28.8 | 28.1 |
| Farm | 1.5 | 27.4 | 25.8 |
| Region | | | |
| Northeast | 20.1 | 35.1 | 34.5 |
| Midwest | 24.8 | 31.1 | 31.2 |
| South | 34.6 | 30.7 | 30.8 |
| West | 20.5 | 27.2 | 27.3 |

*Table 2.12—Continued next page*

*Table 2.12—Continued*

| | Percent distribution | Percent screened for diabetes | Age-standardized percent screened for diabetes |
|---|---|---|---|
| Currently working | | | |
| Yes | 69.2 | 28.1 | 30.0 |
| No | 30.8 | 37.4 | 30.9 |
| Family income | | | |
| <$10,000 | 10.7 | 28.9 | 26.7 |
| $10,000-19,999 | 17.1 | 29.2 | 27.5 |
| $20,000-39,999 | 29.6 | 30.0 | 31.1 |
| ≥$40,000 | 28.2 | 33.7 | 34.6 |
| Unknown | 14.6 | 31.2 | 29.1 |
| Education (grade) | | | |
| <9 | 9.2 | 31.4 | 22.2 |
| 9-12 | 50.4 | 29.2 | 29.2 |
| >12 | 40.4 | 33.0 | 35.0 |
| Health insurance | | | |
| Yes | 86.9 | 33.0 | 32.3 |
| No | 13.1 | 17.9 | 21.0 |
| Number of doctor visits in past 12 months | | | |
| Zero | 26.0 | 10.4 | 10.2 |
| 1-2 | 38.2 | 32.6 | 33.2 |
| 3-4 | 15.6 | 41.8 | 39.9 |
| ≥5 | 20.3 | 47.5 | 45.1 |
| Hospitalization in past 12 months | | | |
| Yes | 7.7 | 49.0 | 45.4 |
| No | 92.3 | 29.6 | 29.9 |
| Parity (women) | | | |
| Zero | 27.5 | 30.7 | 34.1 |
| 1-2 | 40.5 | 34.2 | 33.8 |
| 3-4 | 23.3 | 37.0 | 33.3 |
| ≥5 | 8.6 | 36.9 | 24.2 |

PDW, percent desirable weight. Table shows data for adults age ≥18 years who had no medical history of diabetes, based on the 1989 National Health Interview Survey Diabetes Risk Factor Supplement.

*Source*: Reference 53

Even after age adjustment, screening rates remained higher in those with risk factors or complications. Rates were highest in the Northeast compared with other regions. Rates increased with higher levels of socioeconomic status and health care utilization.

Figure 2.15 shows screening rates among U.S. nondiabetic adults according to the number of risk factors and diabetes-related complications[53]. Screening rates increased with a greater number of risk factors and diabetes-related complications. Among those with three and those with four or more risk factors and complications, screening rates were 38.6% and 57.1%, respectively.

*Figure 2.12*

Percent Distribution and Number of Nondiabetic Adults with NIDDM Risk Factors, U.S., 1989

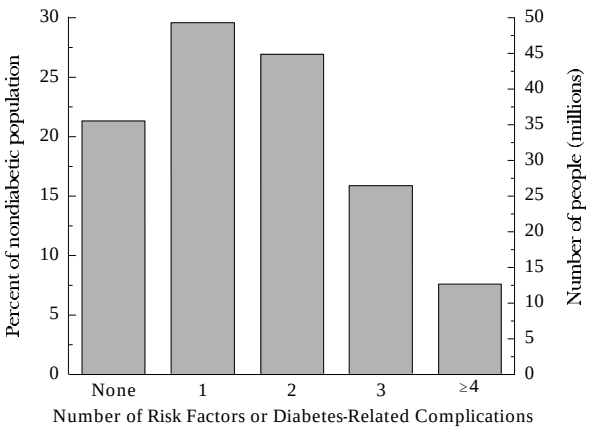
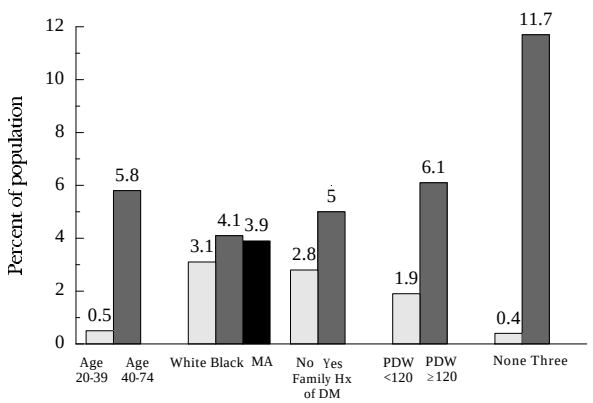



Figure shows data for adults age ≥18 years with no medical history of diabetes, according to number of risk factors for NIDDM or complications related to NIDDM (Figure 2.11), based on self-report by a representative sample of adults in the 1989 National Health Interview Survey Diabetes Risk Factor Supplement.

*Source*: Reference 53

*Figure 2.13*

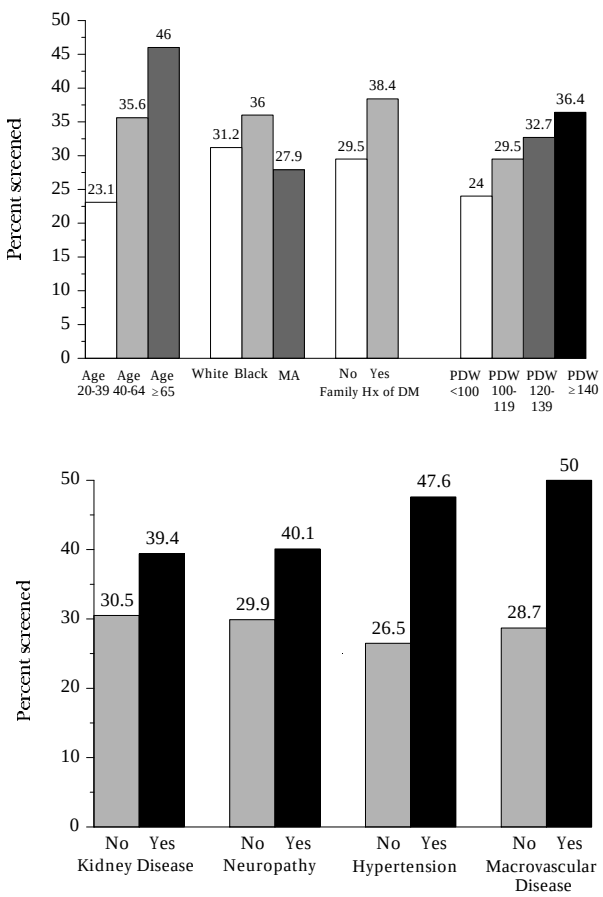
Prevalence of Undiagnosed NIDDM Determined by OGTT According to NIDDM Risk Factors, U.S., 1976-80




MA, Mexican American; PDW, percent desirable weight; hx, history; DM, diabetes; OGTT, oral glucose tolerance test. Undiagnosed NIDDM was determined by a 2-hour OGTT using World Health Organization criteria in a representative sample of U.S. adults age 20-74 years in the 1976-80 Second National Health and Nutrition Examination Survey; estimates for Mexican Americans are from the 1982-84 Hispanic Health and Nutrition Examination Survey. "None" and "Three" refer to the risk factors: age 40-74 years, positive family history of diabetes, and PDW ≥120.

*Source*: Reference 53

*Figure 2.14*
Frequency of Screening for NIDDM in High-Risk Groups, U.S., 1989




PDW, percent desirable weight; hx, history; DM, diabetes; MA, Mexican American. Figure shows percent of U.S. adults age ≥18 years with no medical history of diabetes who were screened for diabetes in the previous year, according to risk factors for NIDDM (top panel) and complications related to NIDDM (bottom panel), based on self-report by a representative sample of adults in the 1989 National Health Interview Survey Diabetes Risk Factor Supplement.

*Source*: Reference 53

*Figure 2.15*
Frequency of Screening for NIDDM According to Number of NIDDM Risk Factors, U.S., 1989

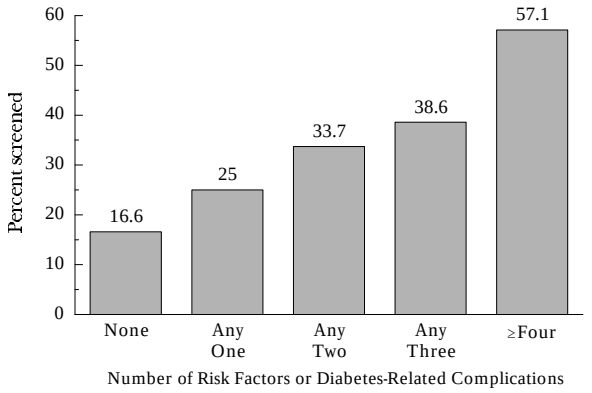



Figure shows percent of U.S. adults age ≥18 years with no medical history of diabetes who were screened for diabetes in the previous year, according to number of risk factors for and complications related to NIDDM, based on self-report by a representative sample of adults in the 1989 National Health Interview Survey Diabetes Risk Factor Supplement. Risk factors/complications include age ≥40 years, parental history of diabetes, percent desirable weight ≥120, black or Mexican American, hypertension, and diabetes-related complications (kidney disease/proteinuria, neuropathy, and macrovascular disease).

*Source*: Reference 53

## SCREENING YIELDS IN HIGH-RISK POPULATIONS

Information on screening in high-risk populations is shown in Table 2.13, which demonstrates how the proportion of the population who have undiagnosed NIDDM is enriched when age, obesity, and family history of diabetes are considered[59]. Among all persons age 40-69 years in the total U.S. population, 5.5% have undiagnosed NIDDM. If all of these were screened, all people with undiagnosed NIDDM would be detected. If screening were limited to people with a PDW of ≥120, only 41% of the population would have to be tested, 9.0% would have undiagnosed NIDDM and this would detect 67% of all cases of undiagnosed NIDDM. If family history of diabetes were added as a criterion, only 14% of the population would be tested and 12% would have undiagnosed NIDDM, but only 29% of all undiagnosed cases would be detected. This shows that most people with undiagnosed NIDDM do not have or do not know they have a family history of diabetes, which is probably a major reason why they remain undiagnosed. If a PDW of ≥140 were used, only 16% of the population would be screened, the prevalence of undiagnosed NIDDM would be 14.4%, and this would capture ~42% of all cases. If family

*Table 2.13*
Screening for Undiagnosed NIDDM by 2-Hour Post-Challenge Glucose, U.S., Age 40-69 Years

| Population screened | Percent of total | Percent with undiagnosed NIDDM | Percent of all undiagnosed NIDDM |
|---|---|---|---|
| Total | 100 | 5.5 | 100 |
| PDW ≥120 | 41 | 9.0 | 67 |
| PDW ≥120 and family hx of DM | 14 | 11.7 | 29 |
| PDW ≥140 | 16 | 14.4 | 42 |
| PDW ≥140 and family hx of DM | 6 | 24.6 | 25 |

PDW, percent desirable weight; hx, history; DM, diabetes. Data are based on a representative sample of adults age 40-69 years in the 1976-80 Second National Health and Nutrition Examination Survey. NIDDM was defined by fasting plasma glucose ≥140 mg/dl and/or 2-hour oral glucose tolerance test glucose ≥200 mg/dl. Subjects with a medical history of diabetes were excluded.

*Source*: Reference 59

history were added as a criterion, 6% of the population would be screened and the prevalence of NIDDM in this high-risk group would be as high as 25%; that is, one in every four people who were screened would be found to have undiagnosed NIDDM, although this would capture only 25% of all cases. Whichever high-risk group is chosen, or whether clinicians choose to screen all patients who they think might have NIDDM, the data in Table 2.13 can provide several scenarios for screening.

The choice of screening method and criteria to be used depends on the screening situation. In public screening programs, considerations of cost and efficiency are important and it might be considered important to screen only very high-risk groups to ensure high yields of positive screenees, although this would miss significant numbers of persons with NIDDM (Table 2.13). In physician's offices, where the focus is on care of the individual patient, it would appear appropriate to relax the screening exclusions and be more inclusive. Screening for undiagnosed NIDDM can also be accomplished in the context of programs directed toward other medical conditions that are frequent in people with diabetes, such as hypertension and hypercholesterolemia.

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## REFERENCES


1. National Diabetes Data Group: Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. *Diabetes* 28:1039-57, 1979
2. World Health Organization: *Report of the Expert Committee on Diabetes.* WHO Technical Report Series, no. 646, Geneva, Switzerland, 1980
3. World Health Organization: *Diabetes Mellitus, Report of a Study Group.* WHO Technical Report Series, no. 727, Geneva, Switzerland, 1985
4. National Center for Health Statistics: Current estimates from the National Health Interview Survey, United States, 1992. *Vital and Health Statistics*, Series 10, no. 189, 1994
5. Harris MI, Cowie CC, Howie LJ: Self monitoring of blood glucose by adults with diabetes in the U.S. population. *Diabetes Care* 16:1116-23, 1993
6. Harris MI, Robbins DC: Prevalence of adult-onset IDDM in the U.S. population. *Diabetes Care* 17:1337-40, 1994
7. Melton LJ, Palumbo PJ, Chu C: Incidence of diabetes by clinical type. *Diabetes Care* 6:75-86, 1983
8. Melton LJ, Ochi JW, Palumbo PJ, Chu CP: Sources of disparity in the spectrum of diabetes at incidence and prevalence. *Diabetes Care* 6:427-31, 1983
9. Harris MI, Hadden WC, Knowler WC, Bennett PH: Prevalence of diabetes and impaired glucose tolerance and plasma glucose levels in U.S. population aged 20-74 yr. *Diabetes* 36:523-34, 1987
10. Harris MI, Hadden WC, Knowler WC, Bennett PH: International criteria for the diagnosis of diabetes and impaired glucose tolerance. *Diabetes Care* 8:562-67, 1985
11. Harris MI, Klein RE, Welborn TA, Knuiman MW: Onset of NIDDM occurs at least 4-7 years before clinical diagnosis. *Diabetes Care* 15:815-19, 1992
12. Klein R, Klein BEK, Moss SE, Davis MD, DeMets DL: The Wisconsin Epidemiologic Study of Diabetic Retinopathy. III. Prevalence and risk of diabetic retinopathy when age at diagnosis is 30 or more years. *Arch Ophthalmol* 102:527-32, l984
13. Haffner SM, Fong D, Stern MP, Pugh JA, Hazuda HP, Patterson JK, Van Heuven WAJ, Klein R: Diabetic retinopathy in Mexican Americans and non-Hispanic whites. *Diabetes* 37:878-84, 1988
14. Hamman RF, Mayer EJ, Moo-Young G, Hildebrandt W, Marshall JA, Baxter J: Prevalence and risk factors of diabetic retinopathy in non-Hispanic Whites and Hispanics with NIDDM: San Luis Valley diabetes study. *Diabetes* 38:1231-37, 1989
15. Klein R, Klein BEK, Moss S, DeMets DL: Proteinuria in diabetes. *Arch Intern Med* 148:181-86, 1988
16. Fabre J, Balant LP, Dayer PG, Fox HM, Vernet AT: The kidney in maturity-onset diabetes mellitus, a clinical study of 510 patients. *Kidney Int* 21:730-38, l982
17. Haffner SM, Mitchell BD, Pugh JA, Stern MP, Kozlowski MK, Hazuda HP, Patterson JK, Klein R: Proteinuria in Mexican Americans and non-Hispanic whites with NIDDM. *Diabetes Care* 12:530-36, 1989
18. Siitonen O, Uusitupa M, Pyorala K, Voutilainen E, Lansimies E: Peripheral arterial disease and its relationship to cardiovascular risk factors and coronary heart disease in newly diagnosed non-insulin-dependent diabetics. *Acta Med Scand* 220:205-12, 1986
19. Uusitupa M, Siitonen O, Aro A, Pyorala K: Prevalence of coronary heart disease, left ventricular failure and hypertension in middle aged newly diagnosed type 2 (non-insulin-dependent) diabetic subjects. *Diabetologia* 28:22-27, 1985
20. Siitonen O, Uusitupa M, Pyorala K, Lansimies E, Voutilainen E: Aortic calcifications and their relationship to coronary heart disease and cardiovascular risk factors in patients with newly diagnosed non-insulin-dependent diabetes and in nondiabetic subjects. *Cardiology* 74:335-43, l987
21. Al Sayegh H, Jarrett RJ: Oral glucose tolerance tests and the diagnosis of diabetes—results of a prospective study based on the Whitehall Survey. *Lancet* 1:431, 1979
22. Bennett PH, et al.: Epidemiologic studies of diabetes in the Pima Indians. *Recent Prog Horm Res* 32:333, 1976
23. Fitzgerald MG, Malins JM: Ten-year follow-up report on the Birmingham Diabetes Survey of 1961. *Br Med J* 2:35, 1976
24. Keen H, Jarrett RJ, McCartney P: The ten-year follow-up of the Bedford Survey (1962-72): Glucose tolerance and diabetes. *Diabetologia* 22:73-78, 1982
25. O'Sullivan JM, Mahan CM: Prospective study of 352 young patients with chemical diabetes. *N Engl J Med* 278:1038, 1968
26. Rushforth NB, Miller M, Bennett PH: Fasting and two-hour post-load glucose levels for the diagnosis of diabetes. The relationship between glucose levels and complications of diabetes in the Pima Indians. *Diabetologia* 16:373-79, 1979
27. Knowler WC, Pettitt DJ, Saad MF, Bennett PH: Diabetes mellitus in the Pima Indians: Incidence, risk factors and pathogenesis. *Diabetes Metabolism Reviews* 6:1-27, 1990
28. Zimmet P, Whitehouse S: Bimodality of fasting and two-hour glucose tolerance distributions in a Micronesian population. *Diabetes* 27:793-800, 1978
29. Rosenthal M, McMahan CA, Stern MP, Eifler CW, Haffner SM, Hazuda HP, Franco LJ: Evidence of bimodality of two hour plasma glucose concentrations in Mexican Americans: Results from the San Antonio Heart Study. *J Chron Dis* 38:5-16, 1985
30. Bennett PH, Knowler WC, Pettitt DJ, Carraher MJ, Vasquez B: Longitudinal studies of the development of diabetes in the Pima Indians. In *Advances in Diabetes Epidemiology*, Eschwege E, ed. Amsterdam, The Netherlands, Elsevier, p. 65-74, 1982
31. Massari V, Eschwege E, Valleron AJ: Imprecision of new criteria for the oral glucose tolerance test. *Diabetologia* 24:100-06, 1983
32. Modan M, Halkin H, Karasik A, Lusky A: Effectiveness of glycosylated hemoglobin, fasting plasma glucose, and a single post load plasma glucose level in population screening for glucose intolerance. *Am J Epid* 119:431-44, 1984
33. Sasaki A: Assessment of new criteria for diabetes according to ten-year survival rates. *Diabetologia* 20:195, 1981
34. Pettitt DJ, Knowler WC, Lisse JR, Bennett PH: Development of retinopathy and proteinuria in relation to plasma glucose concentration. *Lancet* ii:1050-52, 1980
35. McCance DR, Hanson RL, Charles MA, Jacobsson LTH, Pettitt DJ, Bennett PH, Knowler WC: Comparison of tests for glycated haemoglobin and fasting and two hour plasma glucose concentration as diagnostic methods for diabetes. *Brit*

*Med J* 308:1323-28, 1994

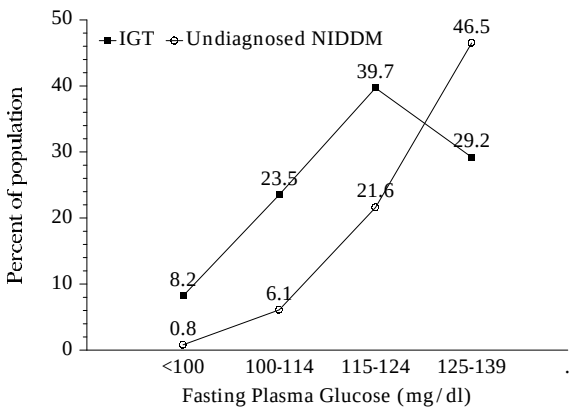
36. O'Sullivan JM, Mahan CM: Criteria for the oral glucose tolerance test in pregnancy. *Diabetes* 13:278, 1964
37. O'Sullivan JM, Mahan CM, Charles D, Dandrow RV: Screening criteria for high-risk gestational diabetic patients. *Am J Obstet Gynecol* 116:895-900, 1973
38. Second International Workshop Conference on Gestational Diabetes: Summary and recommendations. *Diabetes* 34 (Suppl. 2):123-26, 1985
39. Hamman RF, Bennett PH, Miller M: Incidence of diabetes among the Pima Indians. *Adv Metab Dis* 9:49-63, 1978
40. Jarrett RJ, Keen H, Fuller JH, McCartney M: Worsening to diabetes in men with impaired glucose tolerance ("borderline diabetes"). *Diabetologia* 16:25-30, 1979
41. Jarrett RJ, Keen H, McCartney P: The Whitehall study: Ten-year follow-up report on men with impaired glucose tolerance with reference to worsening to diabetes and predictors of death. *Diabetic Medicine* 1:279-83, 1984
42. Sartor G, Schersten B, Carlstrom S, Melander A, Norden A, Persson G: Ten-year follow-up of subjects with impaired glucose tolerance. Prevention of diabetes by tolbutamide and diet regulation. *Diabetes* 29:41-49, 1980
43. Eriksson KF, Lindegarde F: Impaired glucose tolerance in a middle-aged male urban population: A new approach for identifying high-risk cases. *Diabetologia* 33:526-31, 1990
44. Niskanen LK, Uusitupa MI, Sarlund H, Siitonen O, Pyorala K: Five-year follow-up study on plasma insulin levels in newly diagnosed NIDDM patients and nondiabetic subjects. *Diabetes Care* 13:41-48, 1990
45. Haffner SM, Stern MP, Mitchell BD, Hazuda HP, Patterson JK: Incidence of type II diabetes in Mexican Americans predicted by fasting insulin and glucose levels, obesity, and body-fat distribution. *Diabetes* 39:283-88, 1990
46. Riccardi G, Vaccaro O, Rivellese A, Pignalosa S, Tutino L, Mancini M: Reproducibility of the new diagnostic criteria for impaired glucose tolerance. *Am J Epidemiology* 121:422-29, 1985
47. Glatthaar C, Welborn TA, Stenhouse NS, Garcia-Webb P: Diabetes and impaired glucose tolerance, a prevalence estimate based on the Busselton 1981 survey. *Medical Journal of Australia* 143:436-40, 1985
48. Balkau B, Eschwege E: Repeatability of the oral glucose tolerance test for the diagnosis of impaired glucose tolerance and diabetes mellitus. *Diabetologia* 34:201-03, 1991
49. Bourn DM, Williams SM, Mann JI: Distinguishing between persistent and transient impaired glucose tolerance using a prediction model. *Diabetic Medicine* 9:744-48, 1992
50. Jarrett RJ: Duration of non-insulin-dependent diabetes and development of retinopathy: Analysis of possible risk factors. *Diabetic Medicine* 3:261-63, 1986
51. Fuller JH, Shipley MJ, Rose G, Jarrett RJ, Keen H: Coronary heart disease risk and impaired glucose tolerance: The Whitehall study. *Lancet* 1:1373-76, 1980
52. Harris MI: Frequency of oral glucose tolerance testing in the U.S. *Diabetes Care* 18:134-35, 1995
53. Cowie CC, Harris MI, Eberhardt MS: Frequency and determinants of screening for diabetes in the United States. *Diabetes Care* 17:1158-63, 1994
54. Harris MI: Testing for blood glucose by office-based physicians in the U.S. *Diabetes Care* 13:419-26, 1990
55. Centers for Disease Control: *Diabetes Surveillance*, 1993. Atlanta, GA, 1994
56. National Center for Health Statistics 1990: Annual summary of births, marriages, divorces, and deaths, United States, 1989. *Monthly Vital Statistics Report*, Vol. 38, no. 13, 1990
57. National Center for Health Statistics: Annual summary of births, marriages, divorces, and deaths, United States, 1990. *Monthly Vital Statistics Report*, Vol. 39, no. 13, 1991
58. Wilson JMG, Junger G: *Principles and Practice of Screening for Disease*. Geneva, World Health Organization, 1968
59. Harris MI: Undiagnosed NIDDM: Clinical and public health issues. *Diabetes Care* 16:642-52, 1993
60. Knowler WC, Bennett PH, Hamman RF, Miller M: Diabetes incidence and prevalence in Pima Indians: A 19-fold greater incidence than in Rochester, Minnesota. *Am J Epidemiol* 108:497-505, 1978
61. Knowler WC, Pettitt DJ, Savage PJ: Diabetes incidence in Pima Indians: Contributions of obesity and parental diabetes. *Am J Epidemiol* 113:144-56, 1981
62. Fujimoto WJ: Unpublished data from the Seattle, WA Japanese-America community-based study of diabetes, 1994
63. Barrett-Connor E: Unpublished data from the Rancho Bernardo, CA, community-based study of diabetes, 1994
64. Hamman RF: Unpublished data from the San Luis Valley Study, CO community-based study of diabetes, 1994
65. Lee ET: Unpublished data from the Strong Heart Study, 1994
66. Eschwege E, Richard JL, Thibult N, Ducimetiere P, Warnet JM, Claude JR, Rossselin GE: Coronary heart disease mortality in relation with diabetes, blood glucose, and plasma insulin levels, the Paris prospective study ten years later. *Hormone and Metab Res* 15 (Suppl.):41-46, 1985
67. Jarrett RJ, Shipley MJ: Type 2 (non-insulin-dependent) diabetes mellitus and cardiovascular disease—putative association via common antecedents; further evidence from the Whitehall study. *Diabetologia* 31:737-40, 1988
68. Harris MI, Modan M: Screening for NIDDM: Why is there no national program? *Diabetes Care* 17:440-44, 1994
69. American Diabetes Association: Position statement—screening for diabetes. *Diabetes Care* 12:588-90, 1989
70. Knowler WC: Screening for NIDDM. Opportunities for detection, treatment, and prevention. *Diabetes Care* 17:445-50, 1994
71. Bennett PH, Knowler WC: Early detection and intervention in diabetes mellitus: Is it effective? *J Chron Dis* 37:653-66, 1984
72. Singer DE, Samet JH, Coley CM, Nathan DM: Screening for diabetes mellitus. *Ann Int Med* 109:639-49, 1988
73. Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329:977-86, 1993
74. Eastman RC, Siebert CW, Harris M, Gorden P: Clinical review 51. Implications of the Diabetes Control and Complications Trial. *J Clin Endo Metab* 77:1105-07, 1993
75. Modan M, Harris MI: Fasting plasma glucose in screening for NIDDM in the U.S. and Israel. *Diabetes Care* 17:436-39, 1994
76. Blunt BA, Barrett-Connor E, Wingard DL: Evaluation of fasting plasma glucose as a screening test for non-insulin-dependent diabetes mellitus in older adults: Rancho Bernardo study. *Diabetes Care* 14:989-93, 1991
77. Haffner SM, Rosenthal M, Hazuda HP, Stern MP, Laercio J,

Franco LJ: Evaluation of three potential screening tests for diabetes in a biethnic population. *Diabetes Care* 7:347-53, 1984

78. Clements JP, French LR, Goetz FC: A re-evaluation of the effectiveness of a single fasting plasma glucose sample as a screening test for diabetes mellitus: The Wadena City health study. *Diabetes* 42 (Suppl. 1):31A, 1993
79. Hanson RL, Nelson RG, McCance DR, Beart JA, Charles MA, Pettitt DJ, Knowler WC: Comparison of screening tests for non-insulin-dependent diabetes mellitus. *Arch Intern Med* 153:2133-40, 1993
80. Taylor R, Zimmet P: Limitation of fasting plasma glucose for the diagnosis of diabetes mellitus. *Diabetes Care* 4:556-58, 1981
81. Finch CF, Zimmet PZ, Alberti KGMM: Determining diabetes prevalence: A rational basis for the use of fasting plasma glucose concentration? *Diabetic Medicine* 7:603-10, 1990
82. Simon D, Coignet MC, Thibult N, Senan C, Eschwege E: Comparison of glycosylated hemoglobin and fasting plasma glucose with two-hour post-load plasma glucose in the detection of diabetes mellitus. *Am J Epidemiol* 122:589-93, 1985
83. Orchard TJ, Daneman B, Becker DJ, Kuller LH, LaPorte RE, Drash AL, Wagener D. Glycosylated hemoglobin: A screening test for diabetes mellitus? *Prev Med* 11:595-601, 1982
84. Lester E, Frazer AD, Shepherd CA: Glycosylated hemoglobin as an alternative to the glucose tolerance test for the diagnosis of diabetes mellitus. *Ann Clin Biochem* 22:74-78, 1985
85. Little RR, England JD, Wiedmeyer HM, McKenzie EM, Pettitt DJ, Knowler WC, Goldstein DE: Relationship of glycosylated hemoglobin to oral glucose tolerance. *Diabetes* 37:60-64, 1988
86. Guillausseau PJ, Charles MA, Paolaggi F, Timsit J, Chanson P, Peynet J, Godard V, Eschwege E, Rousselet F, Lubetzki J: Comparison of HbA1 and fructosamine in diagnosis of glucose-tolerance abnormalities. *Diabetes Care* 13:898-900, 1990
87. Liu QZ, Pettitt DJ, Hanson RL, Charles MA, Klein R, Bennett PH, Knowler WC: Glycated haemoglobin, plasma glucose and diabetic retinopathy: Cross-sectional and prospective analysis. *Diabetologia* 36:428-32, 1993

*Appendix 2.1*

## Prevalence of IGT and Undiagnosed NIDDM According to Fasting Plasma Glucose, U.S., Age 20-74 Years

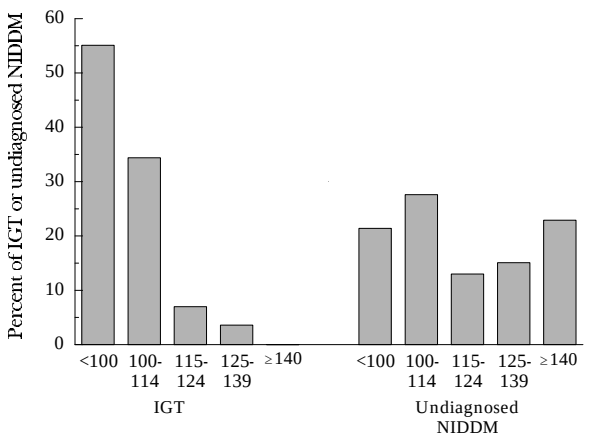



IGT, impaired glucose tolerance. IGT and undiagnosed NIDDM were ascertained by oral glucose tolerance test using World Health Organization criteria in a representative sample of U.S. adults age 20-74 years.

*Source*: 1976-80 Second National Health and Nutrition Examination Survey

*Appendix 2.2*

## Percent Distribution of IGT and Undiagnosed NIDDM According to Fasting Plasma Glucose (mg/dl), Age 20-74 Years, U.S., 1976-80




IGT, impaired glucose tolerance. IGT and undiagnosed NIDDM were ascertained by oral glucose tolerance test using World Health Organization criteria in a representative sample of U.S. adults age 20-74 years.

*Source*: 1976-80 Second National Health and Nutrition Examination Survey